THE JOURNAL
OF THE
AMERICAN CHEMICAL SOCIETY

VOL. LXX

JANUARY—MARCH
1948

EASTON, PA.
MACK PRINTING COMPANY
1948

JOURNAL OF THE
AMERICAN CHEMICAL SOCIETY

VOLUME 70 FEBRUARY 3, 1948 NUMBER 1

[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

The Isolation of the Fermentation *Lactobacillus casei* Factor

BY BRIAN L. HUTCHINGS, E. L. R. STOKSTAD, NESTOR BOHONOS,[1] NATHAN H. SLOANE[2] AND Y. SUBBAROW

On aerobic culture an unidentified organism belonging to the genus *Corynebacterium*[3] produces a compound that is essential for the growth of *Lactobacillus casei* under the conditions described for the detection of the "norite eluate factor."[4,5] The compound, therefore, belongs to the group of substances variously known as the "norite eluate factor,"[4,5] folic acid[6] and vitamin Bc.[7] A preliminary note on the isolation of the fermentation *L. casei* factor has appeared.[8]

The fermentation *L. casei* factor has been isolated as described herein. Before crystallization could be induced the solution had to contain small amounts of electrolytes. If the electrolytes were not present in the crystallizing solvent, gels were invariably formed. Under these specified conditions the compound was crystallized as the free acid, barium salt and methyl ester.

Difficulty has been experienced in obtaining consistent analyses. Therefore, from combustion data no empirical formula could be derived. However, the analyses do serve to distinguish this compound from any related compound previously reported.[7,9]

The ultraviolet absorption spectrum of the fermentation *L. casei* factor is presented in Fig. 1. The compound exhibits the same absorption characteristics as the liver *L. casei* factor.[10] The extinction coefficients are somewhat lower indicating that the fermentation *L. casei* factor is a higher molecular weight compound. The extinction coefficient at 365 mμ in 0.1 *N* sodium hydroxide is 134.

The fermentation compound has the same biological activity for animals as does the liver *L. casei* factor with the proviso that increased amounts are necessary to compensate for the higher molecular weight.[11]

The fermentation *L. casei* factor differs from the liver *L. casei* factor by its relative activity for *Lactobacillus casei* and *Streptococcus faecalis* R. The fermentation compound is 60–80% as active as the liver compound for *L. casei* but only 4–6% as active for *S. faecalis* R. The amounts of the fermentation compound required per ml. for half-maximum growth of *L. casei* and *S. faecalis* R., respectively, are 0.000061 and 0.0042 microgram.

The analyses and biological activity serve to distinguish this compound from any of the com-

---

(1) Present address: Department of Agricultural Chemistry, Purdue University, Lafayette, Indiana.

(2) Present address: Department of Bacteriology, Harvard University, Boston, Massachusetts.

(3) The organism was classified as *Corynebacterium sp.* One of the criteria of classification was the absence of spores. This was determined by heating the organism at 90° for varying lengths of time. The organism was killed even with short periods of heating.

Later studies have shown that the organism is not killed by heating at 85° for periods up to thirty minutes. This evidence introduces the possibility of the presence of spores and, of necessity, questions the validity of the previous classification. Attempts to demonstrate the presence of spores by staining techniques have not been successful. Until the question of the presence or absence of spores is answered, the above classification must be designated as tentative.

Sub-cultures of the organism will be sent on request. All requests should be directed to Dr. B. L. Hutchings, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

The organism can be cultured under aerobic conditions on a medium of the following composition: glucose, 20 g.; glycine, 4.0 g.; dipotassium hydrogen phosphate, 0.5 g.; potassium dihydrogen phosphate, 0.5 g.; ferrous sulfate heptahydrate, 0.04 g.; magnesium sulfate heptahydrate, 0.20 g.; thiamine, 0.40 mg., and tap water to 1 liter. A solid medium can be obtained by the addition of 20 g. of agar to the above medium.

(4) Snell and Peterson, *J. Bact.*, **39**, 273 (1940).

(5) Hutchings, Bohonos and Peterson, *J. Biol. Chem.*, **141**, 521 (1941).

(6) Mitchell, Snell and Williams, THIS JOURNAL, **63**, 2284 (1941).

(7) Pfiffner, *et al.*, *Science*, **97**, 404 (1943).

(8) Hutchings, *et al.*, *ibid.*, **99**, 371 (1944).

(9) Stokstad, *J. Biol. Chem.*, **149**, 573 (1943).

(10) Stokstad, *et al.*, THIS JOURNAL, **70**, 3 (1948).

(11) Hutchings, *et al.*, *J. Biol. Chem.*, **163**, 447 (1946).

pounds previously reported as influencing the growth of *L. casei* or *S. faecalis* R. under conditions of the test.

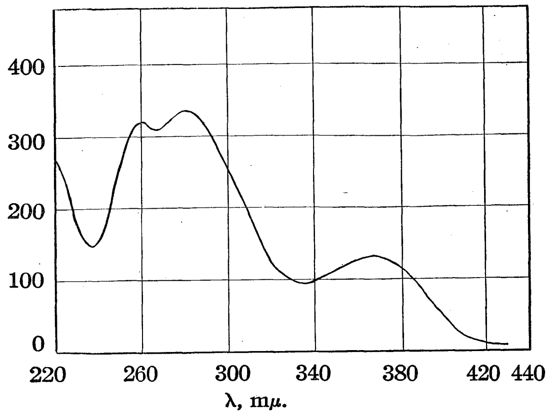


Fig. 1.—Ultraviolet absorption spectrum of fermentation *L. casei* factor in 0.1 *N* sodium hydroxide.

Experimental

Adsorption and Elution from Charcoal.—After removal of the bacterial cells the solution which contained from 3–5 γ of the active compound per ml. was adjusted to *p*H 3.0 and 6 g. of Norite A added per liter of filtrate. After thirty minutes adsorption, the charcoal was filtered off and washed well with water. The charcoal was eluted with 50% ethanol (6 liters per kg. of charcoal). This eluate was discarded. The charcoal was then eluted with 50% ethanol and 10% ammonium hydroxide (by volume) at 70° for one hour (12 liters per kg. of charcoal). The elution was repeated once. The eluates were combined. The recovery approximated 65%.

Precipitation of the Barium Salt.—The ammonia-ethanol eluates were adjusted to *p*H 8.0 with concentrated hydrochloric acid and ethanol added to a concentration of 85%. A saturated aqueous solution of barium chloride was added until complete precipitation occurred, meanwhile maintaining the *p*H at 8.0. After cooling to 0–5° the precipitate was centrifuged out and washed with methanol. The active compound was completely precipitated by this procedure.

Esterification and Extraction with Butanol.—The barium precipitate was suspended in 0.25 *N* methanol–hydrogen chloride (one-fifteenth the volume of the original filtrate) and esterified at room temperature. At the end of twenty-four hours the esterification mixture was adjusted to *p*H 4.5 by cautious addition of 5 *N* sodium hydroxide, and then concentrated to dryness under reduced pressure. The residue was suspended in a volume of water equivalent to a concentration of 15 micrograms per ml. of the active compound. The water insolubles were centrifuged out and discarded.

The aqueous solution was extracted 3 times with 2 volumes of butanol. Each butanol extract was in turn extracted with one-half volume of water. The combined butanol extracts were concentrated to one-sixth of their volume and extracted with one-half volume of water. This water wash was extracted with 2 volumes of butanol. The butanol extracts were combined and concentrated to dryness under reduced pressure. The esterification and butanol extraction gave a yield of 50–90%.

Fractionation from Methanol.—The residue after removal of the butanol was dissolved in the minimum amount of hot methanol. After thorough chilling to −5° the precipitated ester was collected. The precipitate was extracted two times (total volume was one-fifth the volume of methanol necessary to dissolve the residue after removal of butanol) with 0.1 *N* methanol–hydrogen chloride. The extracts were diluted with 2 volumes of methanol and 2 moles of sodium acetate were added per mole of hydrogen chloride. The solution was heated to 60°, centrifuged and the supernatant chilled at −10° for twenty-four hours. The precipitate which formed was centrifuged, then dissolved in hot methanol and sodium chloride was added to a concentration of 0.05 *N*. The solution was centrifuged at 60° and the insoluble fraction discarded. The supernatant was cooled at −10° for twenty-four hours and then centrifuged at 2°. The precipitated ester was obtained in yields approximating 65%.

Clarification with Florisil.—The ester was washed free of methanol, suspended in water and 0.1 *N* barium hydroxide was added until the solution was faintly alkaline to phenolphthalein. The hydrolysis of the ester was extremely rapid. The hydrolysate was centrifuged and the supernatant treated with florisil (1 g. per 100 mg. of active compound) for thirty minutes to remove extraneous pigments. The florisil was filtered off and washed with dilute barium hydroxide. The filtrate and washings were combined. Yield was 85–90%.

Crystallization of the Free Acid.—One-tenth volume of 1 *N* barium chloride was added to the above filtrate, the solution was cooled to 0–5° and ethanol was added to a concentration of 50%. The solution was chilled overnight, then centrifuged and the precipitate washed with alcohol, ether and dried.

The barium precipitate was extracted with small portions of hot water until all of the active compound was in solution. The resulting extracts were combined and 1 *N* hydrochloric acid was added to *p*H 2.8. The solution was cooled to 5° and the precipitate collected. The precipitate was dissolved in hot water previously adjusted to *p*H 2.8 and containing a small amount of calcium or sodium chloride. On cooling the acid crystallized as very short needles or long threads. The acid could be repeatedly crystallized in this manner.

Anal.[12] Found: C, 48.6, 48.0, 47.7; H, 4.8, 4.4, 4.7; N, 16.2, 15.5, 15.5.

Crystallization of the Barium Salt.—The amorphous barium salt obtained by precipitation with 50% ethanol was dissolved in hot 0.1 *N* barium chloride. On cooling the compound crystallized as small needles.

Crystallization of the Methyl Ester.—The compound was re-esterified by dissolving in 0.1 *N* methanol–hydrogen chloride and allowing to stand at 32° for twelve hours.

The ester crystallized as short needles or long threads from methanol 0.05 *N* with sodium chloride.

Table I

Solubility of the Fermentation *L. casei* Factor

Compound	Solvent	Temp., °C.	Concn. mg. per ml.
Methyl ester	Methanol	60	5.00
Methyl ester	Methanol	−5	0.30
Methyl ester	Methanol–0.05 *N*	60	2.00
Methyl ester	sodium chloride	−5	0.11
Methyl ester	Water	80	1.00
Methyl ester	Water	5	0.12
Free acid	Water	80	3.00
Free acid	Water	5	0.10

Solubility.—The methyl ester and the free acid were soluble under the conditions noted in Table I.

Microbiological Assays.—The microbiological activity of the compound was determined for *Lactobacillus casei* and *Streptococcus faecalis* R. according to established procedures.

Ultraviolet Absorption.—The ultraviolet absorption spectra of the fermentation *L. casei* factor was determined using a Beckman Spectrophotometer.

Acknowledgment.—We are indebted to the Misses E. Boggiano and B. Eames for the micro-

---

(12) Analytical figures are given for three different lots.

biological assays and the spectrophotometric determinations, and to Mr. L. Brancone and coworkers for the microanalyses.

The authors are especially indebted to Dr. J. H. Williams for his constant interest and counsel and for his efforts in coördinating the work performed in the various laboratories.

Summary

An isolation procedure for the fermentation *L. casei* factor is outlined. The analyses and biological activity distinguish the fermentation *L. casei* factor from any similar compound previously reported.

PEARL RIVER, NEW YORK RECEIVED JANUARY 24, 1947

[CONTRIBUTION FROM LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

The Isolation of the *Lactobacillus casei* Factor from Liver

BY E. L. R. STOKSTAD, BRIAN L. HUTCHINGS AND Y. SUBBAROW

Pfiffner, *et al.*,[1] and Stokstad[2] have described compounds isolated from liver which are active in promoting the growth of *L. casei* and *S. faecalis* R. The synthesis of this compound has recently been described by Angier, *et al.*[3] It is the purpose of this communication to describe the isolation of this compound from liver.

Experimental

Assays for the *L. casei* factor were made by the method of Landy and Dicken.[4] The assay results were expressed originally in terms of an arbitrary standard Solvamin.[5] One-tenth milligram of this constituted one unit and corresponded to approximately the amount required per 10 ml. of medium to give three-fourths maximum growth. The pure liver *L. casei* factor was later found to have an activity very close to 1,000,000 units per mg.

The starting material for this isolation was a commercial preparation of a dried 85% ethanol precipitate of an aqueous extract of liver. Different preparations of liver extract contained between 20,000 and 30,000 units per gram which corresponds to 20 to 30 micrograms of the pure liver *L. casei* factor per gram.

In the isolation of this compound, four essential steps were used. They were: adsorption and elution of the free acid, esterification and extraction of the methyl ester with immiscible solvents, chromatographic adsorption of the ester, and fractional precipitation of the ester from water and methanol. The results of all these isolation steps are presented in Table I.

Eighty kg. of liver extract was dissolved in 1600 liters of water, sodium hydroxide was added to *p*H 8.5, 80 liters of 2 *N* calcium chloride added and the mixture heated to 85° to flocculate the precipitate. The mixture was filtered while hot with the aid of filter cell. The filtrate was cooled to 25° and adjusted to *p*H 3.00. The *L. casei* factor was adsorbed with 16 kg. of Norit A. This adsorbate was washed, first, with 320 liters of neutral 60% ethanol at 25° to remove inert materials and then with two 320-liter portions of 0.5 *N* ammonium hydroxide in 60% ethanol at 70° to remove the activity.

The ammoniacal eluate was concentrated to 80 liters and adjusted to *p*H 3.5 and the precipitate which formed on standing removed by centrifuging. The precipitate was redissolved in 40 liters of water with the aid of sodium hydroxide and reprecipitated at *p*H 3.5. A large amount of inert material was removed by the precipitate but almost half the activity was carried down with it.

This filtrate was adsorbed at *p*H 1.3 on Superfiltrol[6] by

TABLE I

CONCENTRATION OF *L. casei* FACTOR FROM LIVER

Fraction	Units per gram equiv. liver extr.	Units per mg. solids
Liver extr: starting material	20,000	20
Norit eluate	7,000	......
Filtrate after *p*H 3 precipitation	3,500	......
Superfiltrol eluate (from Superfiltrol adsorbate of *L. casei* factor free acid)	3,500	340
Barium salt	2,100	420
Esterified mixture of barium salt	2,000	
Butanol extract of methyl ester	2,000	3,450
Methanol solution of butanol extract.	2,000	3,450
Methanol filtrate from Superfiltrol adsorption of *L. casei* factor methyl ester	0	......
1st eluate: 92.5% acetone 10 ml. eluant per g. adsorbent	30	......
2nd eluate: 75% acetone 10 ml. eluant per g. adsorbent	1,200	47,000
3rd eluate: 75% acetone 10 ml. eluant per g. adsorbent	325	24,000
Precipitate obtained by concentrating 75% acetone eluates to give aqueous solution	1,000	370,000
1st methanol extract of aqueous precip.: 1 ml. *cold* methanol per kg. equiv. liver	90	35,000
2nd methanol extract of aqueous precip.: 1 ml. *cold* methanol per kg. equiv. liver	100	380,000
3rd methanol extract of aqueous precip.: 4 ml. *hot* methanol per kg. equiv. liver	780	950,000
1st precip. formed by cooling hot methanol extract	270	1,030,000
2nd precip. formed by concentrating filtrate from 1st methanol precipitate	313	870,000

---

(1) Pfiffner, Binkley, Bloom, Brown, Bird, Emmett, Hogan and O'Dell, *Science*, **97**, 404 (1943).

(2) Stokstad, *J. Biol. Chem.*, **149**, 573 (1943).

(3) Angier, Boothe, Hutchings, Mowat, Semb, Stokstad, SubbaRow, Waller, Cosulich, Fahrenbach, Hultquist, Kuh, Northey, Seeger, Sickels and Smith, *Science*, **103**, 667 (1946).

(4) Landy and Dicken, *J. Lab. Clin. Med.*, **27**, 1086 (1942).

(5) Solvamin, a vitamin concentrate manufactured by Commercial Solvents Corporation.

(6) Superfiltrol, an adsorbent supplied through the coöperation of the Filtrol Corporation, Los Angeles.

Fig. 1.—Crystals of liver *L. casei* factor.

percolation through a column of the granular adsorbent. Forty liters of the filtrate, equivalent to 40 kg. of liver extract, was percolated through 100 to 200 mesh Superfiltrol in a column 5 inches deep and 8 inches in diameter. The maximum rate of flow was 100 ml. per sq. cm. of filter surface per hour. The column was then eluted by percolation with 20 liters of 1.0 *N* ammonium hydroxide in 60% ethanol. After elution the column was rewashed with 0.1 *N* hydrochloric acid and then reused several times for subsequent adsorptions and elutions. When an adsorbent is used only once a certain amount of activity is adsorbed which cannot be eluted. In subsequent adsorptions and elutions this loss apparently does not occur. After six such cycles no decrease in efficiency of the adsorbent was observed and almost complete recovery of activity was obtained. From the table it can be seen that the Superfiltrol eluate contained 3,500 units per gram equivalent of liver extract and 340 units per mg. of solids. This represents a 17-fold increase in activity with a recovery of 17%.

The barium salt was next prepared by concentrating the superfiltrol eluates and adjusting to *p*H 7.0. The *L. casei* factor was precipitated as the barium salt by adding 9 volumes of ethanol and an excess of barium chloride solution. Little or no increase in activity was achieved but it did convert the material into a form which could be dried finely ground and then esterified.

It might be noted that while the *L. casei* factor can be precipitated by heavy metals such as lead and silver, and by basic precipitants such as phosphotungstic acid, no large increases in activity could be effected at this stage by the use of these reagents.

The next step consisted in esterification and extraction of the methyl ester with *n*-butanol. Two hundred grams of the finely ground barium salt were esterified in 20 liters of 0.2 *N* hydrochloric acid in methanol for sixteen hours at 25°. Esterification proceeds very rapidly going to completion in one hour at 25° if anhydrous reagents are used. This ester is approximately 10% as active for *L. casei* as the free acid. Part of the activity of the ester may be due to partial hydrolysis of the ester during autoclaving of the sample with the medium as the ester is very rapidly hydrolyzed. Four hours hydrolysis at 100° at *p*H 8.0 produced 75% hydrolysis, and 0.1 *N* sodium hydroxide at 25° gave complete hydrolysis in half an hour. Since the ester possesses only partial activity, assays for potency were preceded by ten minutes saponification with 0.1 *N* sodium hydroxide at 100°.

The esterified mixture was neutralized and evaporated to almost dryness, redissolved in 20 liters of water and adjusted to *p*H 6 to 7. It was then extracted three times with 2 volumes of *n*-butanol. Each butanol extract was washed successively with the same portion of half a volume of water. The distribution coefficient of the *L. casei* factor methyl ester for butanol to water is 3 to 1. The final butanol extract contained 2,000 units per gram equivalent of liver and 3,450 units per mg. of solids.

While chromatographic adsorption of the free acid from aqueous solution proved ineffective, chromatographic adsorption of the ester in organic solvents was highly efficient. Superfiltrol[6] proved the best adsorbent; Brockman alumina and calcium carbonate were much less effective. The *L. casei* factor methyl ester could be adsorbed on Superfiltrol from *n*-butanol, methanol, acetone and water. The only efficient eluant was aqueous acetone. Aqueous methanol, aqueous methyl ethyl ketone, acetone–methanol mixtures, acetone–ethanol mixtures and methyl ethyl ketone–methanol mixtures were ineffective.

Chromatographic separation was carried out as follows: The butanol extract was evaporated to dryness and redissolved in methanol. An aliquot of this methanol solution, equivalent to 0.5 kg. of liver extract, was passed through a 3.5 × 13.0 cm. column containing 75 g. of 200 to 325 mesh Superfiltrol. This was eluted first with 750 ml. of 92.5% acetone and then with three portions of 750-ml. of 75% acetone. The 92.5% acetone elution removed a large amount of highly colored impurities without removing appreciable activity. The 75% acetone rapidly eluted the active factor. The first 75% acetone eluate which had an activity of 47,000 units per mg. was concentrated to 200 ml. during which most of the acetone had been removed. On cooling the aqueous solution most of the activity precipitated out. This contained 1,000 units per gram of original liver extract and 370,000 units per mg. of solids.

This precipitate which formed from aqueous solution was extracted with a small amount of cold methanol using 1 ml. of solvent per kg. of original liver. This removed very little activity but removed most of the dark brown pigment. The *L. casei* factor methyl ester was then dissolved by extraction with a larger amount of boiling methanol (4 ml. per kg. of liver extract). This hot methanol extract was almost colorless and highly active. On cooling the hot methanol extract to 2° the methyl ester separated out in a nearly pure form as a gelatinous precipitate which had an activity of 1,030,000 units per mg. Reprecipitation from hot methanol yielded a preparation whose activity could not be increased by further purification. The solubility of the methyl ester in methanol is approximately 60 micrograms per ml. at 2°. The results obtained by methanol fractionation are shown in Table I. The analysis of two preparations of the methyl ester as obtained by this method are as follows

	C	H	N (Dumas)
Sample 1	53.0	4.6	21.2
Sample 2	53.1	5.1	20.5

The free acid was prepared by saponifying 2.0 mg. of a nearly pure preparation of the ester with 5.0 ml. of 0.01 *N* sodium hydroxide. The solution was treated with 4 mg. of Darco. On acidifying the filtrate to *p*H 3.0, the free acid precipitated out, which was then redissolved by heating to 90°. On cooling slowly the free acid of the *L. casei* factor crystallized out. The solubility of the free acid at *p*H 3.0 at 2° is approximately 10 micrograms per ml. and more than 0.5 mg. per ml. at 100°. These were recrystallized once from 0.1 *n* sodium chloride and two times from water.

The crystal form of the free acid is shown in Fig. 1.

The extinction coefficients in 0.1 *N* sodium hydroxide were determined with a Beckman spectrophotometer and found to be as follows: $E^{1\%}_{1\ \text{cm.}}$ 255 mμ, 565; 282 mμ, 350; 365 mμ, 195.

The amount required per ml. of medium for half maximum growth was 0.00007 microgram for *L. casei* and 0.0003 for *S. faecalis* R. This amount required for half maximum growth is not an accurately reproducible value and varies from one experiment to another.

Acknowledgment.—The authors wish to acknowledge the assistance of Barbara Eames in making the microbiological assays and to express their thanks to Dr. T. H. Jukes for his constant interest and counsel.

Summary

The isolation of the *Lactobacillus casei* factor from liver has been described. This was accomplished by the use of adsorption and elution of the free acid on Norit, esterification and extraction of the methyl ester with *n*-butanol. The methyl ester was chromatographed on Superfiltrol using aqueous acetone as the developer. Final purification of the ester was accomplished by fractional precipitation from water and methanol. The free acid was crystallized from hot water.

PEARL RIVER, NEW YORK RECEIVED JANUARY 24, 1947

[CONTRIBUTION FROM LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

The Degradation of the Fermentation *Lactobacillus casei* Factor. I

BY E. L. R. STOKSTAD, BRIAN L. HUTCHINGS, JOHN H. MOWAT, JAMES H. BOOTHE, COY W. WALLER, ROBERT B. ANGIER, JOSEPH SEMB AND Y. SUBBAROW

The isolation of two *Lactobacillus casei* factors, one from liver[1,2] and one from a fermentation product[3,4] has been described.

These two *L. casei* factors differ in biological activities and physical properties. Extinction coefficients indicated that the fermentation *L. casei* factor has the larger molecular weight. The structure and synthesis of the liver *L. casei* factor have been described in a preliminary communication.[5] The synthetic liver *L. casei* factor has been reported to be the same as vitamin B_c[6] which had previously been isolated from liver and yeast.[7,8]

The relationship of the liver *L. casei* factor to folic acid[9] has not been definitely established although available evidence indicates they are the same.[10]

The liver *L. casei* factor also appears to be the same as the factor designated as the norite eluate factor.[11]

This communication deals with the degradation of the fermentation compound by alkaline hydrolysis under aerobic and anaerobic conditions and by acid hydrolysis.

In experiments on the degradation of the *L. casei* factor from liver and fermentation sources, it was soon observed that hydrolysis with acid or alkali led to the formation of a diazotizable aromatic amine which could be estimated by the method of Bratton and Marshall.[12] The liberation of amine was most rapid in alkaline solutions and it was found that oxygen had a marked effect on the course of the reaction. When the fermentation *L. casei* factor was heated with 1.0 *N* sodium hydroxide at 100° in the presence of oxygen there was a marked change in the absorption spectrum, a diazotizable aromatic amine was produced, a fluorescent pigment was formed and rapid biological inactivation occurred. The *L. casei* factor before hydrolysis has three absorption maxima in 0.1 *N* sodium hydroxide at 257, 282 and 365 mμ. After aerobic alkaline hydrolysis it has two maxima at 263 and 365 mμ.

When the hydrolysis was carried out anaerobically with 1.0 *N* sodium hydroxide at 100° there

---

(1) Stokstad, *J. Biol. Chem.*, **149**, 573 (1943).

(2) Stokstad, Hutchings and SubbaRow, THIS JOURNAL, **70**, 3 (1948).

(3) Hutchings, Stokstad, Bohonos and Slobodkin, *Science*, **99**, 371 (1944).

(4) Hutchings, Stokstad and SubbaRow, THIS JOURNAL, **70**, 1 (1948).

(5) Angier, Boothe, Hutchings, Mowat, Semb, Stokstad, SubbaRow, Waller, Cosulich, Fahrenbach, Hultquist, Kuh, Northey, Seeger, Sickels and Smith, Jr., *Science*, **103**, 667 (1946).

(6) Pfiffner, Calkins, Bloom and O'Dell, THIS JOURNAL, **68**, 1392 (1946).

(7) Pfiffner, Binkley, Bloom, Brown, Bird, Emmett, Hogan and O'Dell, *Science*, **97**, 404 (1943).

(8) Binkley, Bird, Bloom, Brown, Calkins, Campbell, Emmett and Pfiffner, *ibid.*, **100**, 36 (1944).

(9) Mitchell, Snell and Williams, THIS JOURNAL, **63**, 2284 (1941).

(10) Johnson, *J. Biol. Chem.*, **163**, 255 (1946).

(11) Snell and Peterson, *J. Bact.*, **39**, 273 (1940).

(12) Bratton and Marshall, *J. Biol. Chem.*, **128**, 537 (1939).

was no change in the absorption spectrum and very little aromatic amine or fluorescent pigment was produced. The activity for *L. casei* was only slightly decreased during anaerobic hydrolysis while the activity for *S. faecalis* R was greatly increased. After prolonged anaerobic alkaline hydrolysis the ratio of activities for *L. casei* and *S. faecalis* R was approximately the same as that for the liver *L. casei* factor. A summary of results of anaerobic and aerobic alkaline cleavage appear in Table I. It should be noted here that while *p*-aminobenzoic acid (PABA) was used as the standard in the Bratton and Marshall determination, the analytical data are reported in terms of PABA as the arbitrary standard; and that the diazotizable amine was not PABA. The aromatic amine was not extractable from aqueous solutions at *p*H 3.0 with ether, while PABA under the same conditions was extracted readily.

TABLE I

EFFECT OF OXYGEN ON ALKALINE HYDROLYSIS OF *L. casei* FACTOR

	Temperature and time of heating Hr.	°C.	Bio act. for *L. casei*, units per mg.	*S. faecalis* R act. coef.[a]	Aromatic amine liberated; expressed as PABA, %	Pteridine liberated,[b] %	α-Amino acid nitrogen in % of total N
	None		710	0.075	0.14	2.3	4.3
No O_2	10	100	750	.66	0.90	3.0	27.0
	20	100	730	.70	1.05	3.25	28.0
	40	100	720	.52	1.02	3.25	27.0
	10	120	780	.61	1.14	2.8	29.0
O_2	0.5	100	lost	.07	3.9	5.0	8.6
	1.0	100	550	.09	9.0	13.8	9.7
	2.0	100	170	.08	14.4	25.0	9.2
	3.0	100	83	.15	15.9	27.2	10.2
	4.0	100	0	...	16.9	29.5	13.5

[a] S. faecalis activity coefficient = $\frac{\textit{S. faecalis}\text{ activity of 1.0 }\textit{L. casei}\text{ unit of unknown}}{\textit{S. faecalis}\text{ activity of 1.0 }\textit{L. casei}\text{ unit of liver }\textit{L. casei}\text{ factor}}$

[b] Results of pteridine analysis expressed as 2-amino-4-hydroxy-6-pteridine carboxylic acid.

The α-amino acid which was formed during anaerobic hydrolysis had been cleaved from the rest of the molecule because it could be separated from the biologically active fragment. This alpha amino acid could be precipitated by barium hydroxide and 75% ethanol which indicated a dicarboxylic α-amino acid.[13]

The biologically active compound obtained by anaerobic hydrolysis with 1.0 *N* sodium hydroxide at 120° for ten hours was isolated and crystallized as the magnesium salt. It could not be crystallized as the free acid by the method previously employed to yield the crystalline liver *L. casei* factor. The ultraviolet absorption spectrum of this compound was identical with that of the liver *L. casei* factor. However, it was only 57% as active biologically as the liver compound by *S. faecalis* R assay and 58% by *L. casei* assay. The low microbiological activity suggested a racemic product. The identification of this compound as racemic liver *L. casei* factor was accomplished later by comparison of its infrared absorption spectrum with that of a synthetic specimen of racemic liver *L. casei* factor. The infrared absorption spectra of the racemic and natural isomers, which were significantly different, appear in a subsequent paper of this series. It is probable that racemization occurred during the extended alkaline hydrolysis.

The fluorescent pigment which was produced by aerobic alkaline hydrolysis was isolated by the following procedure. It was precipitated by acidifying the hydrolysate to *p*H 3.0 and crystallized as the sodium salt from 2.0 *N* sodium hydroxide. It could not be crystallized from weakly alkaline solutions. The free acid prepared by precipitation at *p*H 3.0 appeared amorphous but did show a micro-crystalline structure by X-ray diffraction. The elementary analysis suggested the empirical formula $C_7H_5N_5O_3$.

The presence of a guanidine group in the fluorescent pigment was observed. Oxidation with chlorine water and subsequent hydrolysis with 0.1 *N* hydrochloric acid at 140° or three hours yielded guanidine which was estimated colorimetrically. The Weber test[14] which is given by guanidine and methyl guanidine was positive. The Sullivan test[15] which is given by guanidine but not by methylguanidine was positive. The Sakaguchi test[16] which is given by methylguanidine but not by guanidine was negative. These colorimetric tests indicated the presence of a non-substituted guanidine in the hydrolyzed chlorine oxidation product. The formation of guanidine by chlorine oxidation constitutes evidence for a pyrimidine ring with an amino group in the 2-position.[17]

A titration curve of the sodium salt showed the presence of two acid groups with *pKa* values of 3.9 and 7.7. The presence of a carboxylic acid group was demonstrated by decarboxylation at 300° for three hours with the liberation of 0.8 mole of carbon dioxide. From this decarboxylated mixture a new fluorescent monobasic compound with a *pKa* of 8.0 was obtained. This decarboxylation of a dibasic acid to a monobasic acid with a *pKa* of 8.0 showed that the original compound contained a carboxylic and an enolic group.

This decarboxylated fraction had an ultraviolet absorption spectrum in 0.1 *N* sodium hydroxide with absorption maxima at 252 and 365 mμ while the original dibasic acid had maxima at 262 and 365 mμ. The absorption spectra of these two compounds in alkaline and acid solutions are shown in Figs. 1 and 2, respectively.

The empirical formula of $C_5H_7N_5O_3$, based on elementary analysis and titration data, and the formation of guanidine suggested a 2-aminopurine or 2-aminopteridine. The absorption spectra,

---

(13) Dakin, *J. Biol. Chem.*, **44**, 499 (1920).

(14) Andes and Meyer, *ibid.*, **118**, 137 (1937).

(15) Sullivan, *Proc. Soc. Exptl. Biol. Med.*, **33**, 106 (1935).

(16) Dubnoff, *J. Biol. Chem.*, **141**, 711 (1941).

(17) Wieland, Metzger, Schopf and Bulow, *Ann.*, **507**, 226 (1933).

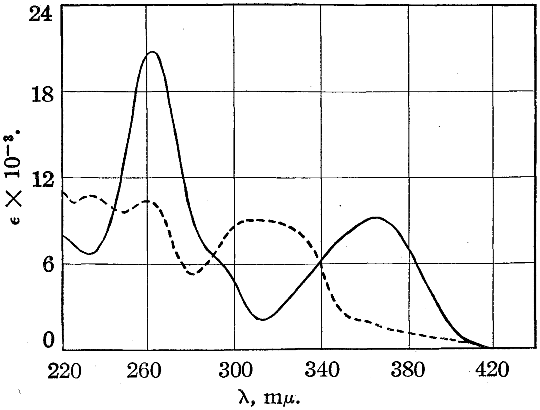


Fig. 1.—Ultraviolet absorption spectra of 2-amino-4-hydroxypteridine-6-carboxylic acid: ——, 0.1 *N* sodium hydroxide; ----, 0.1 *N* hydrochloric acid.

however, eliminated the possibility of a purine because purines do not have absorption maxima above 300 mμ. Thus the available evidence pointed toward 2-aminopteridine with an enolic and a carboxy group. Attempts were made to synthesize pteridines having these functional groups. With this objective, 2-amino-4-hydroxy-6-pteridinecarboxylic acid was synthesized and found to be identical with the fluorescent dibasic pigment. Identity was established by comparison of ultraviolet absorption spectra Fig. 1 and X-ray diffraction patterns. The synthesis and proof of structure of this compound will be given in a subsequent paper. The monobasic fluorescent pigment produced by decarboxylation was identified as 2-amino-4-hydroxypteridine.

Hydrolysis of fermentation *L. casei* factor with 1.0 *N* sulfuric acid anaerobically for eight hours at 100° yielded a fluorescent monobasic acid which was extracted from the hydrolysate with *n*-butanol at *p*H 7.0. This procedure left the dibasic pteridine in the aqueous phase. The monobasic compound was crystallized as the sodium salt from 10.0 *N* sodium hydroxide and then converted to the free acid. This was identified as 2-amino-4-hydroxy-6-methylpteridine by comparison of the ultraviolet and infrared absorption spectra of the natural and synthetic compounds. The synthesis and proof of structure of this compound will be given in a later paper.

The aromatic amine fraction was obtained by first hydrolyzing the fermentation compound anaerobically with alkali to give the racemic liver *L. caesi* factor and then further hydrolyzing aerobically to liberate the aromatic amine. After removal of pteridines the dried amine fraction was extracted as the free acid with ethanol. The aromatic amine obtained from racemic liver *L. casei* factor contained 2.1 atoms of total nitrogen for each atom of aromatic amine nitrogen as measured by the Bratton and Marshall method. On hydrolysis with 2.0 *N* sulfuric acid for sixteen hours at 100°, 45% of the total nitrogen appeared as alpha amino acid nitrogen. *p*-Aminobenzoic acid was isolated from this hydrolysate by extraction with ethyl acetate, crystallized from water and identified by mixed melting points and microbiological assay.

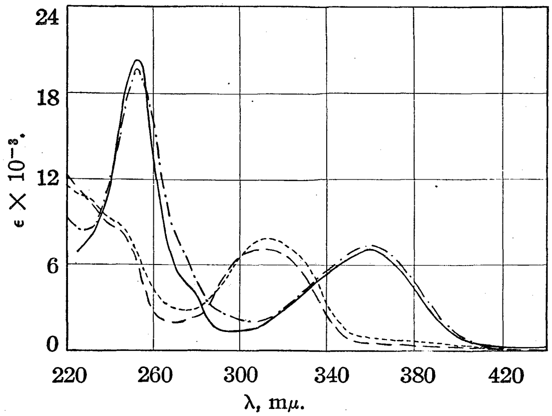


Fig. 2.—Ultraviolet absorption spectra of 2-amino-4-hydroxypteridine, synthetic: ———, in 0.1 *N* sodium hydroxide; — — —, in 0.1 *N* hydrochloric acid. Product obtained from decarboxylation of natural 2-amino-4-hydroxypteridine-6-carboxylic acid; — · — · — in 0.1 *N* sodium hydroxide; ------ in 0.1 *N* hydrochloric acid. The absorption spectra of the decarboxylated product were determined on an aliquot of a solution of an unweighed sample and the values are arbitrarily plotted on the same scale to show similarity.

This evidence indicated that the aromatic amine from the racemic liver *L. casei* factor is a dipeptide of *p*-aminobenzoic acid and an α-amino acid. This peptide linkage must involve the carboxyl group of the *p*-aminobenzoic acid, as the aromatic amine group must be free in order to react in the Bratton and Marshall test.

Some evidence regarding the mode of linkage is furnished by the results of aerobic alkaline hydrolysis. The absence of fluorescence and of free aromatic amine in the original *L. casei* factor, and the simultaneous appearance of these two during aerobic alkaline hydrolysis suggests that the pteridine is linked to the aromatic amine nitrogen. As hydrolysis proceeds, the liberation of pteridine and amine, and biological inactivation proceed at approximately the same rate. No method of cleavage has been found which will liberate the aromatic amine without forming a pteridine. A linkage which can be cleaved only by oxidative hydrolysis is also demanded. This excludes the possibility of a peptide linkage between the carboxy group of the pteridine and the aromatic amine nitrogen. It also eliminates the possibility of the aromatic amine nitrogen being attached to the 4 position of the pteridine. Cleavage of such a bond to give a 4-hydroxypteridine would be simple hydrolysis and would not require oxidation.

Experimental

Effect of Oxygen on Alkaline Hydrolysis.—A solution of 17.4 mg. of fermentation *L. casei* factor in 0.5 ml. of 1.0 *N* sodium hydroxide was hydrolyzed in a sealed 8-mm. test-tube. The tube was evacuated for anaerobic hydrolysis and filled with oxygen for aerobic hydrolysis. After hydrolysis for the times and temperatures indicated in Table I, the solutions were assayed microbiologically with *L. casei* and *S. faecalis* R, using the method of Tepley and Elvehjem.[18] α-Amino acid nitrogen was determined by the method of Van Slyke and aromatic amine by the method of Bratton and Marshall,[12] using *p*-aminobenzoic acid as the standard. The ultraviolet absorption spectra were measured in a Beckman spectrophotometer, and the fluorescence was measured in 0.05 *M* borate buffer with a fluorophotometer. The results were later recalculated in terms of 2-amino-4-hydroxypteridine-6-carboxylic acid.

Isolation of Racemic Liver *L. casei* Factor.—Fermentation *L. casei* factor, 170 mg. in 6 ml. of 1.0 *N* sodium hydroxide, was hydrolyzed for ten hours at 120° anaerobically in an evacuated sealed tube. The hydrolysate contained 39 mg. of liver *L. casei* factor. The biologically active material was precipitated twice with zinc acetate at *p*H 6.7 at 80°. The final zinc precipitate was dissolved in alkali, the zinc hydroxide removed, and the *L. casei* factor precipitated at *p*H 3.0. The precipitate was dissolved in 25 ml. of 0.025 *N* sodium hydroxide, the solution was treated with 100 mg. of activated charcoal (Darco) and the *L. casei* factor precipitated with barium chloride and 3 volumes of methanol.

The barium salts were extracted with hot water, and the extracts heated to 100° and acetic acid added to *p*H 3.0. The active material precipitated on cooling and was reprecipitated twice in a similar manner. These amorphous precipitates of the free acid, 18 mg., were converted into the crystalline magnesium salts by boiling with 5.0 mg. of magnesium oxide and 3.0 ml. of water, and separating off the excess magnesium oxide. On cooling the hot extract the magnesium salt crystallized. This was recrystallized from water. The final magnesium salt, when converted into the free acid by precipitation from a hot solution at *p*H 3, yielded spherulites which exhibited birefringence but which did not form the typical spear-shaped crystals characteristic of the natural isomer of the liver *L. casei* factor; yield of free acid, 5.0 mg. $E^{1\%}_{1\,\mathrm{cm.}}$ for free acid of racemic liver *L. casei* factor as determined in 0.1 *N* sodium hydroxide, 257 mμ, 591; 285 mμ, 575; 365 mμ, 207. Biological activity compared with natural isomer of liver *L. casei* factor: *L. casei* assay, 58.0%; *S. faecalis* R assay, 57.0%. The infrared absorption spectrum of the free acid of the isolated racemic liver *L. casei* factor matched exactly that of the synthetic racemic liver *L. casei* factor.

Isolation of Fluorescent Dibasic Pigment.—Two hundred mg. of fermentation *L. casei* factor in 10.0 ml. 1.0 *N* sodium hydroxide was hydrolyzed six hours at 100° with a stream of oxygen bubbling through the solution. The hot hydrolysate was centrifuged to remove some brown pigment. On cooling the filtrate to 2° a crystalline precipitate (10 mg.) formed which later proved to be the disodium salt of 2-amino-4-hydroxypteridine-6-carboxylic acid. The greater part of the pteridine remained in the filtrate. This filtrate was adjusted to *p*H 5.0 with sulfuric acid and diluted to 20 ml., heated to 70° and the hot solution centrifuged to remove insoluble impurities. The filtrate containing 48 mg. of pteridine was adjusted to *p*H 2.3. The pteridine which precipitated as the free acid at this *p*H was redissolved in dilute alkali and reprecipitated at *p*H 2.3. This free acid (44 mg.) was dissolved at *p*H 11 in 2.0 ml. of water plus sodium hydroxide. After standing at 2° for sixteen hours, impurities were removed by centrifuging and the filtrate brought to 1.0 *N* with sodium hydroxide. On cooling to 2° for sixteen hours the crude sodium salt crystallized. This was recrystallized three times from 1.0 *N* sodium hydroxide.

At this point the products of five such hydrolyses (1.0 g. total fermentation *L. casei* factor) were combined and precipitated twice as the free acid at *p*H 2. The final product was washed with water, methanol and finally ether and dried two hours at 60° in high vacuum over phosphorus pentoxide; yield was 69 mg.

Anal. Found: C, 40.11, 41.03, av., 40.57; H, 1.75, 3.23, av., 2.50; N Kjeldahl, 32.2, 31.8; N Dumas, 32.4, 32.75, av., 32.3. Calcd. for $C_7H_5N_5O_3$: C, 40.58; H, 2.42; N, 32.3.

Formation of Guanidine by Chlorine Oxidation.—A fine suspension of 5 mg. of the fluorescent dibasic acid was treated with 10 ml. of 0.15 *N* chlorine water at 40° for fifteen minutes. The solution was evaporated to dryness, water added, and the solution again evaporated to remove excess chlorine. The residue was dissolved in 4.0 ml. of 0.1 *N* hydrochloric acid and heated three hours at 140°. Guanidine was estimated qualitatively by the method of Sullivan[15] and quantitatively by the method of Weber.[14] Under these conditions of oxidation and hydrolysis the fluorescent dibasic acid yielded 0.24 mole of guanidine, while xanthopterin gave 0.09 mole and leucopterin gave 0.27 mole of guanidine.

Decarboxylation.—The fluorescent dibasic acid (2.562 mg.) was heated at 250–300° for three hours in a stream of nitrogen and the carbon dioxide collected in barium hydroxide solution. The barium carbonate which formed was converted into barium sulfate and weighed. The results were as follows

Wt. of sample, mg.	2.562
Loss on heating, mg.	0.448
Wt. barium sulfate, mg.	1.852
Moles carbon dioxide (based on weight loss on heating and assuming mol. wt. 207)	0.82
Moles carbon dioxide based on barium sulfate found	.64

An electrometric titration of this heated product indicated that complete decarboxylation had not occurred.

A larger sample of 6.63 mg. was decarboxylated and fractionated as follows: It was dissolved in excess alkali, adjusted to *p*H 5.0 and diluted to 10.0 ml. The solution was heated to 90° and centrifuged hot. The filtrate was chilled to 2°. The precipitate which formed had a *pKa* of 8.0 and showed no evidence of an acid group with a *pKa* of 3.7. The absorption spectrum in 0.1 *N* sodium hydroxide was determined on an aliquot of this solution and the new decarboxylated pteridine was found to have maxima at 252 and 365 mμ. As insufficient material was present to be weighed, the absorption spectrum was based on an unknown weight of material. This absorption spectrum was found to be very similar to that of 2-amino-4-hydroxypteridine. The absorption curves of these two compounds appear in Fig. 2.

Isolation of Monobasic Fluorescent Pigment.—Fermentation *L. casei* factor (227 mg.) was dissolved in 25 ml. of 1.0 *N* sulfuric acid and hydrolysed anaerobically for eight hours at 100°. A large amount of black precipitate formed which was centrifuged off. The supernatant was adjusted to *p*H 7.0 and extracted five times with 10 volumes of butanol, using one portion of water to wash each butanol extract. The butanol extract, which contained *ca.* 17.0 mg. of pteridine by spectrophotometric analysis, was evaporated to 9.0 ml. and 3.0 ml. of ether added. The precipitated pteridine was centrifuged, dried and redissolved in 10.0 ml. of water and reextracted three times with 10 volumes of butanol. The combined butanol extracts were concentrated to 5.0 ml., 5.0 ml. ether added and the solution chilled to 0°. The precipitate, containing *ca.* 8.7 mg. pteridine was dried, dissolved in 5.0 ml. of hot water, centrifuged while hot and the supernatant chilled to 0°. The pteridine, which was soluble in hot water, precipitated on cooling. The precipitate, containing *ca.* 6.7 mg. of pteridine was dissolved in 6.0 ml. of dilute sodium hydroxide and treated with 30 mg. of activated charcoal (Darco). The filtrate (3.4 mg. pteridine) was adjusted to *p*H 5.0. On cooling to 0° the pteridine precipitated out. The precipitate was dried, and crystallized two times from 0.5 ml. of 10.0 *N* sodium hydroxide. Crystallization proceeded rapidly from 10.0 *N* sodium hydroxide but not from 5.0 *N*. The final crystalline product was dissolved in

---

(18) Tepley and Elvehjem, *J. Biol. Chem.*, **157**, 303 (1945).

0.55 ml. water. The amount of material present was so small, *ca.* 0.57 mg. by spectrophometric analysis at 365 mμ, that an aliquot of the solution was used to determine the complete absorption spectrum. The absorption spectrum matched with that of 2-amino-6-hydroxy-6-methyl pteridine. The remainder was converted to the free acid, dried and its infrared absorption spectrum determined. This was found to be identical with that of a synthetic specimen of 2-amino-4-hydroxy-6-methylpteridine. The ultraviolet and infrared absorption spectra of this compound will be given in the following paper of this series.

Isolation of Amine Fractions.—Fermentation *L. casei* factor (162 mg.) was dissolved in 9.5 ml. of 1.0 *N* sodium hydroxide and hydrolyzed anaerobically for ten hours at 120°. The racemic liver *L. casei* which formed was precipitated with silver nitrate at *p*H 3.0 and the precipitate freed of silver with hydrochloric acid. The silver precipitate fraction contained 92 mg. of racemic liver *L. casei* factor on the basis of a spectrophotometric determination.

This racemic liver *L. casei* factor was then hydrolyzed aerobically for six hours in 11 ml. of 1.0 *N* sodium hydroxide at 100°. The pteridine was removed by precipitation with silver sulfate at *p*H 5.0. The filtrate, after being freed of silver with hydrochloric acid, was adjusted to *p*H 3.0 and evaporated to dryness. The residue was extracted twice with a total of 75 ml. of hot absolute ethanol to extract this amine. The ethanol extracts were evaporated to dryness and extracted twice with 25-ml. portions of hot isopropanol. This extracted the amine without removing appreciable amounts of inorganic salts. This isopropanol solution was evaporated to dryness and the residue dissolved in 10 ml. of water. This solution analysed as follows:

Aromatic amine calcd. as PABA, mg.	19.0
Aromatic amine nitrogen, mg.	1.94
Alpha amino acid nitrogen, mg.	0.42
Total nitrogen, mg.	4.50
Distribution coefficient for aromatic amine at *p*H 3.0; ethyl acetate to water	0.20

This amine could be hydrolyzed by either 2.0 *N* sulfuric acid at 100° for sixteen hours or by 5.0 *N* sodium hydroxide for thirteen hours at 120°. After hydrolysis with acid, the distribution coefficient at *p*H 3.0 for ethyl acetate to water was 8.1; after alkaline hydrolysis, it was 11.0, while that for PABA under the same conditions was 11.0. *p*-Aminobenzoic acid was isolated by hydrolyzing 7.8 mg. of the amine fraction (calcd. as PABA) in 5.0 ml. of 2.0 *N* sulfuric acid for sixteen hours at 100°. The hydrolysate contained 6.7 mg. of amine (as PABA). The solution was diluted to 50 ml. and freed of sulfuric acid with barium carbonate, the filtrate concentrated to 10 ml. and adjusted to *p*H 8.0. Extraction at this *p*H with two 10-ml. portions of ethyl acetate removed no amine. The solution was adjusted to *p*H 3.0 and again extracted with ethyl acetate in the same way. The two *p*H 3.0 ethyl acetate extracts were each washed successively with one 5-ml. portion of water.

The ethyl acetate extract and the water phase analyzed as follows:

Ethyl acetate extract.	
Aromatic amine (as PABA), mg.	4.5
Aromatic amine nitrogen, mg.	0.47
Total nitrogen, mg.	.42
Aqueous residue plus washings.	
Aromatic amine (as PABA), mg.	0.10
Aromatic amine nitrogen, mg.	.01
Total nitrogen, mg.	.70

On evaporating the ethyl acetate extract to dryness, a crystalline product was obtained which was recrystallized from 0.3 ml. of hot water: yield was 0.8 mg.; m. p. unknown (hot stage), 183.5–184.5° uncor.; m. p. *p*-aminobenzoic acid (hot stage), 185.5–186.5° uncor.; mixed melting point (hot stage), 185.5–186.5° uncor.

Microbiological assays for *p*-aminobenzoic acid were made by the methods using *Clostridium acetobutylicum*[19] and *Acetobacter suboxydans*[20] which gave values of 95 and 81%, respectively.

Acknowledgment.—The authors wish to acknowledge the assistance of Barbara Eames, Edythe Brogan and Anna Buxó for spectrophotometric determinations, Louis Brancone and coworkers for elementary analysis, and Dan McLachlan[21] for X-ray diffraction studies. The authors are especially indebted to Dr. J. H. Williams for his constant interest and counsel and for his efforts in coördinating the work performed in the various laboratories.

Summary

1. Anaerobic alkaline hydrolysis of the fermentation *L. casei* factor gives racemic liver *L. casei* factor and 2 moles of a dicarboxylic alpha amino-acid.

2. Aerobic alkaline hydrolysis gives 2-amino-4-hydroxypteridine-6-carboxylic acid and an aromatic amine.

3. The aromatic amine obtained by aerobic alkaline hydrolysis of the racemic liver *L. casei* factor consists of a dipeptide of *p-aminobenzoic* acid and an α-amino acid.

4. Anaerobic acid hydrolysis of the fermentation *L. casei* factor yields 2-amino-4-hydroxy-6-methylpteridine.

5. Linkage of the pterin to the amino group of *p*-aminobenzoic acid is indicated by the rates of liberation of pteridine and amine during aerobic alkaline hydrolysis.

PEARL RIVER, NEW YORK RECEIVED JANUARY 24, 1947

---

[19] Landy and Streightoff, *Proc. Soc. Exptl. Biol. Med.*, **52**, 127 (1943).

[20] Lampen and Peterson, *J. Biol. Chem.*, **153**, 193 (1944).

[21] Address: American Cyanamid Company, Stamford, Connecticut.

[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Degradation of the Fermentation *L. casei* Factor. II

BY BRIAN L. HUTCHINGS, E. L. R. STOKSTAD, JOHN H. MOWAT, JAMES H. BOOTHE, COY W. WALLER, ROBERT B. ANGIER, JOSEPH SEMB AND Y. SUBBAROW

In the previous paper[1] data were presented indicating that 2-amino-4-hydroxypteridine-6-carboxylic acid, 2-amino-4-hydroxy-6-methylpteridine and *p*-aminobenzoic acid were degradation products of the fermentation *L. casei* factor. In this paper further degradation products are presented and evidence for the structure of the liver *L. casei* factor is outlined.

When the fermentation *L. casei* factor was dissolved in water at *p*H 4.0 and autoclaved at 120° for six hours, the activity of the compound was destroyed. From this inactive solution a crystalline product was isolated. The analysis, chemical properties, and melting point suggested that the substance was *l*-pyrrolidonecarboxylic acid. However, a cryoscopic determination of the molecular weight offered the possibility of a diketopiperazine of glutamic acid.

Synthetic *l*-pyrrolidonecarboxylic acid caused no depression of the melting point of the unknown compound. Further corroborative evidence of the identity of the degradation product with *l*-pyrrolidonecarboxylic acid was furnished by comparison of their infrared absorption spectra (Fig. 1).

When the fermentation *L. casei* factor was dissolved in water and the resulting solution made 0.5 *N* with sulfur dioxide, the growth-promoting properties of the compound were destroyed. There was a marked increase in the fluorescence of the solution and an aromatic amine was formed that could be detected by the method of Bratton and Marshall.[2]

After removal of the sulfur dioxide, the fluorescent moiety reacted rapidly with such typical aldehyde reagents as hydroxylamine, phenylhydrazine and semicarbazide to form insoluble products. The condensation products exhibited no fluorescence. These derivatives were extremely insoluble and quite unstable but analyses indicated the condensation product with phenylhydrazine to be a hydrazone. If the fluorescent compound arising from sulfurous acid hydrolysis was allowed to stand in dilute alkali anaerobically, approximately equal amounts of 2-amino-4-hydroxypteridine-6-carboxylic acid and a compound which was identified as 2-amino-4-hydroxy-6-methylpteridine were formed. The presence of 2-amino-4-hydroxy-6-methylpteridine was unexpected and its mode of formation is obscure. The ability to form insoluble precipitates with typical aldehyde reagents and the dismutation in dilute alkali indicate the presence of an aldehyde group in the pteridine arising from sulfite cleavage of the fermentation *L. casei* factor.

By appropriate manipulations the aromatic amine fragment could be purified. The aromatic amine nitrogen as determined by the method of Bratton and Marshall was found to be approximately 25% of the total nitrogen. The remaining 75% of the nitrogen could be converted into α-amino acid nitrogen by acid or alkaline hydrolysis. From such hydrolysates the aromatic amine was isolated and identified as *p*-aminobenzoic acid. Microbiological assay of the hydrolysate indicated the presence of 3 moles of glutamic acid. Analytical figures suggested that the amino acids are joined in peptide linkage as *p*-aminobenzoyldiglutamylglutamic acid. The mode of linkage of the glutamic acids will be discussed in a subsequent communication.

After sulfurous acid hydrolysis of the fermentation *L. casei* factor no one or two carbon-containing fragments could be detected. Aerobic ultraviolet inactivation of the fermentation *L. casei* factor which cleaves the compound into a pteridine fraction and an aromatic amine fraction failed to yield any carbon dioxide. The evidence suggests that the carbon content of the fermentation *L. casei* factor is that represented by the degradation products.

The fermentation *L. casei* factor was not measurably inactivated by hydrogenation over regular Raney nickel, Raney nickel containing aluminum, or over palladium on barium sulfate if the hydrogenation was carried out at a *p*H of 7.0 or greater and at atmospheric pressure. If the compound was hydrogenated at *p*H 1.0 or 3.0 and at atmospheric pressure using a palladium–barium sulfate catalyst, there was rapid biological inactivation with the simultaneous formation of an aromatic amine. The ultraviolet absorption at 365 mμ was greatly decreased indicating the reduction of the pteridine to a compound that exhibited no absorption at this wave length. The absorption and fluorescence of the pteridine moiety could be regenerated by oxidation with manganese dioxide in acid solution.

The reductive reaction can be carried out chemically with zinc dust and either dilute hydrochloric or sulfuric acids. From chemically reduced solutions of the fermentation *L. casei* factor, 2-amino-4-hydroxy-6-methylpteridine has been isolated and characterized.

In a summation of the data presented in this and the previous paper of this series the following salient points serve as a guide to the formulation of the structure of the liver *L. casei* factor:

A. Aerobic alkaline hydrolysis, sulfite cleavage and chemical or catalytic reduction each give

---

[1] Stokstad, *et al.*, THIS JOURNAL, **70**, 5 (1948).

[2] Bratton and Marshall, *J. Biol. Chem.*, **128**, 537 (1939).

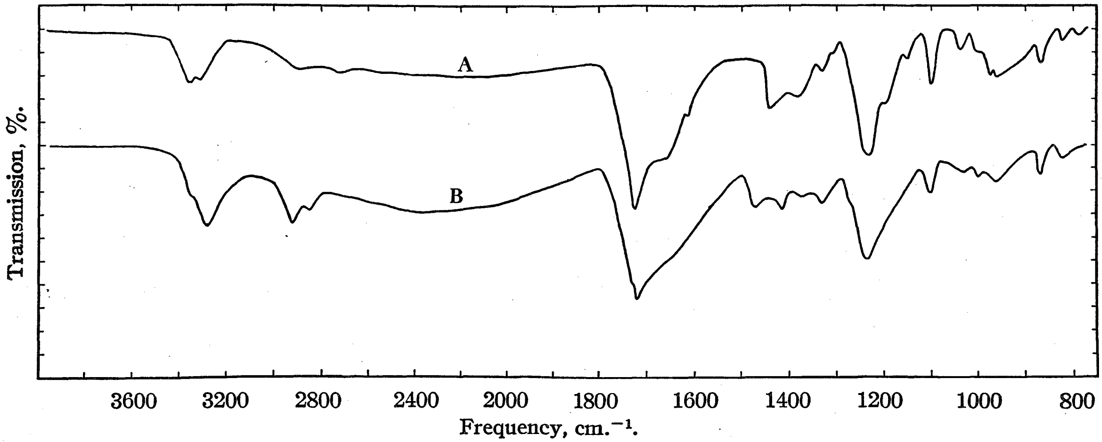


Fig. 1.—Infrared absorption spectra of *l*-pyrrolidonecarboxylic acid: A, synthetic; B, natural.

rise to a pteridine fraction and a primary aromatic amine. This indicates that the point of linkage is probably through the aromatic amine group to the pteridine.

B. A single carbon atom serves as a linkage between the pteridine and aromatic amine. This is indicated by obtaining either 2-amino-4-hydroxypteridine-6-carboxylic acid or 2-amino-4-hydroxy-6-methylpteridine or a compound that could be converted into them as degradation products in several methods of cleavage. Further indicative evidence is the inability to detect any one or two carbon-containing fragments arising from two degradative reactions. The evidence suggests that the one carbon is present as a methylene group. Thus, the necessity of oxygen for the alkaline cleavage is more rational. The reductive formation of 2-amino-4-hydroxy-6-methylpteridine is in accord with this hypothesis.

C. The aromatic amine arising from sulfite-cleavage is a tetrapeptide composed of one mole of *p*-aminobenzoic acid and three moles of glutamic acid. In the previous paper of this series it was observed that in degrading the fermentation *L. casei* factor to the *dl*-liver *L. casei* factor, two moles of α-amino acid nitrogen were liberated. Thus, the liver *L. casei* factor contains one mole of glutamic acid and the fermentation compound three moles of glutamic acid.

Experimental[3,4,5]

Aqueous Hydrolysis of the Fermentation *L. casei* Factor.—Two hundred mg. of the fermentation *L. casei* factor was dissolved in 125 ml. of water and autoclaved at 120° for six hours. The resulting clear solution was allowed to stand at 5° for twenty-four hours. The material that precipitated was centrifuged out and discarded. The water solution was concentrated to dryness and the residue extracted with 4–15 ml. portions of hot absolute ethanol. The ethanol extracts were concentrated to dryness and the residue extracted with 125 ml. of acetone. The acetone was evaporated and the residue sublimed in high vacuum at 148° for six hours. The sublimate was contaminated with a brown pigment that was removed by extracting the sublimate with several 0.1-ml. portions of ice-cold ethanol. The residue was re-sublimed at 138° for six hours. There was obtained a colorless crystalline sublimate (wt. 28 mg.) which melted at 147–148°. A cryoscopic determination of the molecular weight using camphor as the solvent gave a value of 284.

Anal. Found: C, 47.05; H, 5.14; N, 10.93.

Titration data for the compound indicated the presence of a strong carboxylic acid group. The equivalent weight calculated at *p*H 7.0 was 129.2. The compound exhibited no ultraviolet absorption. The substance gave no color with ferric chloride in aqueous or alcoholic solution. The sample adsorbed no hydrogen over Adams platinum oxide catalyst.

The compound contained no α-amino acid nitrogen. However, when 1.794 mg. of the compound was dissolved in 2 ml. of 1 *N* sodium hydroxide and heated at 100° for three hours, the following figures were obtained: total nitrogen, 0.196 mg.; α-amino acid nitrogen before hydrolysis, negative; α-amino acid nitrogen after hydrolysis, 0.174 mg. Because of the small sample used and the accuracy of the Van Slyke determination, these values are indicative of complete conversion of the nitrogen into α-amino acid nitrogen.

A semi-quantitative microbiological determination of the glutamic acid content of a 1 *N* sodium hydroxide hydrolysate of the sublimate was carried out using *Lactobacillus casei* as the test organism. A glutamic acid control was run under identical conditions to determine the extent of racemization. This factor was used in calculating the results. The sublimate analyzed for 81.5% glutamic acid.

l-Pyrrolidonecarboxylic acid was synthesized according to the procedure of Abderhalden and Kautzsch.[6] The *l*-pyrrolidonecarboxylic acid melted not sharply at 144–148°.[7] A mixture of *l*-pyrrolidonecarboxylic acid and the unknown melted at 145–147°.

A cryoscopic determination of the molecular weight of the synthetic *l*-pyrrolidonecarboxylic acid gave a value of 284 indicating polymerization of the compound.

Reaction of the Sulfite-cleaved Pteridine with Phenylhydrazine.—One hundred mg. of the fermentation *L. casei* factor was dissolved in 50 ml. of water with slight warming and a solution of sulfurous acid added. The final volume was 200 ml. and was 0.5 *N* with respect to sulfurous acid. The solution was kept at 32° for sixteen hours. The solu-

---

(3) All concentrations carried out in vacuum.

(4) All melting points are uncorrected.

(5) The ultraviolet absorption was determined with a Beckman Spectrophotometer. The fluorescence of the pteridines was determined in 0.05 *M* sodium borate buffer with a Pfaltz and Bauer Fluorophotometer.

(6) Abderhalden and Kautzsch, *Z. physiol. Chem.*, **68**, 487 (1910).

(7) On further fractional crystallization the m. p. of the synthetic compound was raised to 160–162°. A lack of material precluded further purification of the isolated *l*-pyrrolidonecarboxylic acid. Partial racemization could account for the low m. p. of the isolated compound (see ref. 3).

tion was concentrated to one-half volume under nitrogen to remove the sulfur dioxide, warmed to 80° and a solution of phenylhydrazine in dilute acetic acid was added. There was an immediate formation of a red precipitate. The solution was warmed for thirty minutes, then cooled and centrifuged. The precipitate was dissolved in a mixture of piperidine and water (0.4:10) and precipitated by the addition of acetic acid. The solution and precipitation were repeated twice.

Anal. Calcd. for $C_{13}H_{11}N_7O$: C, 55.5; H, 3.92. Calcd. for $C_{20}H_{17}N_9O$: C, 48.1; H, 3.41. Found: C, 54.2; H, 3.86.

The analyses indicate the formation of a hydrazone rather than a dihydrazone.

Effect of Alkali on the Sulfite-cleaved Pteridine.—Two hundred and fifty mg. of the fermentation *L. casei* factor was treated with sulfurous acid as described above. After hydrolysis the solution was concentrated to dryness under nitrogen and the residue dissolved in 6.0 ml. of 1 *N* sodium hydroxide. The flask was evacuated and then stored in a vacuum desiccator at 4°. After fourteen days the precipitate which had formed was centrifuged off and washed with 2 *N* sodium hydroxide. The absorption spectra of this precipitate in both 0.1 *N* sodium hydroxide and 0.1 *N* hydrochloric acid were identical with the absorption spectra of the 2-amino-4-hydroxypteridine-6-carboxylic acid. The amount of the 2-amino-4-hydroxypteridine-6-carboxylic acid as determined by ultraviolet absorption was 17 mg.

The solution after removal of the precipitated 2-amino-4-hydroxypteridine-6-carboxylic acid was adjusted to *p*H 7.0 and a volume of 30 ml. and extracted five times with ten volume portions of butanol. The total amount of pteridine extracted by the butanol as measured by fluorescence was 30 mg. The butanol was concentrated and the compound precipitated by the addition of ether. The precipitate was dissolved in 20 ml. of hot water at *p*H 7.0. A small amount of brown insoluble pigment was removed by centrifugation. The solution was cooled and the precipitate collected; yield was 25 mg. The pteridine was crystallized from 2.0 ml. of 5 *N* sodium hydroxide. The crystalline precipitate was collected and recrystallized from 1.3 ml. of 5 *N* sodium hydroxide. The crystals were suspended in water, adjusted to *p*H 7.0 and dissolved by heating. After cooling the pteridine was collected.

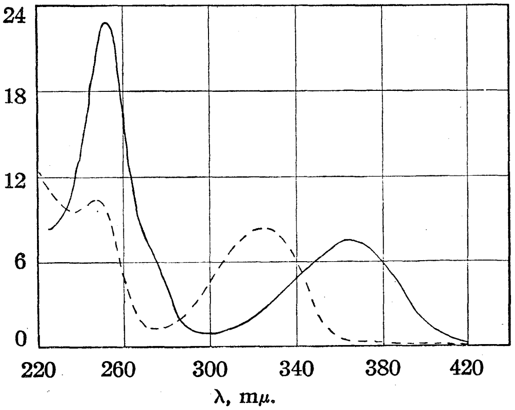


Fig. 2.—Ultraviolet absorption spectra of 2-amino-4-hydroxy-6-methylpteridine: ——, in 0.1 *N* sodium hydroxide; – – – –, in 0.1 *N* hydrochloric acid.

Anal. Calcd. for $C_7H_7N_5O_2$: C, 43.5; H, 3.63; N, 36.3. Calcd. for $C_7H_7N_5O$: C, 47.4; H, 3.95; N, 39.5. Found: C, 47.4; H, 4.43; N, 39.6.

A comparison of the ultraviolet absorption spectra of this compound with the absorption spectra of various pteridines indicated its identity with 2-amino-4-hydroxy-6-methylpteridine (Fig. 2). The synthesis of this compound will be described in the following paper of this series. The infrared absorption spectra of the natural and synthetic 2-amino-4-hydroxy-6-methylpteridine are identical (Fig. 3).

The pteridine remaining in the water layer after butanol extraction was precipitated twice by silver at *p*H 5.0 to remove it from the amine in solution. The yield was 10 mg. as determined by ultraviolet absorption. The absorption spectra of this pteridine were similar to those for the 2-amino-4-hydroxypteridine-6-carboxylic acid.

The total amount of pteridines obtained from the fermentation *L. casei* factor that had been cleaved with sulfurous acid and subsequently treated anaerobically with 1 *N* sodium hydroxide is presented in Table I.

TABLE I

PTERIDINE OBTAINED ON ALKALINE DISMUTATION

	Milligrams	Moles per mole of F. L. C. F.
Fermentation *L. casei* factor used	250	
Amine (calcd. as PABA)	48	0.98
2-Amino-4-hydroxypteridine-6-carboxylic acid		
a. Precipitated by 1.0 *N* sodium hydroxide	17	.23
b. Remaining after extraction with butyl alcohol and precipitated by silver	10	.14
Total	27	.37
2-Amino-4-hydroxy-6-methylpteridine		
a. Total amount extracted by butanol	30	.47

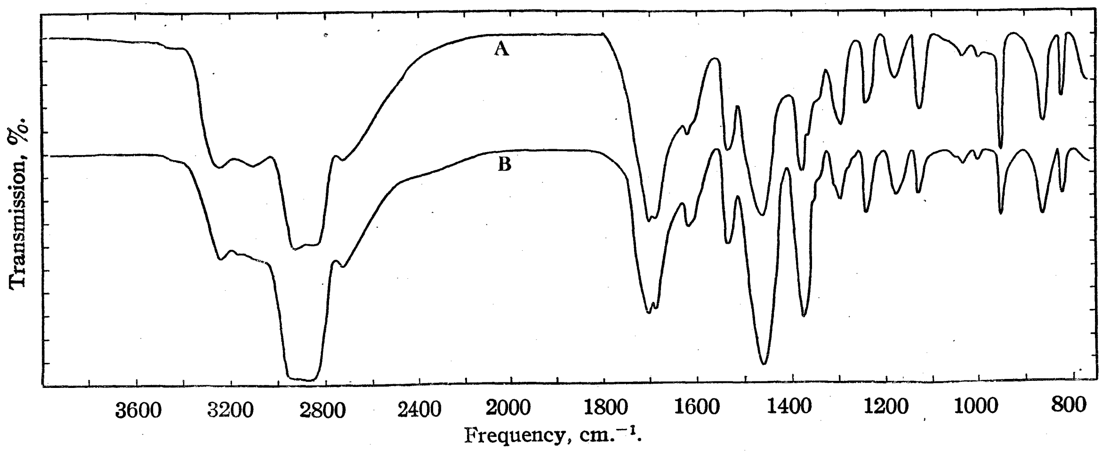


Fig. 3.—Infrared absorption spectra of 2-amino-4-hydroxy-6-methylpteridine: A, natural; B, synthetic.

Purification of the Aromatic Amine.—One gram of the fermentation *L. casei* factor was hydrolyzed with sulfurous acid. After cleavage, the solution was concentrated to one-half volume to remove the sulfur dioxide. The pteridine fraction was removed by precipitation with silver sulfate at *p*H 2.0. Excess silver and sulfate ions were removed from the filtrate; yield was 115 mg. calculated as *p*-aminobenzoic acid. The solution was adjusted to *p*H 2.0 and concentrated to dryness. The residue was dried thoroughly and the amine extracted from the solid with absolute isopropanol. The isopropanol solution was concentrated to dryness and the residue dissolved in 30 ml. of water. Excess lead acetate was added. After standing overnight at 5°, the lead precipitate was collected and washed with 5 ml. of cold water containing a little lead acetate. The precipitate was suspended in water and the lead removed as the sulfide; yield was 96.5 mg. calculated as *p*-aminobenzoic acid. The solution was adjusted to *p*H 2.0 and concentrated to dryness. The amine was extracted into absolute isopropanol. The isopropanol was evaporated and the residue dissolved in 50 ml. of water. Barium hydroxide was added to *p*H 10.0 and the slight precipitate removed. Ethanol was added to 50% concentration and the material kept at 5° overnight. The barium precipitate was collected, dissolved in water, adjusted to *p*H 2.0 and concentrated to dryness. The amine was extracted with isopropanol and then precipitated by the addition of one volume of petroleum ether. The precipitate was centrifuged off, dissolved in 35 ml. of water and concentrated slightly to remove the isopropanol and petroleum ether. Barium hydroxide was added to *p*H 10.0 and ethanol to 50% concentration. After thorough chilling the precipitate was collected, washed thoroughly with 50% ethanol, absolute ethanol and acetone; yield was 71 mg. calculated as *p*-aminobenzoic acid.

Anal. Calcd. for $C_{22}H_{28}N_4O_{11}$: C, 50.5; H, 5.35; N, 10.69. Found: C, 29.42; H, 4.20; N, 6.64; ash, 50.00. Cor. for C in ash: C, 32.46; H, 4.20; N, 6.64; Ba, 34.80. Ba-free: C, 49.8; H, 6.44; N, 10.17.

As the ash is barium carbonate, the carbon values have been corrected for the amount of carbon retained in the ash.

The free acid is extremely soluble in water or alcohol. The compound could not be crystallized from various solvents or combinations thereof.

Aromatic Amine Nitrogen.—Duplicate weighings were dissolved equivalent to 13.62 micrograms of total nitrogen per ml.; 29.1 microgram equivalents of *p*-aminobenzoic acid was found per ml., which is equivalent to 2.97 micrograms of aromatic amine nitrogen. Therefore 22.39% of the total nitrogen was present as aromatic amine nitrogen.

Effect of Acid and Alkaline Hydrolysis on the Amine Fragment.—All samples were hydrolyzed for sixteen hours at 120° in a sealed tube. One normal sodium hydroxide, 5 *N* sodium hydroxide, 1 *N* hydrochloric acid and 2.5 *N* hydrochloric acid liberated 57.6, 73.0, 72.2, and 74%, respectively, of the nitrogen as α-amino acid nitrogen. Glutamic acid analysis of the 2.5 *N* hydrochloric acid hydrolysate was carried out using *Lactobacillus arabinosus*.

Anal. Calcd. for 3 moles of glutamic acid in the amine fragment (as the free acid): 84.25. Found: 81.8, 82.5.

Isolation of *p*-Aminobenzoic Acid from the N_4 Amine.—One hundred and eighty-seven mg. of the amine fragment was dissolved in 6 ml. of 5 *N* sodium hydroxide and hydrolyzed anaerobically for thirteen hours at 120°. The resulting hydrolysate was diluted to 100 ml. and adjusted to *p*H 3.0. The solution was extracted with 100 ml. of ethyl acetate and the ethyl acetate extract washed with 25 ml. of water. The ethyl acetate was removed by distillation and the residue dissolved in 0.5 ml. of hot water. On cooling the compound crystallized as needles. The precipitate was recrystallized from 0.25 ml. of hot water, m. p. 180.5–182.5°. In admixture with an authentic specimen of *p*-aminobenzoic acid (m. p. 183.5–184.5°) it melted at 182.5–183.5°.

Anal. Calcd. for $C_7H_7O_2N$: C, 61.3; H, 5.11. Found: C, 61.5; H, 4.93.

Detection of One or Two Carbon-atom-containing Fragments.—From sulfurous acid hydrolysates of the fermentation *L. casei* factor no carbon dioxide, glyoxal, glycolic aldehyde or ethylene glycol could be detected by appropriately controlled tests. No carbon dioxide was formed on aerobic ultraviolet irradiation of the fermentation *L. casei* factor.

Reductive Cleavage of the Fermentation *L. casei* Factor.—Two hundred and sixteen mg. of the fermentation *L. casei* factor was dissolved in 250 ml. of 0.4 *N* sulfuric acid and 5 g. of zinc dust was added. After twenty-five minutes the excess zinc dust was removed by filtration and 5 g. of manganese dioxide added. After ten minutes of oxidation the solution was filtered and enough dipotassium hydrogen phosphate was added to the filtrate to raise the *p*H to 6.5. The zinc phosphate was centrifuged off, washed with water and discarded. The centrifugate and washings were combined The distribution of the pteridine between butanol and water at various *p*H values was determined. The results suggested that the compound contained no carboxylic acid group. The solution (*p*H 6.5) was extracted with three ten-volume portions of butanol. The butanol extracts were concentrated and the pteridine precipitated by the addition of ether. The compound was crystallized twice from 4 *N* sodium hydroxide, converted to the free compound and dried.

The ultraviolet absorption spectra of the isolated pteridine were identical with the spectra of an authentic sample of the 2-amino-4-hydroxy-6-methylpteridine.

Acknowledgment.—It is a pleasure to acknowledge the assistance of the Misses E. Boggiano, B. Eames, E. Brogen and A. Buxó for the microbiological assays and the spectrophotometric determinations. The authors extend their appreciation to Dr. R. C. Gore of the Stamford Research Laboratories, American Cyanamid Company, for the infrared determinations, and to Mr. L. Brancone and co-workers for the microanalyses.

The authors are especially indebted to Dr. J. H. Williams for his constant interest and counsel and for his efforts in coördinating the work performed in the various laboratories.

Summary

l-Pyrrolidonecarboxylic acid, 2-amino-4-hydroxypteridine-6-carboxylic acid, 2-amino-4-hydroxy-6-methylpteridine and *p*-aminobenzoic acid have been isolated as degradation products of the fermentation *L. casei* factor. Evidence for the existence of 2-amino-4-hydroxypteridine-6-carboxaldehyde and glutamic acid has been presented.

The significance of these products in formulating the structure of the *L. casei* factors has been discussed.

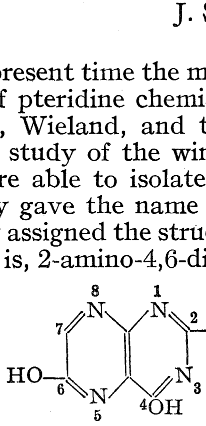
PEARL RIVER, NEW YORK RECEIVED JANUARY 24, 1947

[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

The Structure of the Liver *L. casei* Factor

BY J. H. MOWAT, J. H. BOOTHE, B. L. HUTCHINGS, E. L. R. STOKSTAD, C. W. WALLER, R. B. ANGIER, J. SEMB, D. B. COSULICH[1] AND Y. SUBBAROW

Up to the present time the major reported work in the field of pteridine chemistry has been that of Purrmann, Wieland, and their collaborators, who, in their study of the wing pigments of the butterfly, were able to isolate a yellow pigment to which they gave the name xanthopterine and to which they assigned the structure[2] shown in the formula, that is, 2-amino-4,6-dihydroxypteridine.[3]



Earlier reports[4,5,6,7] of the biological relationship between xanthopterine and the *L. casei* factors, as well as a comparison of the ultraviolet absorption spectra of these factors with the spectra of a number of known pteridines, suggested the presence of a pteridine nucleus in the *L. casei* factors. This possibility warranted more serious consideration when we were able to isolate from the fermentation *L. casei* factor a number of degradation products having pteridine-like absorption curves and having chemical properties consistent with such a hypothesis.

The first of these pteridine-like compounds (V) whose isolation and properties have been described in Paper III[8] of this series, after cleavage with chlorine water and hydrochloric acid gave a positive test for guanidine,[8] thus indicating the presence of a 2-aminopyrimidine. Furthermore, a titration curve indicated the presence of two acidic groups of *pKa* 3.9 and 7.7, probably a carboxyl group and another less acidic group of the enolic type.

Elementary analyses[9] indicated a compound having an empirical formula $C_7H_5O_3N_5$. Neither methoxyl groups nor N-methyl groups could be detected.

Decarboxylation of a few milligrams of the material gave a product which appeared to be identical with 2-amino-4-hydroxypteridine (II), prepared from 2,4,5-triamino-6-hydroxypyrimidine[10] (I) and glyoxal.

The total synthesis of (V) was then accomplished by chlorination and reduction of the previously known iso-xanthopterinecarboxylic acid (III)[11] and also by the condensation of 2,4,5-triamino-6-hydroxypyrimidine (I) and ethyl α-bromo-β,β-diethoxypropionate.[12] These syntheses established the nature of the ring skeleton and the positions of the 2-amino group and the 4-hydroxyl group, and by directly relating the position of the carboxyl group to that of iso-xanthopterinecarboxylic acid (III), showed that the carboxyl group was attached to the pyrazine ring, very probably in the 6-position. The position of the carboxyl group required further proof, however, since the structures postulated by Purrmann[2,11] for xanthopterine and iso-xanthopterinecarboxylic acid were still open to question.

A method of degrading substituted lumazines to pyrazines has been described by Weijlard, Tishler and Erickson[13] and by following this procedure, using 2-amino-4-hydroxy-7-methylpteridine (XIII) we obtained 2-amino-6-methylpyrazine. Subsequently this work was repeated, using the corresponding 2-amino-4-hydroxy-6-methylpteridine (VII), and the product was found to be identical with an authentic sample of 2-amino-5-methylpyrazine (IX) prepared from the known 2,5-dimethylpyrazine (X).

The structure of the so-called "fluorescent dibasic acid[8] obtained from the fermentation *L. casei* factor after aerobic alkaline hydrolysis was therefore conclusively proven to be 2-amino-4-hydroxypteridine-6-carboxylic acid (V).

Another pteridine-like compound[8,14] isolated from hydrolysates of the fermentation *L. casei* factor gave an analysis leading to the empirical formula $C_7H_7ON_5$, a formula which corresponded to that of 2-amino-4-hydroxy-6-methylpteridine. This assumption was proved to be correct by the synthesis of an identical compound through the following series of reactions.

---

(1) Calco Chemical Division, American Cyanamid Company, Bound Brook, New Jersey.

(2) Purrmann, *Ann.*, **546**, 98 (1940).

(3) The system of numbering recommended by "Chemical Abstracts" and the "Ring Index" will be used instead of the older system of numbering which has been used by Purrmann and his collaborators.

(4) Mitchell, THIS JOURNAL, **66**, 274 (1944).

(5) Wright and Welch, *Am. J. Med. Sci.*, **206**, 128 (1943).

(6) Totter, *et al.*, *Federation Proc.*, **2**, 72 (1943).

(7) Wright, Skeggs and Welch, *ibid.*, **3**, 88 (1944).

(8) Stokstad, *et al.*, THIS JOURNAL, **70**, 5 (1948).

(9) For some time we experienced considerable difficulty in obtaining correct and reproducible analysis of the pteridines, particularly in the case of nitrogen determinations. Wieland and Purrmann, *Ann.*, **545**, 163 (1940), have reported similar difficulties. An investigation of this problem by our microanalytical department appears to have resulted in a satisfactory procedure which may be the subject of a later communication.

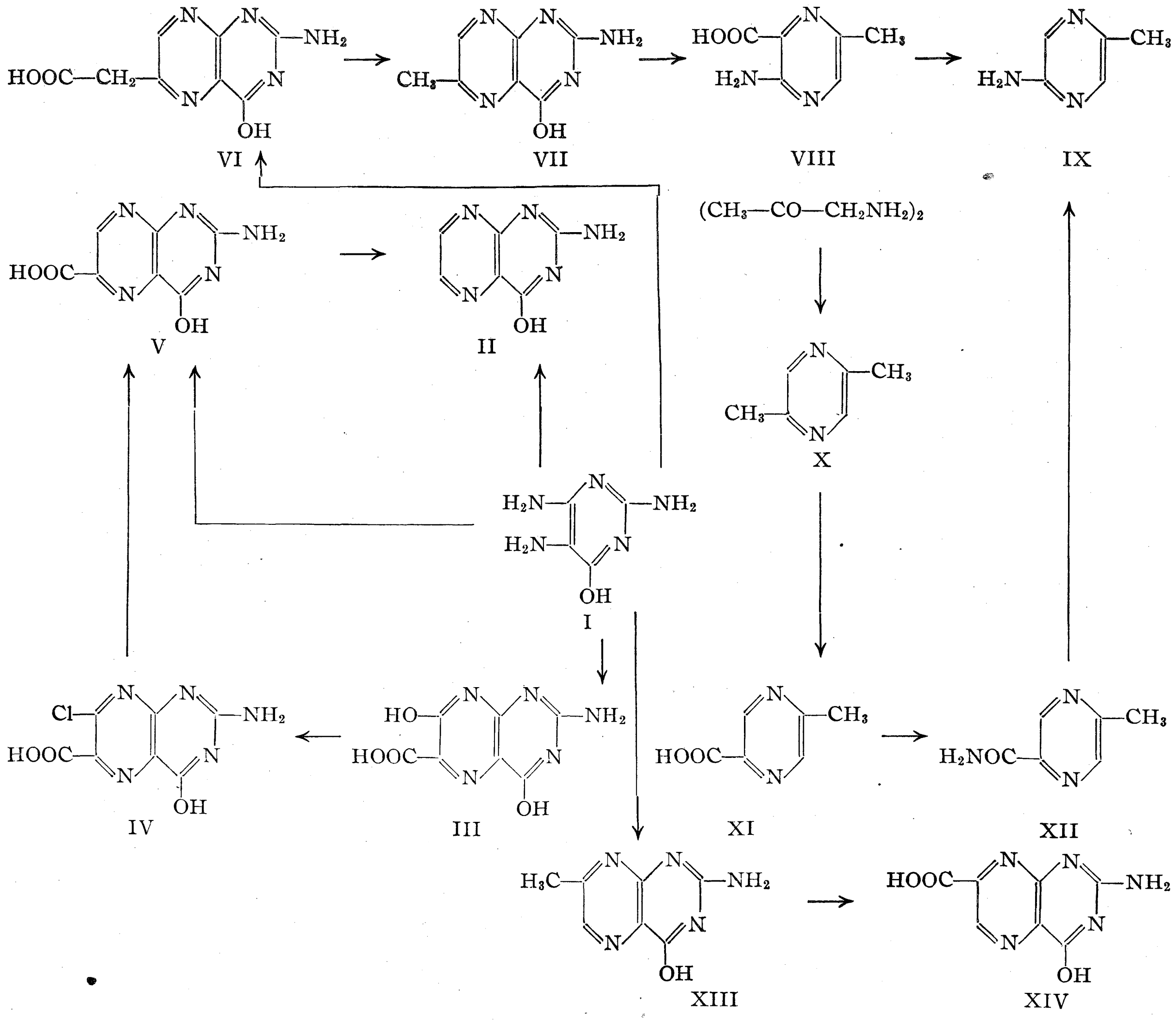
(10) Traube, *Ber.*, **33**, 1371 (1900).

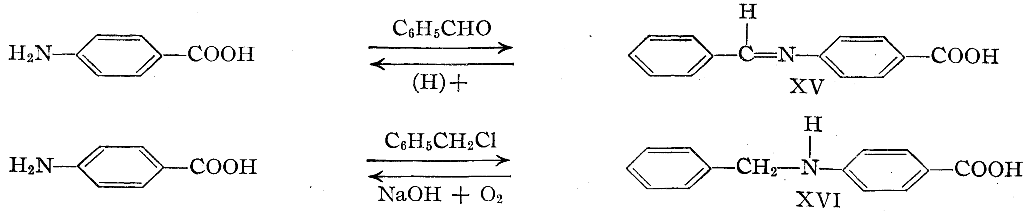
(11) Purrmann, *Ann.*, **548**, 284 (1941).

(12) Direct halogenation of ethyl-β,β-diethoxypropionate appeared to give a mixture of the mono- and di-halogen compounds which could not be readily separated, but which was satisfactory for the synthesis described. The pure mono-halogenated compound has been prepared recently by Oroshnik and Spoerri, THIS JOURNAL, **67**, 721 (1945), using another method.

(13) Weijlard, Tishler and Erickson, THIS JOURNAL, **67**, 802 (1945).

(14) Hutchings, *et al.*, *ibid.*, **70**, 1 (1948).





Methyl γ,γ-dimethoxyacetoacetate, prepared from methyl dimethoxyacetate and methyl acetate by the procedure of Johnson and Mikeska,[15] was condensed with 2,4,5-triamino-6-hydroxypyrimidine (I), to give 2-amino-4-hydroxypteridine-6-acetic acid (VI), (Fig. 5) which could be easily oxidized with alkaline potassium permanganate to 2-amino-4-hydroxypteridine-6-carboxylic acid (V). Decarboxylation of (VI) gave the desired 2-amino-4-hydroxy-6-methylpteridine (VII).

The isomeric 2-amino-4-hydroxy-7-methylpteridine (XIII) was prepared by the condensation of 2,4,5-triamino-6-hydroxypyrimidine (I) with the acetal of methyl glyoxal.[16] This 7-methylpteridine was then converted to the corresponding 2-amino-4-hydroxypteridine-7-carboxylic acid (XIV) by oxidation with alkaline potassium permanganate.

The ultraviolet absorption curves of the 6- and 7-methylpteridines are shown in Figs. 1 and 2.

Since the pteridine nucleus appears to be stable in the presence of alkaline potassium permanganate, various side chains in the 6 or 7 position may usually be oxidized to the corresponding pteridinecarboxylic acid which may then be identified by comparing its ultraviolet absorption spectrum

---

(15) Johnson and Mikeska, THIS JOURNAL, **41**, 812 (1919).

(16) Madelung and Oberwegner, *Ber.*, **65**, 940 (1932).

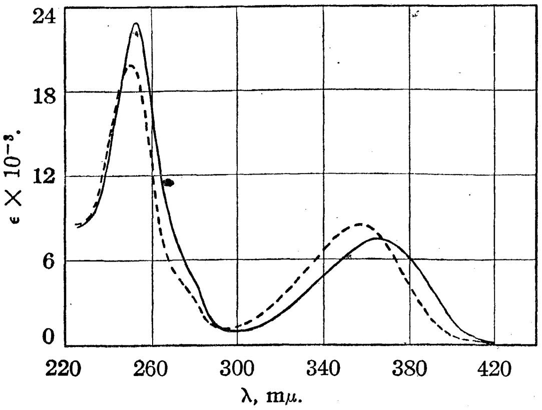


Fig. 1.—Ultraviolet absorption spectra in 0.1 *N* sodium hydroxide: ——, 2-amino-4-hydroxy-6-methylpteridine; – – – –, 2-amino-4-hydroxy-7-methylpteridine.

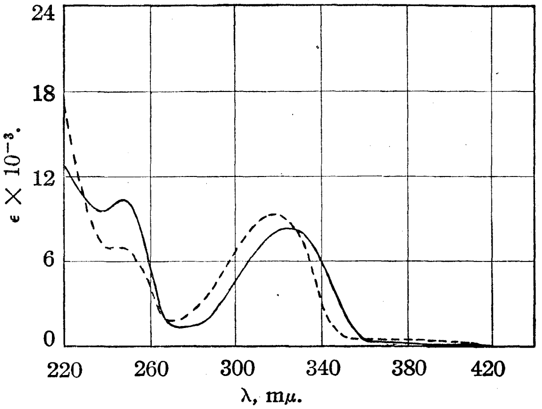


Fig. 2.—Ultraviolet absorption spectra in 0.1 *N* hydrochloric acid: ——, 2-amino-4-hydroxy-6-methylpteridine; – – – – –, 2-amino-4-hydroxy-7-methylpteridine.

with that of a known sample. The ultraviolet absorption curves of these pteridinecarboxylic acids are shown in Figs. 3 and 4.

The structure of the cleavage products of the *L. casei* factors having been determined, it then became necessary to consider the linkages by which these fragments were joined. Evidence has been presented in a previous paper[14] of this series which indicates that the pteridine ring system must be joined at the 6-position to the amino group of *p*-aminobenzoylglutamic acid (or its homologs) through a one-carbon atom linkage. Two simple model compounds were prepared, namely, N-(benzylidene)-*p*-aminobenzoic acid[17] (XV), and N-(benzyl)-*p*-aminobenzoic acid (XVI). The anil linkage of (XV) was found to cleave with extreme rapidity in the presence of even traces of weak acids, whereas the methylene linkage of (XVI) was stable when subjected to acids or to anaerobic alkaline hydrolysis but was rapidly cleaved by aerobic alkaline hydrolysis, just as in the case of the *L. casei* factors. Such a linkage also appears to explain the role of oxygen in the aerobic alkaline hydrolysis, since it has been reported[18] that compounds of this type are cleaved by hydrolysis in the presence of hydrogen acceptors.

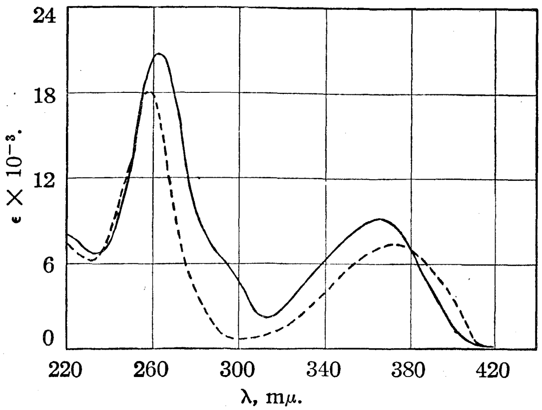


Fig. 3.—Ultraviolet absorption spectra in 0.1 *N* sodium hydroxide: ——, 2-amino-4-hydroxypteridine-6-carboxylic acid; – – – –, 2-amino-4-hydroxypteridine-7-carboxylic acid.

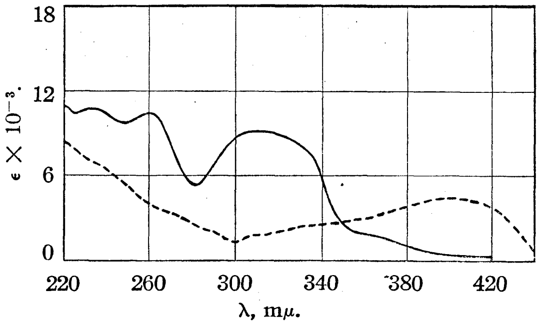


Fig. 4.—Ultraviolet absorption spectra in 0.1 *N* hydrochloric acid: ——, 2-amino-4-hydroxypteridine-6-carboxylic acid; – – – – – –, 2-amino-4-hydroxypteridine-7-carboxylic acid.

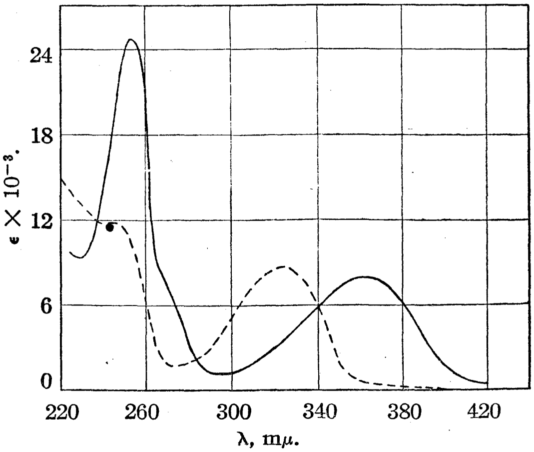


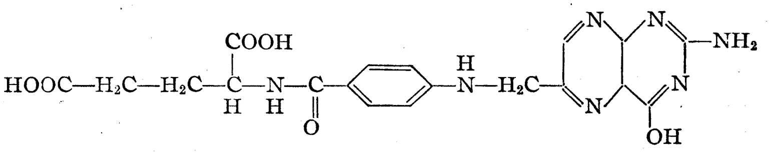
Fig. 5.—Ultraviolet absorption spectra of 2-amino-4-hydroxypteridine-6-acetic acid: ——, in 0.1 *N* sodium hydroxide; – – – – –, in 0.1 *N* hydrochloric acid

---

(17) Reddelien and Danilof, *Ber.*, **54**, 3132 (1921).

(18) Gilman, "Organic Chemistry, An Advanced Treatise," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 881.

In view of these considerations the structure of the liver *L. casei* factor was therefore postulated to be N-[4-{[(2-amino-4-hydroxy-6-pteridyl)-methyl]-amino}-benzoyl]-*l*(+)-glutamic acid, that is



The validity of this formula has been proved by the synthesis of this compound by a number of methods, several of which are described in the following communications.

Experimental

2-Amino-4-hydroxypteridine (II).—A solution of 14.1 g. of 2,4,5-triamino-6-hydroxypyrimidine[10] in 200 cc. of 1 *N* hydrochloric acid was heated to 70° and treated with 22 cc. of a 26.5% solution of glyoxal. After twenty-four hours the precipitate was collected, washed with water, alcohol and ether and dried; weight was 13.4 g. This material was dissolved in a mixture of 50 cc. of water and 10 cc. of 10 *N* sodium hydroxide solution, filtered and then diluted with an equal volume of 10 *N* sodium hydroxide. The sodium salt crystallized rapidly. The sodium salt was collected, washed with alkali and again dissolved in water. Acidification to *p*H 3 precipitated the crude 2-amino-4-hydroxypteridine; weight was 13 g. A portion of this material was recrystallized several times from alkali and then precipitated at *p*H 3, thoroughly washed with hot water, alcohol and ether, and dried *in vacuo*.

Anal. Calcd. for $C_6H_5ON_5$: C, 44.10; H, 3.07; N, 42.94. Found: C, 43.65, 44.04; H, 2.82, 3.50; N, 42.88, 42.75.

2-Amino-4-hydroxy-7-chloropteridine-6-carboxylic Acid (IV).—A mixture of 0.59 g. of 2-amino-4,7-dihydroxy-pteridine-6-carboxylic acid (iso-xanthopterinecarboxylic acid),[11] (III) 3.0 g. of phosphorus pentachloride and 30 cc. of phosphorus oxychloride was heated on the steam-bath under a reflux condenser for twenty minutes. The mixture was then refluxed over a gas burner for about thirty minutes. In order to effect complete solution of the starting material, an additional 15 cc. of phosphorus oxychloride was then added and refluxing was continued for fifteen minutes. The hot solution was filtered and evaporated to dryness *in vacuo*. The residue was then triturated with 5 cc. of cold water for about forty-five minutes. The solid product was collected on a filter and washed with a little water and finally with a little ether; weight was 0.56 g.

Anal. Calcd. for $C_7H_4O_3N_5Cl$: Cl, 14.7. Found: Cl, 13.9. Attempts to further purify a portion of this material resulted in the loss of halogen.

2-Amino-4-hydroxypteridine-6-carboxylic Acid (V): A.—A mixture of 1.5 g. of 2-amino-4-hydroxy-7-chloropteridine-6-carboxylic acid, 21 cc. of glacial acetic acid and 21 cc. of hydriodic acid (sp. gr. 1.7) was heated on the steam-bath with stirring for five minutes. The cooled solution was diluted with 150 cc. of cold water. After a short time, the precipitate was collected in the centrifuge, washed with water and then with very dilute sulfurous acid. The product was then washed with water, alcohol and ether and dried; wt. 0.400 g. This material was dissolved in about 30 cc. of very dilute sodium hydroxide solution, and decolorized with charcoal. The clarified solution was acidified to *p*H 2 and the precipitate was collected and recrystallized several times from 2 *N* sodium hydroxide solution. The pure, crystalline sodium salt was then dissolved in warm water and converted to the free acid by acidification to *p*H 2. After thorough washing with water, alcohol and ether, the product was dried *in vacuo*. Weight was 0.060 g. *Anal.* Calcd. for $C_7H_5O_3N_5$: C, 40.58; H, 2.42; N, 33.82. Found: C, 40.24; H, 2.80; N, 33.37.

B.—A mixture of 100 g. of 2,4,5-triamino-6-hydroxypyrimidine, 192 g. of ethyl α-bromo-β,β-diethoxypropionate,[12] 112 g. of silver carbonate and 2500 cc. of absolute alcohol was refluxed under an atmosphere of nitrogen for five hours. After distilling off most of the alcohol the residue was suspended in a mixture of 2500 cc. of water and 250 cc. of concentrated hydrochloric acid, refluxed for one hour and then filtered while hot. To the filtrate was added a solution of 125 g. of iodine in 800 cc. of alcohol and the mixture was then adjusted to *p*H 2 by the addition of ammonium hydroxide. After thorough cooling, the precipitate was collected in the centrifuge and washed once with dilute sulfurous acid and then with water. This crude product was dissolved in 1 liter of hot water containing 16 g. of sodium hydroxide, decolorized with charcoal and then precipitated by acidification of the solution to *p*H 2. The precipitate was collected, washed with water, alcohol, and ether and dried; weight was 15.5 g. Further purification was effected by crystallization from 1 *N* sodium hydroxide. The pure, crystalline sodium salt was then converted to the free acid. *Anal.* Calcd. for $C_7H_5O_3N_5$: C, 40.58; H, 2.42; N, 33.82. Found: C, 40.54; H, 2.75; N, 33.80.

2-Amino-4-hydroxypteridine-6-acetic Acid (VI).—A stirred mixture of 7.5 g. of 2,4,5-triamino-6-hydroxypyrimidine, 50 cc. of glacial acetic acid and 9.0 g. of methyl γ,γ-dimethoxyacetoacetate[15] (b. p. 92° (5 mm.)) was heated on the steam-bath for twenty minutes; then 50 cc. of water was added and the mixture was heated for an additional thirty minutes. After cooling thoroughly, the precipitate was collected, washed with a little water and then dissolved in 250 cc. of very dilute sodium hydroxide solution. The solution was clarified with charcoal and the crude product was precipitated by the addition of acetic acid; weight was 6.1 g. A portion of this crude material (1.0 g.) was dissolved in 10 cc. of dilute sodium hydroxide solution, filtered, and then treated with an equal volume of 10 *N* sodium hydroxide solution. After cooling, the crystalline sodium salt was collected, washed with 5 *N* sodium hydroxide solution and then recrystallized twice more by the same procedure. The pure, crystalline sodium salt was then dissolved in water at *p*H 10–12, decolorized with charcoal and the free acid was precipitated by the addition of hydrochloric acid to *p*H 2. The washed and dried product weighed 0.355 g. *Anal.* Calcd. for $C_8H_7O_3N_5$: C, 43.44; H, 3.17; N, 31.67. Found: C, 43.75; H, 3.82; N, 32.05.

Oxidation of 2-Amino-4-hydroxypteridine-6-acetic Acid.—A stirred solution of 0.11 g. of 2-amino-4-hydroxypteridine-6-acetic acid, 0.25 cc. of 10 *N* sodium hydroxide solution and 10 cc. of water was heated in a water-bath to a temperature of about 75°. To this hot solution was then added 5 cc. of a 0.2 *M* solution of potassium permanganate during ninety minutes. After stirring at 75° for an additional thirty minutes, the mixture was cooled and treated with a few drops of sulfurous acid to destroy any excess permanganate. The manganese dioxide was removed by filtration and the oxidation product was precipitated by acidification to *p*H 2. The precipitate was collected, washed with water, and recrystallized from about 5 cc. of 2 *N* sodium hydroxide solution. The crystalline sodium salt was then dissolved in water and acidified. The product was collected, washed with water, alcohol and ether and dried; weight was 0.060 g. This material was identical with the previously described 2-amino-4-hydroxypteridine-6-carboxylic acid.

2-Amino-4-hydroxy-6-methylpteridine (VII).—A dry, finely powdered sample of 2-amino-4-hydroxypteridine-6-acetic acid (0.200 g.) was heated for about seven hours at 280° in an atmosphere of nitrogen. The residue was dissolved in 150 cc. of dilute sodium hydroxide solution, decolorized with charcoal and then adjusted to *p*H 7.0. The mixture was then boiled for a few minutes and filtered through a heated funnel. The filtrate was thoroughly cooled and the precipitate was collected; weight was 0.105 g. This material was again dissolved in very dilute alkali, adjusted to *p*H 7.0, heated to boiling, filtered and allowed to cool. The precipitate was collected, washed with cold water and finally recrystallized from 90 cc. of hot water; weight was 0.068 g. *Anal.* Calcd. for $C_7H_7ON_5$: C, 47.46; H, 3.96; N, 39.55. Found: C, 47.82; H, 4.75; N, 39.56.

2-Amino-4-hydroxy-7-methylpteridine (XIII).—A mixture of 0.5 g. of 2,4,5-triamino-6-hydroxypyrimidine and 0.6 g. of methylglyoxal diethyl acetal[16] was dissolved in 25 cc. of warm 4 *N* hydrochloric acid. After heating on the steam-bath for ninety minutes the solution was cooled and neutralized to *p*H 3.0. The precipitate was collected in the centrifuge, washed with water, alcohol and ether and dried; weight was 0.6 g. This crude product was dissolved in 30 cc. of dilute sodium hydroxide solution and then treated with an equal volume of 10 *N* sodium hydroxide solution. The crystalline precipitate was collected and recrystallized twice more by the same procedure. The crystalline sodium salt was then dissolved in water, decolorized with charcoal and precipitated at *p*H 3.0. *Anal.* Calcd. for $C_7H_7ON_5$: C, 47.46; H, 3.96; N, 39.55. Found: C, 47.18; H, 4.45; N, 39.42.

2-Amino-4-hydroxypteridine-7-carboxylic Acid (XIV).—A stirred solution of 0.200 g. of 2-amino-4-hydroxy-7-methylpteridine in 20 cc. of water containing 0.3 cc. of 10 *N* sodium hydroxide solution was heated in a water-bath to 90° and treated with small portions of a 0.2 molar solution of potassium permanganate until no further reaction occurred. The excess potassium permanganate was destroyed with a little sodium sulfite and the manganese dioxide was removed by filtration. The filtrate was adjusted to *p*H 2.0 and the precipitate was collected, washed with water, methanol and ether; weight was 0.195 g. This material was purified by crystallization from alkali as previously described and finally converted to the free acid. *Anal.* Calcd. for $C_7H_5O_3N_5$: C, 40.58; H, 2.42; N, 33.82. Found: C, 40.50; H, 3.11; N, 33.30, 33.49. This compound appears to be very hygroscopic and rapidly takes up water to form a very stable monohydrate.

2-Amino-5-methylpyrazine-3-carboxylic Acid (VIII).—A mixture of 7.0 g. of 2-amino-4-hydroxy-6-methylpteridine (VII), 22 cc. of water and 16 cc. of 10 *N* sodium hydroxide solution was heated in a sealed bomb at 170° for twenty hours. After being removed from the bomb, the reaction mixture was heated to effect solution and filtered while still hot. The hot filtrate was then acidified to *p*H 2.5 with hydrochloric acid, and on cooling the crude product crystallized; weight was 4.1 g. This material was recrystallized from 45 cc. of hot water after clarification with charcoal; weight was 3.2 g. An analytical sample was recrystallized twice more from hot water, m. p. 171.5–172.0°. *Anal.* Calcd. for $C_6H_7O_2N_3$: C, 47.05; H, 4.60; N, 27.45. Found: C, 46.75; H, 4.49; N, 27.40.

2-Amino-5-methylpyrazine (IX).—A solution of 1.0 g. of 2-amino-5-methylpyrazine-3-carboxylic acid (VIII) in 5 cc. of butyl cellosolve was refluxed for forty-five minutes. The solution was then clarified with charcoal, diluted with about 40 cc. of heptane and cooled. The precipitate was filtered off and discarded and the filtrate was then treated with gaseous hydrogen chloride. The precipitated hydrochloride was collected, dissolved in water and made alkaline by the addition of sodium hydroxide solution. This solution was extracted with ether several times. The ether solution was evaporated to dryness and the yellow crystalline residue (0.3 g.) was then recrystallized from a mixture of ether and petroleum ether and then sublimed twice *in vacuo* at 70° and 1–2 mm. pressure. The white sublimate melted at 116–117°. This melting point was not depressed by mixture with a sample of 2-amino-5-methylpyrazine prepared from 2-methylpyrazine-5-carboxylic acid by the method of Weijlard, Tishler and Erickson.[13] *Anal.* Calcd. for $C_5H_7N_2$: C, 55.00; H, 6.47; N, 38.53. Found: C, 55.58; H, 6.68; N, 38.40.

N-(Benzyl)-*p*-aminobenzoic Acid (XVI).—A mixture of 1.4 g. of *p*-aminobenzoic acid, 0.7 g. of potassium carbonate, 20 cc. of absolute ethanol and 1.3 cc. of benzyl chloride was refluxed on the steam-bath for several hours and then allowed to stand overnight at room temperature. The reaction mixture was diluted with water and the precipitate was collected and washed with water, then with a little cold alcohol and then again with water. The material may be recrystallized from hot, aqueous ethanol. *Anal.* Calcd. for $C_{14}H_{13}O_2N$: C, 74.00; H, 5.77; N, 6.16. Found: C, 74.10; H, 5.40; N, 6.13.

Acknowledgment.—We wish to acknowledge the technical assistance of Miss Barbara Eames and Miss Edith Brogan. The microanalyses were carried out by Mr. Louis Brancone and coworkers. The authors are especially indebted to Dr. J. H. Williams for his constant interest and counsel and for his efforts in coördinating the work performed in the various laboratories.

Summary

The structure of the pteridine nucleus of the *L. casei* factors has been established and a structure for the liver *L. casei* factor consistent with all of the experimental evidence has been postulated.

Experimental methods and reference compounds of known structure have been described which allow rapid and certain distinction between pteridines which are isomeric in the 6- and the 7-positions.

PEARL RIVER, NEW YORK RECEIVED JANUARY 24, 1947

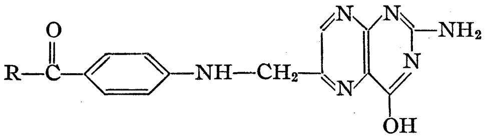
[CONTRIBUTION FROM LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, AND CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

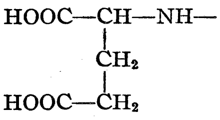
Synthesis of Pteroylglutamic Acid (Liver *L. casei* Factor) and Pteroic Acid. I

BY COY W. WALLER,[1] BRIAN L. HUTCHINGS,[1] JOHN H. MOWAT,[1] E. L. R. STOKSTAD,[1] JAMES H. BOOTHE,[1] ROBERT B. ANGIER,[1] JOSEPH SEMB,[1] Y. SUBBAROW,[1] DONNA B. COSULICH,[2] M. J. FAHRENBACH,[2] M. E. HULTQUIST,[2] ERWIN KUH,[2] E. H. NORTHEY,[2,3] DORIS R. SEEGER,[2] J. P. SICKELS[2] AND JAMES M. SMITH, JR.[2]

In a preliminary note[4] it was announced that the total synthesis of the liver *L. casei* factor had been accomplished. In a second note[5] the structure was given and the method of synthesis was outlined. The purpose of this communication is to describe in detail this method of synthesis of the liver *L. casei* factor.

The present status of the nomenclature of the *L. casei* factors and related compounds is extremely ambiguous. Mitchell, Snell and Williams[6] used the term "Folic Acid" to represent a product obtained from spinach and defined folic acid "as the material responsible for growth stimulation of *Streptococcus lactis* R on a given medium." Folic acid has become popular as a term to represent any material with such activity without regard for differences in chemical nature; this usage makes it unsuited to represent a chemical entity. The complexity of these compounds precludes the general usage of their chemical names. Therefore, it would be desirable to have a short, pseudochemical name for the basic compound from which the name of any related compound can be derived. The name suggested for the liver *L. casei* factor[5] and its structure is as represented by I. The basic compound whose synthesis is reported in detail herein is represented by II.



Compound	R—	Name
I	 $HOOC-CH(NH-)-CH_2-CH_2-COOH$	Liver *L. casei* factor, pteroylglutamic acid, N-[4-{[(2-amino-4-hydroxy-6-pteridyl)-methyl]-amino}-benzoyl]-glutamic acid
II	HO—	Pteroic acid, 4-{[(2-amino-4-hydroxy-6-pteridyl)-methyl]-amino}-benzoic acid

In Table I the compounds which have been obtained in a pure state are summarized according to their biological activities and the number of glutamic acid residues in each molecule. The number of glutamic acid residues ranges from none for pteroic acid to seven for pteroylhexaglutamylglutamic acid with one and three for pteroylglutamic acid and the fermentation *L. casei* factor, respectively. Pteroic acid has the basic structure found in all of these compounds. The exact name of the fermentation *L. casei* factor will be given when the nature of the peptide linkage is reported.

TABLE I

	No. of glutamic acid residues	Activities in micrograms per ml. for half maximum growth		Active for chicks	Refs.
		S. faecalis R	*L. casei*		
Pteroic acid	0	0.0008	0.07	No	5
Pteroylglutamic acid (liver *L. casei* factor)	1	.0003	.00007	Yes	4, 5, 7, 8, 9
Fermentation *L. casei* factor	3	.0042	.000061	Yes	5, 7, 8, 12
Pteroylhexaglutamylglutamic acid (B_c conjugate)	7	Slight[a]	Slight[a]	Yes	10, 11

[a] One microgram is equivalent to 0.003–0.006 microgram of vitamin B_c when measured with *L. casei* and 0.002 microgram when using *S. faecalis*.

In a previous publication[9] the pteridines were synthesized from 2,4,5-triamino-6-hydroxypyrimidine and a compound in which adjacent carbons contained functional groups capable of reacting with amines. By analogy a reaction should occur between the 2,4,5-triamino-6-hydroxypyrimidine and a three-carbon compound in which the *p*-aminobenzoylglutamic acid is attached to a terminal carbon atom and functional groups such as bromine or oxygen are on each of the other two carbons to give pteroylglutamic acid.

The first reaction attempted in this synthesis was to combine α,β-dibromopropionaldehyde and diethyl *p*-aminobenzoylglutamate and then to treat the product with 2,4,5-triamino-6-hydroxypyrimidine. When diethyl *p*-aminobenzoylglutamate reacted with the dibromopropionaldehyde, a crude, hygroscopic, non-crystalline product (III) was obtained. This material appeared to contain an anil structure because it hydrolyzed readily to diethyl *p*-aminobenzoylglutamate and a tar. Upon condensation of III with 2,4,5-triamino-6-hydroxypyrimidine, a very low yield of biologically active material was obtained.

---

[1] Lederle Laboratories Division, American Cyanamid Company.

[2] Calco Chemical Division, American Cyanamid Company.

[3] Present address: Stamford Research Laboratories, American Cyanamid Compay.

[4] Angier, *et al.*, *Science*, **102**, 227 (1945).

[5] Angier, *et al.*, *ibid.*, **103**, 667 (1946).

[6] Mitchell, Snell and Williams, THIS JOURNAL, **66**, 267 (1944).

[7] Stokstad, *et al.*, *ibid.*, **70**, 3, 5 (1948).

[8] Hutchings, *et al.*, *ibid.*, **70**, 1, 10 (1948).

[9] Mowat, *et al.*, *ibid.*, **70**, 14 (1948).

[10] Pfiffner, *et al.*, *Science*, **102**, 228 (1945).

[11] Pfiffner, *et al.*, THIS JOURNAL, **68**, 1392 (1946).

[12] Hutchings, *et al.*, *Science*, **99**, 371 (1944).

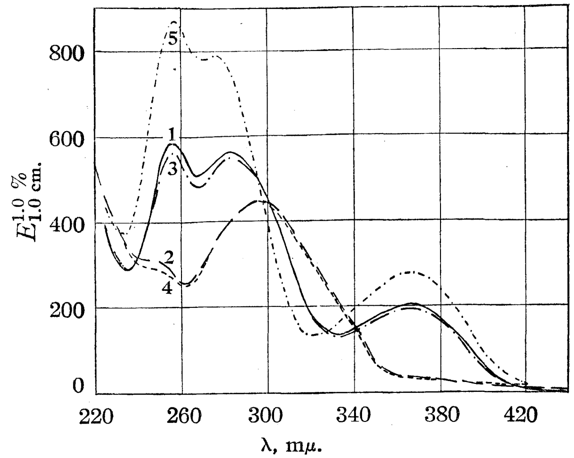


Fig. 1.—Ultraviolet absorption spectra: (1) synthetic liver *L. casei* factor (pteroylglutamic acid[a]) in 0.1 *N* sodium hydroxide; (2) synthetic liver *L. casei* factor (pteroylglutamic acid[a]) in 0.1 *N* hydrochloric acid; (3) natural liver *L. casei* factor in 0.1 *N* sodium hydroxide; (4) natural liver *L. casei* factor in 0.1 *N* hydrochloric acid; (5) pteroic acid in 0.1 *N* sodium hydroxide.

[a] *Anal.* Calcd. for $C_{19}H_{19}O_6N_7 \cdot H_2O$: C, 49.6; H, 4.15; N, 21.4. Found: C, 49.5, 49.5; H, 4.36, 4.16; N, 21.40, 21.5.

In view of the failure of the first reaction to give appreciable yields of pteroylglutamic acid, the dibromopropionaldehyde was then treated with the 2,4,5-triamino-6-hydroxypyrimidine in an attempt to obtain a 6-bromomethylpteridine or a 6-hydroxymethylpteridine. From this condensation a crude product was obtained and separated into two fractions. One fraction was identified as 2-amino-4-hydroxy-7-methylpteridine. The other fraction (IV) could be characterized only to the extent that it was a 6-substituted-pteridine since it could be oxidized with alkaline permanganate to 2-amino-4-hydroxypteridine-6-carboxylic acid.

In a final attempt to obtain pteroylglutamic acid by the use of dibromopropionaldehyde, equal molecular amounts of 2,4,5-triamino-6-hydroxypyrimidine and the *p*-aminobenzoylglutamic acid were dissolved in water and treated with the dibromopropionaldehyde which was dissolved in an organic solvent. The yields were 30–50% of crude material which was shown to contain 10–25% of pteroylglutamic acid. A series of experiments at various acidities showed that the best yields were obtained when the *p*H was maintained at 4. The addition of the *p*-aminobenzoylglutamic acid to a reaction mixture of the 2,4,5-triamino-6-hydroxypyrimidine and the dibromopropionaldehyde gave much less pteroylglutamic acid than when all reactants were mixed together.

The synthesis of pteroic acid, which is reported herein, was accomplished by substituting *p*-aminobenzoic acid for *p*-aminobenzoylglutamic acid in the above reaction.

Pteroylglutamic and pteroic acids were purified in the same general way. The crude materials were dissolved in alkali, brought to *p*H 7, filtered and brought to *p*H 3 to precipitate the active compounds. The products were purified further by repeated treatments with charcoal in alkaline solution and recrystallizations from water at *p*H 3.

A comparison of pteroylglutamic acid with the liver *L. casei* factor indicated that the two compounds are identical.[13]

The crystalline structure of pteroylglutamic acid and the liver compound are identical. The ultraviolet absorption spectra for pteroic acid, pteroylglutamic acid and the liver *L. casei* factor are plotted in Fig. 1. The infrared absorption spectra for pteroylglutamic acid, the liver *L. casei* factor, racemic pteroylglutamic acid, racemic liver *L. casei* factor from the anaerobic alkaline hydrolysis of the fermentation *L. casei* factor and pteroic acid are given in Fig. 2. The infrared absorption spectrum of the liver *L. casei* factor is identical with that of pteroylglutamic acid and this spectrum of the racemic liver *L. casei* factor is identical with that of the racemic pteroylglutamic acid.

Degradation of pteroylglutamic acid and pteroic acid with alkali and oxygen gave 2-amino-4-hydroxypteridine-6-carboxylic acid which was the same acid obtained from the natural liver and fermentation *L. casei* factors.

Experimental

Materials.—The 2,4,5-triamino-6-hydroxypyrimidine was prepared by nitrosation and reduction of 2,4-diamino-6-hydroxypyrimidine.[14] The *p*-aminobenzoyl-*l*(+)-glutamic acid and the *p*-aminobenzoyl-*d,l*-glutamic acid were prepared by nitrobenzoylation and reduction of *l*(+)-glutamic acid and *d,l*-glutamic acid according to the method of Van Der Scheer and Landsteiner.[15] The dihalopropionaldehydes were prepared by direct halogenation of acrolein in carbon disulfide[16] or in carbon tetrachloride.[17] The dihalopropionaldehydes were purified by repeated fractionation; the fractions boiling at 53 to 54° at 2.5 mm. pressure and 46 to 49° at 12 to 14 mm. pressure for the dibromopropionaldehyde and dichloropropionaldehyde, respectively, were used.

Diethyl *p*-Aminobenzoyl-*l*(+)-glutamate.—The *p*-aminobenzoyl-*l*(+)-glutamic acid (25 g.) was slurried in 200 ml. of 95% ethanol which had previously been saturated with hydrogen chloride at 0°. This mixture was allowed to stand for two days during which time the *p*-aminobenzoylglutamic acid gradually dissolved. The excess hydrogen chloride and part of the ethanol were removed by evaporation under reduced pressure at room temperature. The residual solution was diluted to 1 liter with cold water and neutralized with ammonia to about *p*H 8. A slightly colored crystalline product was filtered off at once, washed and dried; yield 24 g. (75%); m. p. 139–141°.

This crude product is satisfactory for most purposes. For analytical sample it was recrystallized twice from ethanol after decolorizing the solution with charcoal; yield 16 g.; m. p. 143–144°.

---

[13] Pfiffner[11] found that pteroylglutamic acid and vitamin B_c were identical.

[14] Traube, *Ber.*, **33**, 1371 (1900).

[15] Van Der Scheer and Landsteiner, *J. Immunology*, **29**, 373 (1935).

[16] Fischer and Tafel, *Ber.*, **20**, 3389 (1887).

[17] Moureu and Boismenu, *Ann. Chim.*, [9] **15**, 209 (1921).

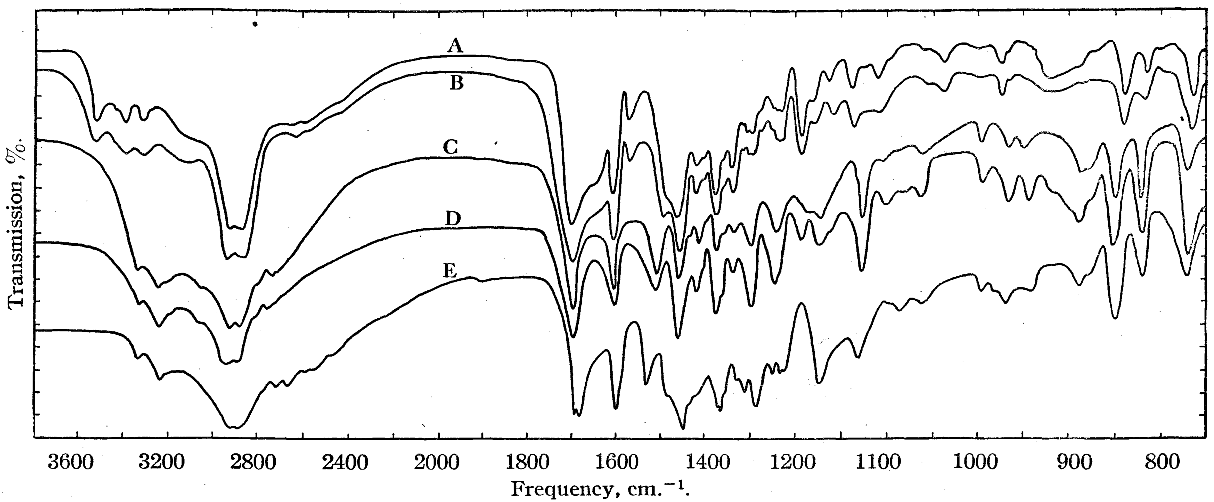


Fig. 2.—Infrared absorption spectra: A, natural liver *L. casei* factor; B, synthetic liver *L. casei* factor (pteroylglutamic acid; C, synthetic racemic liver *L. casei* factor (racemic pteroylglutamic acid); D, natural racemic liver *L. casei* factor; E, pteroic acid.

Anal. Calcd. for $C_{16}H_{22}O_5N_2$: C, 59.61; H, 6.89; N, 8.69. Found: C, 59.2; H, 6.7; N, 8.84.

Preparation of Anil (III).—A solution of 5 g. of diethyl *p*-aminobenzoyl-*l*(+)-glutamate and 3.35 g. of α,β-dibromopropionaldehyde in 200 ml. of diethyl ether was refluxed for four hours. After standing overnight the red oil was separated from the ether solution, dissolved in 15 ml. of ethanol and precipitated with 500 ml. of ether. The resulting oily product was dried to a powder.

A sample of the above anil and an equal weight of sodium bisulfite when heated in water for twenty minutes deposited a tar. This tar was collected and discarded. The solution deposited a crystalline material when cooled which melted at 138 to 140°. It was diethyl *p*-aminobenzoylglutamate.

Diethyl Pteroylglutamate from Anil (III).—To a solution of 0.5 g. of 2,4,5-triamino-6-hydroxypyrimidine and 0.88 g. of sodium acetate in 50 ml. of water was added a solution of 2.3 g. of anil (III) in 50 ml. of ethanol. After standing overnight a very small amount of precipitate was collected, washed and dried. After alkaline hydrolysis this crude product was shown to contain 1.9% of biologically active material calculated as pteroylglutamic acid.

Preparation of (IV).—To a solution of 3 g. of 2,4,5-triamino-6-hydroxypyrimidine in 300 ml. of 10% sodium acetate solution was added dropwise with stirring 4.7 g. of α,β-dibromopropionaldehyde dissolved in 150 ml. of ethanol. Fifteen minutes after completion of the addition 2 g. of the precipitated product was collected. When the acidity of this reaction was maintained at *p*H 4 by the gradual addition of sodium hydroxide solution instead of using the acetate buffer, a comparable yield of the same product was obtained.

Attempted purification and identification of this material was unsuccessful; however, when a sample was oxidized with hot alkaline permanganate solution 2-amino-4-hydroxypteridine-6-carboxylic acid[9] was obtained.

2-Amino-4-hydroxy-7-methylpteridine and (IV).—To a solution of 30 g. of 2,4,5-triamino-6-hydroxypyrimidine dihydrochloride in 300 ml. of 1 *N* hydrochloric acid was added a solution of 30 g. of α,β-dibromopropionaldehyde in 300 ml. of ethanol. After standing for one hour, 6 g. of the precipitated product was collected and identified as 2-amino-4-hydroxy-7-methylpteridine.[9] The filtrate after buffering with a slight excess of sodium acetate deposited 4 g. more of the above 7-methylpteridine.

The above filtrate on standing with the excess acetate buffer for two hours deposited 1.7 g. of material which had the properties of compound IV.

Pteroylglutamic Acid: A.—Ten grams of 2,4,5-triamino-6-hydroxypyrimidine and 19 g. of *p*-aminobenzoyl-*l*(+)-glutamic acid were dissolved in 1 liter of 10% sodium acetate solution. To this solution was added slowly with stirring a solution of 15.3 g. of α,β-dibromopropionaldehyde in 100 ml. of ethanol. After stirring for ninety minutes 4.8 g. of the precipitated product was collected. This crude product was shown to contain 10% of pteroylglutamic acid by bioassaying with *S. faecalis* R.

A reaction was run as above except the *p*-aminobenzoylglutamic acid was added five minutes after the addition of the dibromopropionaldehyde was complete. The resulting crude was found to contain only 4% of pteroylglutamic acid.

B.—Fifty grams (0.355 mole) of 2,4,5-triamino-6-hydroxypyrimidine and 95 g. (0.355 mole) of *p*-aminobenzoylglutamic acid were dissolved in 7.5 liters of water. The acidity of this solution was adjusted and maintained at *p*H 4 throughout the reaction. To this solution was added slowly with stirring over a ninety-minute period a solution of 77 g. (0.355 mole) of α,β-dibromopropionaldehyde in 7.5 liters of ethanol. The resulting mixture was then stirred for two hours more. The precipitated product was collected, washed with water and alcohol and dried. The yield of crude material was 50 g. which was shown to contain 20.8% of pteroylglutamic acid by the bioassay.

This synthesis was repeated using 0.007 mole each of 2,4,5-triamino-6-hydroxypyrimidine, *p*-aminobenzoylglutamic acid and α,β-dichloropropionaldehyde. The crude product weighed 0.8 g. and contained 14.5% pteroylglutamic acid. Further repetition of this synthesis using benzene, chloroform, carbon tetrachloride, acetic acid or acetone as solvents for the dibromopropionaldehyde instead of ethanol gave yields of the crude material ranging from 0.8 g. to 1.5 g. using 0.007 mole of each of the reactants. The pteroylglutamic acid in these crudes was about 20%.

A series of condensations was run at various acidities using 0.0035 mole of each of 2,4,5-triamino-6-hydroxypyrimidine-α,β-dibromopropionaldehyde and *p*-aminobenzoylglutamic acid. At *p*H 2, 3, 4 and 5 the yields of the crude products were 0.24, 0.30, 0.35 and 0.33 g.; and were shown by bioassay to contain 13, 24, 35 and 14%, respectively, of pteroylglutamic acid. At *p*H 6, 7, 8 and 10 there were no appreciable amounts of precipitates formed; however, pteroylglutamic acid was found by bioassay to be present in the reaction mixtures to the extent of 20 to 30% as much as the condensation usually yielded at *p*H 4.

Racemic Pteroylglutamic Acid.—This compound was prepared by the method given above for pteroylglutamic acid (method B) except that the *p*-aminobenzoyl-*l*(+)-glutamic acid was replaced by *p*-aminobenzoyl-*d,l*-glutamic acid.

Purification of Pteroylglutamic Acid.—A sample of crude material (5.85 g.) containing 0.755 g. of pteroylglutamic acid was dissolved in 3500 ml. of hot water at *p*H 10–12. This alkaline solution was brought to *p*H 7, cooled and filtered. The filtrate was adjusted to *p*H 3 and the active material was collected. This partially purified material was dissolved in 200 ml. of water at *p*H 10–12, clarified with 1 g. of activated charcoal and diluted with 800 ml. of hot water containing enough acetic acid to bring the acidity to *p*H 3–3.5. After cooling 0.61 g. of product was obtained. A bioassay showed the presence of 76.8% pteroylglutamic acid giving a 62% recovery.

Two hundred milligrams of the above 76.8% material was dissolved in 100 ml. of water at *p*H 10–12, clarified with 0.4 g. of charcoal, diluted to 700 ml. with boiling water containing enough acetic acid to bring to *p*H 3–3.5, filtered and cooled. The active material crystallized as rosets. This was collected and dried; yield, 166.2 mg.; bioassay, 92% pteroylglutamic acid. Recrystallization from water gave needle-like crystals.

Anal. As magnesium salt, calcd. for $C_{19}H_{15}O_6N_7$-$Mg_{1.5}\cdot 2H_2O$: C, 44.8; H, 3.74; N, 19.4; Mg, 7.06. Found: C, 44.8; H, 3.8; N, 19.3; Mg, 6.6.

Degradation of Synthetic Pteroylglutamic Acid.—A 0.275-g. sample of purified synthetic pteroylglutamic acid when hydrolyzed for eight hours at 100° with 10 ml. of 1 *N* solution of sodium hydroxide in a current of oxygen as described[4] for the natural *L. casei* factor, gave 0.058 g. (46%) of pure 2-amino-4-hydroxypteridine-6-carboxylic acid. No 2-amino-4-hydroxypteridine-7-carboxylic acid was detected in the hydrolysate.

Pteroylglutamic acid (0.5 g.) was cleaved with sulfite as described for the fermentation *L. casei* factor.[5] The solution when freed of sulfur dioxide and treated with phenylhydrazine gave 0.206 g. of the red phenylhydrazone. Analytical figures agree with those given for the hydrazone from the fermentation compound.

Pteroic Acid.—A vigorously stirred solution of 1 g. each of 2,4,5-triamino-6-hydroxypyrimidine and *p*-aminobenzoic acid in 150 ml. of water was adjusted and maintained at *p*H 4 throughout the reaction. A solution of 1.53 g. of α,β-dibromopropionaldehyde in 150 ml. of ethanol was then added dropwise. The resulting mixture was stirred for ninety minutes after the addition of the aldehyde was complete. The precipitated product was collected, washed with water and alcohol and dried. A yield of 0.59 g. of crude containing 19.2% of pteroic acid was obtained.

This synthesis using the same amounts of the reactants and substituting benzene for ethanol as the solvent for the dibromopropionaldehyde gave 0.9 g. of crude product containing 13.5% of pteroic acid as shown by bioassay with *S. faecalis* R.

Synthesis of Ethyl Pteroate.—A vigorously stirred solution of 1 g. of 2,4,5-triamino-6-hydroxypyrimidine and 1.2 g. of ethyl *p*-aminobenzoate in a mixture of 150 ml. of water and 100 ml. of ethanol was adjusted and maintained at *p*H 4 while 1.53 g. of α,β-dibromopropionaldehyde in 50 ml. of ethanol was added over a twenty-minute period. The mixture was stirred for an additional ninety minutes and filtered. A yield of 0.38 g. of crude was obtained. This crude after hydrolyzing with sodium hydroxide solution in the cold was shown to contain 14.3% pteroic acid.

Purification of Pteroic Acid.—The crude material containing 15% of pteroic acid was dissolved in 0.01 *N* sodium hydroxide solution at a concentration of 1 mg. of crude per ml., brought to *p*H 7, filtered and brought to *p*H 3. The precipitated material at *p*H 3 was collected and shown by bioassay to contain 60% pteroic acid. This represented a recovery of 11%. The precipitate at *p*H 7 contained the bulk of the active material which can be largely recovered by repeating the procedure several times.

Final purification was accomplished by the following procedure: The partially purified pteroic acid was clarified in 0.2 *N* sodium hydroxide solution with charcoal at a concentration of 1 mg. per ml. The resulting alkaline filtrate was diluted to 0.1 mg. per ml., heated to boiling and neutralized slowly with dilute hydrochloric acid to *p*H 3. The crystals of pteroic acid formed in the hot solution. After cooling this material was collected and recrystallized three times by dissolving in hot sodium hydroxide solution at a concentration of 0.1 mg. per ml. and bringing to *p*H 3 with dilute hydrochloric acid.

Anal. Calcd. for $C_{14}H_{12}O_3N_6$: C, 53.85; H, 3.85. Found: C, 53.3; H, 4.15.

Degradation of Pteroic Acid.—When 0.1 g. of purified pteroic acid was hydrolyzed with 5 ml. of 1 *N* solution of sodium hydroxide in the presence of oxygen at 100° for six hours, 0.0225 g. (37.5%) of pure 2-amino-4-hydroxypteridine-6-carboxylic acid was obtained. No 2-amino-4-hydroxypteridine-7-carboxylic acid was detected in the hydrolysate.

Acknowledgment.—The authors wish to thank the following for their work on this project: Dr. R. C. Gore and assistants of Stamford Research Laboratories, American Cyanamid Company, for infrared spectrographs; Dr. A. F. Kirkpatrick of Stamford Research Laboratories, American Cyanamid Company, for the microscopical examinations: Miss Edythe Brogan[1] and Miss Anna Buxó[1] for ultraviolet spectrographs; Miss Eleanora Boggiano[1] for microbiological assays; and Mr. L. Brancone[1] and Mr. O. Sundberg[2] and their assistants[1,2] for the microanalyses. The authors are especially indebted to Dr. J. H. Williams for his constant interest and counsel and for his efforts in coördinating the work performed in the various laboratories.

Summary

The preparation of pteroic acid and pteroylglutamic acid is given. This method of preparation illustrates a general procedure for the synthesis of pteroyl derivatives.

Physical, chemical and biological data on pteroylglutamic acid and the liver *L. casei* factor appear to show that the two compounds are identical.

PEARL RIVER, NEW YORK RECEIVED JANUARY 24, 1947

[CONTRIBUTION FROM CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY, AND LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Synthesis of Pteroylglutamic Acid (Liver *L. casei* Factor) and Pteroic Acid. II

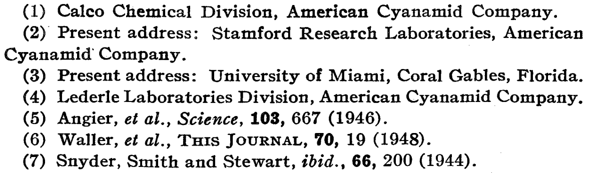
BY MARTIN E. HULTQUIST,[1] ERWIN KUH,[1] DONNA B. COSULICH,[1] MARVIN J. FAHRENBACH,[1] ELMORE H. NORTHEY,[1,2] DORIS R. SEEGER,[1] JACKSON P. SICKELS,[1,3] JAMES M. SMITH, JR.,[1] ROBERT B. ANGIER,[4] JAMES H. BOOTHE,[4] BRIAN L. HUTCHINGS,[4] JOHN H. MOWAT,[4] JOSEPH SEMB,[4] E. L. R. STOKSTAD,[4] Y. SUBBAROW[4] AND COY W. WALLER[4]

In a previous publication,[5,6] pteroylglutamic acid and pteroic acid were synthesized by reactions involving 2,4,5-triamino-6-hydroxypyrimidine, 2,3-dibromopropionaldehyde and *p*-aminobenzoylglutamic or *p*-aminobenzoic acid. It was felt that preparation of a 6-substituted pteridine capable of alkylating the above amino acids was desirable. Descriptions in the literature suggest the use of quaternary ammonium salts as alkylating agents, such as the procedure of Snyder, Smith and Stewart[7] in alkylating malonic and similar esters with benzyl trimethylammonium salts or gramine to obtain the corresponding C-benzyl malonic ester or substituted esters of β-(3-indole)-propionic acid.

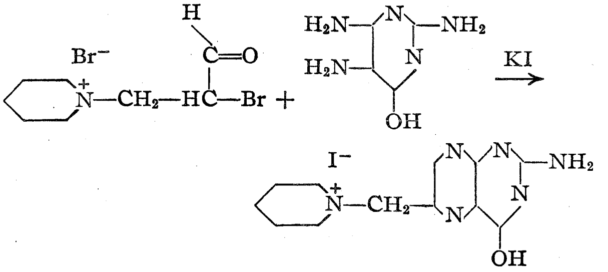
The above workers and others made use of this type of reaction in the preparation of synthetic *dl*-tryptophan[8,9,10]; and the use of simple quaternary salts in the preparation of sulfur[11] and oxygen[12,13,14,15] alkylated derivatives has also been described.

The use of a tertiary amine to alkylate another amine is reported by Howe, *et al.*[10] The effectiveness of pyridine as the tertiary base component of the quaternary ammonium salt was shown by Snyder and Speck.[11]

α,β-Dibromopropionaldehyde was condensed with pyridine to give the intermediate, N-(2-formyl-2-bromoethyl)-pyridinium bromide



and this compound was then condensed with the 2,4,5-triamino-6-hydroxypyrimidine to give the desired N-[(2-amino-4-hydroxy-6-pteridyl)-methyl]-pyridinium bromide for use in alkylation.



Presumably a dihydro derivative was formed which, during the course of the reaction, was converted to the aromatic form. The product was isolated as the less soluble iodide.

Oxidation of the N-[(2-amino-4-hydroxy-6-pteridyl)-methyl]-pyridinium iodide gave the corresponding 2-amino-4-hydroxypteridine-6-carboxylic acid,[16] showing the substituted methyl group to be in the 6- position. No 2-amino-4-hydroxypteridine-7-carboxylic acid was detected.

Pteroylglutamic acid or pteroic acid was then prepared by heating the N-[(2-amino-4-hydroxy-6-pteridyl)-methyl]-pyridinium iodide, *p*-aminobenzoylglutamic acid or *p*-aminobenzoic acid and sodium methylate in anhydrous ethylene glycol. After isolation of the crude material, purification was carried out as described by Waller, *et al.*[6] The crystalline structure, ultraviolet absorption spectra, and bioassay of the synthetic pteroylglutamic acid were identical with those same properties of the liver *L. casei* factor. The properties of the synthetic pteroic acid were identical with those of the pteroic acid prepared by Waller, *et al.*[6]

Experimental

Materials.—The 2,4,5-triamino-6-hydroxypyrimidine, *p*-aminobenzoyl-*l*(+)-glutamic acid and dibromopropionaldehyde were prepared as described in the previous paper in this series.[6]

N-(2-Formyl-2-bromoethyl)-pyridinium Bromide.—To a solution of 21.6 g. (0.1 mole) of freshly distilled 2,3-dibromopropionaldehyde in 100 ml. of anhydrous ether at 0° was added slowly 8.8 g. (0.11 mole) of dry pyridine in 100 ml. of anhydrous ether, with stirring and cooling to keep the temperature of the reaction mixture at 0 to 10°. There was an immediate precipitation of a white product at the start of the addition, and, after allowing the mixture to stand for one or two hours, the hygroscopic solid was filtered, washed with ether and dried in a vacuum desiccator, or extracted with water for use directly in the next step. The crude material melted at 66–69°.

---

(1) Calco Chemical Division, American Cyanamid Company.

(2) Present address: Stamford Research Laboratories, American Cyanamid Company.

(3) Present address: University of Miami, Coral Gables, Florida.

(4) Lederle Laboratories Division, American Cyanamid Company.

(5) Angier, *et al.*, *Science*, **103**, 667 (1946).

(6) Waller, *et al.*, THIS JOURNAL, **70**, 19 (1948).

(7) Snyder, Smith and Stewart, *ibid.*, **66**, 200 (1944).

(8) Snyder and Smith, *ibid.*, **66**, 350 (1944).

(9) Albertson, Archer and Suter, *ibid.*, **66**, 500 (1944); **67**, 36 (1945).

(10) Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945).

(11) Snyder and Speck, *ibid.*, **61**, 668, 2895 (1939).

(12) Hla Baw, *Quart. J. Indian Chem. Soc.*, **3**, 101 (1926) [*C. A.*, **20**, 3695 (1926)].

(13) Tarbell and Vaughan, THIS JOURNAL, **65**, 231 (1943).

(14) Willstätter, *Ber.*, **35**, 584 (1902).

(15) Griess, *ibid.*, **6**, 585 (1873); **13**, 246 (1880).

(16) Mowat, *et al.*, THIS JOURNAL, **70**. 14, (1947).

Anal. Calcd. for C_8H_9NBr: Br, 27.09. Found: Br, 29.8.

It was recrystallized from absolute 2-propanol, and then melted to a milky liquid at 55–65°, cleared at 80–90°, became partially crystalline again at 105–110°, and melted at 120–125°.

Anal. Calcd.: Br, 27.09. Found: Br, 27.55, 27.59.

N-[(2-Amino-4-hydroxy-6-pteridyl)-methyl]-pyridinium Iodide.—To a solution of 14.1 g. (0.1 mole) of 2,4,5-triamino-6-hydroxypyrimidine in 150 ml. of water and 20 ml. of concd. hydrochloric acid was added the N-(2-formyl-2-bromoethyl)-pyridinium bromide prepared as above in a 0.1-mole run and extracted from the ether with 50 ml. of water. The yellowish-brown solution became almost purple. There was then added 10 g. of potassium iodide, and the solution was allowed to stand overnight. After addition of sodium hydroxide solution to bring the *p*H to 3 to 4, the mixture of brown, amorphous material and lighter crystalline product was filtered off and recrystallized from water, using activated charcoal to decolorize the hot solution. The addition of potassium iodide aided in obtaining more complete crystallization of the less soluble iodide. The purified material consisted of bright yellow, thin plates and rosets of plates.

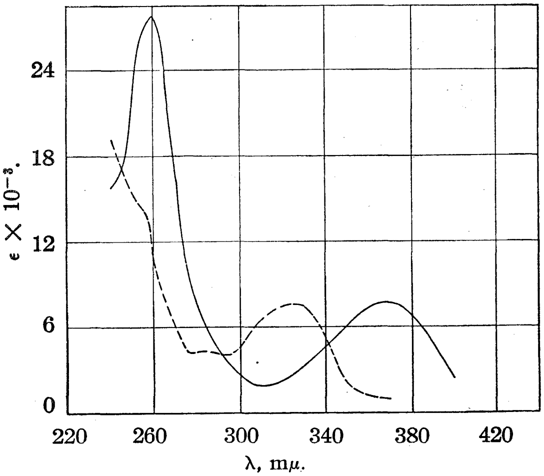


Fig. 1.—Ultraviolet absorption spectra of N-[(2-amino-4-hydroxy-6-pteridyl)-methyl]-pyridinium iodide: ——— 0.1 *N* sodium hydroxide; - - - - - - - 0.1 *N* hydrochloric acid.[a]

[a] ε is the molecular extinction coefficient as defined by $I = I_0\ 10^{-\epsilon c l}$ where *c* is the concentration in moles/liter and *l* is the cell length in centimeters. Transmittancy (I/I_0) measurements of 10 mg./liter solutions were made in 1-cm. cells at 5 mμ intervals on a Model DU Beckmann Spectrophotometer using a solvent filled cell in the reference position. Additional data were obtained at 2 mμ intervals at maxima, minima and points of inflection.

Anal. Calcd. for $C_{12}H_{11}ON_6I$: N, 22.0; I, 33.2. Found: N, 21.9; I, 32.7.

The ultraviolet absorption curve for this compound is given in Fig. 1.

Oxidation of the above product with hot alkaline permanganate yielded 2-amino-4-hydroxypteridine-6-carboxylic acid.[16] An odor of pyridine was noted during the oxidation step.

Pteroylglutamic Acid.—To a solution of 10.8 g. (0.2 mole) of sodium methylate in 75 ml. of anhydrous ethylene glycol was added 26.6 g. (0.1 mole) of *p*-aminobenzoyl-*l*(+)-glutamic acid and 38.2 g. (0.1 mole) of N-[(2-amino-4-hydroxy-6-pteridyl)-methyl]-pyridinium iodide. A solution of 5.4 g. (0.1 mole) of sodium methylate in 25 ml. of anhydrous ethylene glycol was added, and the resulting solution was heated at 140–145° for three hours. The brown solution obtained was poured into one liter of water at 70°, and acidified to *p*H 3 to 4 with hydrochloric acid. The precipitated product filtered from the cooled solution weighed 9 g., and was shown to contain 25% pteroylglutamic acid by bioassaying with *S. faecalis* R.

Purification of this crude material as described by Waller, *et al.*,[6] gave pteroylglutamic acid showing crystalline structure, ultraviolet absorption spectra and bioassay identical with those same properties of liver *L. casei* factor.

Pteroic Acid.—This was prepared as described under pteroylglutamic acid, substituting *p*-aminobenzoic acid for *p*-aminobenzoyl-*l*(+)-glutamic acid, and decreasing the sodium methylate usage by one mole per mole of N-[(2-amino-4-hydroxy-6-pteridyl)-methyl]-pyridinium iodide.

Purification as described by Waller, *et al.*,[6] gave pteroic acid. The ultraviolet spectra in alkaline solution showed this to be identical with Waller's material.

Acknowledgment.—We are indebted to Dr. R. C. Gore of the Stamford Research Laboratories, American Cyanamid Company, for the infrared spectra; to Dr. A. F. Kirkpatrick of the same laboratories for crystallographic comparisons; to Miss Ruth Abbott for ultraviolet spectrographs; and to Mr. O. Sundberg and assistants for the microanalyses. Dr. P. F. Dreisbach assisted in the preparation of certain compounds.

The authors are especially indebted to Dr. J. H. Williams for his constant interest and counsel and for his efforts in coördinating the work in the various laboratories.

Summary

1. N-[(2-Amino-4-hydroxy-6-pteridyl)-methyl]-pyridinium iodide has been prepared by the reaction of N-(2-formyl-2-bromoethyl)-pyridinium bromide with 2,4,5-triamino-6-hydroxypyrimidine.

2. Pteroylglutamic acid and pteroic acid have been prepared by alkylating the appropriate amino acid with N-[(2-amino-4-hydroxy-6-pteridyl)-methyl]-pyridinium iodide.

BOUND BROOK, N. J. RECEIVED JANUARY 24, 1947

[CONTRIBUTION FROM LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, AND CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Synthesis of Pteroylglutamic Acid. III

BY ROBERT B. ANGIER,[1] E. L. R. STOKSTAD,[1] JOHN H. MOWAT,[1] BRIAN L. HUTCHINGS,[1] JAMES H. BOOTHE,[1] COY W. WALLER,[1] JOSEPH SEMB,[1] Y. SUBBAROW,[1] DONNA B. COSULICH,[2] M. J. FAHRENBACH,[2] M. E. HULTQUIST,[2] ERWIN KUH,[2] E. H. NORTHEY,[2,3] DORIS R. SEEGER,[2] J. P. SICKELS,[2] AND JAMES M. SMITH, JR.[2]

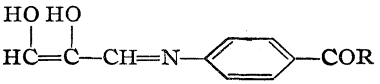
Two methods of synthesizing pteroylglutamic acid have been described.[4] Another approach to the synthesis of this compound involves the reaction of N-(*p*-aminobenzoyl)-glutamic acid with a three carbon compound to form a stable intermediate which after isolation could be condensed with 2,4,5-triamino-6-hydroxypyrimidine to form the desired product.

The most satisfactory intermediate of this type was prepared from the three carbon compound, reductone (2,3-dihydroxyacrylaldehyde).[5] Euler and Martius[6] described the reaction of reductone with urea in a dilute mineral acid solution to form the two expected products, 2,3-dihydroxy-2-ene-propylideneurea and bis-(2,3-dihydroxy-2-ene-propylidene)-urea. O'Meara, *et al.*,[7] described the reaction of an impure reductone solution with *p*-aminobenzoic acid to obtain a crystalline compound but no analyses or physical data were given for the product.

In this Laboratory reductone reacted with diethyl N-(*p*-aminobenzoyl)-glutamate in a dilute hydrochloric acid solution to produce diethyl N-{*p*-(2,3-dihydroxy-2-ene-propylideneamino)-benzoyl}-glutamate (VI). In a similar way a number of other derivatives of *p*-aminobenzoic acid were treated with reductone to form compounds which might be used as intermediates in the preparation of various analogs of pteroylglutamic acid. These compounds are listed in Table I. As is evident from the formula these compounds could exist in several tautomeric forms. However, in writing the formula of the product the enediol structure of the starting compound has been retained since it is at least the initial product of the reaction. Irrespective of the tautomeric nature of the solid it was thought probable that in solution there would be present at least a small percentage of the keto-aldehyde tautomer. The fact that compounds (II) and (VI) were found to react readily with an alcoholic solution of phenylhydrazine to form the corresponding diphenylhydrazones indicated that this might be true. In contrast to these results attempts at treating the ester (VI) with 2,4,5-triamino-6-hydroxypyrimidine[8] in aqueous or methanolic solution gave little or no product. However, when hot ethylene glycol was used as a solvent the reaction proceeded satisfactorily and the product was obtained by diluting with water and filtering. As was true in the first synthesis[4a] this material was very impure and contained 10 to 30% pteroylglutamic acid (5 to 21% molal yield) as determined with *S. faecalis* R. The best yield was obtained either by using a one to three mole excess of 2,4,5-triamino-6-hydroxypyrimidine or by using a 0.5 mole excess of the pyrimidine and one equivalent of a basic condensing agent such as sodium acetate or disodium phosphate.

TABLE I

p-(2,3-DIHYDROXY-2-ENE-PROPYLIDENEAMINO)-BENZOIC ACID AND DERIVATIVES



R =	M. p., °C.[a]	Yield, %	Analyses, % Calcd. C			Found C		
			C	H	N	C	H	N
—OH (I)	255–258	90	57.96	4.38	6.76	57.97	4.46	6.72
$—OC_2H_5$ (II)	189–190	95	61.27	5.57	5.96	61.71	5.34	6.19
$—NH_2$ (III)	>200 dec.	90	58.24	4.89	13.59	57.95	5.65	13.85
$—NHCH_2COOH$ (IV)	>210 dec.	94	54.54	4.58	10.61	53.72	4.18	10.11
$—NHCH_2COOC_2H_5$ (V)	196–198	75	57.51	5.52	9.59	56.93	5.35	9.56
$—NHCHCOOC_2H_5$ (VI) | $CHCH_2COOC_2H_5$	121–125	80	58.16	6.17	7.14	58.32	6.78	7.18
—NHCHCOOH[b] (VII) | CH_2CH_2COOH	195–200	40–65						

[a] Corrected for exposed stem of thermometer. [b] Obtained only in a crude state.

Compounds (I), (II) and (VII) have each been

---

(1) Lederle Laboratories Division, American Cyanamid Company.

(2) Calco Chemical Division, American Cyanamid Company.

(3) Present address: Stamford Research Laboratories, American Cyanamid Company.

(4) (a) Waller, *et al.*, THIS JOURNAL, **70**, 19 (1948); (b) Hultquist, *et al.*, *ibid.*, **70**, 23 (1948).

(5) Euler and Martius, *Ann.*, **505**, 73 (1933).

(6) Euler and Martius, *C. A.*, **28**, 3382 (1934).

(7) O'Meara, McNally and Nelson, *Nature*, **154**, 796. (1944).

(8) Traube, *Ber.*, **33**, 1371 (1900).

reacted with 2,4,5-triamino-6-hydroxypyrimidine in the manner described above. The crude product obtained from VII was active in stimulating the growth of both *S. faecalis* R and *L. casei*. The products obtained from I and II were active in stimulating the growth of *S. faecalis* R but were only very slightly active for *L. casei*. The yield of the expected pteroic acid from I and II compared favorably with the yield of pteroylglutamic acid from VI. The reaction appears to be generally applicable to intermediates of the type described.

Experimental[9]

Ethyl N-(*p*-Aminobenzoyl)-glycinate.—N-(*p*-Aminobenzoyl)-glycine[10] (4.0 g.) was suspended in a solution of 50 cc. of absolute ethanol and 3 cc. of concentrated hydrochloric acid and refluxed for two hours. The solution was evaporated to a sirup which crystallized. This was dissolved in 60 cc. of water, filtered and then neutralized with a saturated sodium carbonate solution. The material oiled out but soon crystallized. This was recrystallized once from a water–ethanol solution.

For purposes of analysis this was recrystallized twice from benzene; white crystals, m. p. 93–95°.

Anal. Calcd. for $C_{11}H_{14}O_3N_2$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.83; H, 6.71; N, 12.78.

Diethyl N-{*p*-(2,3-Dihydroxy-2-ene-propylideneamino)-benzoyl}-glutamate (VI).—Reductone (5.0 g.) (0.057 mole) prepared by the method of Euler and Martius[5] was dissolved in 100 cc. of water and added to a mixture of 16 g. (0.05 mole) of diethyl N-(*p*-aminobenzoyl)-glutamate[4a] and 7 cc. of concentrated hydrochloric acid in a solution of 1600 cc. of water and 100 cc. of ethanol. This was stirred rapidly for two hours and then stood in the refrigerator for several hours. It was then filtered, washed with ether, and dried; yield 16.7 g. (85%). This was sufficiently pure for subsequent reactions but may have contained water of crystallization since it had the rather low melting range of about 65–73°.

For analyses this was purified by dissolving it in chloroform at room temperature and then adding petroleum ether. The product oiled out but crystallized after standing. This purification was repeated once; cream colored crystals, m. p. 121–125°.

General Procedure for the Preparation of *p*-(2,3-Dihydroxy-2-ene-propylideneamino)-benzoic Acid (I) and Its Derivatives.—Compounds (I), (II), (III), (IV), (V) and (VII) were prepared by methods analogous to that described above for compound (VI) except that no ethanol was used in the solvent. With the exception of the acid (VII) these products were all crystalline and pale yellow to light orange in color. The acids (I) and (IV) and the amide (III) were rather insoluble in most solvents but they analyzed satisfactorily without purification. The esters (II) and (V) were readily recrystallized from ethanol or chloroform.

The Diphenylhydrazones of the Esters (II) and (VI).—A. Ethyl *p*-(2,3-dihydroxy-2-ene-propylideneamino)-benzoate (II) (0.2 g.) and 0.2 cc. of phenylhydrazine were dissolved in 10 cc. of ethanol containing 2 drops of acetic acid and refluxed for twenty minutes. Upon cooling the product separated; yield 0.2 g. This was recrystallized once from benzene and once from chloroform; long, yellow thread-like needles; m. p. 203–205°.

Anal. Calcd. for $C_{24}H_{25}O_2N_5$: C, 69.36; H, 6.07; N, 16.86. Found: C, 69.84; H, 5.42; N, 17.21.

B. Diethyl N-{*p*-(2,3-dihydroxy-2-ene-propylideneamino)-benzoyl}-glutamate (VI) (0.5 g.) and 0.9 cc. of phenylhydrazine were dissolved in 10 cc. of ethanol containing 3 drops of acetic acid and refluxed for twenty minutes. Upon cooling the product separated; yield 0.42 g. This was recrystallized once from benzene and once from ethanol; m. p. 157–159°.

Anal. Calcd. for $C_{31}H_{36}O_5N_6$: C, 65.01; H, 6.34; N, 14.68. Found: C, 64.79; H, 5.95; N, 15.06.

Pteroylglutamic Acid.—Seven grams (0.018 mole) of diethyl N-{*p*-(2,3-dihydroxy-2-ene-propylideneamino-benzoyl}-glutamate (VI), 5.0 g. (0.036 mole) of 2,4,5-triamino-6-hydroxypyrimidine[8] and 200 cc. of ethylene glycol were placed in a 250-cc. flask and heated to 135° for thirty minutes with continuous stirring. The solution was cooled almost to room temperature and poured into 600 cc. of water. A little concentrated hydrochloric acid was added to bring it to *p*H 3–4. The mixture was then filtered, washed with water, methanol and ether and dried; yield of crude 5.5 g. (63%). This was shown to be 20% pteroylglutamic acid by bioassay with *S. faecalis* R. Real yield was 12.6%.

This material was purified by the method of Waller, *et al.*,[4a] to obtain a crystalline product. The ultraviolet and infrared spectra, crystallography and biological activity of this compound, the previously prepared synthetic pteroylglutamic acid,[4] and the naturally occurring liver *L. casei* factor were found to be identical.

Acknowledgment.—We are indebted to Dr. R. C. Gore of the Stamford Research Laboratories, American Cyanamid Company, for infrared spectra and to Dr. A. F. Kirkpatrick of the same Laboratories for crystallographic comparisons. We also acknowledge the technical assistance of the Misses E. Boggiano and A. Buxó and the microanalytical work performed by L. Brancone and his co-workers.[1]

The authors are especially indebted to Dr. J. H. Williams for his constant interest and counsel and for his efforts in coördinating the work performed in the various laboratories.

Summary

1. *p*-(2,3-Dihydroxy-2-ene-propylideneamino)-benzoic acid and six of its derivatives have been prepared by treating reductone (2,3-dihydroxyacrylaldehyde) with *p*-aminobenzoic acid or a derivative.

2. Pteroylglutamic acid has been prepared by condensing diethyl N-{*p*-(2,3-dihydroxy-2-ene-propylideneamino)-benzoyl}-glutamate with 2,4,5-triamino-6-hydroxypyrimidine.

PEARL RIVER, NEW YORK RECEIVED JANUARY 24, 1947

---

[9] All melting points are corrected.

[10] Purchased from the National Aniline Division of Allied Chemical and Dye Corporation.

[CONTRIBUTION FROM LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, AND CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Synthesis of Pteroylglutamic Acid. IV

BY JAMES H. BOOTHE,[1] COY W. WALLER,[1] E. L. R. STOKSTAD[1], BRIAN L. HUTCHINGS,[1] JOHN H. MOWAT,[1] ROBERT B. ANGIER,[1] JOSEPH SEMB,[1] Y. SUBBAROW,[1] DONNA B. COSULICH,[2] M. J. FAHRENBACH,[2] M. E. HULTQUIST,[2] ERWIN KUH,[2] E. H. NORTHEY,[2,3] DORIS R. SEEGER,[2] J. P. SICKELS[2] AND JAMES M. SMITH, JR.[2]

The structure of pteroylglutamic acid requires the presence of a methylene group connecting the pteridine nucleus and N-(*p*-aminobenzoyl)-glutamic acid. The methods of synthesis previously reported[4] have made use of the reaction of a three-carbon compound between 2,4,5-triamino-6-hydroxypyrimidine and N-(*p*-aminobenzoyl)-glutamic acid, or the alkylation of N-(*p*-aminobenzoyl)-glutamic acid with 2-amino-4-hydroxy-6-pteridylmethylpyridinium iodide.

This communication deals with the halogenation of 2-amino-4-hydroxy-6-methylpteridine, and the alkylation of N-(*p*-aminobenzoyl)-glutamic acid with the crude halomethylpteridine. It includes an improved method of synthesis of 2-amino-4-hydroxy-6-methylpteridine and a description of the dihydro form of this compound.

The previously described method of preparation of 2-amino-4-hydroxy-6-methylpteridine[5] was difficult to adapt to large scale preparative work. A more convenient method of preparing this pteridine was found to be by the reduction of 2-amino-4-hydroxy-6-pteridylmethylpyridinium iodide.[4b] The reduction was accomplished by dissolving the compound in 1 *N* sodium hydroxide and stirring with zinc dust. During the reduction the pteridine ring was reduced to a dihydro form which could be oxidized readily to the aromatic form with hydrogen peroxide, iodine or potassium permanganate. It was proved to be a dihydro form and not a more highly reduced form by oxidation to 2-amino-4-hydroxy-6-methylpteridine with the theoretical amount of potassium permanganate. This dihydro compound has an ultraviolet absorption spectrum quite different from the ordinary aromatic form of the pteridines (Fig. 1).

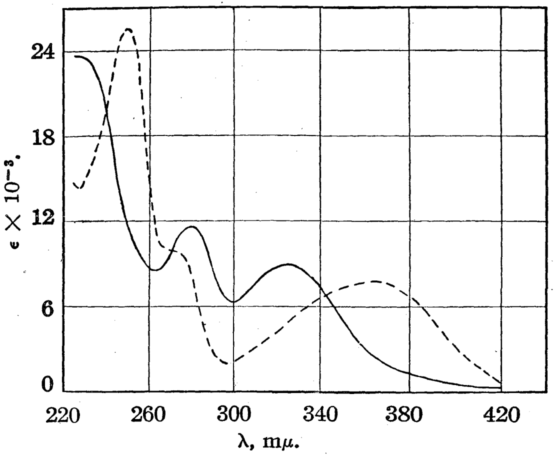
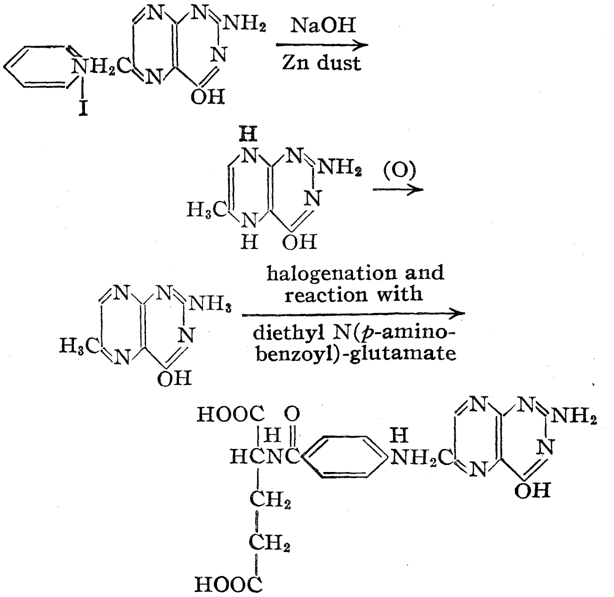


Fig. 1.—Ultraviolet absorption spectra of 2-amino-4-hydroxy-6-methyldihydropteridine hydrochloride monohydrate: ——— in 0.1 *N* sodium hydroxide; - - - - - - in 0.1 *N* hydrochloric acid.

Several methods of halogenation have been used with varying degrees of effectiveness. Bromination was accomplished by heating the 2-amino-4-hydroxy-6-methylpteridine in a sealed tube with bromine at temperatures of from 100–150°. Catalytic amounts of benzoyl peroxide and concentrated hydrochloric acid were each tried but both resulted in lowered yields. The most effective temperature seemed to be 150°. Bromination was also accomplished by heating the methylpteridine in 48% hydrobromic acid and bromine. Chlorination was effected to a very limited extent by refluxing the methylpteridine in sulfuryl chloride and benzoyl peroxide. These crude halogenation products then reacted with diethyl N-(*p*-aminobenzoyl)-glutamate[4a] by heating in ethylene glycol at 100–110°. The products of this condensation were then assayed microbiologically



---

[1] Lederle Laboratories Division, American Cyanamid Company.

[2] Calco Chemical Division, American Cyanamid Company.

[3] Present address: Stamford Research Laboratories, American Cyanamid Company, Stamford, Connecticut.

[4] (a) Waller, *et al.*, THIS JOURNAL, **70**, 19 (1948). (b) Hultquist, *et al.*, *ibid.*, **70**, 23 (1948). (c) Angier, *et al.*, *ibid.*, **70**, 25 (1948).

[5] Mowat, *et al.*, THIS JOURNAL, **70**, 14 (1948).

against *S. faecalis* R after hydrolysis of the ester groups.

Experimental

2-Amino-4-hydroxy-6-methyldihydropteridine.—Ten grams of 2-amino-4-hydroxy-6-pteridylmethylpyridinium iodide was dissolved in 500 cc. of 1 *N* sodium hydroxide. Twenty grams of zinc dust was added and the reaction mixture was stirred twenty minutes at room temperature. The excess zinc was filtered out and the solution was adjusted to *p*H 2.7 with concentrated hydrochloric acid. The light yellow precipitate was removed by filtration and dried; weight was 6 g. This product contained some zinc oxide. It was purified by dissolving in the minimum amount of 0.5 *N* sodium hydroxide, treating with Norite, and then adding an equal volume of 10 *N* sodium hydroxide solution. On cooling, the sodium salt crystallized and was removed by filtration. The sodium salt was then dissolved in the minimum amount of warm water and enough concentrated hydrochloric acid was added to make the solution 0.5 *N*. The yellow crystalline hydrochloride separated and was filtered out. For an analytical sample this purification was repeated once more. The hydrochloride crystallizes as a monohydrate, from which water is not removed by heating at 60° *in vacuo*.

Anal. Calcd. for $C_7H_{10}ON_5 \cdot HCl \cdot H_2O$: C, 36.05; H, 5.14; N, 30.00. Found: C, 36.20; H, 5.47; N, 30.20.

2-Amino-4-hydroxy-6-methylpteridine.—(a) Two hundred mg. of 2-amino-4-hydroxy-6-methyldihydropteridine was dissolved in 10 cc. of dilute sodium hydroxide. A solution of 0.2 *M* potassium permanganate was added dropwise at room temperature until a light green color persisted when the manganese dioxide was centrifuged out. This required 3.7 cc. After discharging the green color with sodium sulfite, the manganese dioxide was filtered out and the clear yellow solution was acidified with hydrochloric acid. The precipitated product was centrifuged and washed with water. It was crystallized by dissolving in 6 cc. of dilute sodium hydroxide and adding 6 cc. of 10 *N* sodium hydroxide. The crystalline sodium salt was dissolved in water and the solution was acidified. The product was collected and dried. Weight was 130 mg. The ultraviolet absorption spectrum was identical to that of authentic samples of 2-amino-4-hydroxy-6-methylpteridine.[5]

(b) One hundred grams of 2-amino-4-hydroxy-6-pteridylmethylpyridinium iodide was dissolved in 4 liters of 1 *N* sodium hydroxide and 100 g. of zinc dust was added. The mixture was stirred twenty minutes and the excess zinc was filtered out. Sixteen cc. of 30% hydrogen peroxide was added and stirred ten minutes at room temperature. The solution was then heated on the steam-bath and treated with Norite. The clarified solution was then added dropwise to a heated, stirred solution of 600 cc. of acetic acid in 2 liters of water. After standing overnight the supernatant liquid was siphoned off and the product collected on a filter, washed and dried. Weight was 32.4 g. This material was pure enough for most work but could be crystallized from 5 *N* sodium hydroxide as described above. For an analytical sample the material was crystallized twice from boiling water.

Anal. Calcd. for $C_7H_7N_5O$: C, 47.45; H, 3.96; N, 39.6. Found: C, 47.40; H, 4.32; N, 39.45.

The ultraviolet and infrared absorption spectra were identical with authentic samples of 2-amino-4-hydroxy-6-methylpteridine.[5]

Pteroylglutamic acid.—(a) Two grams of 2-amino-4-hydroxy-6-methylpteridine was sealed in a glass tube with 2.5 g. of bromine. The tube was heated at 150–155° for five hours, cooled and opened. The contents were dried in vacuum over potassium hydroxide for twenty-four hours and then washed out of the tube with a solution of 1 g. of diethyl N-(*p*-aminobenzoyl)-glutamate in 100 cc. of hot ethylene glycol. This mixture was heated one hour at 100–110°, cooled, and diluted with 300 cc. of ethanol. The insoluble product was removed by centrifuging, washed with alcohol and ether, and dried. Weight was 1.75 g. After hydrolysis of the ester groups by standing in 0.1 *N* sodium hydroxide for twelve hours, the crude material was shown to contain 14% pteroylglutamic acid by microbiological assay against *S. faecalis* R. The active material was isolated by the method previously described[6] and found to be identical with pteroylglutamic acid by comparison of the microbiological assay, the ultraviolet and infrared absorption spectra.

(b) Twelve grams of 2-amino-4-hydroxy-6-methylpteridine was suspended in 500 cc. of 48% hydrobromic acid and 12 cc. of bromine was added. The suspension was heated on a steam-bath under a reflux condenser with occasional stirring for five hours. The methylpteridine was nearly all in solution at this point. After standing overnight at room temperature, the solution was concentrated in vacuum until all the excess bromine had been removed. The solution was then treated with Norite, filtered, and concentrated in vacuum until the product began to crystallize (30–40 cc.). To this concentrated solution was added 2.5 liters of cold water which precipitated the product. It was filtered and dried; weight was 14 g. One hundred mg. of this material was heated three hours at 100° with 400 mg. of diethyl N-(*p*-aminobenzoyl)-glutamate in 8 cc. of ethylene glycol. The solution was cooled and diluted with 30 cc. of acetone. The insoluble product was centrifuged, washed and dried. Weight was 60 mg. After hydrolysis of the ester groups in 0.1 *N* sodium hydroxide at room temperature for twelve hours, the material was bioassayed with *S. faecalis* R and found to contain 14.8% pteroylglutamic acid.

(c) Five hundred mg. of 2-amino-4-hydroxy-6-methylpteridine was suspended in 10 cc. of sulfuryl chloride and a small amount of benzoyl peroxide was added. The mixture was refluxed five hours, evaporated to dryness and dry benzene was added and evaporated to dryness again. One gram of diethyl N-(*p*-aminobenzoyl)-glutamate in 10 cc. of hot ethylene glycol was added and heated one hour at 100–110°. The mixture was cooled and diluted with 30 cc. of ethanol and the product centrifuged, washed, and dried. Weight was 500 mg. This product after hydrolysis was shown to contain 0.5–1.0% pteroylglutamic acid by bioassay against *S. faecalis* R.

Acknowledgment.—The authors wish to acknowledge the technical assistance of E. Boggiano, and A. Buxó in obtaining ultraviolet absorption data and microbiological assays. Infrared absorption comparisons were made by R. C. Gore, Stamford Research Laboratories, American Cyanamid Company. Microanalyses were done by Louis Brancone and co-workers.

The authors are especially indebted to Dr. J. H. Williams for his constant interest and counsel and for his efforts in coördinating the work performed in the various laboratories.

Summary

A new synthesis of 2-amino-4-hydroxy-6-methylpteridine is described which includes a description of the dihydro form of this compound as an intermediate.

A synthesis of pteroylglutamic acid from 2-amino-4-hydroxy-6-methylpteridine by halogenation and reaction with diethyl N-(*p*-aminobenzoyl) glutamate is described.

PEARL RIVER, NEW YORK RECEIVED JANUARY 24, 1947

---

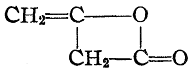
[6] Angier, *et al.*, *Science*, **103**, 667 (1946).

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

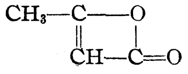
Studies Relating to the Structure of Ketene Dimer[1]

BY A. T. BLOMQUIST AND FRANKLIN H. BALDWIN

Ziegler's[2] development of specific reagents for halogenation of the allyl position suggested a useful application in securing additional chemical evidence for the structure of ketene dimer. Consideration of the most reliable evidence to date indicates structures I and II as being the most likely ones for ketene dimer.[3]

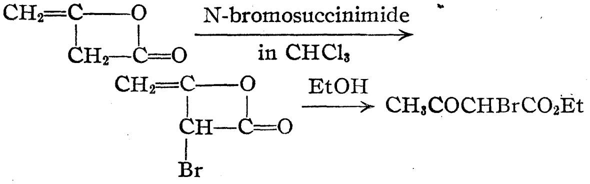


I

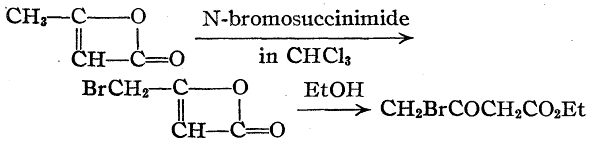


II

If structure I is the correct representation of ketene dimer, halogenation with Ziegler's reagents should afford halogen derivatives directly convertible to α-haloacetoacetic esters



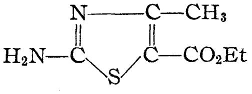
However, should structure II be the true one for ketene dimer, a similar series of reactions would lead to γ-haloacetoacetic esters



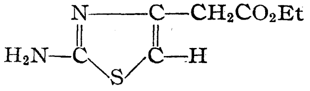
These formulations are, of course, also based on the assumption that Ziegler's reagents halogenate the allyl position in oxygenated unsaturated compounds as in unsaturated hydrocarbons.

Treatment of ketene dimer in chloroform solution with N-bromosuccinimide gave a highly unstable bromo derivative which reacted smoothly with ethyl alcohol to yield exclusively α-bromoacetoacetic ester. Similarly, chlorination with N,2,4-trichloroacetanilide followed by reaction with ethyl alcohol gave only α-chloroacetoacetic ester.

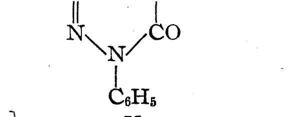
The two α-haloacetoacetic esters were characterized by conversion to two known solid derivatives. Reaction with thiourea gave, in each case, ethyl 2-amino-4-methylthiazole-5-carboxylate (III)[4] and none of the ethyl-2-aminothiazolyl-4-acetate (IV) derivable from γ-haloacetoacetic esters.[5] Phenylhydrazine converted both α-halogen esters into 3-methyl-1-phenyl-4-phenylhydrazono-5-pyrazolone (V).[6]



III



IV



V

It is significant that there was no evidence for the presence of γ-haloacetoacetic esters in the reaction products. Although it has been demonstrated that there is no tendency for α-chloroacetoacetic ester to rearrange to its γ-isomer, α-bromoacetoacetic ester may rearrange to γ-bromoacetoacetic ester under certain conditions. The rearrangement of γ-haloacetoacetic esters to the α-isomers has not been observed.[7]

The isolation of the direct products of halogenation of ketene dimer in pure form has not been realized as yet but work along this line is being continued.

Experimental[8]

Materials.—Ketene dimer was prepared as described in "Organic Syntheses."[9] N-Bromosuccinimide, m. p. 160–161°, was prepared by the method of Lengfeld and Stieglitz.[10] N,2,4-Trichloroacetanilide was prepared as described by Orton and Reed.[11]

Bromination of Ketene Dimer.—To a solution of 8.4 g. (0.1 mole) of freshly distilled ketene dimer in 200 cc. of chloroform there was added, at room temperature with vigorous stirring, a solution of 17.8 g. (0.1 mole) of N-bromosuccinimide in 700 cc. of chloroform. The volume of the mixture was reduced to 400 cc. by distillation at atmospheric pressure from a steam-bath. The succinimide which precipitated was removed by filtration and to the filtrate there was added 10 cc. of absolute alcohol and 2 drops of triethylamine. After refluxing for one hour the reaction mixture was fractionated under reduced pressure. α-Bromoacetoacetic ester (9 g., 43% based on ketene dimer) was obtained as a fraction boiling at 125–127° at 25 mm. It was characterized by the following two derivatives:

Ethyl 2-Amino-4-methylthiazole-5-carboxylate.—Using the method of Epprecht[4] 0.5 g. of α-bromoacetoacetic ester gave 0.5 g. (80%) of the thiazole derivative: m. p. 171–172° (Epprecht[4] gave the m. p. as 175–176°).

---

[1] This paper is an abstract of a portion of the thesis submitted by Franklin H. Baldwin to the Graduate Faculty of Cornell University for the M.S. degree in June, 1947.

[2] Ziegler, *et al.*, *Ann.*, **551**, 80 (1942).

[3] "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, pp. 127–128.

[4] Epprecht, *Ann.*, **278**, 79 (1894); Conrad, *Ber.*, **29**, 1044 (1896).

[5] Steude, *Ann.*, **261**, 30 (1891); Conrad and Schmidt, *Ber.*, **29**, 1043 (1896).

[6] Schönbrodt, *Ann.*, **253**, 193 (1889); Buchka and Sprague, *Ber.*, **22**, 2548 (1899).

[7] Hantzsch, *Ber.*, **27**, 356, 3168 (1894).

[8] All boiling points and melting points reported are uncorrected.

[9] "Organic Syntheses," **21**, 64 (1941).

[10] Lengfeld and Stieglitz, *Am. Chem. J.*, **15**, 215 (1893).

[11] Orton and Reed, *J. Chem. Soc.*, **91**, 1554 (1909).

3-Methyl-1-phenyl-4-phenylhydrazono-5-pyrazolone. Following the procedure of Buchka and Sprague,[6] 1.3 g. of α-bromoacetoacetic ester gave 1.5 g. (50%) of the pyrazolone derivative: m. p. 154° (Buchka and Sprague[6] reported the m. p. at 157°).

Chlorination of Ketene Dimer.—In a flask protected against atmospheric moisture there was placed a solution of 8.4 g. (0.1 mole) of ketene dimer in 100 cc. of chloroform, a solution of 23.8 g. (0.1 mole) of N,2,4-trichloroacetanilide in 200 cc. of chloroform was added, and the mixture refluxed for twenty hours. The reaction mixture was then reduced to a volume of 150 cc., cooled in an ice–salt-bath, the precipitated 2,4-dichloroacetanilide filtered, and 4.6 cc. of absolute alcohol added to the chloroform solution. This mixture was then refluxed for six hours, concentrated to 50 cc., and again cooled to precipitate additional dichloroacetanilide. The liquid residue was then fractionated under reduced pressure giving 6.0 g. (35% based on ketene dimer) of α-chloroacetoacetic ester: b. p. 100–110° (25 mm.).

This chloroester was characterized in the same manner as described for α-bromoacetoacetic ester: ethyl 2-amino-4-methylthiazole-5-carboxylate, m. p. 172–173°; 3-methyl-1-phenyl-4-phenylhydrazono-5-pyrazolone, m. p. 155–157°.

Summary

Chemical evidence, based on halogenation of the allyl position, is presented in support of that lactone structure for ketene dimer which has the exocyclic carbon–carbon double bond.

ITHACA, N. Y. RECEIVED JUNE 6, 1947

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

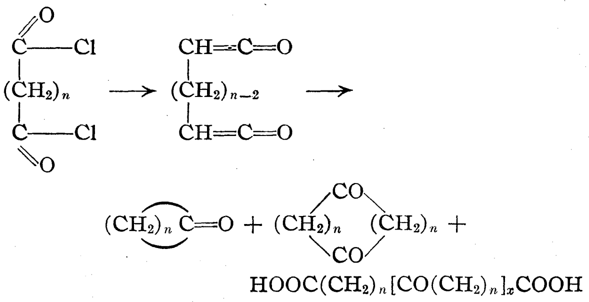
Many-membered Carbon Rings. I. Cyclization of Some Bifunctional Ketenes[1]

BY A. T. BLOMQUIST AND R. D. SPENCER[2]

In the course of investigations in this Laboratory with respect to certain derivatives of many-membered carbon rings it was decided to investigate the possibilities of a new method of cyclization involving bifunctional ketenes. Sauer[3] in his investigation of ketene dimers from acid halides observed that the bifunctional ketene derived from adipyl chloride gave a 40% yield of α-carbethoxycyclopentanone when treated with ethyl alcohol while sebacyl chloride yielded only a polymeric ketene derivative with no evidence of the formation of cyclic compounds. In these experiments no attempt was made to achieve significantly greater dilution than that employed in the preparation of monofunctional ketene dimers. Ziegler[4] and subsequently Hunsdiecker[5] have shown that high dilution is essential for the formation of many-membered rings in satisfactory yields by their methods. Ruzicka's method[6] was not adaptable to the application of the dilution principle and, consequently, the yields of the larger rings formed by his method were quite low.

We reported in a recent communication[7] the results obtained when the dilution principle was applied to the formation of the bifunctional ketene prepared from sebacyl chloride by dehydrohalogenation with triethylamine. There was some evidence for the formation of traces of cyclononanone as a product of the reaction, but none was isolated. A 16% yield of crude 1,10-cycloöctadecanedione was obtained. We have now prepared cycloheptanone and 1,8-cyclotetradecanedione from suberic acid as well as cyclopentadecanone and 1,16-cyclotriacontanedione from thapsic acid.

The following general equation indicates the products obtained upon hydrolysis and decarboxylation of the ketene derivatives without making any attempt to show the structure of these intermediates themselves. The structure of ketene dimer and the aldoketene dimers is still a controversial issue.[8,9]



In the course of the cyclization reaction much ketene polymer is formed. Part of this is ether insoluble and remains with the triethylamine hydrochloride. The ether soluble polymeric material is easily separable from the desired cyclic products after the mixture has been hydrated and decarboxylated with alcoholic potassium hydroxide. Presumably the polymers afford polyketodibasic acids which are soluble in aqueous alkali.

The original experimental procedure has been

---

(1) Abstracted from a dissertation submitted by R. D. Spencer in June, 1947, to the Graduate Faculty of Cornell University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) du Pont Postgraduate Fellow in Chemistry, 1946–1947.

(3) Sauer, THIS JOURNAL, **69**, 2444 (1947).

(4) Ziegler, Eberle and Ohlinger, *Ann.*, **504**, 94–130 (1933), and succeeding papers by Ziegler and his co-workers.

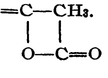
(5) Hunsdiecker, *Ber.*, **75B**, 1190–1197 (1942), and succeeding papers.

(6) Stoll and Rouve, *Helv. Chim. Acta*, **27**, 1570–1583 (1944).

(7) Blomquist and Spencer, THIS JOURNAL, **69**, 472 (1947).

(8) Hanford and Sauer, "Organic Reactions," John Wiley and Sons, New York, Vol. III, 1946, pp. 127–128.

(9) Recent work in this Laboratory, *cf.* Blomquist and Baldwin, THIS JOURNAL, **69**, 29 (1947), supports the following structure for ketene dimer



$$\begin{array}{l}CH_2{=}C{-}CH_3\\ \;\;\;\;\;\;|\;\;\;\;\;|\\ \;\;\;\;\;\;O{-}C{=}O\end{array}$$

simplified by using crude acid chlorides.[10] Traces of thionyl chloride have no apparent effect on the reaction but the presence of larger amounts are undesirable.

Three tertiary amines have been tried as the dehydrohalogenating and condensing agents. Triethylamine gave the best yields, even though it was possible to achieve considerably greater dilution with N-ethylpiperidine by using apparatus (B) (see Experimental). Tributylamine of uncertain purity gave negative results in a cyclization of sebacyl chloride. However, even with carefully purified tributylamine, low yields of the desired product were obtained with pelargonyl chloride and with the crude acid chloride from lauric acid and thionyl chloride.

A second approach to the problem of formation of macrocyclic ketene dimers is under study at the present time. It is known that several keto- and aldoketene dimers can be reconverted to the monomers by heat.[11] On the other hand, Sauer has reported[3] that the ketene derivative obtained from adipyl chloride resinified when its distillation was attempted. An analogous observation was made by Hill and Carothers,[12] when they attempted to depolymerize a linear polyanhydride (sebacic "α-anhydride") by heating it under greatly diminished pressure in a Claisen flask; but, by molecular distillation at 200°, they obtained a twenty-two-membered cyclic dimer. Preliminary experiments in this Laboratory on the ketene polymer from sebacyl chloride indicate that it does indeed depolymerize on heating. The results of these investigations will be the subject of a future communication. In addition to the high temperature depolymerization there is some evidence that the "dimerization" reaction is reversible or, possibly, that a further condensation of some sort occurs even at the temperature of refluxing ether.

Comparison to Other Methods of Formation of Large Ring Ketones

In the cyclization step the yields of large ring ketones by the ketene method are generally superior to those of Ruzicka, but inferior to those of Ziegler and Hunsdiecker. The discrepancy is not so great, however, when the over-all yields are compared, since the synthesis of dibasic acids generally involves fewer steps than do the syntheses of the corresponding nitriles and ω-iodo-β-keto-esters. The lower yields obtained by the ketene method are probably due very largely to the lower dilution employed. It is shown in the experimental section that an increase in the reaction time during the cyclization step has the effect of materially reducing the yield. This phenomenon could be caused either by reversibility of the ketene dimerization reaction in the presence of the catalyst or by a further condensation of the dimer. The authors favor the first explanation and experiments are under way to test this theory. It can readily be seen that if the dimerization reaction is appreciably reversible under the conditions of the cyclization, a point of diminishing returns may be reached. At this point the cyclic dimers open up and react with the linear ketene polymer (present in solution in ever-increasing concentration) more rapidly than they are formed by the intramolecular condensation of the monomer. Consequently, with this in mind, it was necessary to avoid prolonging the reaction time. This was accomplished partly by making small runs, but, nevertheless, the advantages of extremely high dilution had to be sacrificed.

The ketene method is surpassed in convenience only by that of Ruzicka. The necessity of maintaining rigorously anhydrous conditions makes the ketene method somewhat more tedious. However, this inconvenience is offset by the greater ease of separating the cyclic ketones from the accompanying by-products. In this respect the ketene method far surpasses the other three. Although the cyclic diketones have been somewhat difficult to purify (possibly because of the presence of small amounts of the cyclic tri- and polyketones), the cyclic monoketones have been obtained in a relatively high state of purity after simple vacuum distillation.

Experimental[13]

Materials.—The thionyl chloride used in the cyclization step was carefully purified.[14] Commercial anhydrous ether was further purified by distillation from an ether solution of *n*-butylmagnesium bromide. A good grade of commercial triethylamine was purified by drying over potassium hydroxide pellets, refluxing over successive portions of sodium wire until a fresh portion retained its luster and, finally, fractioning it from the sodium wire through a 50-cm., vacuum-jacketed column packed with glass helices. The main fraction boiled at constant temperature. It was stored in a glass-stoppered bottle over sodium wire. N-Ethylpiperidine was prepared from piperidine by alkylation with ethyl iodide, and freed from the secondary amine by treatment with benzoyl chloride followed by fractional distillation. It was stored over sodium wire in the dark, but after about a month it had become light yellow in color.

The sebacyl chloride used in these experiments was prepared from commercial acid which had been purified through the ethyl ester. The suberic acid was from old Kahlbaum stock, m. p. 139.5–141°. The thapsic acid was prepared by the saponification of dimethyl thapsate.[15]

Apparatus.—(A) The apparatus which gave the most satisfactory results was very unpretentious. A one-liter, three-necked flask with ground joints was used. When in operation one neck was stoppered with a glass stopper. In the center neck was an efficient, all-glass stirrer equipped with a small condenser which effectively prevented the ether from distilling up into the mercury seal during the long periods of continuous operation. To the third neck was attached, by means of a bent adapter tube, a 30-cm. bulb condenser. The adapter was used simply to place the

---

[10] This was first tried in the preparation of civetone. Blomquist, Holley and Spencer, THIS JOURNAL, **70**, 34 (1948).

[11] Ref. 8, p. 119.

[12] Hill and Carothers, THIS JOURNAL, **54**, 1574 (1932).

[13] Boiling points are uncorrected. Melting points are corrected.

[14] "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, New York, 1943, p. 570.

[15] This ester was prepared by Mr. George Kossel by electrolysis of methyl hydrogen azelate.

Table I

Summary of Properties of Cyclic Ketones

Cyclic ketone	M. p., °C.		B. p., °C.		M. p. semicarbazone, °C.		M. p. oxime, °C.		Yield of cyclic ketone, %
	Found[a]	Reported	Found[b]	Reported	Found[a]	Reported	Found[a]	Reported	
Cycloheptanone			176[c]	179–180[d]	163.5–164.5	163–164[d]	Not prepd.	23[d]	33
1,8-Cyclotetradecanedione[e]	147.5–148				261 dec.		234–235 dec.		10
1,10-Cycloöctadecanedione	96–97	96–97[f]			225–227 dec.[g]	>230 dec.[f]	163–165[g]	166–168[f]	16[h]
Cyclopentadecanone	Not detd.	63[i]	107–108[j]	*ca.* 120[i,k]	190.5–191.5	187–188[i]			14–20
1,16-Cyclotriacontanedione	77–78	74–75[l]			216.5–219	218–219[l]	144.5–145.5	141–142[m]	1.3–5.3

[a] Melting points are corrected. [b] Boiling points are uncorrected. [c] At 735 mm. [d] Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1934. [e] Not previously reported. [f] Ruzicka, *et al.*, *Helv. Chim. Acta*, **11**, 506 (1928). [g] Ref. 7. [h] This yield is on once-crystallized diketone. The crude yield was 22.5%. [i] Ref. 21. [j] At 0.25 mm. [k] At 0.3 mm. [l] Ref. 20. [m] Ruzicka, *et al.*, *Helv. Chim. Acta*, **16**, 1342 (1933).

condenser and the dropping funnel at a convenient distance from the stirring motor. At the top of the condenser, by means of a well-rolled cork, was attached a U-tube bearing a calcium chloride drying tube and a Hershberg–Hinman dropping funnel.[16] The dropping funnel was protected with a calcium chloride tube.

(B) A more complicated cyclization apparatus was devised in which ether was distilled from the reaction flask through a short fractionating column and condensed into a second flask where it was used to further dilute the solution of the acid chloride before eventually returning to the reaction flask. It was estimated that fifty-fold dilution was easily realized by this arrangement. However, triethylamine distilled too readily with the ether despite the fractionation employed and, consequently, could not be used successfully as the condensing agent with this apparatus. A condensing agent of higher molecular weight, N-ethylpiperidine, although it did not distil appreciably with the ether (of the order of one part of amine per one hundred thousand parts of ether)[17] gave a much lower yield than that obtained when triethylamine was used in apparatus (A).

(C) When the simplified Ziegler apparatus[18] was used, with triethylamine and three times as much ether in the reaction flask, there was troublesome clogging of the dropping funnel and the yield was not improved over (A). The clogging was probably due to the greater ease of diffusion of triethylamine vapor to the funnel tip, with consequent formation of the hydrochloride in the capillary.

General Procedure.—A cyclization run is conveniently made with from 3–5 g. of dibasic acid or a correspondingly larger amount of the bifunctional acid chloride. If the acid is used it is first converted to the crude acid chloride by the following procedure. To the acid is added one and one-half to two times the theoretical amount of purified thionyl chloride.[19] The mixture is heated in a water-bath maintained at about 55° for two hours and is then heated on the steam-bath until evolution of hydrogen chloride and sulfur dioxide has ceased. This usually requires from one to three hours longer. When the reaction is complete the excess thionyl chloride is removed as completely as possible without subjecting the acid chloride to excessive heating. This is best accomplished by applying cautiously the direct suction of a good glass aspirator (10–15 mm.) shaking and swirling gently for three to four minutes at room temperature and for four to five minutes more on the steam-bath. The flask must be swirled constantly in order to prevent bumping and should be protected with a small Kjeldahl safety trap. If a sufficiently efficient aspirator is not available, addition of a small amount of anhydrous ether and repetition of the above evacuation is suggested. As previously mentioned, a large excess of thionyl chloride present in the crude acid chloride causes the cyclization mixture to become orange or brown in color and seems to reduce the yield materially. If the removal of thionyl chloride has been essentially complete, the cyclization mixture is almost colorless or is a very light yellow. The crude acid chloride which is usually a light yellow color, is transferred by means of a pipet to a carefully dried Hershberg–Hinman dropping funnel to which 200–300 cc. of dry ether has previously been added. The two liquids must be thoroughly mixed before the addition is started.

While the acid chloride is being prepared, the apparatus for the cyclization is assembled and thoroughly dried for one to two hours with air or nitrogen which has previously passed through an efficient drying tower. To the flask is added 500–600 cc. of dry ether and 10–20 cc. (three to four times the calculated amount) of pure triethylamine. Stirring is started and the "glass-col" heating mantle adjusted to a temperature which causes the ether to reflux gently. Addition is started at such a rate that it is usually complete at the end of twenty–forty hours. (Longer periods were sometimes required because of the occasional clogging of the dropping funnel.) The dropping funnel is rinsed with 50 cc. of dry ether and this is run in rapidly and is used to rinse down the sides of the condenser. Refluxing is continued for an hour longer. The subsequent operations differ somewhat and will be discussed under the individual cases.

Cyclization of Thapsic Acid.—The apparatus used were those described under (A), (B) and (C). The procedure for working up the reaction product was essentially the same in all three cases. In each run 4.00 g. (0.014 mole) of thapsic acid was used. The addition time varied from thirty-eight hours for (A) to forty-eight and fifty-three hours for (B) and (C), respectively. The reaction mixture was distilled until about 300 cc. of solution remained. This was decanted from the precipitated amine salt and ketene polymer and shaken with a slight excess of dilute hydrochloric acid in a separatory funnel to remove the excess amine. The ether solution was washed with water, dried and distilled on the steam-bath. The viscous orange or amber oil was refluxed for three hours with a solution of 1.5 g. (0.027 mole) of potassium hydroxide in 25 cc. of alcohol. During the first hour, an incrustation, presumably potassium carbonate, formed around the sides of

---

(16) "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, 1943, p. 129. The capillary stem of Hershberg's funnel was modified by L. Hinman as follows. A tungsten wire (about 0.5–0.6 mm. in diameter) with a sharpened tip was placed in a lathe and used as the grinding tool to enlarge a capillary of smaller diameter. The stem was 7 cm. long and the wire, when completely seated, extended slightly beyond the glass tip, thus making it possible to clear the capillary when it became clogged. This modification permitted a very fine adjustment of flow ranging from complete stoppage to a steady stream.

(17) This was determined by a simple test. A 1-cc. portion of the ether solution of N-ethylpiperidine is placed in a small test-tube containing a piece of red litmus paper about 5 mm. square. One drop of boiled, distilled water is allowed to fall through the ether solution onto the litmus paper. The tube is shaken gently and the time required for the paper to become perceptibly blue (as compared with a blank) serves as a rough indication of the concentration of N-ethylpiperidine in the solution. The test was sensitive enough to detect one part by volume of the amine in at least two hundred thousand parts of ether.

(18) Schroeder, Ph.D. Dissertation, Harvard University, 1938.

(19) An equal volume of anhydrous ether may also be added to accelerate the solution of the acid and thereby speed the reaction. If this is done the ether is allowed to distil slowly through the uncooled condenser during the first hour.

the flask. The reaction mixture was diluted with 50 cc. of water and thoroughly extracted with ether. The ether extract was washed with water, dried over magnesium sulfate and distilled. Removal of the ether left an aqueous-alcoholic residue which deposited 1,16-cyclotriacontanedione in needles. The yield ranged from 1.3% of tan crystals sintering at 68° and melting at 74–76° when apparatus (C) was used, to 5.3% of white crystals melting at 76–77° when apparatus (B) was used. Apparatus (A) gave 2.9% m. p. 76.5–78°. Recrystallization from alcohol did not appreciably raise the melting points, 77–78° (Ruzicka reports 74–75°[20]). The yield of diketone obtained seemed to bear no relation at all to the yield of monoketone.

The cyclopentadecanone (Exaltone) was isolated by distillation of the filtrate from the diketone in a 5-cc. flask provided with a sausage side arm. The white, waxy ketone distilled at 107–108° (0.25 mm.). The yields ranged from 14 (B) to 20% (C) and (A). The ketone was converted directly to the semicarbazone, which, after one crystallization from methanol melted at 190.5–191.5° (Ruzicka gives 187–188°).[21]

Cyclization of Suberic Acid.—The apparatus was that described under (A). The addition of the solution of crude acid chloride from 3.00 g. of suberic acid required twenty-six hours. The ether solution from the cyclization was decanted from the precipitated triethylamine hydrochloride and trace of insoluble polymer into a separatory funnel. After shaking with a slight excess of dilute hydrochloric acid, it was washed with water until the washings were neutral to congo red. The solution was dried over magnesium sulfate and then fractionally distilled through a 50-cm., vacuum-jacketed column packed with glass helices. To the residual light yellow oil was added 5 cc. of alcohol, and, *very slowly*,[22] with cooling, a solution of 1.8 g. (0.032 mole) of potassium hydroxide in 20 cc. of alcohol. The solution was allowed to stand at room temperature for ten hours and was then refluxed for two hours more. A precipitate, presumably potassium carbonate, started to form shortly after addition of the alcoholic potassium hydroxide. The mixture was worked up in the same manner as the thapsic acid cyclization product with the exception that the ether solution was fractionally distilled through the above-mentioned fractionating column. From the alcoholic solution which remained was isolated 93 mg. of shining white plates, m. p. 144–145.5°. Distillation of the filtrate gave 642 mg. (33.3%) of cycloheptanone, b. p. 176° (735 mm.). An additional 100 mg. of slightly yellow crystals, m. p. 143–146.5°, was isolated by crystallization from alcohol of the residue from the distillation of the cycloheptanone. The two crops represent a yield of 10% of 1,8-cyclotetradecanedione. Crystallization from alcohol raised the melting point to 147.5–148° and this was not changed by a vacuum sublimation.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78; mol. wt., 224.34. Found: C, 74.89; H, 10.89; mol. wt., 231 (micro Rast).

The disemicarbazone of 1,8-cyclotetradecanedione was prepared by treating 50 mg. of the diketone in 3 cc. of warm methanol with semicarbazide reagent. A yield of 75 mg. of fine, white powder was obtained (the theoretical yield on the basis of disemicarbazone). This, being very insoluble in the common solvents, was purified by extraction with two portions of boiling alcohol, m. p. 261° dec. in a copper block with rapid heating (about five degrees per minute).

Anal. Calcd. for $C_{16}H_{30}O_2N_6$: N, 24.83. Found: N, 23.73, 23.84.

The dioxime of 1,8-cyclotetradecanedione was prepared by the pyridine method.[23] The white material was crystallized from a large volume of alcohol, m. p. 234–235° dec.

Anal. Calcd. for $C_{14}H_{26}O_2N_2$: N, 11.01. Found: N, 11.10, 10.93.

Evidence for Reversibility of the Dimerization Reaction.—The stability of the cyclic ketene derivatives was tested in the following manner. To a solution of 50 cc. (36.5 g., 0.36 mole) of triethylamine in 100 cc. of dry ether was added over a period of fifty-seven hours a solution of 11.90 g. (0.0498 mole) of sebacyl chloride in 600 cc. of dry ether. The apparatus described under (A) was used. The funnel was rinsed with dry ether and the mixture allowed to stand overnight at room temperature. The ether was siphoned into a one-liter graduated cylinder through a glass tube in the end of which was placed a plug of fine glass wool. Care was taken to minimize the exposure of the ether solution to the atmosphere. Half of the ether was returned to the flask by means of a pipet and refluxed for three more days. The other half was worked up as follows.

Most of the ether was distilled on the steam-bath. When the volume became small the remainder of the ether and most of the excess triethylamine was removed with suction at room temperature and finally for a short period at 50–60°. A solution of 3 g. (0.053 mole) of potassium hydroxide in 50 cc. of alcohol was added and the resulting solution was refluxed on the steam-bath for three hours. A precipitate, presumably potassium carbonate, started to come down at once. Upon the addition of 50 cc. of water the potassium carbonate readily dissolved, but the 1,10-cycloöctadecanedione was precipitated. This solution was steam distilled until 200 cc. of liquid had been collected in the distillate. This was acidified to congo red. A pronounced sweetish odor was detected, but extraction with ether and fractionation through a 12-cm., helix-packed column, followed by treatment with semicarbazide reagent, failed to yield any cyclononanone semicarbazone. Filtration of the residue from the steam distillation gave 783 mg. (22.5%) of crude, faintly brown 1,10-cycloöctadecanedione, m. p. 80–90° with sintering at about 75°. One crystallization from ether gave 446 mg. of almost white cubes, m. p. 93–96°. Concentration of the mother liquor yielded an additional 117 mg., m. p. 92.5–95°. This represents a yield of 16% of relatively pure diketone. The melting point can be raised to 96–97° by sublimation at 110° (0.45 mm.).

The ether solution which had been returned to the flask for further refluxing was worked up the same way as the first half. The crude diketone weighed 478 mg. (13.7%) and melted at 75–85° with previous sintering at about 70°.

Summary

Acid chlorides of suberic, sebacic and thapsic acids have been dehydrohalogenated by tertiary aliphatic amines to form the bifunctional ketene derivatives. These condense linearly to give ketene polymers, but under conditions of high dilution, moderate yields of macrocyclic compounds are obtained. Hydrolysis and decarboxylation of these cyclic ketene derivatives gives the large ring ketones and diketones.

ITHACA, NEW YORK RECEIVED JUNE 12, 1947

---

[20] Ruzicka, *et al.*, *Helv. Chim. Acta*, **11**, 509–510 (1928).

[21] Ruzicka, *ibid.*, **9**, 260 (1926).

[22] A vigorous exothermic reaction ensues and if great care is not taken there is likely to be a loss of product.

[23] Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., p. 167.

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Many-membered Carbon Rings. II. A New Synthesis of Civetone and *dl*-Muscone

BY A. T. BLOMQUIST, ROBERT W. HOLLEY[1] AND R. D. SPENCER[2]

The only recorded synthesis of civetone is that of Hunsdiecker in which intramolecular alkylation of an ω-iodoacylacetic ester was effected to form the appropriate many-membered carbon ring.[3] Ruzicka, Plattner and Widmer[4] as well as Hunsdiecker[5] reported the preparation of suitable intermediates for the synthesis of civetone by Ziegler's method[6] but have not described cyclization experiments leading to the complete synthesis.

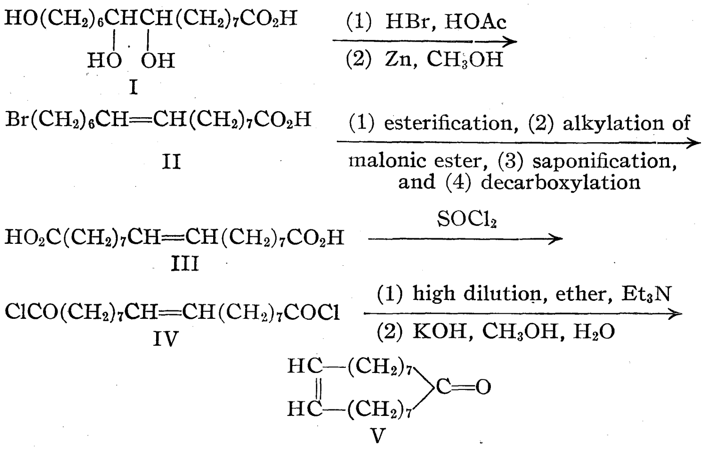
Ziegler and Weber[7] and Ruzicka and Stoll[8] announced, practically simultaneously, the synthesis of *dl*-muscone by the Ziegler method although the two groups used different syntheses for the requisite ω,ω′-dinitrile used in the cyclization. Hunsdiecker also has synthesized *dl*-muscone through his intramolecular alkylation method.[9]

It was of interest to attempt the synthesis of civetone and *dl*-muscone through the intramolecular condensation, under conditions of high dilution, of suitable bifunctional ketenes. This synthetic method for many-membered rings is described in preceding articles.[10]

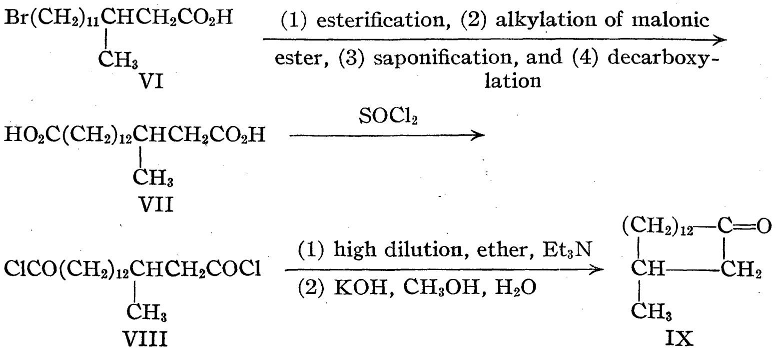
The reactions employed in the syntheses here reported are indicated in the accompanying diagram. Using aleuritic acid (I) as the starting material for the civetone synthesis, 9-octadecene-1,18-dioic acid (III) was prepared essentially by Hunsdiecker's procedure.[5] The crude acid chloride (IV) derived therefrom was cyclized through the bifunctional ketene. Civetone (V) was obtained in 33% yield from 9-octadecene-1,18-dioic acid (III).

The starting material for the synthesis of *dl*-muscone was 14-bromo-3-methyltetradecanoic acid (VI).[11] It was converted to 3-methyl-1,16-hexadecanedioic acid (VII) as indicated and the corresponding crude acid chloride (VIII) cyclized through the bifunctional ketene. *dl*-Muscone (IX) was obtained in 22% yield from 3-methyl-1,16-hexadecanedioic acid.

SYNTHESIS OF CIVETONE



SYNTHESIS OF *dl*-MUSCONE



In the present study the yields of civetone and *dl*-muscone from the appropriate dicarboxylic acids are lower than those reported by Hunsdiecker[3] and by Ziegler and Weber[7] for the cyclization steps of their respective syntheses. However, a consideration of such factors as ease of synthesis of necessary intermediates, convenience in laboratory manipulation, and over-all yield from the starting materials may favor the new syntheses somewhat. In repeating Hunsdiecker's synthesis of civetone we effected certain simplifications and improvements in yield in some of the steps and realized an 8.5% over-all yield of civetone, as its semicarbazone, from aleuritic acid. By the present method a 9.8% yield of civetone, as its semicarbazone, from aleuritic acid was obtained. Nicely crystalline inter-

---

(1) National Research Council Predoctoral Fellow, 1946–1947.

(2) du Pont Postgraduate Fellow, 1946–1947.

(3) Hunsdiecker, *Ber.*, **76B**, 142 (1943).

(4) Ruzicka, Plattner and Widmer, *Helv. Chim. Acta*, **25**, 1086 (1942).

(5) Hunsdiecker, *Ber.*, **77B**, 185 (1944).

(6) Ziegler, Eberle and Ohlinger, *Ann.*, **504**, 94 (1933).

(7) Ziegler and Weber, *ibid.*, **512**, 164 (1934).

(8) Ruzicka and Stoll, *Helv. Chim. Acta*, **17**, 1308 (1934).

(9) Hunsdiecker, *Ber.*, **75B**, 1197 (1942).

(10) Blomquist and Spencer, THIS JOURNAL, **69**, 472 (1947); **70**, 30 (1948).

(11) Prepared in the Cornell Laboratories by Miss M. Burg (ref. 15) according to Hunsdiecker's procedure (ref. 9).

mediates were encountered in the present syntheses.

Experimental

Preparation of Civetone

16-Bromo-9-hexadecenoic Acid (II).—This acid was prepared from aleuritic acid according to Hunsdiecker's procedure.[3] The 9,10,16-tribromopalmitic acid was treated, in methanol solution, with zinc dust at reflux temperature for five and a half hours. The yield of crude acid from aleuritic acid was 62%; the yield of acid m. p. 40.5–42° was 39%.

Methyl 16-Bromo-9-hexadecenoate.—The acid described above on treatment with an excess of an ethereal solution of diazomethane gave a quantitative yield of the liquid methyl ester.

8-Hexadecene-1,1,16-tricarboxylic Acid.—The procedure was that of Hunsdiecker.[5] The tricarboxylic acid, m. p. 67–69°, was used without purification.

9-Octadecene-1,18-dioic Acid (III).—The tricarboxylic acid described above was decarboxylated by heating *in vacuo* to 200°, as described by Hunsdiecker.[5] The unpurified acid, m. p. 95.5–98°,[12] was recrystallized from ethyl acetate, m. p. unchanged, yield 82% from 16-bromo-9-hexadecenoic acid. The acid was used without further purification in the cyclization step. Neutral equivalent was 163 (calcd. 156).

Civetone (V). Cyclization of 9-Octadecene-1,18-dioic Acid.—A mixture of 1.8 g. (5.8 millimoles) of 9-octadecene-1,18-dioic acid, 2 cc. (3.3 g., 28 millimoles) of thionyl chloride and 5 cc. of absolute ether was warmed gently. Sulfur dioxide and hydrogen chloride distilled gradually. After half an hour the temperature was raised to *ca.* 70° and kept there for one hour. Removal of excess thionyl chloride *in vacuo* at 50–60° gave 2.03 g. of the crude acid chloride which still had an odor of thionyl chloride.

A solution of the crude acid chloride in 200 cc. of absolute ether (Grignard-dried) was added over a period of fifteen hours from a Hershberg[13] dropping funnel down the condenser into a stirred, refluxing mixture of 500 cc. of absolute ether (Grignard-dried) and 10 cc. of triethylamine. At the end of this time the dropping funnel and condenser were rinsed with absolute ether and 500 cc. of ether was removed by distillation of the combined ethereal solution. The remaining ethereal solution, triethylamine hydrochloride, and polymer was washed with 50-cc. and 30-cc. portions of 3 *N* hydrochloric acid and finally with water until the washes were neutral to congo red. The ethereal solution was dried over anhydrous magnesium sulfate.

The ether was distilled and the residue weighed 1.72 g. In order to hydrolyze ketene dimers, this material was dissolved in a solution of 2.0 g. of potassium hydroxide in 2.0 cc. of water and 30 cc. of methanol. The solution was kept at room temperature for forty hours and then was refluxed one and one-half hours. The saponification mixture was cooled, diluted with water to about 200 cc., and the neutral organic material extracted repeatedly with ether. The ethereal solution was washed with water and dried over anhydrous magnesium sulfate. The ether was distilled and 545 mg. of residue, crude civetone, was obtained. The material remaining in the aqueous layer was investigated sufficiently to insure that no civetone was being lost as α-civetonecarboxylic acid.

The civetone was distilled at 0.2 mm. pressure with a bath temperature of about 160°. A nearly colorless distillate was obtained; yield, 476 mg. (33% from 9-octadecene-1,18-dioic acid).

Civetone Semicarbazone.—The distilled civetone (476 mg.) was dissolved in 5 cc. of acetone-free methanol and a solution of 700 mg. of semicarbazide hydrochloride and 1.05 g. of sodium acetate trihydrate in 2.1 cc. of water was added dropwise. The semicarbazone started to crystallize after 15 to 20% of the semicarbazide solution had been added. The mixture was allowed to stand at room temperature overnight.

The semicarbazone was collected, washed with water and was dried four hours in the air and finally *in vacuo;* yield, 575 mg. It was recrystallized from 35 cc. of methanol. The recrystallized semicarbazone, shining leaflets, weighed 497 mg.; m. p. 189.5–191.5° (Ruzicka[14] reported 185–186°, Hunsdiecker[3] reported 190–191°). The melting point was not changed when this semicarbazone was mixed with the semicarbazone of civetone obtained according to Hunsdiecker's[3] procedure.

Anal. Calcd. for $C_{18}H_{33}ON_3$: N, 13.67. Found: N, 13.64; 13.71.

The mother liquors were concentrated to about 5 cc. and the second crop of semicarbazone was recrystallized; 48 mg. were obtained; m. p. 190–192°. The total yield of civetone semicarbazone was 31% from 9-octadecene-1,18-dioic acid. This was a 25% yield from 16-bromo-8-hexadecenoic acid and a 9.8% yield from aleuritic acid.

Civetone may be regenerated from its semicarbazone in quantitative yield by heating the semicarbazone with an oxalic acid solution as described by Ruzicka.[14]

Preparation of *dl*-Muscone

14-Bromo-3-methyltetradecanoic Acid (VI).—This acid was prepared in the Cornell laboratories by Miss M. Burg[15] according to the procedure described by Hunsdiecker.[9]

Methyl 14-Bromo-3-methyltetradecanoate.—The liquid ester was obtained in quantitative yield by treatment of the acid described above with an excess of diazomethane.

2-Methyl-1,14,14-tetradecanetricarboxylic Acid.—The alkylation of diethyl malonate was carried out in exactly the same way as in the preparation of 8-hexadecene-1,1,16-tricarboxylic acid from methyl 16-bromo-9-hexadecenoate, the procedure described by Hunsdiecker.[5] The crude 2-methyl-1,14,14-tetradecanetricarboxylic acid was an oil, and no attempt was made to purify it.

3-Methyl-1,16-hexadecanedioic Acid (VII).—The tricarboxylic acid described above was decarboxylated at 200°. The resulting dicarboxylic acid was recrystallized from ethyl acetate and from a mixture of ethyl acetate and 60–70° petroleum ether. The yield from 14-bromo-3-methyltetradecanoic acid was 46%; m. p. 74–76° (Chuit, *et al.*,[16] reported the melting point as 77.2–77.4°). Neutral equivalent was 152 (calcd. 150).

***dl*-Muscone (IX). Cyclization of 3-Methyl-1,16-hexadecanedioic Acid.**—The di-acid chloride was prepared from 1.8 g. (6.0 millimoles) of 3-methyl-1,16-hexadecanedioic acid exactly as the corresponding di-acid chloride was prepared in the synthesis of civetone. The cyclization procedure was exactly the same except that the solution of di-acid chloride was added over twenty-three hours. The product was isolated as before. The saponification mixture was allowed to stand at room temperature for five and one-half days.

The saponification mixture was diluted with 250 cc. of water and the *dl*-muscone was extracted into ether; 450 mg. was obtained. The *dl*-muscone was distilled at 0.2 mm. pressure with a bath temperature of about 140°. The colorless *dl*-muscone weighed 315 mg. (22% from 3-methyl-1,16-hexadecanedioic acid).

***dl*-Muscone Semicarbazone.**—The distilled *dl*-muscone (315 mg.) was dissolved in 4 cc. of acetone-free methanol and a solution of 500 mg. of semicarbazide hydrochloride and 750 mg. of sodium acetate trihydrate in 1.5 cc. of water was added over ten minutes. The solution was maintained at 65° for fifteen minutes, at which time the semicarbazone began to precipitate. The mixture was allowed to stand at room temperature for twenty-four hours.

The semicarbazone was collected and was allowed to dry in air; yield 400 mg. It was recrystallized from 5 cc. of

---

[12] From the fractionated dimethyl ester Hunsdiecker obtained the free acid melting at 99.5–100.3°.

[13] "Organic Syntheses," **18,** 16 (1938).

[14] Ruzicka, *Helv. Chim. Acta*, **9,** 239 (1926).

[15] Burg, Thesis, Cornell University, 1947.

[16] Chuit, Boelsing, Hausser and Malet, *Helv. Chim. Acta*, **10,** 167 (1937).

boiling methanol. The recrystallized semicarbazone weighed 319 mg.; m. p. 131.5–132.5°. (Hunsdiecker[9] reported 133–133.5°; Ruzicka[8] reported 136–137°.)

Anal. Calcd. for $C_{17}H_{33}ON_3$: N, 14.22. Found: N, 14.38, 14.39.

A second crop of semicarbazone (54 mg.) was obtained from the mother liquors; m. p. 127–128.5°. The total yield of *dl*-muscone semicarbazone from 14-bromo-3-methyltetradecanoic acid was 9.7%.

dl-Muscone may be regenerated from its semicarbazone by heating the semicarbazone with an oxalic acid solution, as in the regeneration of civetone from its semicarbazone.

Summary

A new synthesis for civetone and *dl*-muscone is described in which the appropriate many-membered carbon rings are formed by the intramolecular condensation of bifunctional ketenes.

ITHACA, NEW YORK RECEIVED JUNE 12, 1947

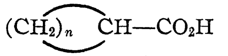
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Many-membered Carbon Rings. III.[1] Carboxylic Acid Derivatives of Cycloheptadecane[2]

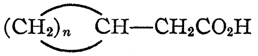
BY A. T. BLOMQUIST AND ROBERT W. HOLLEY[3]

The extensive researches in the chemistry of higher fatty acids have resulted in the discovery of therapeutic agents of some promise against tuberculosis and leprosy.[4] Recently, activity in the field has been stimulated by the interesting study of phthioic acid, isolated from the tubercle bacillus.[5] Accordingly, it seemed of interest to undertake an investigation of the properties of carboxylic acids containing many-membered carbon rings.

The present paper records exploratory studies on synthetic methods for the preparation of large-ring carboxylic acids of the type A and B.



A

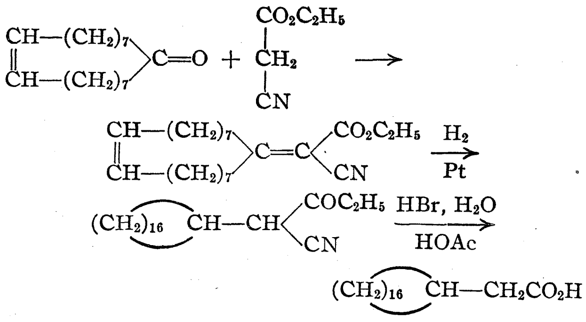


B

The relative availability of the seventeen-carbon cyclic ketone, civetone, suggested its use in developing synthetic methods for the type of acids described above. These methods should be applicable to the synthesis of higher homologs with the carbon ring containing from twenty to thirty members.

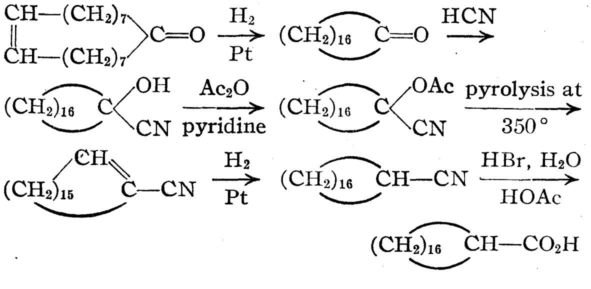
Hunsdiecker's synthesis of civetone from aleuritic acid[6] was selected as a suitable method for obtaining the C_{17} ring. Unfortunately, his published procedure is incomplete and considerable experimentation was necessary before a useful synthesis was developed. A number of modifications were worked out and these are described in the experimental section. Through the use of unpurified intermediates in many of the steps it was possible not only to achieve a considerable saving of labor but also to improve the over-all yield of civetone from aleuritic acid, 8.5% as compared with 5.3% obtained by Hunsdiecker.

Cycloheptadecaneacetic acid was readily obtained from the condensation product of civetone with ethyl cyanoacetate as indicated by the equations



The over-all yield of purified cycloheptadecaneacetic acid from civetone was 57%.

The preparation of cycloheptadecanecarboxylic acid presented more difficulties. It was eventually obtained by way of cycloheptadecanone cyanohydrin as indicated below.



The over-all yield of cycloheptadecanecarboxylic acid was 40%.

Attempts to obtain the above acid by carbonation of the appropriate Grignard reagent or

---

[1] Preceding paper in this series: Blomquist, Holley and Spencer, THIS JOURNAL, **70**, 34 (1948).

[2] This paper is an abstract of part of the doctoral dissertation presented by Robert W. Holley to the Graduate Faculty of Cornell University in June, 1947.

[3] National Research Council predoctoral fellow in Chemistry, 1946–1947. Present address: Department of Chemistry, State College of Washington, Pullman, Washington.

[4] (a) Emmart, *Am. Rev. Tuberculosis*, **53**, 83 (1946). (b) Stanley, Jay and Adams, THIS JOURNAL, **51**, 1261 (1929). (c) Stanley and Adams, *ibid.*, **54**, 1548 (1932).

[5] (a) Henshall, *Ann. Reports*, **37**, 224 (1940). (b) Polgar and Robinson, *J. Chem. Soc.*, 389 (1945). (c) Stenhagen and Ställberg, *J. Biol. Chem.*, **139**, 345 (1941); **148**, 685 (1943). (d) Velick and Anderson, *ibid.*, **152**, 523 (1944).

[6] Hunsdiecker, *Ber.*, **76B**, 142 (1943).

organolithium compound were unsuccessful as the chief products were neutral, halogen-free oils. Degradation of cycloheptadecaneacetic acid according to the Barbier–Wieland procedure[7] gave a low yield of the carboxylic acid. Although 1-hydroxycycloheptadecanecarboxamide was obtained in excellent yield from cycloheptadecanone cyanohydrin its conversion to the carboxylic acid did not appear promising. Further, since methyl α-civetonecarboxylate, an intermediate in the civetone synthesis, could not be readily purified, it was not used as a starting material for the synthesis of the carboxylic acid.

Civetol, characterized as its acid phthalate ester, was obtained in 95% yield by reduction of civetone with aluminum isopropoxide and was converted quantitatively into cycloheptadecanol by hydrogenation over platinum.

Civetone was converted smoothly into an hydantoin derivative by treatment with sodium cyanide and ammonium carbonate.

Experimental[7a]

Preparation of Civetone

16-Bromo-9-hexadecenoic Acid.—A mixture of 190 g. (2.9 moles) of commercial zinc dust, 1800 cc. of methanol and 5 cc. of 14.5% hydrogen bromide solution in acetic acid was placed in a 5-liter, three-necked flask equipped with a stirrer, reflux condenser, and a thermometer which dipped below the surface of the liquid. The mixture was heated to gentle reflux and then was cooled to about 55°. A solution of 286 g. of crude 9,10,16-tribromopalmitic acid (prepared from 182 g. of aleuritic acid exactly as described by Hunsdiecker[6]) in 300 cc. of methanol was added slowly. The mixture was warmed and refluxed for 5.5 hours during which time additional 10-g. portions of zinc dust were added at one-hour intervals. The hot solution was decanted from unreacted zinc and cooled.

The zinc salt was collected, recrystallized from 6400 cc. of boiling methanol (heated on a steam-bath to avoid overheating the solid zinc salt) and dried in air: yield 136 g., 62% from aleuritic acid.

The acid was liberated by shaking the zinc salt with a mixture of 6 *N* hydrochloric acid and ether. The 16-bromo-9-hexadecenoic acid weighed 125 g., m. p. 38–41° (62% from aleuritic acid). It was recrystallized from 160 cc. of pure methanol: first crop 72 g., m. p. 40.5–42°, second crop 7 g., m. p. 40–42°. The second crop was recrystallized from 25 cc. of methanol by cooling the solution first in the refrigerator and then in Dry Ice: weight 6.6 g., m. p. 40.5–42°. The total yield was 39% from aleuritic acid.

Methyl 18-Bromo-3-oxo-11-octadecenoate.—The acylation of ethyl acetoacetate was carried out in a three-necked, 500-cc. flask equipped with a stirrer, reflux condenser and dropping funnel. The sodium enolate was prepared from 38 g. (0.29 mole) of freshly distilled ethyl acetoacetate by adding small pieces of sodium totalling 5.75 g. (0.25 mole) to a solution of ethyl acetoacetate in 40 cc. of absolute ether. About three-quarters of the sodium dissolved before the sodium enolate began to precipitate. The remainder of the sodium was added, the mixture diluted with 100 cc. of absolute ether, and stirring was continued for three hours.

While the above mixture was being stirred, 72 g. (0.22 mole) of 16-bromo-9-hexadecenoic acid was mixed with 18.5 cc. (30.3 g., 0.25 mole) of pure thionyl chloride and 30 cc. of absolute ether was added. The mixture was warmed very slightly on a steam-bath until the rapid evolution of sulfur dioxide and hydrogen chloride had slowed. The remaining ether was distilled and the temperature raised to approximately 80° over an additional hour. The excess thionyl chloride was removed at water pump pressure, finally at 80°. The acid chloride, 76 g., was dissolved in 75 cc. of absolute ether.

The suspension of sodium enolate of ethyl acetoacetate was diluted to give a total volume of 200 cc. A few small pieces of unreacted sodium remained. The solution of acid chloride in ether was added to this suspension through the dropping funnel over a period of about five minutes. The mixture was refluxed for two hours and then was allowed to stand at room temperature overnight.

The reaction mixture was added to a mixture of 30 cc. of concentrated sulfuric acid and 250 cc. of ice and water. An additional 100 cc. of ether was added. The last traces of solid dissolved with some difficulty. The ether layer was separated and the aqueous layer was extracted with two additional 50-cc. portions of ether. The combined ether extracts were washed with water until the washes were neutral to congo red. The ethereal solution was dried over anhydrous magnesium sulfate. The ether was distilled and volatile material remaining was removed *in vacuo*, first at water pump pressure with a bath temperature of 120° and finally by heating at 120° for fifteen minutes at a pressure of 0.2 mm. The residue of crude ethyl 2-acetyl-18-bromo-3-oxo-11-octadecenoate, 90 g., was dissolved in a solution of sodium methylate prepared from 5.75 g. of sodium and 250 cc. of methanol (dried by distillation from magnesium methylate). The solution was left at room temperature for five hours.

The solution was added to a mixture of 30 cc. of concentrated sulfuric acid and 500 cc. of ice and water. The gummy solid which precipitated was extracted into ether (400-cc. total). The ethereal solution was washed with water, until the washes were neutral to congo red, and was dried over anhydrous magnesium sulfate. After removal of the ether, 82 g. of crude methyl 18-bromo-3-oxo-11-octadecenoate was obtained (97.5% from 16-bromo-9-hexadecenoic acid).

Methyl 18-Iodo-3-oxo-11-octadecenoate.—The crude methyl 18-bromo-3-oxo-11-octadecenoate (82 g., 0.21 mole) was dissolved in a solution of 37.5 g. (0.25 mole) of sodium iodide in 250 cc. of reagent grade acetone. The mixture was left at room temperature overnight.

About two-thirds of the acetone was distilled *in vacuo*. A mixture of 100 cc. of water and 200 cc. of ether was added to the residue. The ether layer was separated and the aqueous layer was extracted twice with additional ether. The combined ether extracts were dried over anhydrous magnesium sulfate. The ether was distilled *in vacuo*. The residue was taken up in methanol and this was removed *in vacuo* (for comparison of the m. p. with samples recrystallized from methanol). The crude methyl 18-iodo-3-oxo-11-octadecenoate was a mushy solid at 25° and liquified completely at 30°, weight 86 g. (93.5% from methyl 18-bromo-3-oxo-11-octadecenoate).

Civetone.—A solution of 25 g. (0.057 mole) of crude methyl 18-iodo-3-oxo-11-octadecenoate in 300 cc. of methyl ethyl ketone was added over sixty hours from a Hershberg dropping funnel[8] into the returning stream of condensate from a stirred, refluxing mixture of 3300 cc. of methyl ethyl ketone and 500 g. of potassium carbonate. After the addition was complete, the mixture was stirred and refluxed an additional twenty-four hours.

The mixture was cooled and the potassium carbonate was removed by filtration and washed several times with methyl ethyl ketone. The methyl ethyl ketone was distilled: the last 50 cc. was removed *in vacuo*, weight of residue 33 g. This material was shaken with 100 cc. of 15% formic acid as described by Hunsdiecker[6] to remove products of the condensation of methyl ethyl ketone with itself. The insoluble material weighed 27.5 g. The more volatile fraction of this crude cyclization product was distilled by heating at 70° at 0.2 mm. pressure for ten min-

---

[7] Hoehn and Mason, THIS JOURNAL, **60**, 1493 (1938).

[7a] All melting points and boiling points are uncorrected unless otherwise specified.

[8] "Organic Syntheses," **18**, 16 (1938).

utes. The residue, crude methyl α-civetonecarboxylate, weighed 19 g. It was dissolved in a solution prepared from 30 g. of potassium hydroxide, 30 cc. of water and 450 cc. of methanol. The solution was allowed to stand at room temperature (about 25°) for five days.

The saponification mixture was added to 1200 cc. of 10% sulfuric acid and the organic material was extracted with portions of ether totalling 500 cc. The ether extracts were washed with water, and then 100 cc. of 3% potassium hydroxide solution was poured through the ether solution in a fine stream. The aqueous layer became orange. The separatory funnel was tipped on its side and rotated slowly in order to expose most of the ether layer to the alkali. Care was taken not to shake the mixture since a very stable emulsion formed if this was done. Considerable acidic material went into the alkaline extract. Investigation indicated that no α-civetonecarboxylic acid was present at this point. The alkaline layer was drawn off and the ether layer was washed twice with water, pouring the water through the ether and down the sides of the funnel. The ethereal solution was dried over anhydrous magnesium sulfate. The ether was distilled and the residue, crude civetone, weighed 8 g.

The civetone was distilled, weight 4.58 g., boiling chiefly at 144–150° at 0.2 mm. (probably superheated). The vapor temperature was allowed to rise to 175° because of the large amount of residue.

Civetone Semicarbazone.—The civetone (4.58 g.) was converted to its semicarbazone by the method described by Ruzicka.[9] It was recrystallized from 250 cc. of boiling methanol, weight 4.16 g., m. p. 189–191°. (Ruzicka[9] reported 185–186°; Hunsdiecker[9] reported 190–191°.) The yield was 74% from the distilled civetone, 23.8% from methyl 18-iodo-3-oxo-11-octadecenoate, and 8.5% over-all from aleuritic acid. Civetone, m. p. 35–36.5°, was obtained in quantitative yield from the semicarbazone by the method described by Ruzicka.[9]

Cycloheptadecanone.—Civetone was reduced catalytically using ethanol as the solvent and 3% by weight of platinum oxide catalyst. Reduction was complete in one hour at 20° and atmospheric pressure. Only 90% of the theoretical amount of hydrogen was absorbed. This low value was also obtained in the catalytic reduction of civetol. The cycloheptadecanone (quantitative yield) was used in subsequent reactions without purification. Recrystallized from methanol, it melted at 64–65°. (Hunsdiecker[6] reported 64–64.5°.)

Preparation of Cycloheptadecaneacetic Acid

Condensation of Civetone with Ethyl Cyanoacetate.—The procedure was essentially the same as that described by Cope, *et al.*[10]

A mixture of 3.4 g. (13.5 millimoles) of civetone, 1.6 g. (14 millimoles) of ethyl cyanoacetate, 155 mg. (2 millimoles) of ammonium acetate, 1.7 cc. of glacial acetic acid and 14 cc. of dry benzene was heated in an oil-bath at 125–130°. The benzene was distilled slowly to remove water; 8 cc. were distilled during nine hours of heating. The reaction mixture was cooled, diluted with ether, and the solution was washed three times with water. The washes were extracted once with ether and this was washed again with water. The ethereal solutions were dried over anhydrous magnesium sulfate. The ether was distilled and the residue, weight 4.65 g., crystallized. The product was recrystallized once from 15 cc. of methanol. The once recrystallized product weighed 3.49 g. (74% from civetone) and melted on the microscope hot stage at 65–68° (cor.).

Anal. Calcd. for $C_{22}H_{35}O_2N$: N, 4.06. Found: N, 4.26.

The condensation product was reduced catalytically in ethanol solution using 4% by weight of platinum oxide catalyst. The theoretical amount of hydrogen (for two double bonds) was absorbed in four hours at room temperature and atmospheric pressure, and practically no more hydrogen was absorbed during two additional hours. The reduced product was an oil (quantitative yield) and was used without purification.

Cycloheptadecaneacetic Acid.—A solution of 253 mg. of reduced condensation product in 3 cc. of glacial acetic acid and 1 cc. of 48% hydrobromic acid was refluxed for forty-eight hours. The mixture was cooled, diluted with water and extracted with ether. The ethereal solution was washed with water and then was extracted with 3% potassium hydroxide solution. The cycloheptadecaneacetic acid, weight 196 mg., was a light brown oil which crystallized within a few days when stored at 5°. The unpurified acid melted at 20–25°. It was recrystallized from acetone by cooling the solution with Dry Ice, first crop, 147 mg., m. p. 27–28° (Calcd. neut. equiv., 296.5. Found: 289; second crop, 20 mg., m. p. 26.5–28°, neut. equiv., found, 294). The yield (167 mg.) was 77% from the civetone–ethyl cyanoacetate condensation product, and 57% from civetone.

Cycloheptadecaneacetamide.—Unpurified cycloheptadecaneacetic acid was converted to the acid chloride using purified thionyl chloride. The crude acid chloride was treated with cold concentrated aqueous ammonia. The amide was extracted with a small volume of petroleum ether and was recrystallized from ether. The yield of once recrystallized amide was 62%; micro m. p. 134–134.8° (cor.).

Anal. Calcd. for $C_{19}H_{37}ON$: N, 4.74. Found: N, 4.68, 4.72.

Preparation of Cycloheptadecanecarboxylic Acid

Acetate of Cycloheptadecanone Cyanohydrin.—The entire reaction was carried out in the hood.

Excess anhydrous hydrogen cyanide[11] (from 600 mg., 12.2 millimoles, of sodium cyanide) was condensed on top of 700 mg. (2.78 millimoles) of cycloheptadecanone at 0° to give a clear solution. A tiny droplet of piperidine was added as a catalyst[12] and the reaction mixture soon became viscous. The temperature was allowed to rise to room temperature during half an hour and was kept there three hours.

A solution of 1 cc. of acetic anhydride in 2.5 cc. of pyridine was added to the reaction mixture and the solution was heated at 125° for four hours. The reaction mixture was diluted with 20 cc. of water and the insoluble material was extracted into ether. The ether solution was washed successively with 1.5 *N* hydrochloric acid, water, 10% sodium carbonate solution and finally with water. The ethereal solution was dried over anhydrous magnesium sulfate and the ether was distilled. The crude acetate of cycloheptadecanone cyanohydrin, 825 mg. (92% from cycloheptadecanone), was used in the subsequent pyrolysis without purification. It reduced potassium permanganate in acetone solution only slightly and very slowly. In a micro hydrogenation apparatus, it took up only 10% of one mole of hydrogen during five hours.

Pyrolysis of the Acetate of Cycloheptadecanone Cyanohydrin.—The pyrolysis was similar to those carried out by Burns, Jones and Ritchie.[13]

The acetate (500 mg.) was refluxed at atmospheric pressure for ten minutes (Wood's metal bath at 360°). The pyrolyzed product gave a strong unsaturation test with potassium permanganate in acetone solution. It was reduced in a micro hydrogenation apparatus using 50 mg. of platinum oxide as the catalyst and 10 cc. of ethanol as the solvent. About 5% more than the theoretical amount of hydrogen (1 mole) was absorbed in 1.7 hours. The catalyst was removed by filtration and the crude cycloheptadecyl cyanide was isolated, yield 418 mg.

Cycloheptadecanecarboxylic Acid. Hydrolysis of Cycloheptadecyl Cyanide.—A solution of 316 mg. of crude cycloheptadecyl cyanide in 6 cc. of glacial acetic acid and

---

[9] Ruzicka, *Helv. Chim. Acta*, **9**, 239 (1926).

[10] Cope, Hofmann, Wyckoff and Hardenberg, THIS JOURNAL, **63**, 3452 (1941).

[11] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, N. Y., 1941, p. 314.

[12] Stoughton, THIS JOURNAL, **63**, 2376 (1941).

[13] Burns, Jones and Ritchie, *J. Chem. Soc.*, 400, 714 (1935).

1.2 cc. of 48% hydrobromic acid was refluxed seventy hours. A small amount of insoluble oil separated during the hydrolysis. The mixture was diluted with water and the insoluble material was extracted into ether. The ethereal solution was washed thoroughly with water and then was diluted with more ether to about 50 cc. A total of 50 cc. of 3% potassium hydroxide solution was used to extract acidic material. This alkaline solution was washed once with ether and then was acidified to congo red. The acidic material was extracted into ether and the ethereal solution was washed thoroughly with water and was dried over anhydrous magnesium sulfate. The cycloheptadecanecarboxylic acid was isolated, yield 144 mg. (40% of the theoretical amount from cycloheptadecanone).

The unpurified liquid cycloheptadecanecarboxylic acid gave a neutral equivalent of 295; calcd., 282.5.

Cycloheptadecanecarboxamide.—Unpurified cycloheptadecanecarboxylic acid was converted to the acid chloride using an excess of purified thionyl chloride. The crude acid chloride reacted with cold concentrated aqueous ammonia. The brown amide was extracted with a small volume of petroleum ether and then was dissolved in hot 85% ethanol and insoluble tar was separated. The amide was precipitated by the addition of water and was dried. It was dissolved in ethanol and treated with charcoal. The amide, re-isolated, was colorless; yield 48% from the acid; micro m. p. 158–163°. It was recrystallized from ether; yield 25% from the acid; micro m. p. 165–167°.

Anal. Calcd. for $C_{18}H_{35}ON$: N, 4.98; Found, N, 4.78, 4.92.

1-Hydroxycycloheptadecanecarboxamide.—The procedure was essentially the same as that described by Stoughton.[12] The entire reaction was carried out in a hood.

Anhydrous hydrogen cyanide (from 300 mg. of sodium cyanide) was condensed on top of 95 mg. (0.38 millimole) of cycloheptadecanone at 0°. A tiny droplet of piperidine was added and the mixture was kept at 0° for one and a half hours. The mixture was cooled in an ice–salt-bath and 0.4 cc. of 90% sulfuric acid was added. The mushy solid was stirred occasionally at 0° for one and a half hours and then was allowed to stand at room temperature overnight.

Cracked ice was added to the somewhat mushy mixture until the total volume was about 3 cc. The precipitated solid was extracted into ether: a total of 8 cc. of ether was used. The ether solution was washed with water until the washes were neutral to congo red and then the solution was dried over anhydrous magnesium sulfate. The ether was distilled until about 1 cc. remained. Beautiful white needles separated and, after the mixture was kept at 5° for two hours, the crystals were collected, weight 70 mg., micro m. p. 146–147° (cor.). A second crop of 9 mg. of less pure material was obtained by concentrating the mother liquors to 0.3 cc. and cooling again. The second crop was recrystallized and 7 mg. of fine crystals was obtained. The total yield (72 mg.) was 64% from cycloheptadecanone.

For analysis, part of the first crop was recrystallized from ether, micro m. p. 147–147.7° (cor.).

Anal. Calcd. for $C_{18}H_{35}O_2N$: N, 4.71; Found: N, 4.72.

Reaction of Cycloheptadecanone with Sodium Cyanide and Ammonium Carbonate. 5,5-Hexadecamethylenehydantoin.—The procedure was essentially that of Bucherer and Lieb.[14]

A solution of 100 mg. of cycloheptadecanone in 2 cc. of 95% ethanol was mixed with a solution of 50 mg. of sodium cyanide and 200 mg. of ammonium carbonate in 1 cc. of water. The mixture was warmed at 50–55° for twelve hours. The mixture was cooled and then was extracted with a mixture of ether and 60–70° petroleum ether. The ether–petroleum ether layer was washed with water and was dried over anhydrous magnesium sulfate. The ether was distilled and the petroleum ether-insoluble needles, presumably hydantoin, were collected and washed with petroleum ether, yield 46 mg. The petroleum ether-soluble material, presumably unchanged cycloheptadecanone, weighed 64 mg.

For analysis, the hydantoin was recrystallized from absolute ether, micro m. p. 251–252°, dec. (cor.).

Anal. Calcd. for $C_{19}H_{34}O_2N_2$: N, 8.69. Found: N, 8.61, 8.73.

Civetol. Reduction of Civetone with Aluminum Isopropoxide.—The procedure was similar to those described in "Organic Reactions."[15]

A mixture of 1.2 g. (4.8 millimoles) of civetone, 10 cc. of dry isopropanol, and 10 g. of distilled aluminum isopropoxide was placed in a 25-cc. distilling flask and was heated in an oil-bath at 125°. The aluminum isopropoxide dissolved and the opalescent solution was refluxed at such a rate that 1 to 2 cc. of isopropanol distilled per hour. A total of 20 cc. of isopropanol was added during the reaction and about 25 cc. was distilled. The test for acetone in the distillate was negative after about eight hours and heating was discontinued at fifteen hours.

The reaction mixture was added to 20 cc. of 10% sulfuric acid and the civetol was extracted with a total of 50 cc. of ether. The ethereal solution was washed with water until the washes were neutral to congo red. The washes were extracted with a little more ether and this was washed free of acid. The ethereal solution of civetol was dried over anhydrous magnesium sulfate. The ether was distilled, finally *in vacuo* at 60°; 1.22 g. of crude, solid civetol was obtained.

The civetol was recrystallized from 10 cc. of 60–70° petroleum ether by cooling the solution slowly with Dry Ice. A second crop of crystals was obtained by concentrating the mother liquors and cooling again with Dry Ice. The first crop weighed 1.00 g.; m.p. 64–65° with sintering at 62°; the second crop weighed 165 mg.; m. p. 62–65° (Rusicka, *et al.*,[16] reported the melting point of civetol at 65°). The yield of recrystallized civetol was 95% of the theoretical from civetone.

The half-ester of phthalic acid was prepared by heating phthalic anhydride with civetol at 125° for sixteen hours. The product was recrystalized from methanol–water and then from 60–70° petroleum ether; yield 53%, beautiful needles; micro m. p. 117.5–119° (cor.); neut. equiv. cald., 400.5; found, 397.

Cycloheptadecanol. Catalytic Reduction of Civetol.—Civetol was hydrogenated, using ethanol as the solvent and 1% by weight of platinum oxide catalyst. The reduction was complete in two hours at room temperature and atmospheric pressure; only 86% of the theoretical amount of hydrogen was absorbed. The crude cycloheptadecanol was isolated and solidified immediately. The yield was quantitative, m. p. 79–81° (Ruzicka, *et al.*,[16] reported the m. p. as 80°).

Summary

Procedures have been developed for the synthesis of carboxylic acids containing many-membered carbon rings. The acids prepared have the general formulas RCH_2CO_2H and RCO_2H, where R is a seventeen-membered carbon ring.

The synthesis of civetone by Hunsdiecker's procedure has been improved.

ITHACA, N. Y. RECEIVED JUNE 12, 1947

---

(14) Bucherer and Lieb, *J. prakt. Chem.*, **141**, 5 (1934).

(15) Wild's chapter in "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 178.

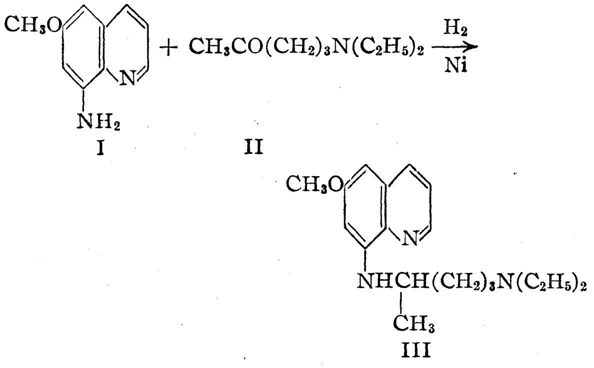
(16) Ruzicka, Schinz and Seidel, *Helv. Chim. Acta*, **10**, 695 (1927).

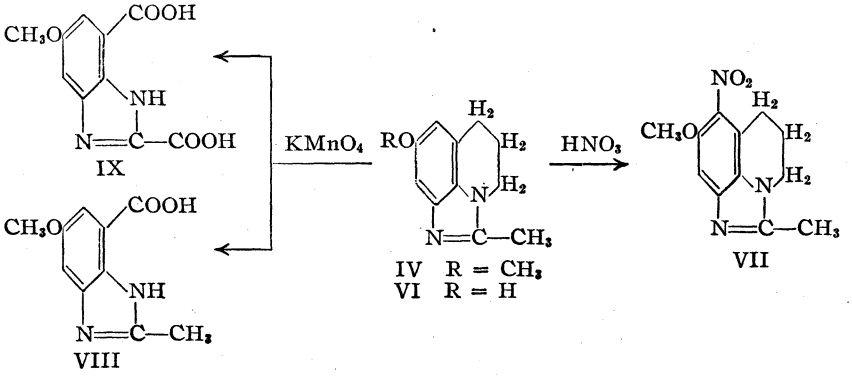
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY AND THE RESEARCH LABORATORIES OF SHARPLES CHEMICALS, INC.]

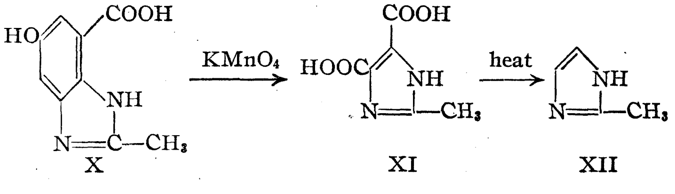
A Study of the Synthesis of Plasmochin by the Reductive Amination Method with Raney Nickel[1]

BY ROBERT C. ELDERFIELD, FRANK J. KREYSA, JAMES H. DUNN AND DAVID D. HUMPHREYS

Commercial Plasmochin (6-methoxy-8-[4-diethylamino-1-methylbutylamino]-quinoline) (III) as commonly manufactured contains significant amounts of an isomeric substance[2] to which the name Isoplasmochin and the tentative structure of 6-methoxy-8-(3-diethylamino-1-ethylpropylamino)-quinoline have been given.[2] The source of this isomer apparently may be found in the relatively large amounts of 1-diethylamino-3-bromopentane with which commercial 1-diethylamino-4-bromopentane, the intermediate for Plasmochin, is contaminated. Pure 1-diethylamino-4-bromopentane, from which pure Plasmochin may be prepared, can be made by the action of thionyl bromide on the corresponding alcohol[2,3] rather than by the action of hydrobromic acid on the alcohol as has been the commercial practice.







The use of the reductive amination reaction involving 6-methoxy-8-aminoquinoline and 1-diethylaminopentanone-4 (I–III) for the synthesis of Plasmochin presents attractive possibilities from the viewpoint of relatively accessible materials, simplicity of operation and potential formation of a product which should be free from isomers. Accordingly the reactions I–III have been the subject of intensive investigation.

Three general methods which are described in detail later were used in carrying out the reaction between I and II; *viz.*, (A) the ketone, II, was pumped into a solution of I at a specified pressure and temperature in the presence of hydrogen and Raney nickel; (b) I and II were refluxed with a substance such as ethylbenzene for azeotropic removal of water eliminated in the formation of the pertinent Schiff base and the latter was then hydrogenated; (c) I and II were heated with stirring in the presence of a dehydrating agent such as magnesium methoxide and the resulting crude product was hydrogenated. Although several variations of the above procedures were investigated, the high boiling products from all runs were roughly similar in composition. On fractionation, the material boiling in the Plasmochin range consisted of a yellow semi-solid which melted at about 104–109° and darkened rapidly on exposure to the air. Investigation of this in a typical case showed the presence of 4–5% of I, 26–29% of III and 50% of a substance which was subsequently shown to be 2-methyl-8-methoxy-5,6-dihydro-4-imidazo-[ij]-quinoline (IV). Material from other runs was of the same general composition.

After IV had been chemically identified, the substance was described by Price and Herbrandson[4] and by Barber and Wragg.[5] Although compounds of the type of IV have been previously reported[4,6] from the reaction of 8-amino-derivatives of 1,2,3,4-tetrahydroquinoline with acetic acid

---

(1) The work described in this paper was done under contracts recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Columbia University and Sharples Chemicals, Inc. A preliminary note on this material has already appeared, THIS JOURNAL, **69**, 186 (1947).

(2) Elderfield, *et al.*, *ibid.*, **68**, 1516 (1946).

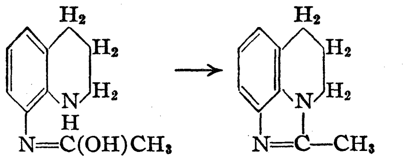
(3) Elderfield, *et al.*, *ibid.*, 1579 (1946).

(4) Price and Herbrandson, *ibid.*, **68**, 910 (1946).

(5) Barber and Wragg, *J. Chem. Soc.*, 610 (1946).

(6) Hazlewood, Hughes and Lions, *Proc. Roy. Soc. N. S. Wales*, **71** 467 (1937–1938).

under mild dehydrating conditions in accordance with XIII–XIV it seemed improbable that such a reaction would occur when a ketone was substituted for acetic acid. In the latter case rupture of a carbon–carbon linkage under relatively mild conditions must occur. Therefore, prior to the appearance of Price and Herbrandson's note,[4] the constitution of IV was established by a study of its chemical reactions.


XIII XIV

The presence of the methoxyl group was shown by its cleavage to the corresponding phenol VI. Attempted oxidation with 35% nitric acid resulted in the formation of a mononitro derivative for which the most likely structure is VII by analogy with the behavior of other quinoline compounds on nitration. Oxidation of IV with potassium permanganate in pyridine resulted in cleavage of the reduced pyridine ring with the formation of 2-methyl-5-methoxybenzimidazole-7-carboxylic acid (VIII) as the major product together with a small amount of 5-methoxybenzimidazole-2,7-dicarboxylic acid (IX). Attempted decarboxylation of the acid, VIII, did not lead to the isolation of any definite compound. However, when 2-methyl-5-hydroxybenzimidazole-7-carboxylic acid (X), obtained from VIII by cleavage of the ether, was oxidized further with potassium permanganate, 2-methylimidazole-4,5-dicarboxylic acid (XI) was obtained. XI, on decarboxylation, gave 2-methylimidazole XII. The identities of XI and XII were established by comparison with known samples synthesized by the methods of Fargher and Pyman[7] and Dedichen,[8] respectively.

On the basis of the above degradation, the structure IV must be assigned to the major product arising from the reductive amination reaction with I and II. This was confirmed by comparison of the substance with a sample prepared by known methods.[4,6]

It is obvious that the elements of N,N-diethylpropylamine must have been eliminated during the course of the formation of the imidazole from I and II. Therefore the solvent removed from the crude hydrogenation reaction mixture was examined. From this it was indeed possible to isolate the above amine which was identified by comparison with a sample synthesized by known methods. Thus, the at first seemingly unlikely formation of the imidazole IV from I and II has been definitely confirmed. A further study of the formation of such imidazoles is reported in the succeeding paper.

Since the empirical formula of the imidazole IV is the same as that of 6-methoxy-8-ethylaminoquinoline (XV) and since formation of the latter was conceivable by a transethylation during the reaction of I and II, we have prepared XV which has not been reported previously. Ethylation of 6-methoxy-8-(*p*-toluenesulfonylamino)-quinoline according to the general method of Gawron and Spoerri[9] for the amination of aminoquinoxalines followed by hydrolysis of the tosyl group readily yielded XV.

Experimental[10,11]

Reaction of 6-Methoxy-8-aminoquinoline with 1-Diethylaminopentanone-4 in the Presence of Nickel and Hydrogen.—Three general methods have been used.

Procedure A.—A 2-gallon hydrogenation autoclave was charged with 800 ml. of methanol, 60 g. of Raney nickel and 348 g. (2 moles) of 6-methoxy-8-aminoquinoline (I). After heating to 130° at 600 lb. hydrogen pressure, 628 g. (4 moles) of 1-diethylaminopentanone-4 (II) was pumped in. A pressure drop of about 150 lb. took place over about two and one-half hours. The reaction mixture, after filtration from the catalyst was distilled up to a temperature of 135° (1 mm.) for removal of excess amino ketone and alcohol derived from it by reduction. An intermediate fraction (about 200 g.) consisting of unreacted 6-methoxy-8-aminoquinoline, and probably some of its tetrahydroderivative, followed. The so-called "Plasmochin fraction[11] (96 g.) was collected at 182–194° (1 mm.). It consisted of a mush of crystalline material in an oil which rapidly discolored on exposure to the air. The residue in the flask was a hard brittle resin and was not investigated further. The 182–194° fraction was redistilled under nitrogen and examined spectrographically in the ultraviolet using a Beckman quartz spectrophotometer. The curves obtained are shown in Figs. 1 and 2 in which it has been necessary to depart from the conventional manner of plotting to secure the information desired.[12]

At 390 mμ neither the pure imidazole, IV, nor 6-methoxy-8-aminoquinoline (I) has an appreciable extinction coefficient. The amount of Plasmochin (III) present calculated by the extinction coefficient at this wave length is 29%. At about 360 mμ, 6-methoxy-8-aminoquinoline and Plasmochin have the same extinction coefficient whereas the imidazole, IV, has a coefficient of O. Calculations at this wave length indicate a total of 34% 8-aminoquinolines, assuming Plasmochin and 6-methoxy-8-aminoquinoline to be the only 8-aminoquinolines present. At 295 mμ the imidazole, IV, has a sharp maximum. By correcting for the absorption of the 8-aminoquinolines at this wave length, calculations show the presence of about 50% of the imidazole on the assumption that no other compound present absorbs at this wave length.

Colorimetric analysis of the crude reaction product substantiated the above results. Direct coupling of the material with diazotized sulfanilic acid indicated a total of 30% 8-aminoquinolines in terms of Plasmochin. Direct diazotization and coupling indicated the presence of about 4% of 6-methoxy-8-aminoquinoline. The difference is about 26% of Plasmochin.

That there is still another substance or substances present in the crude reaction product is indicated by the fact that the absorption curve is falling at 320 to 330 mμ whereas at these wave lengths the pure imidazole, IV, has an extinction coefficient of zero while the curves for the 8-

---

[7] Fargher and Pyman, *J. Chem. Soc.*, **115**, 229 (1919).

[8] Dedichen, *Ber.*, **39**, 1838 (1906).

[9] Gawron and Spoerri, THIS JOURNAL, **67**, 514 (1945).

[10] All melting points are corrected.

[11] The microanalyses reported in this paper were done by Miss Lois May of the Columbia laboratories.

[12] We wish to acknowledge our indebtedness to Dr. Bernard Brodie of the Goldwater Memorial Hospital for carrying out the spectrographic and colorimetric analyses here reported and for permission to incorporate them in this paper.

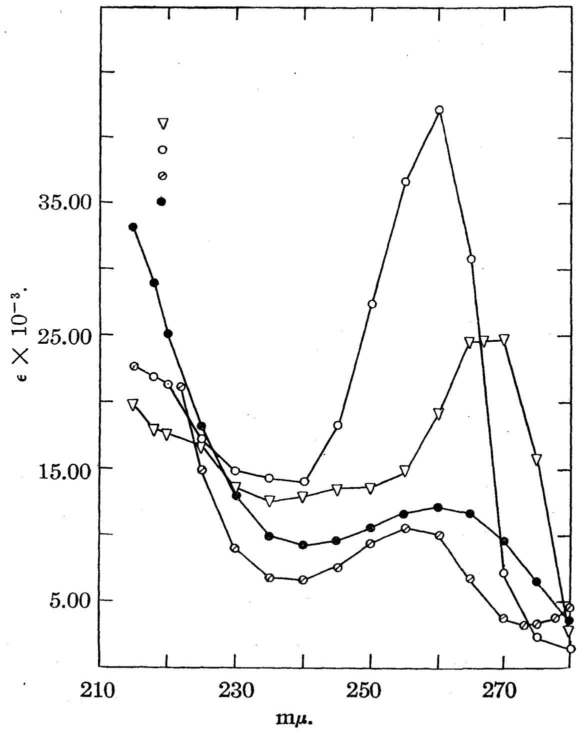


Fig. 1.—Ultraviolet absorption spectra: ▽, Plasmochin; O, 6-methoxy-8-aminoquinoline; ⊘, pure imidazole, IV; ●, twice distilled plasmochin fraction; solvent, heptane; concentration, 10 γ per ml.

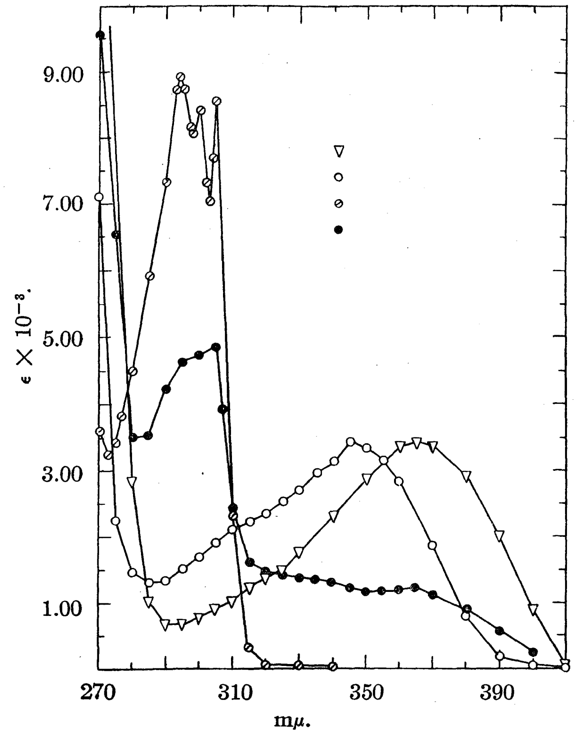


Fig. 2.—Ultraviolet absorption spectra: ▽, Plasmochin; O, 6-methoxy-8-aminoquinoline; ⊘, pure imidazole, IV; ●, twice distilled plasmochin fraction; solvent, heptane; concentration, 100 γ per ml.

aminoquinolines are rising. No attempt was made to isolate other substances which may have been present.

Procedure B.—A 2-gallon autoclave was charged with 348 g. (2 moles) of 6-methoxy-8-aminoquinoline, 60 g. of Raney nickel and a solution of magnesium methylate prepared by dissolving 24 g. of magnesium turnings in 1600 ml. of boiling absolute methanol. At 130° and 780 lb. hydrogen pressure, 628 g. (4 moles) of 1-diethylaminopentanone-4 was pumped in. The temperature was raised to 150° where a pressure drop of 250 lb. was noted. After cooling, water was added to the reaction mixture and the magnesium hydroxide was filtered off with considerable difficulty and some loss of material. Distillation of the product gave a "Plasmochin fraction" of 83 g. which was of the same character as that obtained above.

Procedure C.—The Schiff base (see below) prepared by refluxing 174 g. (1 mole) of 6-methoxy-8-aminoquinoline and 314 g. (2 moles) of 1-diethylaminopentanone-4 with 200 ml. of ethylbenzene for seventy-two hours was reduced at 90–95° and 600 lb. hydrogen pressure with 40 g. of Raney nickel for two and one-half hours. After working up as before 40 g. of a "Plasmochin fraction" having the same characteristics as that described above was obtained.

Several runs by each of the above procedures were made. Temperature limits were from 95 to 180°. In all of the runs the product was essentially the same.

Isolation of N,N-Diethylpropylamine from the Products of the Above Reaction.—The Dry Ice traps in the apparatus in which the crude product from a run similar to that given under Procedure A was distilled contained 30 ml. of liquid. This was fractionated through a small Podbielniak column. The carefully purified material boiled at 111.9–112.2°.

Anal. Calcd. for $C_7H_{17}N$: C, 73.0; H, 14.9; neutral equiv., 115. Found: C, 73.2; H, 15.1; neutral equiv., 115.7.

The amine was definitely identified by mixed melting points of the hydrochloride and methiodide with an authentic sample synthesized as below.

N,N-Diethyl-*n*-propylamine has been described as the chloroplatinate by LeBel[13] but the base has not been described. It was therefore synthesized by the general method described by Caspe[14] for the preparation of the corresponding isopropyl compound.

A mixture of 50 g. of glycerol, 123 g. of *n*-propyl bromide and 95 g. of diethylamine was heated under reflux for sixty hours. The melt was dissolved in 50 ml. of water and the solution was made strongly alkaline with 200 ml. of 50% potassium hydroxide solution, the temperature being kept below 25°. The amine layer was separated and the aqueous layer was repeatedly extracted with ether. The combined amine and ether layers were dried over potassium hydroxide and fractionated yielding 58 g. (50%) of the amine.

Anal. Calcd. for $C_7H_{17}N$: C, 73.0; H, 14.9. Found: C, 73.1; H, 14.7.

N,N-Diethyl-*n*-propylamine hydrochloride formed hygroscopic white needles from ethyl acetate and melted at 205.5–206.5°.

Anal. Calcd. for $C_7H_{17}N \cdot HCl$: C, 55.4; H, 12.0. Found: C, 55.5; H, 12.2.

N,N-Diethyl-*n*-propylamine methiodide formed hygroscopic plates from isopropanol or acetone and melted at 243–244°.

Anal. Calcd. for $C_7H_{17}N \cdot CH_3I$: C, 37.4; H, 7.8. Found: C, 37.6; H, 8.1.

Isolation of 2-methyl-8-methoxy-5,6-dihydro-4-imidazo-[ij]-quinoline, IV, from the "Plasmochin fraction."—The crystalline mush of twice distilled "Plasmochin fraction" obtained by any of the above procedures was washed with cold heptane and the insoluble crystalline material was

---

[13] LeBel, *Compt. rend.*, **125**, 351 (1897).

[14] Caspe, This Journal, **54**, 4457 (1932).

further recrystallized from heptane yielding plates which melted at 119.5–120°.

Anal. Calcd. for $C_{12}H_{14}ON_2$: C, 71.3; H, 7.0; N, 13.9; OCH_3, 15.3. Found: C, 71.2; H, 6.8; N, 14.0; OCH_3, 15.0.

The hydrochloride of the imidazole formed hygroscopic needles from absolute alcohol–carbon tetrachloride (1:1) which melted at 233–233.5°.

Anal. Calcd. for $C_{12}H_{14}ON_2{\cdot}HCl$: C, 60.4; H, 6.3; N, 11.7; Cl, 14.9. Found: C, 60.1; H, 6.2; N, 11.7; Cl, 14.8.

The hydrobromide, from absolute alcohol, was hygroscopic and melted at 242°.

Anal. Calcd. for $C_{12}H_{14}ON{\cdot}HBr$: C, 50.9; H, 5.3; N, 9.9; Br, 28.2. Found: C, 51.0; H, 5.4; N, 9.7; Br, 28.1.

The picrate, from alcohol or dioxane, softened at 243° and decomposed at 248–253°.

Anal. Calcd. for $C_{18}H_{17}O_8N_5$: C, 50.1; H, 4.0. Found: C, 50.2; H, 4.0.

The methiodide, from methanol, darkened at 280° and decomposed at 285–290°.

Anal. Calcd. for $C_{12}H_{14}ON_2{\cdot}CH_3I$: C, 45.4; H, 5.0. Found: C, 45.4; H, 4.9.

The *p*-toluenesulfonic acid salt, from isopropyl ether, alcohol or carbon tetrachloride, melted at 139.5–140.5°.

Anal. Calcd. for $C_{19}H_{22}N_2O_4S$: C, 60.9; H, 5.9; N, 7.5. Found: C, 61.1; H, 5.7; N, 7.4.

The imidazole was identified by mixed melting points of the base and the above derivatives with samples prepared according to the known method of Hazlewood, Hughes and Lions.[6]

Perbromide of the Imidazole, IV.—To a solution of 0.2 g. of the imidazole in 10 ml. of carbon tetrachloride, 5 ml. of a 5% solution of bromine in carbon tetrachloride was added dropwise. Orange crystals separated but no evolution of hydrogen bromide occurred. After recrystallization from methanol, the substance darkened at 265° and decomposed about 285°.

Anal. Calcd. for $C_{12}H_{14}Br_2ON_2$: C, 39.8; H, 3.9. Found: C, 39.8; H, 3.8.

2-Methyl-7(?)-nitro-8-methoxy-5,6-dihydro-4-imidazo[ij]quinoline.—The imidazole, IV, was unattacked when oxidation with 35% nitric acid was attempted. Rather a mononitro derivative was formed during the working up of the reaction mixture.

A solution of 1 g. of the imidazole in 10 ml. of 35% nitric acid was boiled under reflux for five hours. The mixture was transferred to an evaporating dish and 10 ml. of 70% nitric acid was added. It was then evaporated to dryness on the steam-bath after which 10 ml. of water was added and the evaporation was repeated. After triturating with 5 ml. of ice water the crystalline nitro compound was collected and recrystallized from ethyl acetate or alcohol. The substance is soluble in aqueous acid (*p*H 3) and is reprecipitated at *p*H 10. It melted at 238–240° (dec.). Assignment of the nitro group to the 7-position is preferred although the 9-position cannot be excluded.

Anal. Calcd. for $C_{12}H_{13}O_3N_3$: C, 58.3; H, 5.3. Found: C, 58.3; H, 5.2.

2-Methyl-8-hydroxy-5,6-dihydro-4-imidazo[ij]-quinoline.—A solution of 5 g. of the imidazole, IV, in 75 ml. of 48% hydrobromic acid was refluxed for ten hours. On refrigeration a crystalline precipitate separated. This was dissolved in 75 ml. of warm water (*p*H 4) and the solution was adjusted to *p*H 10 with sodium hydroxide during which the hydroxy compound first precipitated and then dissolved. The filtered alkaline solution was saturated with carbon dioxide and the precipitate was recrystallized from isopropanol. It darkened at 285° and decomposed at 295–305° (copper block).

Anal. Calcd. for $C_{11}H_{12}ON_2$: C, 70.2; H, 6.4. Found: C, 70.2; H, 6.4.

Oxidation of the Imidazole, IV, with Potassium Permanganate.—To a boiling well-stirred solution of 6 g. of the imidazole, IV, in 900 ml. of 33% aqueous pyridine was added 1200 ml. of 3% aqueous potassium permanganate solution over two hours. The mixture was boiled and stirred for an additional hour. After cooling, the manganese dioxide was filtered and extracted by boiling it with 500 ml. of 10% aqueous pyridine for half an hour. The combined filtrates from the manganese dioxide were evaporated to dryness on the steam-bath. The residue was dissolved in 200 ml. of warm water (*p*H 10) and the *p*H of the filtered solution was adjusted to 5–6 with hydrochloric acid. After refrigerating, the precipitate was collected and recrystallized from dioxane, water or alcohol. The yield was 70%. On air drying 2-methyl-5-methoxybenzimidazole-7-carboxylic acid was thus obtained as the dihydrate which darkened at 295° and decomposed at 300–305°.

Anal. Calcd. for $C_{10}H_{10}O_3N_2{\cdot}2H_2O$: C, 49.6; H, 5.8; N, 11.6. Found: C, 49.8; H, 5.7; N, 11.6.

On drying at 175° and 15 mm. over calcium chloride for one hour the substance lost 14.72% of water; calcd. 14.87%. The anhydrous acid decomposed at 295–305°.

Anal. Calcd. for $C_{10}H_{10}O_3N_2$: C, 58.3; H, 4.9; N, 13.6. Found: C, 58.5; H, 4.7; N, 13.6.

The aqueous filtrate from the above acid at *p*H 5–6 was acidified to *p*H 2 with hydrochloric acid. After refrigerating, the precipitate was purified by acidification of its hot filtered solution in 10% sodium hydroxide with hydrochloric acid and finally by recrystallization from glacial acetic acid. The yield of 5-methoxybenzimidazole-2,7-dicarboxylic acid monohydrate which darkened about 270° and decomposed at 290–295° was 0.1 g. The air-dried acid, for which analytical figures are given, lost 7.1% of water on drying at 175° and 15 mm. over calcium chloride; calcd. 7.1%.

Anal. Calcd. for $C_{10}H_8O_5N_2{\cdot}H_2O$: C, 47.3; H, 4.0; N, 11.0. Found: C, 47.3; H, 4.0; N, 11.3.

2-Methyl-5-hydroxybenzimidazole-7-carboxylic Acid.—A solution of 5 g. of the methoxy acid, VIII, in 50 ml. of 48% hydrobromic acid was refluxed for forty-five minutes at which time bumping caused by separated crystalline material necessitated stopping the reaction. After cooling, the hydroxy acid was filtered off and dissolved in 50 ml. of warm water (*p*H 2). The *p*H was adjusted to 5 with sodium hydroxide at which point the acid, X, precipitated. It was recrystallized from 900 ml. of boiling water yielding 3 g. of white needles which slowly decomposed without melting at 300–350° (copper block).

Anal. Calcd. for $C_9H_8O_3N_2$: C, 56.3; H, 4.2; N, 14.6. Found: C, 56.2; H, 4.0; N, 14.7.

Oxidation of the Acid, X, to 2-Methylimidazole-4,5-dicarboxylic Acid, XI.—To a stirred suspension of 1 g. of the acid, X, in 200 ml. of water cooled to 5° was added 80 ml. of 4% potassium permanganate solution during the course of one hour. Oxidation was prompt and the temperature was kept below 10° by external cooling. The mixture was then refrigerated for twelve hours and any unreacted permanganate was destroyed with methanol. The filtrate from the manganese dioxide was acidified to *p*H 2–3 with hydrochloric acid and then evaporated to dryness. The residue was dissolved in 40 ml. of 7% ammonium hydroxide solution, and the solution was treated with 0.1 g. of decolorizing carbon (Norit A) in the cold, filtered and evaporated to dryness. If too much Norit is used or if the solution is boiled at this point the ammonium salt of the acid is completely absorbed on the Norit. The solution of the residue in 10 ml. of warm water was acidified to *p*H 2–3 and the crystalline precipitate was collected and recrystallized several times from a small amount of water. The fine white needles decomposed at 275–285°. After drying at atmospheric pressure over calcium chloride, the acid still retained a molecule of water.

Anal. Calcd. for $C_6H_6N_2O_4{\cdot}H_2O$: C, 38.3; H, 4.3. Found: C, 38.3; H, 4.0.

A sample of 2-methylimidazole-4,5-dicarboxylic acid monohydrate prepared according to Fargher and Pyman[7] by condensation of tartaric acid dinitrate with acetaldehyde, and recrystallized in the same manner decomposed at 275–285°.

The acid was decarboxylated by heating it over a small free flame according to Dedichen[8] and the resulting 2-methylimidazole was recrystallized from benzene. The latter compound prepared from the acid from both sources melted at 134–136° and the mixed melting point was not depressed. Dedichen[8] reports the m. p. of 2-methylimidazole as 139°.

6-Methoxy-8-(4-diethylamino-1-methylbutylideneamino)-quinoline.—The Schiff base was used by Barber and Wragg in the preparation of tetrahydropamaquine but neither the method of synthesis nor physical constants of the compound are given by the British workers. A mixture of 157 g. (1 mole) of 1-diethylaminopentanone-4, 87 g. (0.5 mole) of 6-methoxy-8-aminoquinoline and 150 ml. of ethylbenzene was refluxed for one hundred hours in an apparatus equipped with a liquid separator from which the condensed reflux of ethylbenzene was returned to the reaction flask after passing through anhydrous potassium carbonate for removal of water. The bulk of the solvent was distilled off at atmospheric pressure in an atmosphere of nitrogen and 80 g. of the amino-ketone was then removed at water pump vacuum followed by 45 g. of unreacted 6-methoxy-8-aminoquinoline boiling at 175–185° (4 mm.). The crude Schiff base (85 g.) then distilled at 230–240° (4 mm.). Redistillation yielded 55 g. (35%) of orange oil boiling at 184–186° (0.4 mm.).

Anal. Calcd. for $C_{19}H_{27}ON_3$: C, 72.8; H, 8.7. Found: C, 72.8; H, 8.5.

6-Methoxy-8-(*p*-toluenesulfonylamido)-quinoline.—A mixture of 17.5 g. of 6-methoxy-8-aminoquinoline, 19 g. of *p*-toluenesulfonyl chloride and 100 ml. of 10% sodium hydroxide was shaken at room temperature until the acid chloride was all gone. The sulfonamide was recrystallized from isopropanol and melted at 133.5°.

Anal. Calcd. for $C_{17}H_{16}O_3N_2S$: C, 62.2; H, 4.9. Found: C, 62.0; H, 4.8.

6-Methoxy-8-(*p*-toluenesulfonylethylamido)-quinoline. To a stirred solution of 32.8 g. of the above tosyl compound in 350 ml. of absolute alcohol at 75–80° in a flask protected from atmospheric moisture was added a solution of 6.7 g. of potassium hydroxide in 150 ml. of absolute alcohol. After stirring the mixture for thirty minutes at 70–80° and then cooling, the crystalline potassium salt (90%) was filtered off and washed with absolute alcohol.

A stirred mixture of 18.3 g. of the above potassium salt, 8.3 g. of ethyl bromide (no reaction occurred when ethyl iodide was used) and 250 ml. of absolute alcohol was heated under reflux for twenty-four hours. After cooling the filtrate from the potassium bromide was evaporated to dryness. To the residue was added 250 ml. of 5% potassium hydroxide solution and this mixture was extracted with ether. After washing and drying the extract, evaporation of the ether left a yellow residue which was recrystallized from isopropanol or acetone. The substance melted at 125–126°.

Anal. Calcd. for $C_{19}H_{20}O_3NS$: C, 64.0; H, 5.7. Found: C, 64.0; H, 5.6.

6-Methoxy-8-ethylaminoquinoline.—A mixture of 1 g. of the above compound and 3 ml. of 96% sulfuric acid was heated with occasional stirring at 100° for ten minutes. After cooling and standing at room temperature for three hours, 20 ml. of 40% sodium hydroxide solution was added very cautiously. The mixture was extracted with benzene, yielding a yellow oil which gradually solidified. After recrystallization from *n*-heptane, the ethylaminoquinoline melted at 38–40°.

Anal. Calcd. for $C_{12}H_{14}ON_2$: C, 71.3; H, 7.0. Found: C, 71.0; H, 6.9.

Summary

1. Reductive amination of 1-diethylaminopentanone-4 with 6-methoxy-8-aminoquinoline with Raney nickel under various conditions leads to a mixture consisting of Plasmochin and 2-methyl-8-methoxy-5,6-dihydro-4-imidazo[ij]quinoline as principal components.
2. A study of the oxidative degradation of 2-methyl-8-methoxy-5,6-dihydro-4-imidazo[ij]quinoline has been made.
3. N,N-Diethylpropylamine and 6-methoxy-8-ethylaminoquinoline have been prepared.

NEW YORK 27, N. Y.
WYANDOTTE, MICH.

RECEIVED MARCH 21, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

The Reaction of *o*-Phenylenediamine and of 8-Amino-1,2,3,4-tetrahydroquinoline Derivatives with Carbonyl Compounds

BY ROBERT C. ELDERFIELD AND FRANK J. KREYSA

In the preceding paper[1] a study of the reductive amination of 1-diethylamino-pentanone-4 with 6-methoxy-8-aminoquinoline has been described. The major product of the reaction was 2-methyl-8-methoxy-5,6-dihydro-4-imidazo[ij]quinoline (I) and N,N-diethyl-*n*-propylamine was isolated from the products of the reaction. Since the formation of I obviously involves cleavage of a carbon–carbon bond under relatively mild conditions the reaction conditions under which imidazoles of the general type of I are formed from ketones have been the subject of further investigation.

As pointed out by Hazlewood, Hughes and Lions[2] 8-amino-1,2,3,4-tetrahydroquinoline (II) can be regarded as a mono-N-alkyl-*o*-phenylenediamine and the same authors prepared imidazoles of the type of I by the action of acids on II under mild dehydrating conditions. Formation of the imidazole ring in this fashion is easily understood and obviously proceeds by intramolecular elimination of water from an enolic form of an N-acyl derivative of II (III) in accordance with the observations of Phillips[3] on the behavior of *o*-phenylenediamine itself under similar conditions. Whether the acyl derivatives of II involve the ring nitrogen or that of the primary amino group is irrelevant and cannot be stated with certainty at this time. As far as we are aware only three cases of the formation of a 2-substituted benzimidazole

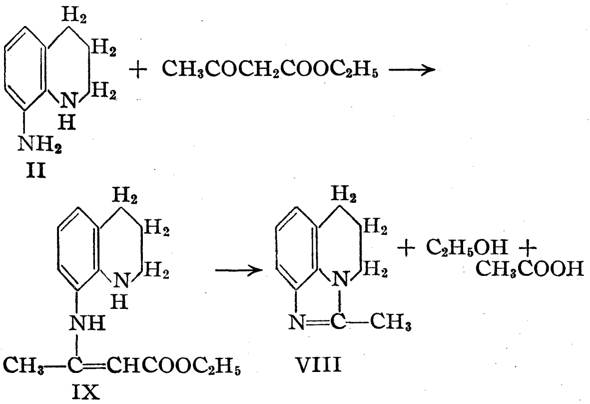
---

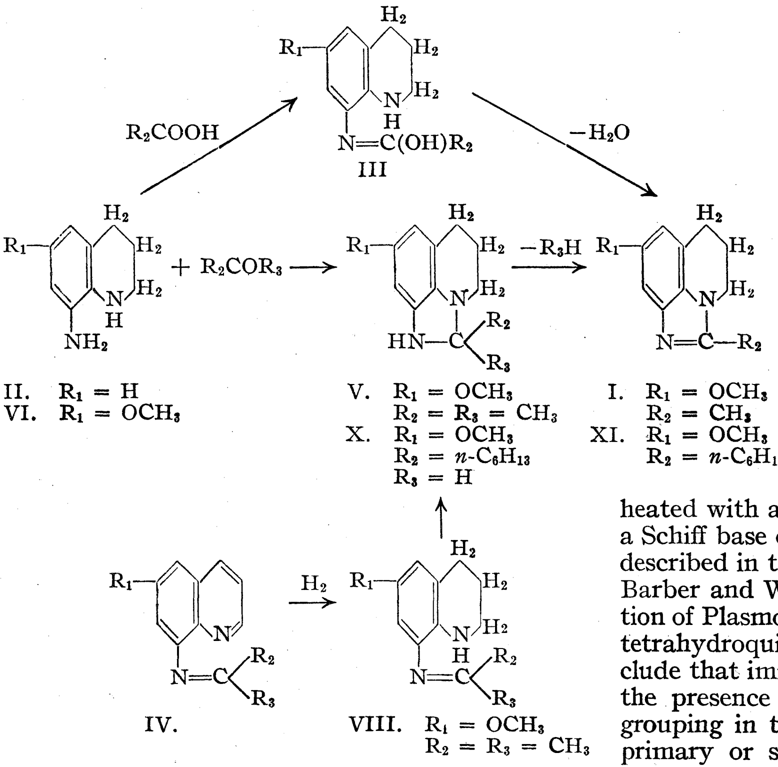
(1) Elderfield, *et al.*, THIS JOURNAL, **70**, 40 (1948).

(2) Hazlewood, Hughes and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 467 (1937–1938).

(3) Phillips, *J. Chem. Soc.*, **173**, 2395 (1928); see also McCoy and Day, THIS JOURNAL, **65**, 2159 (1943).

from the action of a ketone on *o*-phenylenediamine or its derivatives have been reported.[4] Hazlewood, Hughes and Lions[2] describe the formation of the imidazole, VIII, from II and ethyl acetoacetate and suggest the following sequence of reactions for the observed facts.





The formation of IX took place when a mixture of II and ethyl acetoacetate was allowed to stand at room temperature in the presence of a trace of hydrochloric acid and the crotonic ester, IX, on dropping into hot paraffin lost the elements of ethyl acetate to yield VIII. A similar reaction has been noted by Baxter and Spring,[5] who obtained 2-methylbenzimidazole instead of the expected 2-methyl-3-carbethoxyquinoxaline by merely warming *o*-phenylenediamine with ethyl α-chloroacetoacetate in alcoholic solution. Finally, Weil and Marcinkowska[6] describe the formation of 2-phenylbenzimidazole by heating *o*-phenylenediamine with dibenzoylphenylmethane in the presence of hydrochloric acid. Desoxybenzoin must have been eliminated at some stage of this reaction, although its isolation was not reported.

TABLE I

PRODUCTS FROM THE REACTION OF *o*-PHENYLENEDIAMINES WITH CARBONYL COMPOUNDS

Diamine	Carbonyl compd.	R_2 in the 2-position of the resulting imidazole
6-Methoxy-8-amino-tetrahydroquinoline	$CH_3CO(CH_2)_3N(C_2H_5)_2$	CH_3
	$CH_3COCH_2C_6H_5$	CH_3
	$CH_3CO(CH_2)_5CH_3$	CH_3
	$OCCH_2CH_2CH_2CH_2$	$CH_2CH_2CH_2CH_3$
	CH_3COCH_3	CH_3
	$n\text{-}C_6H_{13}CHO$	$n\text{-}C_6H_{13}$
o-Phenylenediamine	$CH_3COCH_2C_6H_5$	CH_3 and $CH_2C_6H_5$
	$CH_3CO(CH_2)_3N(C_2H_5)_2$	Product not isolated

Accordingly the action of representative simple ketones on 6-methoxy-8-amino-1,2,3,4-tetrahydroquinoline and on *o*-phenylenediamine has been investigated. The results are summarized in Table I. We suggest the sequence of reactions shown in formulas VI to I or IV to I as a tentative explanation for the observed results. Imidazole formation occurs when an 8-amino-1,2,3,4-tetrahydroquinoline is heated with a ketone (formulas VI to I), or where a Schiff base of an 8-aminoquinoline is reduced as described in the preceding paper (IV to I). Since Barber and Wragg[7] have shown that hydrogenation of Plasmochin yields an 8-alkylamino-1,2,3,4-tetrahydroquinoline and not an imidazole, we conclude that imidazole formation is contingent upon the presence in the molecule of an azomethine grouping in the proper spatial relationship to a primary or secondary amino group. This conclusion implies that on reduction of IV, the pyridine ring is saturated before any substantial reduction of the azomethine grouping has occurred.

Both reaction paths involve an intermediate for which we propose an imidazoline structure of the type of V. Barber and Wragg[7] have assigned structure V to the product arising from condensation of VI with acetone, and we have now shown that this condensation product does indeed give I

---

(4) An excellent review of the modes of formation of 2-substituted benzimidazoles is given by Wiedenhagen, *Ber.*, **69**, 2263 (1936).

(5) Baxter and Spring, *J. Chem. Soc.*, 229 (1945).

(6) Weil and Marcinkowska, *Roczniki Chem.*, **14**, 1312 (1934); *C. A.*, **29**, 6233 (1935).

(7) Barber and Wragg, *J. Chem. Soc.*, 610 (1946).

in good yield on heating at 250–300° for six hours. Structure V for the condensation product is confirmed by the close similarity of its ultraviolet absorption spectrum to that of VI. If the condensation product possessed the Schiff base structure, VII, the azomethine double bond in conjugation with the benzene ring should have caused a more profound change in absorption characteristics. Furthermore, the instability of the condensation product—alcoholic picric acid cleaves it to the picrate of VI–argues against the Schiff base structure.

The ready conversion of the imidazoline into the imidazole type is noteworthy. We assume that the gain in resonance stabilization[8] accompanying this aromatization provides the driving force for the direct elimination of the alkyl group and a hydrogen atom from the molecule. It is of interest that the benzothiazolines resulting from the reaction of *o*-aminothiophenol and aldehydes or ketones, are relatively stable.[9] The principle of molecular symmetry suggests that the benzothiazoles conceivably can possess a lower level of resonance stabilization than the imidazoles, which would account for the greater reported stability of the thiazolines.

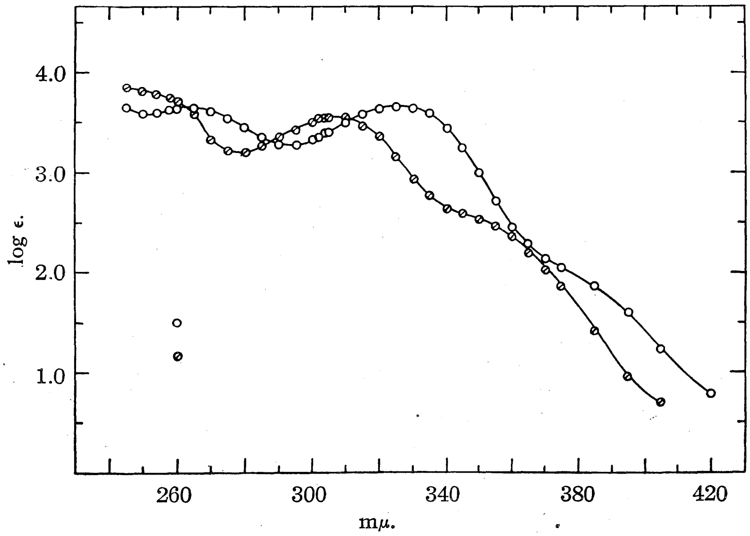


Fig. 1.—Ultraviolet absorption spectra: ○, 6-methoxy-8-amino-1,2,3,4-tetrahydroquinoline; ⊖, the imidazoline, V; solvent, cyclohexane.

The factor determining which of the two substituents in structure V is eliminated, in the formation of the benzimidazole ring, appears to be connected with the degree of substitution on one of the nitrogens of the *o*-phenylenediamine derivative entering into the reaction. Thus in all cases examined in which an N-alkyl-*o*-phenylenediamine, typified by a tetrahydroquinoline derivative (VI), was one of the reactants, the other being a methyl ketone, the only imidazole emerging was the 2-methyl derivative, I, although the results obtained with acetophenone were obscure in the sense that a poor yield of I was obtained. On the other hand, in the reaction of *o*-phenylenediamine with methyl benzyl ketone and, presumably, with 1-diethylaminopentanone-4, elimination of the methyl group of the ketone occurred to a major extent. While it would be attractive to generalize on this point, no such generalization can be more than suggested at this time pending the outcome of further experiments currently in progress in these laboratories.

We have also investigated the reaction of a typical aliphatic aldehyde, *n*-heptaldehyde, on 6-methoxy-8-amino-1,2,3,4-tetrahydroquinoline (VI) and find that hydrogen is eliminated from the proposed intermediate, X, as readily as is a hydrocarbon residue when a ketone is employed with the formation of XI. The use of aldehydes in the synthesis of benzimidazoles from *o*-phenylenediamine has been recorded in the literature. Hinsberg and Koller[10] and Weil and Marcinkowska[6] obtained 2-phenylbenzimidazole from the action of benzaldehyde on *o*-phenylenediamine. As far as we are aware the only instance whereby a 2-substituted imidazole carrying an alkyl substituent has been obtained by this general method using an aliphatic aldehyde as one reactant is that reported by Weidenhagen.[4] In this case cupric salts were added to the reaction mixture which raises the possibility that the aldehyde used might be oxidized to the corresponding acid prior to condensation with *o*-phenylenediamine. Production of imidazoles from acids is a well known reaction. In the present work, such oxidation of the aldehyde to the acid was avoided by working in an atmosphere of nitrogen, a fact which would appear to establish beyond doubt that the imidazole results from the intermediate imidazoline by direct expulsion of hydrogen.

Experimental[11,12]

6-Methoxy-8-amino-1,2,3,4-tetrahydroquinoline.—The preparation of this compound has been described by Price and Herbrandson[13] by the reduction of 6-methoxy-8-aminoquinoline with stannous chloride (62%) or catalytically with copper chromium oxide (78%) and by Barber and Wragg[7] by reduction of the corresponding quinoline derivative catalytically with Raney nickel in dioxane (80%). None of the above workers report a yield or analysis of the free amine, but rather converted it directly into a suitable salt, on which the yield was based, because of the instability of the free amine. In the present work,

---

[8] Hückel, Datow and Simmersbach, *Z. physik. Chem.*, **A186**, 129 (1940); Jensen and Friediger, *Kgl. Danske Videnskab, Selskab, Math.-fys. Medd.*, **20**, No. 20, 1 (1943) [*C. A.*, **39**, 2068 (1945)].

[9] Lankelma and Sharnoff, This Journal, **53**, 2654 (1931); **54**, 379 (1932).

[10] Hinsberg and Koller, *Ber*,. **29**, 1498 (1896).

[11] All melting points are corrected.

[12] The microanalyses reported were done by Miss Lois May of these laboratories.

[13] Price and Herbrandson, This Journal, **68**, 910 (1946).

we have avoided catalytic reduction with nickel in dioxane, because of the inherent danger involved, and have used the sodium and alcohol method first used in the reduction of 8-aminoquinoline by Hazlewood, Hughes and Lions.[2]

To a refluxing solution of 30 g. of 6-methoxy-8-aminoquinoline (m. p. 48.5–49.5°) in 750 ml. of absolute alcohol (distilled from sodium and diethyl phthalate) protected with a calcium chloride tube was added, with stirring, 60 g. of sodium during the course of ninety minutes. Refluxing and stirring was continued for an additional ninety minutes. The flask was then equipped with a condenser set downward and about 250 ml. of alcohol was distilled off. To the contents of the flask 400 ml. of cold water was added and the alkaline solution was extracted with four 100-ml. portions of benzene. The combined extracts were dried with anhydrous potassium carbonate and concentrated in an atmosphere of nitrogen to about 200 ml. The resulting solution was washed with three 20-ml. portions of water and dried with potassium carbonate. After removal of the solvent, the dark, viscous red oil was distilled in an atmosphere of nitrogen at 0.65 mm. pressure. The main fraction, boiling at 148–150°, amounted to 28 g. (90%), of pure 6-methoxy-8-amino-1,2,3,4-tetrahydroquinoline and slowly crystallized as plates which melted at 44–45°. Barber and Wragg[7] give the melting point as 43–45°.

Reaction of 6-Methoxy-8-amino-1,2,3,4-tetrahydroquinoline (VI) with 1-Diethylaminopentanone-4.—A mixture of 18 g. of freshly distilled VI and 31 g. of 1-diethylaminopentanone-4 was heated in a flask equipped with an inside thermometer and a condenser set downward for distillation through the contents of which a stream of dry nitrogen furnished agitation. At an inside temperature of 200° a colorless distillate appeared. The inside temperature was slowly raised during six hours to 265° at which point the heating was interrupted.

The distillate (15–20 g.) was redistilled in an atmosphere of nitrogen. The fraction boiling at 105–115° (5–6 g.) was collected, followed by a second fraction boiling at about 200° which consisted of unreacted 4-diethylamino-1-methylbutylamine. The lower boiling fractions, which separated into two layers, were taken up in 75 ml. of ether and dried over anhydrous potassium carbonate. After removal of the solvent, the main fraction was distilled twice, with drying over potassium hydroxide after the first distillation, yielding 4 g. of material boiling at 111–112°.

Anal. Calcd. for $C_7H_{17}N$: C, 73.0; H, 14.9. Found: C, 73.2; H, 15.1.

The amine was identified as N,N-diethyl-*n*-propylamine by mixed melting points of its hydrochloride and methiodide with authentic samples.[1]

The residue in the original reaction flask solidified on cooling. It was triturated with 50 ml. of cold ether and the insoluble portion was recrystallized from heptane. The product was identified as 2-methyl-8-methoxy-5,6-dihydro-4-imidazo[ij]quinoline by mixed melting point with an authentic sample.[1]

Reaction of 6-Methoxy-8-amino-1,2,3,4-tetrahydroquinoline with Octanone-2.—A mixture of 5 g. of the tetrahydroquinoline and 5 g. of octanone-2 (b. p. 173–174°) was heated in an atmosphere of nitrogen for three hours at 150–250°. The distillate was discarded and the residue in the reaction flask was distilled *in vacuo* under nitrogen, the fraction boiling at 170–175° (0.6 mm.) being collected. This crystallized in the receiver and was identified as the imidazole, I, as in the preceding cases.

Reaction of 6-Methoxy-8-amino-1,2,3,4-tetrahydroquinoline with Methyl Benzyl Ketone.—A mixture of 18 g. of the tetrahydroquinoline and 27 g. of methyl benzyl ketone [b. p. 75° (3 mm.)] was heated in a flask equipped with a thermometer and a condenser set downward in an atmosphere of nitrogen from 150 to 250° during six hours. At 150° water separated in the reaction mixture and the color changed from dark red to a light orange red. During the course of the reaction about 10 ml. of distillate was collected. This was taken up in 20 ml. of ether, dried over anhydrous magnesium sulfate and again distilled. The fraction boiling at 110–111° (3 g.) was identified as toluene by oxidation to benzoic acid with potassium permanganate.[14]

The orange-red residue in the reaction flask was seeded with a crystal of the imidazole, I, and after refrigeration it crystallized for the most part. The crystalline material was isolated and identified as the imidazole, I, as previously described.

Thermal Decomposition of 2,2-Dimethyl-8-methoxy-1,2,5,6-tetrahydro-4-imidazo[ij]quinoline.—This compound was prepared according to Barber and Wragg,[7] whose results were duplicated. Although the substance melts at approximately the same temperature as the imidazole, I, it differs from the imidazole in its easy decomposition to 6-methoxy-8-amino-1,2,3,4-tetrahydroquinoline when warmed with an alcoholic solution of picric acid. The mixed melting point of the two substances is likewise depressed. The British authors report the m. p. of the picrate of the latter substance as 163–164°, whereas Price and Herbrandson[13] give 151.5–152°. This discrepancy has now been found to be due to the rate of heating. On rapid heating of the capillary, the m. p. of 163–164° is observed, whereas on slow heating (several minutes per degree) the decomposition point of 150–152° is observed.

When the acetone condensation product of the tetrahydroquinoline was heated at 250–300° for six hours in a stream of nitrogen, the residue, on distillation at 0.6 mm. yielded 78% of the imidazole, I, which was identified as in the preceding cases.

Reaction of 6-Methoxy-8-amino-1,2,3,4-tetrahydroquinoline with Cyclopentanone.—A mixture of 9 g. of the tetrahydroquinoline and 8.5 g. of cyclopentanone (b. p. 129–130°) was heated under nitrogen in a sealed tube for twenty-four hours at 265°. The black mixture was distilled *in vacuo* under nitrogen and a main fraction of 4 g. boiling at 210–220° (1.5 mm.) was collected. To the solution of this in hot absolute alcohol, 250 ml. of an alcoholic solution of picric acid was added. The yellow needles were recrystallized from alcohol and melted at 171.5–173°.

The picrate was then decomposed with warm potassium hydroxide solution and the liberated imidazole was extracted with ether and benzene. The free imidazole obtained on evaporation of the combined extracts was recrystallized first from ether and then from pentane and formed needles which melted at 60–61°.

Both the 2-*n*-butyl-8-methoxy-5,6-dihydro-4-imidazo-[ij]quinoline and its picrate obtained above were identified by mixed melting points with samples of the same substance prepared according to the general method of Hazlewood, Hughes and Lions[2] as follows.

A mixture of 1 g. of 6-methoxy-8-amino-1,2,3,4-tetrahydroquinoline and 5 ml. of *n*-valeric acid was refluxed in an atmosphere of nitrogen for two hours, after which 25 ml. of water and 25 ml. of ammonium hydroxide (d. 0.9) was added to the red mixture. The ammoniacal mixture was extracted with benzene. The crude imidazole from the extracts was purified by sublimation at 150–175° (0.3 mm.) and then was recrystallized twice from pentane. It melted at 60–61°.

Anal. Calcd. for $C_{15}H_{20}ON_2$: C, 73.7; H, 8.2. Found: C, 73.5; H, 8.0.

The picrate melted at 172–173° after crystallization from absolute alcohol.

Anal. Calcd. for $C_{21}H_{23}O_8N_5$: C, 53.3; H, 4.9. Found: C, 53.4; H, 4.8.

Reaction of 6-Methoxy-8-amino-1,2,3,4-tetrahydroquinoline with Acetophenone.—A mixture of 10 g. of 6-methoxy-8-amino-1,2,3,4-tetrahydroquinoline and 24 g. of acetophenone was heated in a distilling flask in an atmosphere of nitrogen for seven hours during which the temperature was raised from 150 to 265°. From the distillate from this reaction no benzene could be isolated. The reaction mixture was fractionally distilled under re-

---

(14) Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 164.

duced pressure in an atmosphere of nitrogen. Unreacted acetophenone came over at 60–70° (3 mm.) followed by a fraction, a heavy red oil, (4 g.) boiling at 210–225° (1.5–2 mm.). A third fraction (4 g.) boiling at 225–250° (1.5–2 mm.) was a heavy red tar. The second fraction was dissolved in alcohol and treated with a saturated alcoholic solution of picric acid. The red picrate was recrystallized from boiling dioxane, washed with benzene and decomposed with 50% potassium hydroxide solution. The alkaline solution was extracted with benzene and the extract, after drying yielded a semi-solid which was sublimed at 185–235° (0.2 mm.). The sublimate was recrystallized from heptane and again converted to the picrate (0.1 g.). The picrate melted at 248–253° and did not depress the melting point of a known sample of the picrate of the imidazole, I.

Condensation of *n*-Heptaldehyde with 6-Methoxy-8-amino-1,2,3,4-tetrahydroquinoline.—A mixture of 18 g. of 6-methoxy-8-amino-1,2,3,4-tetrahydroquinoline and 23 g. of pure *n*-heptaldehyde was heated in an atmosphere of nitrogen at 150–250° for eight hours. The residue was distilled under reduced pressure, a main fraction (22 g.) boiling at 180–220° (0.3 mm.) being collected. After redistillation, the fraction boiling at 190–210° (0.35 mm.) (19 g.) consisting of a viscous yellow oil was treated with a saturated absolute alcoholic solution of an equal weight of picric acid. The yellow needles of the imidazole picrate were recrystallized from alcohol yielding 20 g. of material melting at 127°.

Anal. Calcd. for $C_{23}H_{27}O_8N_5$: C, 55.1; H, 5.4. Found: C, 55.1; H, 5.4.

The picrate was decomposed with 50% potassium hydroxide as before and the *n*-hexylimidazole derivative crystallized on refrigerating. It melted at 27°. The free base was very hygroscopic which prevented securing satisfactory analytical data. Both the above imidazole and its picrate were identified by mixed melting point with an authentic sample prepared from I and oenanthic acid.

Reaction of *o*-Phenylenediamine with Methylbenzyl Ketone.—A mixture of 10.8 g. of *o*-phenylenediamine and 27 g. of methyl benzyl ketone was heated in an atmosphere of nitrogen in a distilling flask at 200–250°. The distillate was dried over anhydrous magnesium sulfate and redistilled yielding a fraction (1.5 g.) boiling at 110–111° which was identified as toluene by oxidation to benzoic acid. The residue in the distilling flask was poured out while still molten and, after cooling, was rubbed up under ether. The ether insoluble portion was repeatedly recrystallized from 60% methanol–water yielding 8 g. of 2 benzylbenzimidazole melting at 186.5–187.5°. The picrate melted at 214–215° (dec.). Both substances were identified by mixed melting point with an authentic sample synthesized for the purpose. 2-Benzylbenzimidazole is reported as melting at 187° and its picrate at 214°.[15]

From the combined mother liquors of the above 2-benzylbenzimidazole about 1 g. of 2-methylbenzimidazole was obtained by taking advantage of the ready solubility of the latter as compared to the benzyl derivative in hot water. The methyl derivative melted at 175–176° after final recrystallization from benzene and was identified by mixed melting point with an authentic sample. It is reported as melting at 176° by Phillips[3] among other workers.

Reaction of *o*-Phenylenediamine with 1-Diethylaminopentanone-4.—When the reaction was carried out as in the preceding case, no 2-methylbenzimidazole could be isolated from the reaction mixture. On attempted distillation substantially complete decomposition occurred. The reaction was not investigated further.

Summary

1. Direct heating of *o*-phenylenediamine and a mono-N-alkyl derivative with representative aldehydes and ketones leads to 2-substituted benzimidazoles by elimination of one of the atoms or radicals of the carbonyl compound from the intermediate imidazoline.

2. A mechanism for the reaction is suggested.

---

[15] Walther and V. Pulawski, *J. prakt. Chem.*, [2] **59**, 253 (1899).

NEW YORK 27, N. Y.

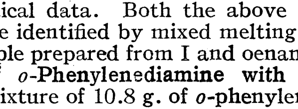
RECEIVED MARCH 21, 1947

[FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, MEDICAL RESEARCH DIVISION, SHARP AND DOHME, INC.]

The Preparation and Rearrangements of 1,2-Dimethylaminochloropropanes

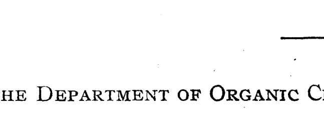
BY EVERETT M. SCHULTZ AND JAMES M. SPRAGUE

Recent work has shown that the chloroamine obtained from 1-dimethylamino-2-propanol reacts with diphenylacetonitrile in the presence of basic condensing agents to yield two isomeric nitriles, I and II.[1] The structures of these nitriles showed that a rearrangement had occurred, otherwise only the nitrile I should have resulted. In view of recent work dealing with the chemistry of chloroethylamines,[2] it seemed probable that, under the influence of the basic condensing agents, the chloroamine gave rise to an ethylenimonium ion which led to the isomeric nitriles on further reaction with diphenylacetonitrile. However, the possibility that the rearrangement occurred during the conversion of the aminoalcohol to the chloroamine was not excluded. More recently, Brode and Hill[3] have raised the question of the identity of the chloroamine employed in this reaction. These investigators failed to obtain different and distinct isomeric chloroamine bases from the treatment of 1-dimethylamino-2-propanol and 2-dimethylamino-1-propanol with thionyl chloride although apparently two distinct hydrochlorides were obtained. They conclude that the chloroamines rearranged, under the conditions used to isolate the bases from their salts,



$(C_6H_5)_2C(CN)CH(CH_3)CH_2N(CH_3)_2$

I



$(C_6H_5)_2C(CN)CH_2CH(CH_3)N(CH_3)_2$

II

---

[1] Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188 (1947); **69**, 2454 (1947).

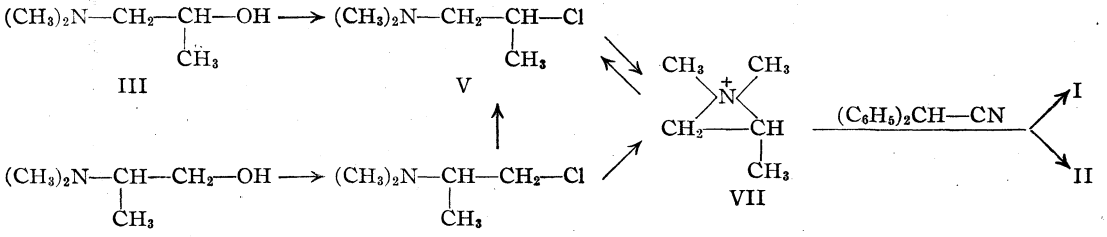
[2] Golumbic, Fruton, Bergmann, *et al.*, *J. Org. Chem.*, **11**, 518–591 (1947).

[3] Brode and Hill, THIS JOURNAL, **69**, 724 (1947).

to yield the same product and suggest that this product may be either of the two isomeric chloroamines or an equilibrium mixture of the two.

The results of work in this Laboratory are not in agreement with the observations and conclusions of Brode and Hill. It has been possible to prepare both of the isomeric chloroamines from the respective aminoalcohols and to show that 2-dimethylamino-1-chloropropane is rearranged by heat into 1-dimethylamino-2-chloropropane, whereas the latter is thermally stable and that both chloroamines give rise to the same mixture of aminonitriles on reaction with diphenylacetonitrile.

1-Dimethylamino-2-propanol (III) was converted by the action of thionyl chloride into a chloroamine hydrochloride, m. p. 185–186°, that is relatively insoluble in chloroform. The chloroamine base (V) obtained from this hydrochloride was characterized both before and after distillation by conversion to the picrate, hydrochloride and methiodide. The properties of these derivatives and of the picrate prepared directly from the original hydrochloride indicated that no rearrangement had occurred either during the liberation of the chloroamine from the hydrochloride or during the distillation. The action of thionyl chloride on the isomeric alcohol IV, or its hydrochloride, gave a chloroamine hydrochloride, m. p. 104°, that is very soluble in chloroform. The properties of the picrate prepared from this hydrochloride or from the undistilled chloroamine as well as the properties of the methiodide of the undistilled base showed this chloroamine to be different from V. After distillation, however, it was identical with V as shown by a comparison of the hydrochloride, picrate and methiodide. Furthermore, the hydrochloride, m. p. 104°, on heating rearranged into the isomer, m. p. 185–186°.

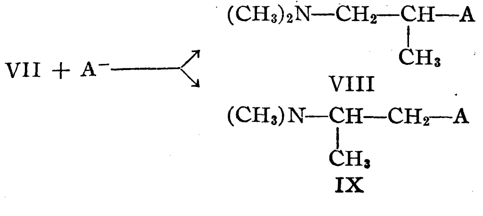


Although no irrefutable evidence is available concerning the structure of these isomeric chloroamines, it seems improbable that a rearrangement also occurred during the treatment of both of the isomeric dimethylaminopropanols with thionyl chloride or during the isolation of the resulting chloroamine hydrochlorides. Therefore, it must be concluded that 1-dimethylamino-2-chloropropane (V) and 2-dimethylamino-1-chloropropane (VI) are obtained from the respective alcohols, III and IV, and, furthermore, that VI, either as the hydrochloride or the free base, rearranges on heating to the more stable isomer, V.

Although a number of runs with IV, as well as its hydrochloride, yielded the hydrochloride of VI, m. p. 104°, one run gave only the hydrochloride of V, m. p. 185–186°. It is evident that some undetermined condition was responsible for the rearrangement in this experiment. When the chloroamine hydrochloride, m. p. 104°, was subjected to conditions comparable to the thionyl chloride reaction, it was recovered unchanged. It seems likely that the results of Brode and Hill may be similar to this anomalous experiment in our series.

In the earlier work, the stable chloroamine, V, was employed in the condensation with diphenylacetonitrile.[1] Therefore, it seems probable that the unexpected nitrile II arose through the intermediate formation of the ethylenimonium ion VII under the influence of the strong alkaline condensing agents. However, the expected nitrile I could arise either directly by replacement of the chlorine of V, or indirectly by the opening of the cyclic imonium ion in a manner opposite to that resulting in nitrile II. Under the conditions of this reaction, VI should yield the same imonium ion VII either directly or by first rearranging to V. In either event this chloroamine would give rise to the same mixture of nitriles on condensation with diphenylacetonitrile. This was found to be the case. The hydrochloride of VI was converted to the base at a low temperature. The dried undistilled base, VI, was condensed with diphenylacetonitrile to yield a mixture of equal amounts of the two isomeric nitriles, I and II.

All of the foregoing results suggest that the rearrangement of 2-dimethylamino-1-chloropropane (VI) into its isomer (V) as well as the reaction of either chloroamine, V or VI, with diphenylacetonitrile proceeds through the cyclic ion VII. The behavior of VII is governed, no doubt, by steric as well as polar factors, both within the cyclic ion and in the anion (A^-) with which it reacts. The rearrangement which involves the reaction of the ethylenimonium ion with a chloride ion leads predominately, if not exclusively, to structure VIII



(A = Cl). However, the reaction of VII with the relatively large anion of diphenylacetonitrile results in virtually equal amounts of the two possible isomers VIII and IX (*cf.* I and II).

Experimental[4,5]

1-Dimethylamino-2-propanol (III) was prepared in two ways: (A) from 1-chloro-2-propanol and dimethylamine in aqueous alkali by the German procedure[6] and (B) by the methylation of 1-amino-2-propanol with formaldehyde and formic acid by the method of Clarke, Gillespie and Weisshaus.[7] The physical constants were: b. p. 120–125°, d^{26}_{26} 0.855, n^{20}_D 1.4210, n^{26}_D 1.4182; molecular refraction: calcd., 30.75; found, 30.37.

The **methiodide** was prepared in ether; m. p. 153–154° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_6H_{16}INO$: N, 5.75. Found: N, 5.68.

1-Dimethylamino-2-chloropropane Hydrochloride. A. In Chloroform.—Dry chloroform (200 ml.) and purified thionyl chloride (68 g., 0.58 mole) were placed in a round-bottomed flask equipped with a stirrer, reflux condenser and dropping funnel. The flask was placed in an ice-bath and 1-dimethylamino-2-propanol (50 g., 0.49 mole) added to the cooled, stirred mixture over a period of one hour. Near the end of the addition, the reaction mixture became semisolid due to the separation of a white precipitate. The mixture then was heated to gentle boiling whereupon the white solid dissolved gradually. After boiling for one-half hour, the whole reaction mixture solidified suddenly. The mixture was cooled at once, the solid collected by filtration and recrystallized from isopropyl alcohol. The product was washed with ether and dried in air at about 60°; yield 47 g. (61.5%) m. p. 185–186°.

B. In Benzene.—The German procedure[6] was followed. From 75 g. (0.56 mole) of thionyl chloride and 50 g. (0.48 mole) of III in 190 ml. of dry benzene there was obtained 51.5 g. (67.5%) of pure white needles, m. p. 185–186° after crystallization from chloroform (Norit) and then from isopropyl alcohol.

This salt is quite soluble in isopropyl alcohol, sparingly soluble in acetone and dissolves in chloroform to the extent of about one gram in 40 ml. at 26°. It is only slightly hygroscopic and sublimes readily without change at temperatures below its melting point.

Anal. Calcd. for $C_5H_{12}NCl{\cdot}HCl$: N, 8.85. Found: N, 8.87.

The **picrate** was prepared from the hydrochloride in water solution. After crystallization from benzene and from water, it melted at 101–103°.

1-Dimethylamino-2-chloropropane (V).—The hydrochloride (30 g.) was dissolved in 40–50 ml. of water and made strongly basic with 20% sodium hydroxide. The chloroamine layer was separated, dried over solid potassium hydroxide and distilled, b. p. 62–63° (100–110 mm.); yield, 19 g., n^{20}_D 1.4250. The recorded boiling point[6] is 60° (110 mm.). On addition of this chloroamine to an acidified solution of silver nitrate, no silver chloride precipitated even after several days at room temperature. Precipitation was rapid when the solution was heated.

The distilled base (2.7 g.) in ether was converted to the **hydrochloride**, (3.35 g., m. p. 181–183°). After crystallization from isopropyl alcohol and from chloroform, it melted at 185–186° (1.6 g.).

Anal. Calcd. for $C_5H_{12}NCl{\cdot}HCl$: C, 37.97; H, 8.24; N, 8.85; Cl (ionic), 22.47. Found: C, 38.0; H, 8.34; N, 8.87; Cl (ionic), 22.45.

The distilled base (2 g.) in chloroform was converted to its hydrochloride, m. p. 185–186°, yield 2.28 g., 97%, after correcting for the solubility in chloroform. Therefore, little, if any, of the isomer, VI, was present since its hydrochloride is very soluble in chloroform, 1 g./2 ml.

The **picrate** was prepared from the distilled base in ether. The melting point was 101–103° and was not changed by crystallization from benzene. The picrate was prepared from the undistilled base as follows: 1-dimethylamino-2-chloropropane hydrochloride (1.0 g.) (m. p. 185–186°) was taken up in a little water, the solution chilled to 0° in an ice-bath and made basic with 20% sodium hydroxide. The oil was removed and the picrate was prepared in alcohol; yellow needles, m. p. 101–103°, 0.84 g. The picrate is very soluble in alcohol and hot water but less soluble in benzene. Crystallization from alcohol or benzene did not change the melting point.

Anal. Calcd. for $C_{11}H_{15}ClN_4O_7$: C, 37.66; H, 4.31; N, 15.97. Found: C, 37.7; H, 4.28; N, 16.00.

The **methiodide** of V was prepared from the undistilled base in the following manner: the hydrochloride was dissolved in water and the cold solution made basic with 20% sodium hydroxide solution. The organic material was taken up in ether and dried over anhydrous sodium sulfate. An excess of methyl iodide was added to the ether solution. After a few hours at room temperature, a white precipitate separated, m. p. 180–181°. After crystallizing once from absolute alcohol and three times from acetone, the rectangular prisms melted at 184–185°. (The melting point depends upon the manner in which it is taken but did not change between the last two crystallizations.) This methiodide was prepared also from the distilled base in ether solution. After crystallization from acetone, it melted at 185–186° with decomposition and a mixed melting point with the previous sample showed no depression.

Anal. Calcd. for $C_6H_{15}ClIN$: C, 27.34; H, 5.73; N, 5.32. Found: C, 27.25; H, 5.76; N, 5.31.

2-Dimethylamino-1-hydroxypropane (IV) was prepared from ethyl α-dimethylaminopropionate[8] by reduction with sodium according to the method of Stoll[9] and also from the reductive methylation[7] of 2-amino-1-propanol that was obtained by the reduction of 2-nitro-1-propanol according to the method of Gakenheimer and Hartung[10]: b. p. 145–148° (765 mm.), n^{20}_D 1.4365, d^{26}_{26} 0.889, molecular refraction, calcd., 30.75; found, 30.16.

The **methiodide** was prepared in absolute alcohol and precipitated with ether,[11] m. p. 293°. The melting point depends upon the rate of heating.

2-Dimethylamino-1-chloropropane Hydrochloride. A. In Benzene.—Dry benzene (200 ml.) and thionyl chloride (63 g., 0.53 mole), were placed in a round-bottomed flask fitted with a reflux condenser, a dropping funnel and a mechanical stirrer. The flask was cooled in an ice-bath and 2-dimethylamino-1-propanol (46 g., 0.448 mole) in dry benzene (100 ml.) was added to the vigorously stirred mixture during a period of thirty minutes. A gummy yellow precipitate formed. The flask was allowed to warm to room temperature and then placed in a water-bath that was heated slowly to 60°. At 60–70° sulfur dioxide was evolved. After heating at 60–70° for one hour, the mixture was refluxed for two hours. During the heating, the original yellow precipitate was converted to a black tarry oil. Upon allowing the reaction mixture to cool, the oil solidified. The solid was collected by filtration and dried *in vacuo* over solid potassium hydroxide and concentrated sulfuric acid. The dark-brown product was taken up in 300 ml. of boiling acetone, the solution filtered and decolorized with charcoal. Upon cooling, pure white crystals separated, 29 g. (41%), m. p. 103–104°. Further recrystallization from acetone did not change the melting point. When the temperature was raised slowly above 104°, the

---

[4] All melting points and boiling points are uncorrected.

[5] We are indebted to Mr. K. B. Streeter, Miss Ruth Lynch and Miss Thelma Plank for the analytical data and to Miss Sally Mickey for assistance with some of the syntheses.

[6] Office of the Publication Board, Department of Commerce, Report PB-981, p. 96.

[7] Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

[8] Major and Kline, *ibid.*, **54**, 242 (1932).

[9] Stoll, *Helv. Chim. Acta*, **26**, 936 (1943).

[10] Gakenheimer and Hartung, *J. Org. Chem.*, **9**, 87 (1944).

[11] Karrer, *et al.*, *Helv. Chim. Acta*, **5**, 477 (1922), reports m. p. 296°.

melt resolidified at 140–150° and then remelted with decomposition at 175–177°. This hydrochloride is exceedingly hygroscopic and it is difficult to obtain a reproducible melting point.

Anal. Calcd. for $C_5H_{12}NCl \cdot HCl$: N, 8.85; Cl, 44.86; Cl (ionic), 22.47. Found: N, 8.90; Cl, 44.35; Cl (ionic), 22.77.

The above salt (0.5 g.) m. p. 104° was sublimed at a pressure of 18 mm. and a bath temperature of 150°. The compound first melted and then resolidified. Sublimation was rapid. The sublimate melted at 185–186° after one crystallization from isopropyl alcohol. A mixed melting point with the chloroamine hydrochloride prepared from 1-dimethylamino-2-propanol showed no depression.

The **picrate** was prepared from the hydrochloride (m. p. 103–104°) in a cold aqueous solution. The solid that separated melted at 153°. After one crystallization from alcohol, it melted at 166–167°, and further recrystallization did not change the melting point.

B. In Chloroform.—Dry chloroform (200 ml.) and purified thionyl chloride (68 g., 0.575 mole) were placed in the apparatus described in A. The flask was placed in an ice-bath and 2-dimethylamino-1-propanol (50 g., 0.485 mole) in chloroform (100 ml.) was added with stirring during one-half hour. A clear, amber, homogeneous solution resulted. The solution was boiled for two and one-half hours. No solid appeared at any time. The reaction mixture was divided into two equal parts.

(a) To the clear solution 500 ml. of dry benzene and 200 ml. of absolute ether were added. A white solid, 36 g., m. p. 98–100°, separated. After crystallization from acetone, using decolorizing charcoal, the product melted at 102–104° (29 g.). The picrate prepared from the hydrochloride melted at 166–167° after purification.

(b) The chloroform was distilled by heating on a steam-bath leaving a dark oil that solidified on cooling. Trituration of the residue with dry benzene gave a tan solid (30 g.) m. p. 95°. After purification as described in a, the product (20 g.) was identical with that obtained in **a**. Total yield from **a** and **b** was 49 g. (64%).

In one run, chlorination of 2-dimethylamino-1-propanol (50 g.) with thionyl chloride (68 g.) in chloroform (300 ml.) gave an anomalous result. The isolation was carried out as in **b**. No difference was observed during the reaction. Upon distillation of the chloroform, the hot mixture solidified when the volume became small. The product (54 g.) melted at 180° and, after crystallization from isopropyl alcohol, using decolorizing charcoal, a pure white product was obtained, 37 g. (52%), m. p. 185–186°. The picrate prepared from the hydrochloride melted at 101–103°. The mother liquors from the reaction mixture and recrystallization were evaporated. The only substances obtained were tar and about 5 g. of hydrochloride melting at 178–180°.

C. In sym-Tetrachloroethane.—2-Dimethylamino-1-propanol (25 g.) was added slowly to *sym*-tetrachloroethane (50 ml.) at 80°. At this temperature the amino-alcohol reacted with the tetrachloroethane to yield the hydrochloride and trichloroethylene. The flask then was placed in an ice-bath and thionyl chloride (34 g.) in *sym*-tetrachloroethane (100 ml.) was added during a period of fifteen minutes. The mixture then was heated to boiling for two hours. The solvent was removed by vacuum distillation and the residual dark sirup solidified on adding dry benzene. After one crystallization from acetone, 26.6 g. (69.5%) of product, m.p. 102–103°, was obtained.

2-Dimethylamino-1-chloropropane (VI).—The picrate and methiodide were prepared from this chloroamine immediately after liberation from the hydrochloride as follows:

A. Picrate.—The hydrochloride (1 g.) was taken up in water (5–6 ml.). The solution was cooled in an ice-bath and made basic by addition of 20% sodium hydroxide. The oil that separated was removed and added to 3 ml. of ethanol. To the resulting solution was added 20 ml. of saturated ethanolic picric acid solution. After the mixture had stood at room temperature for four hours, the product was removed by filtration; yield, 1.1 g., m. p., 162–163°. After one crystallization from alcohol, the m. p. was 166–167° and was not changed by subsequent recrystallizations.

Anal. Calcd. for $C_{11}H_{15}ClN_4O_7$: C, 37.66; H, 4.31; N, 15.97. Found: C, 37.90; H, 4.27; N, 15.89.

B. Methiodide.—The hydrochloride (1 g.) was taken up in 5–6 ml. of water. The solution was cooled in ice and made basic with 20% sodium hydroxide solution. The oil that separated was removed, taken up in ether and the solution dried over anhydrous magnesium sulfate at 0–5°. To the dried solution was added 2 ml. of methyl iodide. After standing at 25–30° for sixteen hours, the white precipitate (1.1 g.) was collected by filtration. It decomposed at 190–191°, with evolution of gas, after extensive darkening at about 170°. The melting behavior was not changed by four crystallizations from absolute alcohol. A mixture with an equal amount of its isomer (m. p. 185–186°) melted at 181–184°.

Anal. Calcd. for $C_6H_{15}ClIN$: C, 27.34; H, 5.73; N, 5.32. Found: C, 27.27; H, 5.63; N, 5.23.

Distillation of 2-Dimethylamino-1-chloropropane (VI).—The hydrochloride (20 g.) was converted to the base and distilled in the manner described for V, b. p. 64–67° (97–100 mm.), $n^{20}D$ 1.4252. The yield of distilled free base was about 10 g. There was some mechanical loss in drying and a few ml. of high boiling, sirupy residue remained in the distilling flask. This chloroamine base, before or after distillation, did not give an immediate precipitate with acidified silver nitrate solution. After long standing or upon heating silver chloride formed.

The **hydrochloride** was prepared from the distilled base (2 ml.) in ether (2.1 g., m. p. 173–175°). After recrystallization from isopropyl alcohol, it melted at 186–187°. The **picrate** of the distilled base (0.8 ml.) was prepared in ether; yield, 1.0 g., m. p. 96–99°. After crystallization from water and from benzene it melted at 101–103°. The **methiodide** was prepared from 0.8 ml. of the distilled base and 3 ml. of methyl iodide in ether solution; yield 1.17 g., m. p. 172°. After crystallization from absolute alcohol and from acetone, the m. p. was 185–186°.

As shown by melting points and mixed melting points, all three derivatives, the hydrochloride, the picrate and the methiodide, of the distilled base were different from the derivatives that were prepared before distillation and were identical with the derivatives of 1-dimethylamino-2-chloropropane, V.

Reaction of 2-Dimethylamino-1-chloropropane with Diphenylacetonitrile.—In a 500-ml. flask equipped with a sealed stirrer, a gas inlet tube and air condenser, potassium metal (4 g., 0.1 mole) was dissolved in hot *t*-butyl alcohol (135 ml.) under an atmosphere of nitrogen. Diphenylacetonitrile (19.3 g., 0.1 mole) was added to the hot solution. The mixture was heated to boiling and undistilled 2-dimethylamino-1-chloropropane (15 g., 0.124 mole) in xylene (12 ml.) was added during a period of twenty-five minutes. After boiling for six hours, the alcohol was distilled and water and ether were added to the residue. The basic substances were extracted from the ether layer with dilute hydrochloric acid. The acid solution was made basic with dilute sodium hydroxide solution and the semisolid organic material was taken up in ether. The ether solution was washed with water, dried over anhydrous sodium sulfate and the ether evaporated. The semisolid residue was triturated with hexane (35 ml.) and cooled in an ice-bath. White crystals of 2,2-diphenyl-4-dimethylaminopentanenitrile were obtained by filtration. After crystallization from benzine, the product was obtained as long needles, m. p. 90–91° (11.05 g., 40%). The evaporation of the hexane filtrate yielded a thick oil that was distilled, b. p. 165° (1–2 mm.). The distillate soon solidified, and was identified as 2,2-diphenyl-3-methyl-4-dimethylaminobutanenitrile by means of its picrate,[1] m. p. 204–205°.

The chloroamine used in this preparation was obtained from 2-dimethylamino-1-chloropropane hydrochloride, m. p. 103–104°. The salt (45 g.) was dissolved in water (20–30 ml.) and, while cooling in an ice-bath, the solution was made basic with 20% sodium hydroxide solution. The base was taken up in ether and the solution was dried over anhydrous magnesium sulfate. The solvent was removed by vacuum distillation at 30–35°. Immediately before using the residual oil in the condensation reaction, a sample was withdrawn and converted to the picrate, (m. p. 158–160°). After crystallization from alcohol, the melting point was 166–167°. Therefore, the chloroamine added to the reaction was 2-dimethylamino-1-chloropropane.

Summary

1-Dimethylamino-2-chloropropane and 2-dimethylamino-1-chloropropane were prepared from the corresponding dimethylaminopropanols by the action of thionyl chloride.

2-Dimethylamino-1-chloropropane, either as the free base or as the hydrochloride, rearranges on heating into 1-dimethylamino-2-chloropropane which is thermally stable.

Both chloroamines reacted with diphenylacetonitrile to give the same mixture of isomeric aminonitriles.

Glenolden, Pa. Received July 7, 1947

[Contribution from the Eastern Regional Research Laboratory[1]]

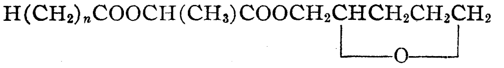
n-Alkanoyl Derivatives of *n*-Butyl and Tetrahydrofurfuryl Lactates

By M. L. Fein and C. H. Fisher

Several alkyl lactates have been acylated[2] with the lower acid anhydrides and chlorides, but little is known about acylated lactic esters of relatively high molecular weight. The present paper describes several homologous acyl derivatives (I and II, *n*-1, 2, 3, 6, 8 and 11) of *n*-butyl lactate and tetrahydrofurfuryl lactate, prepared in high yields by treating the corresponding lactic esters with various aliphatic acid chlorides or anhydrides.

$$H(CH_2)_nCOOCH(CH_3)COO(CH_2)_4H$$

I



$$H(CH_2)_nCOOCH(CH_3)COOCH_2\underbrace{CHCH_2CH_2CH_2}_{O}$$

II

The *n*-alkanoyl derivatives (I and II) were purified carefully by fractional distillation. The resulting colorless liquids were used in the determination of density (*d*), refractive index (*n*), viscosity (η), and boiling points (T) under different pressures. These physical properties of the two homologous series (I and II) were related to the number of carbon atoms, *x* (or molecular weight) by plotting certain functions of the physical properties (x/d, x/n, log η, and T^2) against *x*. The resulting straight line relationships are useful in estimating properties of other homologous members of I and II by interpolation and extrapolation, comparing the properties of I and II with those of other homologous series, and correlating x/d, x/n, log η and T^2 with one another (within a homologous series, *i.e.*, I or II).

Experimental

Materials.—Redistilled *n*-butyl lactate (b.r. 79–80° at 12.4 mm.) from a commercial source and tetrahydrofurfuryl lactate[3] (b.p. 92° at 1 mm.) prepared by alcoholysis of methyl lactate were used. Commercial grades of acetic, propionic, and butyric anhydrides and pelargonyl chloride were used; the *n*-heptanoyl and *n*-dodecanoyl chlorides were Eastman Kodak Co. White Label grade.

Acylation: Acid Anhydrides.—The previously described[2b] method was used to acylate the lactic esters.

Acid Chlorides.—The acid chloride (1 mole per mole of lactic ester) was added slowly with stirring to a mixture of the lactic ester, reagent-grade pyridine (10% excess), and benzene (100 ml. per mole of lactic ester) contained in a 3-necked flask fitted with a condenser, mechanical stirrer, and glass-stoppered funnel. In most instances, the temperature of the reaction mixture was kept at 10 to 20° by external cooling. Cooling is recommended, although it was omitted in some experiments (temperature rose to 80°). When the reaction was complete (shortly after the addition of all the acid chloride), a small quantity of water was added to dissolve the pyridine hydrochloride. The oil layer was separated and washed in succession with dilute hydrochloric acid, saturated brine, and dilute sodium bicarbonate. In some instances, water was removed by drying over anhydrous sulfate; in others this treatment was omitted, and the water was distilled azeotropically with the benzene already present. The low- and high-boiling materials were then distilled under reduced pressures with a water aspirator and oil pump, respectively. Vigreux columns approximately 50 cm. high were used for most of the distillations. Yields and properties of the products are given in Tables I and II.

Determination of Physical Constants.—The boiling points used for the construction of Fig. 1 were determined, as in a previous study,[4] by carefully distilling narrow-boiling fractions either through a 60-cm. Vigreux column or with an alembic flask[5]; pressures were read from a Dubrovin gage.[6] When the same equipment and technique were used to determine boiling points of butyl phthalate at several pressures between 2 and 10 mm., data agreeing with those of Hickman[7] were obtained. The boiling points of the acylated lactic esters (I and II) were plotted on a Cox chart[8]; boiling points at 10 mm. were taken from the chart (Fig. 1).

Refractive indices and specific gravities (Table I) were determined with an Abbe type refractometer and a 10-ml.

---

[1] One of the Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

[2] (a) R. Burns, D. T. Jones, and P. D. Ritchie, *J. Chem. Soc.*, 400 (1935); (b) M. L. Fein and C. H. Fisher, *Ind. Eng. Chem.*, **36**, 235 (1944).

[3] M. L. Fein, W. P. Ratchford and C. H. Fisher, This Journal, **66**, 1201 (1944).

[4] M. L. Fein and C. H. Fisher, *ibid.*, **68**, 2631 (1946).

[5] J. C. Cowan, L. B. Falkenburg and H. M. Teeter, *Ind. Eng. Chem., Anal. Ed.*, **16**, 90 (1944).

[6] J. Dubrovin, *Instruments*, **6**, 194 (1933); F. E. E. Germann and K. A. Gagos, *Ind. Eng. Chem., Anal. Ed.*, **15**, 285 (1943).

[7] K. C. D. Hickman, *J. Franklin Institute*, **221**, 383 (1936); G. E. Barker, G. E. Alter, Jr., C. E. McKnight, J. R. McKlveen and D. M. Hood, A. S. T. M. Bulletin No. 139, 25 (Mar. 1946).

[8] E. R. Cox, *Ind. Eng. Chem.*, **15**, 592 (1923); G. Calingaert and D. S. Davis, *ibid.*, **17**, 1287 (1925).

TABLE I

ACYL DERIVATIVES OF *n*-BUTYL AND TETRAHYDROFURFURYL LACTATES[a]

Acyl deriv.	B. p., °C.	Mm.	d^{20}_4	n^{20}_D	M^{20}_D Found	M^{20}_D Calcd.	Ester equiv. Found	Ester equiv. Calcd.	Analyses, % Carbon Found	Carbon Calcd.	Hydrogen Found	Hydrogen Calcd.
					n-Butyl lactate							
Acetyl[b]	90	7.8	1.0036	1.4163	47.09	47.07	95.2	94.1	...	...	...	...
Propionyl[b]	118	18.7	0.9864	1.4178	51.65	51.69	100.9	101.1	...	...	...	...
n-Butyryl[b]	90	2	.9731	1.4215	56.40	56.31	108.9	108.1	60.91	61.09	9.07	9.32
n-Heptanoyl[c]	122	2	.9477	1.4290	70.27	70.16	129.3	129.2	64.84[d]	65.08	...	...
n-Nonanoyl[e]	143	3	.9353	1.4339	79.70	79.40	142.3	143.2	66.92	67.09	10.05	10.56
n-Dodecanoyl[c]	142	0.6	.9218	1.4388	93.68	93.25	163.8	164.2	69.54	69.47	11.12	11.05
					Tetrahydrofurfuryl lactate							
Acetyl[b]	109	1.2	1.1234	1.4445	51.18	51.13	108.2	108.1	...	...	...	...
n-Butyryl[b]	92	0.2	1.0768	1.4448	60.33	60.39	122.5	122.1	59.07	59.00	8.32	8.25
n-Heptanoyl[c]	171	5.4	1.0300	1.4478	74.38	74.22	143.1	143.2	62.89	62.91	9.14	9.15
n-Nonanoyl[e]	202	10.0	1.0121	1.4498	83.45	83.46	154.8	157.2	64.75	64.94	9.44	9.62
n-Dodecanoyl[c]	205	2.7	0.9843	1.4522	97.74	97.31	180.2	178.3	67.92	67.38	10.41	10.18

[a] Acylation yields of product distilling over approximately 3° range were approximately 90% of the theoretical, except for the nonanoates (15 to 20° range). The authors are indebted to Mary J. Welsh, Mildred Gaspar and C. O. Willits for analytical data. [b] Acid anhydride used for acylation. [c] Acid chloride (Eastman Kodak Co. White Label) used. [d] Carbon determined by wet oxidation (D. D. Van Slyke and J. Folch, *J. Biol. Chem.*, **136**, [2] 509 (1940)). [e] Commercial grade of pelargonyl chloride used.

TABLE II

VISCOSITIES[a] OF ACYL DERIVATIVES OF *n*-BUTYL LACTATE AND TETRAHYDROFURFURYL LACTATE

Acyl deriv.	Viscosity at 20° Centistokes	Viscosity at 20° Centipoises	I at 20°[b] Found	I at 20°[b] Calcd.	I/M[c]
		Butyl Lactate			
Acetyl	3.19	3.20	577.2	571.9	12.25
Propionyl	2.92	2.88	629.0	627.5	12.19
n-Heptanoyl	5.21	4.94	853.1	849.9	12.14
n-Nonanoyl	6.74	6.30	966.2	961.1	12.12
n-Dodecanoyl	10.84	9.99	1140.4	1127.9	12.17
		Tetrahydrofuryl Lactate			
Acetyl	12.09	13.58	621.4	627.8[d]	12.14
n-Butyryl	10.30	11.09	728.1	739.0[d]	12.07
n-Heptanoyl	13.06	13.45	897.6	905.8[d]	12.07
n-Nonanoyl	17.27	17.48	1009.8	1017.0[d]	12.10
n-Dodecanoyl	25.03	24.64	1184.5	1183.8[d]	12.12

[a] A.S.T.M. procedure using modified Ostwald tubes. [b] Souders' viscosity function, I (M. Souders, Jr., THIS JOURNAL, 60, 154 (1938); A. N. Planovskii and V. V. Kafarov, *Khimicheskaya Prom.*, No. 8, 19 (1944)(*C.A.*, 40, 2048 (1946))). [c] According to R. T. Lagemann (THIS JOURNAL, 67, 498 (1945)), I/M should be approximately 12. [d] In calculating I from group and structural values, −24 (recommended by Souders for 5-membered carbon rings) was used for the 5-membered tetrahydrofuran ring.

specific gravity bottle (fitted with a ground glass thermometer and cap), respectively. Viscosities (Table II) were determined by A.S.T.M. procedure,[9] using modified Ostwald tubes and a constant temperature bath[10] capable of maintaining the temperature within ± 0.02° at 20°.

Determination of Boiling Water Stability.—A mixture of 5 g. of ester and 100 ml. of distilled water was refluxed for twenty-four hours and allowed to cool. Approximately 200 ml. of acetone and several drops of cresol red–thymol blue mixed indicator[11] were added, and the resulting solution was titrated with 0.1 *N* sodium hydroxide. This method appeared to have certain advantages (one-phase system and less fading of end-point) over the similar method of Fordyce and Meyer.[12] Water solubilities were determined by a method similar to that of Fordyce and Meyer[12], using Sudan Red No. III dye.

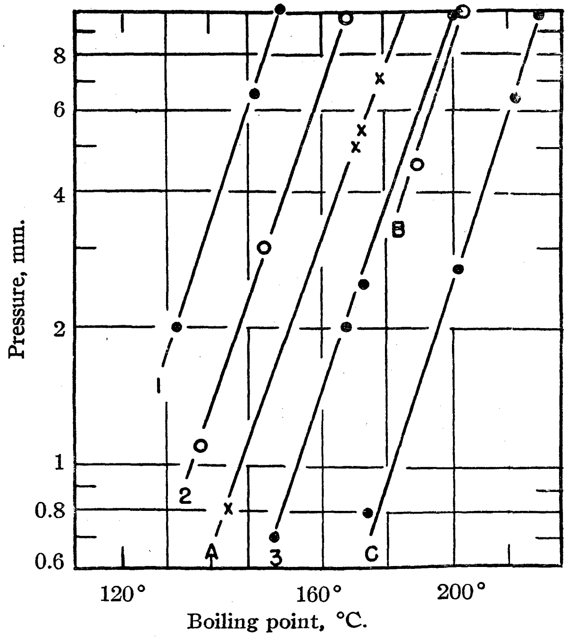


Fig. 1.—Boiling points at various pressures of acyl derivatives of *n*-butyl and tetrahydrofurfuryl lactates: acyl derivatives of *n*-butyl lactate: 1, heptanoate; 2, nonanoate; 3, dodecanoate; acyl derivatives of tetrahydrofurfuryl lactate: A, heptanoate; B, nonanoate; C, dodecanoate.

---

[9] A. S. T. M., D445 and Committee D-2 Report, 1936; M. R. Cannon and M. R. Fenske, *Oil Gas J.*, **33**, 52 (1935); *ibid.*, **34**, 45 (1936).

[10] M. L. Fein, *Chem. Analyst*, **34**, 94 (Nov. 1945).

[11] A. Kleinzeller and A. R. Trim, *Analyst*, **69**, 241 (1944).

[12] C. R. Fordyce and L. W. A. Meyer, *Ind. Eng. Chem.*, **32**, 1053 (1940).

Table III

Properties of Acyl Derivatives of *n*-Butyl Lactate and Tetrahydrofurfuryl Lactate

Acyl deriv.	Vapor press. at 120°., mm.[a]	Solubility in water, g./liter, less than	Boiling water stability[b]	Compatibility[c]			
				Ethyl cellulose, 1:1[d]	Cellulose acetate, 4:1[d]	Cellulose acetate butyrate, 4:1[d]	Polyvinyl chloride, 1:1[d]
		Butyl lactate					
n-Heptanoyl	1.7	0.07	..	C	I	C	C
n-Nonanoyl	0.7	.03	12.3	C	I	CI	C
n-Dodecanoyl	.15	.04	7.8	C	I	CI	C
		Tetrahydrofurfuryl lactate					
n-Heptanoyl	.34	.16	..	C	I	C	C
n-Nonanoyl	.22	.04	8.9	C	I	C	C
n-Dodecanoyl	< .1	.04	5.0	C	I	C	C

[a] Estimated from Fig. 1 by extrapolation; vapor pressure of butyl phthalate at 120° = 0.26 mm. (ref. 7). [b] Volume 0.1 *N* sodium hydroxide (ml.) to neutralize sample (5 g. in 100 ml. of water) that had been refluxed for twenty-four hours; values obtained by this method with methyl and butyl phthalate, respectively, were 1.0 and 0.2 ml. [c] C, compatible; I, incompatible; and CI borderline compatibility (commercially available plastics used for tests). [d] Ratio of polymer to plasticizer.

Compatibilities.—The acylated lactic ester and certain commercially available resins (Table III) were dissolved in a suitable solvent (acetone for ethyl cellulose, cellulose acetate, and cellulose acetate butyrate and dioxane for polyvinyl chloride). The solution was placed in a Petri dish and covered with a watch glass, and the solvent was allowed to evaporate. The resulting film was examined to determine compatibility. The esters were recorded as being compatible (Table III) only when transparent and dry films were obtained.

Correlation of Properties with Number of Carbon Atoms

The experimental data of the present work (Tables I to III) characterize many members of two homologous series (α-carbobutoxyethyl *n*-alkanoates, I, and α-carbotetrahydrofurfuryloxyethyl *n*-alkanoates, II), but several members of both series were not prepared or examined. To provide methods for estimating the properties of the missing members and to facilitate comparison of the *n*-alkanoyllactic esters (Table I) with certain previously-described homologous series, relationships between physical properties and number of carbon atoms (or molecular weight) of the homologous *n*-alkanoyl lactates were developed. Instead of plotting the physical constants as such against the number of carbon atoms and obtaining curved lines, certain functions of the properties that gave straight lines were selected. In agreement with earlier work, it was found that the straight line relationships usually were unsatisfactory for the first two or three members of the homologous series.

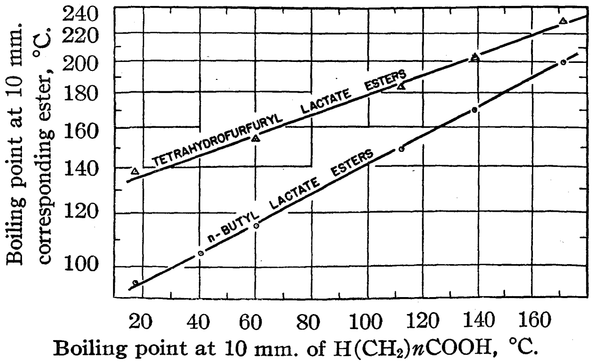


Fig. 2.—Relation of boiling points at 10 mm. of aliphatic acids and the corresponding acyl derivatives of tetrahydrofurfuryl and *n*-butyl lactates.

Boiling points at 10 mm. were taken from Fig. 1 and related[13] to the number of carbon atoms (x) and molecular weight (M) by equations 1, 2, 3 and 4 (T = b.p. at 10 mm., °K.). Observed boiling points vary 2° or less from the values calculated by equations 1 and 3. In the case of equations 2 and 4, the variation is 1° or less.

Butyl esters: $T^2 10^{-4} = 0.061M + 1.96$ (1)

$T^2 10^{-4} = 0.85x + 5.8$ (2)

Tetrahydrofurfuryl esters:

$T^2 10^{-4} = 0.061M + 3.42$ (3)

$T^2 10^{-4} = 0.85x + 8.2$ (4)

Figure 2, constructed by plotting boiling points at 10 mm. of aliphatic acids[14] against the boiling points of the corresponding carbobutoxyethyl (I) and carbotetrahydrofurfuryloxyethyl esters (II) on semilog paper, also can be used to estimate boiling points of the missing homologous esters. Boiling points (°K.) of the acids ($H(CH_2)_{x-1}COOH$) at 10 mm.[14] were used also to derive equations 5 and 6. Boiling points reported[14] in the literature vary 1 degree or less from the values calculated by equations 5 and 6.

$H(CH_2)_{x-1}COOH$: $T^2 10^{-4} = 1.28x + 6.06$ (x = 1 to 7, inclusive) (5)

$T^2 10^{-4} = 0.93x + 8.60$ (x = 8 to 18, inclusive) (6)

The boiling points of the lactic esters (1 and II) are compared with those of other homologous

---

[13] This method for relating the boiling point at 760 mm. and number of carbon atoms or molecular weight has been used by E. Boggia-Lera, *Gazz. chim. ital.*, **29**, 441 (1899); A. H. W. Aten, *J. Chem. Phys.*, **5**, 260 (1937); and F. Klages, *Ber.*, **76**, 788 (1943).

[14] Boiling points were estimated from the vapor pressure data of W. O. Pool and A. W. Ralston (*Ind. Eng. Chem.*, **34**, 1104 (1942)) by the use of Cox charts.[8]

series in Fig. 3, in which boiling points at 10-mm. pressure (°C.) are plotted against the square root of the number of carbon atoms. The *n*-butyl (I) and tetrahydrofurfuryl esters (II) boil lower and higher, respectively, than the diethyl esters[15] ($(CH_2)_n(COOC_2H_5)_2$) having the same number of carbon atoms. The lateral methyl group of the lactic esters and the tetrahydrofurfuryl group are relatively ineffective and effective, respectively, in raising the boiling point.[16] Both homologous series of lactic esters boil higher than the methyl alkanoates ($H(CH_2)_nCOOCH_3$) having an equal number of carbon atoms (with the exception of some of the higher *n*-alkanoyl derivatives of *n*-butyl lactate). The lines in Fig. 3 representing the homologous series having two or more functional groups have less slope than the *n*-paraffin[17] and methyl alkanoate lines.

The boiling points at 760 mm. of the *n*-butyl lactate derivatives (I) were calculated (Table IV) by the methods of Kinney,[16a] Burnop[16b] and Klages.[18] Boiling points at 760 mm. computed by Kinney's method[16a] were used to estimate[19] boiling points at 10 mm. Some of the calculated boiling points at 10 mm. (Table IV) are in close agreement with the experimental values.

The densities ($d^{20}{}_4$) and refractive indices ($n^{20}{}_D$) of the *n*-alkanoyl derivatives of *n*-butyl lactate (I) are given in Table I. They are related to the number of carbon atoms (x) by equations 7 and 8. Observed densities differ 0.0009 or less from the values calculated by equation 7. With the exception of the first member of the series, the observed refractive indices vary 0.0009 or less from the values calculated by equation 8.

$$\text{Butyl esters: } x/d = 1.164x - 1.509 \qquad (7)$$
$$x/n = 0.6845x + 0.2082 \qquad (8)$$

Similarly, equations 9 and 10 may be used to calculate $d^{20}{}_4$ and $n^{20}{}_D$ of the tetrahydrofurfuryl esters (II) from the number of carbon atoms (x). With the exception of the first member of the series, the average deviation of the observed densities from those calculated by equation 9 was 0.002. The average deviation for the refractive indices (equation 10) was 0.0004.

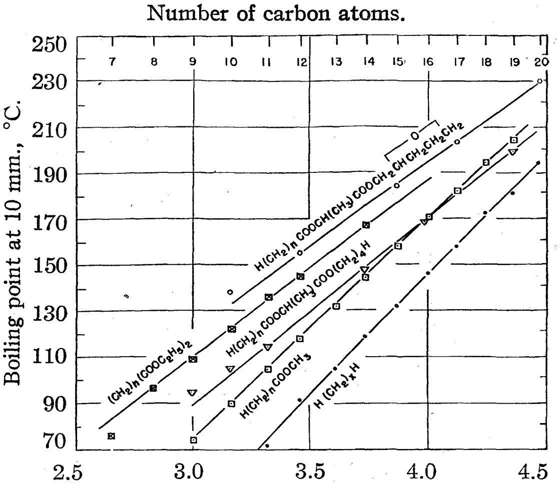


Fig. 3.—Relation between boiling point at 10 mm. and carbon atoms (X) of homologous compounds.

TABLE IV

CALCULATED BOILING POINTS OF THE ACYL DERIVATIVES OF *n*-BUTYL LACTATE

No. of carbon atoms	9	10	11	14	19
Boiling point (760 mm.), °C.					
Kinney's method[a]	222	235	254	304	377
Burnop's method[b]	232	249	266	312	375
Klages' method[c]	230	250	269	323	404
Boiling point (10 mm.), °C.					
Found[d]	95	105	115	148	201
Calcd.[e]	97	107	122	161	219

[a] Ref. 16a. [b] Ref. 16b. [c] Ref. 18. [d] From Fig. 1 or similar charts. [e] On the assumption[19] that esters have the temperature–vapor pressure relationship of group 3 compounds, using the equation: b. p. 10 mm. = (0.786) (b. p. 760 mm.) − 77.6.

$$\text{Tetrahydrofurfuryl esters: } x/d = 1.142x - 2.563 \qquad (9)$$
$$x/n = 0.6845x + 0.0892 \qquad (10)$$

The butyl acyloxypropionates (I) and tetrahydrofurfuryl acyloxypropionates (II) are similar to other homologous series,[20] in that linear relationships (Fig. 4) exist (excluding the first few members) between the logarithm of viscosity and the number of carbon atoms (Table II). The *n*-butyl (I) and tetrahydrofurfuryl esters (II) had lower and higher viscosities, respectively, than the diethyl esters[21] ($(CH_2)_n(COOC_2H_5)_2$) having an

---

[15] Boiling points of the diethyl esters ($(CH_2)_n(COOC_2H_5)_2$) at 10-mm. were estimated from boiling point data of A. I. Vogel, *J. Chem. Soc.*, 333 (1934).

[16] These conclusions are in agreement with the boiling points of somewhat related compounds at 760 mm. (a) C. R. Kinney, This Journal, **60**, 3032 (1938); Lange's "Handbook of Chemistry," 5th ed., 1944, Handbook Publishers, Inc., Sandusky, Ohio, p. 853, (b) V. C. E. Burnop, *J. Chem. Soc.*, 826 (1938).

[17] Boiling points of $H(CH_2)_nCOOCH_3$ and $H(CH_2)_nH$ at 10 mm. may be calculated by the equations: (esters) $T^2 10^{-4} = 1.09x + 2.23$; (*n*-paraffins) $T^2 10^{-4} = 1.19x - 1.0$ (x = 1 to 12, inclusive), and $T^2 10^{-4} = 1.07x + 0.35$ (x = 12 to 20, inclusive); where T = °K., and x = number of carbon atoms. Boiling point data used in deriving these equations were taken from (esters) P. M. Althouse and H. O. Triebold, *Ind. Eng. Chem., Anal. Ed.*, **16,** 605 (1944); F. A. Norris and D. E. Terry, *Oil & Soap*, **22,** 41 (1945); A. W. Weitkamp, This Journal, **67,** 447 (1945); "International Critical Tables," Vol. III, p. 217, and (*n*-paraffins) C. B. Willingham, W. J. Taylor, J. M. Pignocco and F. D. Rossini, *J. Research Natl. Bur. Standards*, **35** (31) 219 (1945); M. P. Doss, "Physical Constants of the Principal Hydrocarbons," 4th ed., The Texas Co., New York, N. Y., 1943. Boiling points reported in the literature differ 2° or less from the values calculated by the *n*-paraffin equations.

[18] F. Klages, *Ber.*, **76,** 788 (1943).

[19] In estimating the boiling points at 10 mm., it was assumed (following the suggestion of C. Bordenca, *Ind. Eng. Chem., Anal. Ed.* **18,** 99 (1946), and S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, **38,** 320 (1946)) that esters fall into Group 3 with respect to temperature–vapor pressure properties.

[20] A. E. Dunstan and F. B. Thole, *J. Chem. Soc.*, **103,** 127 (1913).

[21] Viscosity data of the diethyl esters were taken from R. Cedar, *Ann. Univ. Fennicae Aboensis Series*, **A2,** No. 4, 14 pp. (1926) (*C. A.*, **22,** 3137 (1928)).

equal number of carbon atoms. The lactic esters (I and II) were more viscous than the corresponding ethyl alkanoates[22] and *n*-paraffins[23] (Fig. 4).

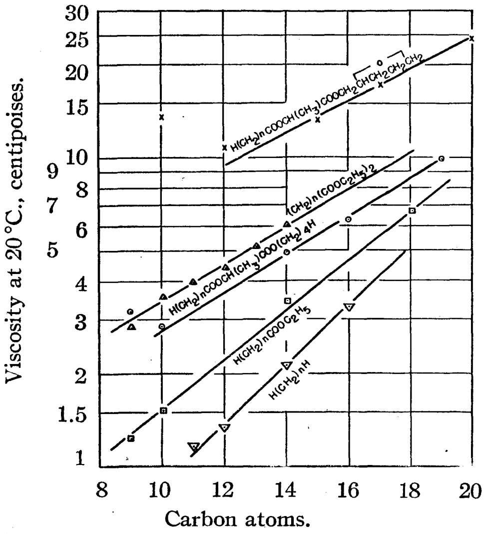


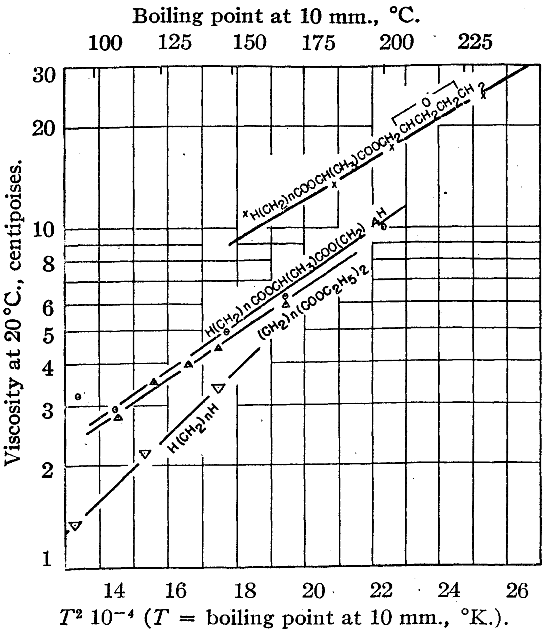
Fig. 4.—Relation between viscosity and carbon atoms of homologous compounds.

The viscosities of the *n*-butyl lactate (I) and tetrahydrofurfuryl lactate (II) derivatives are plotted in Fig. 5 as a function of the boiling points at 10 mm. The viscosities of the higher *n*-alkanoyl derivatives of butyl lactate were similar to those of the diethyl esters ($(CH_2)_n(COOC_2H_5)_2$) and *n*-paraffins of the same boiling point, but the tetrahydrofurfuryl esters (II) had viscosities considerably higher than those of the corresponding linear compounds (Fig. 5).

The values of Souders' viscosity function[24] were calculated (Table II) for the esters (I and II) of lactic acid; the I values calculated from the formula

$$I = \frac{M}{d}\log_{10}(\log_{10}n) + 2.9$$

where M = molecular weight, d = density and n = viscosity agreed moderately well with those estimated from the atomic and group increments.[24] In agreement with Lagemann,[25] the ratios between the I values and molecular refraction were approximately 12.



T^2 10^{-4} (T = boiling point at 10 mm., °K.).

Fig. 5.—Relation between boiling points at 10 mm. and viscosity of homologous compounds.

Several of the compounds of Table I had vapor pressures (Table III and Fig. 1) sufficiently low for use as plasticizers.[26] The suggestion that some of the esters of the present work should be suitable as plasticizers is supported by their relatively low viscosity, moderate stability in the presence of boiling water, and compatibility with certain commercially important plastics (Table III).

Acknowledgment.—W. P. Ratchford demonstrated that the alembic type still is suitable for determining boiling points at relatively low pressures and verified the boiling points of Figure 1. The authors are grateful for this major contribution.

Summary

Several homologous *n*-alkanoyl derivatives of *n*-butyl lactate ($H(CH_2)_nCOOCH(CH_3)COO(CH_2)_4H$) and of tetrahydrofurfuryl lactate ($H(CH_2)_nCOOCH(CH_3)COOCH_2\underbrace{CHCH_2CH_2CH_2}_{O}$) were prepared in high yields by treating the corresponding lactic esters with acid chlorides or anhydrides. Relationships between physical properties and molecular weight are given, from which the density, refractive index, viscosity and boiling point at 10 mm. of the missing members can be calculated.

PHILADELPHIA 18, PA. RECEIVED APRIL 25, 1947

---

[22] Viscosities of ethyl *n*-alkanoates were obtained from A. E. Dunstan, F. B. Thole and P. Benson, *J. Chem. Soc.*, **105**, 782 (1914).

[23] "Landolt–Bornstein Tabellen," 3rd Supplement, p. 162, 1935, Julius Springer, Berlin; E. C. Bingham and H. J. Fornwalt, *J. Rheol.*, **1**, 372 (1930).

[24] M. Souders, Jr., THIS JOURNAL, **60**, 154 (1938); A. N. Planovskii and V. V. Kafarov, *Khimicheskaya Prom.*, No. 8, 19 (1944) (*C. A.*, **40**, 2048 (1946)).

[25] R. T. Lagemann, THIS JOURNAL, **67**, 498 (1945).

[26] This statement is based on a comparison of the esters with *n*-butyl phthalate, a widely used plasticizer having a vapor pressure of 10 mm. at 195°.[7]

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LXXXIV. The High Pressure Hydrogenation of Maple Wood: Hydrol Lignin[1]

BY CHARLES P. BREWER,[2] LLOYD M. COOKE[3] AND HAROLD HIBBERT[4]

In the investigation of the structure of lignin, the techniques of oxidation[5,6] and ethanolysis have been extensively employed. Oxidation of spruce and maple woodmeal gave yields of aldehydes of 25 and 46%, respectively, based on the lignin originally present, but as these compounds are only lignin degradation products, they give no clue to the structure of the side-chains existing in the original lignin unit. On the other hand, while the yields of identifiable lignin products isolated from the ethanolysis procedure are low, they possess a marked significance with respect to the structure of lignin inasmuch as they evidently represent stabilized end-products of the more reactive, true lignin progenitors.[7]

Previous to this investigation, the products of high pressure catalytic hydrogenation of wood and lignin have been isolated mainly in the form of propylcyclohexane derivatives.[8a,b,c,9] This paper describes a method for isolating lignin from wood under hydrogenation conditions in a form believed to be essentially unchanged from that in the wood. In addition, several new products of lignin degradation have been isolated and identified.

This method consists in hydrogenating maple woodmeal over Raney nickel catalyst[10] in a neutral solution of ethanol–water (1:1) under mild conditions (165–170° for four hours) and separating the lignin from the cellulose degradation products by extraction with chloroform. In this way 75–85% of the original lignin is removed from the wood under such conditions that little or no condensation should occur. This new lignin product has been named "hydrol" lignin.

Preliminary investigations show that hydrol lignin contains phenol and methoxyl groups, but no carbonyl groups or ethylenic linkages. It is not degraded when subjected to ethanolysis, and thus appears to be more stable than lignin isolated by ethanolysis.[11] Hydrogenation of hydrol lignin at 205° results in only partial saturation, as indicated by the high yield of phenolic material in the reaction mixture. Since most aromatic derivatives are completely reduced under the conditions of this hydrogenation, this result is considered unusual.

Hydrogenation of hydrol lignin over Raney nickel and copper chromium oxide at 225° yielded a water-soluble fraction containing 4-ethylcyclohexanol to the extent of 9.7% of the original weight of lignin. This product probably resulted from the hydrogenation of 3-(4-hydroxycyclohexyl)-1-propanol, as does ethylcyclohexane from 3-cyclohexyl-1-propanol in 80% yield.[12] No identifiable products were isolated from the water-insoluble portion.

At 250°, hydrogenation of hydrol lignin over copper chromium oxide produced 4-*n*-propylcyclohexanol (I), 3-cyclohexyl-1-propanol (II), and 3-(4-hydroxycyclohexyl)-1-propanol (III), in yields of 3.1, 3.4, and 5.5%, respectively, based on the original Klason lignin. These products have been isolated in previous investigations[8,9] and thus indicate a marked similarity of behavior between hydrol lignin, other isolated lignins and protolignin.

Hydrol lignin was solvent-fractionated by precipitation into 30–50° petroleum ether, yielding 10–15% of a soluble fraction. This product was distilled through a 28-plate column,[13] but the variations in refractive indices and methoxyl contents of the distillate indicated preliminary separation was necessary. Accordingly, a separation into acid-soluble, alkali-soluble and neutral portions was made, and the large, alkali-soluble portion was fractionally distilled. The following products were thereby isolated: 3-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanol, (IV), 3-(4-hydroxy-3-methoxyphenyl)-1-propanol, (V) and 3-(4-hydroxy-3,5-dimethoxyphenyl)-propane (VI) in yields of 1.4, 0.84 and 0.83%, respectively, based on the original lignin.

An additional quantity of IV amounting to 7.4% of the lignin, was obtained by precipitating the petroleum ether-insoluble hydrol lignin into diethyl ether, and fractionally distilling the alkali-soluble portion of the ether-soluble lignin.

Synthesis of IV (not previously reported), was carried out by the following series of reactions

$$\text{Maple wood} \xrightarrow[\text{Nitrobenzene}]{\text{NaOH}} \text{RCHO} \xrightarrow{CH_2(COOH)_2}$$

---

[1] From a thesis submitted to the Graduate Faculty of McGill University by Charles P. Brewer in partial fulfilment of the requirements for the degree of Doctor of Philosophy, October, 1943.

[2] Holder of a Studentship awarded by the National Research Council of Canada, 1941–1942. Present address: Shell Development Laboratories, Emeryville, Calif.

[3] Present address: Visking Corporation, Chicago, Illinois.

[4] Deceased, May 13, 1945.

(5) Freudenberg, Lautsch and Engler, *Ber.*, **73**, 167 (1940).

(6) Creighton, McCarthy and Hibbert, THIS JOURNAL, **63**, 312 (1941).

(7) Hibbert, *Ann. Rev. Biochem.*, **12**, 183 (1942).

(8) (a) Harris, D'Ianni and Adkins, THIS JOURNAL, **60**, 1467 (1938); (b) Adkins, Frank and Bloom, *ibid.*, **63**, 549 (1941); (c) Harris, Salmon and Sherrard, *Ind. Eng. Chem.*, **32**, 440 (1940).

(9) Cooke, McCarthy and Hibbert, *ibid.*, **63**, 3052, 3056 (1941).

(10) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

(11) West, Hawkins and Hibbert, *ibid.*, **63**, 3038 (1941).

(12) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937.

(13) Cooke and Bower, *Ind. Eng. Chem. Anal. Ed.*, **15**, 290 (1943).

$$\mathrm{RCH{=}CHCOOH}^{(13a)} \xrightarrow{\mathrm{H_2}} \mathrm{RCH_2CH_2COOH} \xrightarrow{\mathrm{EtOH,\ H_2SO_4}} \mathrm{RCH_2CH_2COOEt} \xrightarrow{\mathrm{Na,\ EtOH}} \mathrm{RCH_2CH_2CH_2OH}\ \text{(IV)}$$

(R = 4-hydroxy-3,5-dimethoxyphenyl)

The isolation of the previously known saturated compounds, I, II, III, by the hydrogenation of hydrol lignin indicated the similar behavior of this material, wood, and isolated lignins when subjected to the same conditions of hydrogenation. The structure of these isolated products pointed to their derivation from propylphenol derivatives containing terminal oxygen atoms on the side chains, probably in the form of ether or acetal linkages.

Isolation of the aromatic derivatives (IV, V and VI) provides valuable support for the above theory, since 92% of these products contain terminal carbinol groups on the side chain. Furthermore, the methoxyl groups are left intact, thus permitting the isolation of guaiacyl (4-hydroxy-3-methoxyphenyl) and syringyl (4-hydroxy-3,5-dimethoxyphenyl) derivatives as wood hydrogenation–hydrogenolysis products for the first time.

Moreover, the difference in yields between the guaiacyl- and syringyl- containing propylphenol derivatives points to a marked difference in the mode of linkage by which these are united to similar units in protolignin, and supports the theory that in the former we are concerned largely with —C—C— linkages, and in the latter with —C—O—C— linkages between propylphenol units.

Experimental

Preparation of Hydrol Lignin.—Maple woodmeal (22 g. 20.3% Klason lignin, 6.1% $\mathrm{OCH_3}$ and 4–6% water) was mixed with 1:1 ethanol:water (220 cc.) and moist Raney nickel catalyst (16.5 g.) and hydrogenated for four hours at 165–170° with an initial hydrogen pressure of 3000 lb./sq. in. The pulp yield was 65% of the dry wood and the lignin removal was 75–85%, based on the original lignin in the wood. The pulp was filtered from the reaction medium, the solution concentrated to incipient precipitation, and then extracted three times with an equal volume of chloroform. The chloroform solution was dried and concentrated to a clear, red-brown viscous oil containing 24–25% $\mathrm{OCH_3}$ and representing 70–80% of the lignin in the wood. Hydrol lignin prepared in this way was used in all further experiments.

Hydrogenation of Hydrol Lignin. I. At 250°.—Hydrol lignin (7 g.) was hydrogenated in dioxane (150 cc.) for five hours at 250° over copper–chromium oxide catalyst[12] (10 g.) with an initial hydrogen pressure of 3000 lb./sq. in. The catalyst was removed by centrifugation, and the dioxane and lower boiling compounds by distillation. The residual colorless oil was dissolved in ether (20 cc.) and the solution extracted five times with 10-cc. portions of water. The extracted ether solution contained 3.1 g. water-insoluble oils, while the water extract contained 1.4 g.

(a) **Isolation and Identification of 4-*n*-Propylcyclohexanol and 3-Cyclohexyl-1-propanol.**—The water-insoluble oils (3.1 g.) were fractionated through a Podbielniak column[15] at 0.1 mm. pressure and bath temperatures up to 250° to yield two identifiable fractions, 4-*n*-propylcyclohexanol (n^{25}_{D} 1.4640–1.4648) and 3-cyclohexyl-1-propanol (n^{25}_{D} 1.4650–1.4679), identified as their phenylurethans, m. p. 126–127° and 84–85°, respectively. Yields were 0.4 and 0.43 g., respectively.

(b) **Isolation and Identification of 3-(4-Hydroxycyclohexyl)-1-propanol.**—The water-soluble oils (1.4 g.) were fractionated in a semi-micro column[13] to give 0.7 g. of a semi-crystalline fraction n^{53}_{D} 1.4768–1.4786 identified as 3-(4-hydroxycyclohexyl)-1-propanol by oxidation to β-(4-ketocyclohexyl)-propionic acid and preparation of the semicarbazone.[9]

II. **At 225°.**—Hydrol lignin (10.9 g.) was hydrogenated in dioxane (180 cc.) for seven and one-half hours at 225° over Raney nickel (10 g.) and copper–chromium oxide (8 g.) with an initial hydrogen pressure of 3100 lb./sq. in. The products were separated into water-soluble (0.5 g.) and -insoluble (3.9 g.) fractions as described above, and the latter fractionally distilled through a 28-plate column.[13] From the products a fraction with n^{25}_{D} 1.4600–1.4615 was isolated and identified as 4-ethylcyclohexanol by a mixed melting point of the phenylurethan with an authentic sample. Melting point of urethan 113.5–114.5°; yield 1.25 g.

The water-soluble portion (0.5 g.) was not identified.

Fractionation of Hydrol Lignin.—(1) Hydrol lignin (9.5 g.) was dissolved in chloroform (100 cc.) and precipitated by pouring into two liters of 30–50° petroleum ether with stirring. The oily precipitate was allowed to separate, the clear supernatant liquor was decanted, and the residual solvent removed by evaporation, leaving the petroleum ether-soluble fraction as a viscous oil (1.0 g.). The petroleum ether-insoluble material (8.4 g.) was further fractionated by dissolving in chloroform (80 cc.) and extracting four times with 20 cc. of saturated sodium bicarbonate solution. The extracts were combined, neutralized with 10% sulfuric acid and back-extracted with four 20-cc. portions of chloroform, which were then combined, dried over sodium sulfate and the solvent removed; yield of acid fraction 0.6 g. A similar treatment of the residual chloroform solution with 5% sodium hydroxide solution yielded an alkali-soluble fraction of 6.4 g. and left a neutral fraction of 0.8 g. in the residual chloroform solution.

(2) A quantity (17.4 g.) of the petroleum ether-insoluble hydrol lignin obtained according to the above procedure was dissolved in chloroform (100 cc.) and precipitated into 1 liter of diethyl ether. A light buff-colored amorphous precipitate (6.4 g.) was removed by filtration, and evaporation of the filtrate left a reddish oil, 11 g. (42% of Klason lignin). An aliquot (9.6 g.) of this oil was separated into acid (0.95 g.), alkali-soluble (6.6 g.), and neutral fractions (0.7 g.) by the procedure described above in I.

Isolation and Identification of 3-(4-Hydroxy-3,5-dimethoxyphenyl)-1-propanol, IV.—The alkali-soluble fraction (6.4 g.) of petroleum ether-soluble hydrol lignin (from 108 g. of Klason lignin) was fractionated through a 28-plate column[13] (270–290° bath temp. at 0.25 mm. pressure) and yielded a white, crystalline product, m. p. 75.5–76.5° after recrystallization from benzene. A mixed m. p. with a synthetic sample described below showed no depression; yield 1.5 g. (1.4% of lignin).

The alkali-soluble portion (6.6 g.) of the petroleum ether-insoluble, diethyl ether-soluble hydrol lignin was fractionated in the same column to yield an additional quantity of the same crystalline product; yield 1.72 g. (7.4% of the Klason lignin).

Isolation and Identification of 3-(4-Hydroxy-3-methoxyphenyl)-1-propanol (V).—Fractions (1.35 g., n^{50}_{D} 1.5200–1.5380) obtained in the fractionation of the alkali-soluble portion of petroleum ether-soluble hydrol lignin described in the previous section were combined and refractionated in a smaller column,[13] (bath temp. 170° at 0.2 mm. pressure) to yield a clear, colorless oil, n^{50}_{D} 1.5360–1.5380, identified as 3-(4-hydroxy-3-methoxyphenyl)-1-propanol

---

[13a] Sinapic acid melted at 178–183° (reported 191–192°[14]) and could not be further purified by recrystallization.

[14] Graebe and Martz, *Ber.*, **36**, 1031 (1903).

[15] Podbielniak, *Ind. Eng. Chem. Anal. Ed.*, **3**, 177 (1931); **5**, 119 (1933).

by a mixed melting point of the bis-*p*-nitrobenzoate with that of the synthetic derivative; yield was 0.9 g. (0.84% of Klason lignin).

Isolation and Identification of 3-(4-Hydroxy-3,5-dimethoxyphenyl)-propane (VI).—Fractions (1.45 g., n^{50}D 1.5000–1.5150), also obtained from the fractionation of alkali-soluble, petroleum ether-soluble hydrol lignin, were combined and refractionated to yield a clear, colorless oil identified as 3-(4-hydroxy-3,5-dimethoxyphenyl)-propane by a mixed m. p. of the acetate with that of the synthetic product; yield was 0.89 g. (0.83% of Klason lignin).

Synthesis of Products Isolated from Hydrol Lignin. I. 3-(4-Hydroxy-3,5-dimethoxyphenyl)-1-propanol (IV) Syringaldehyde.—A mixture of vanillin and syringaldehyde was prepared by the oxidation of maple woodmeal, using the method of Creighton.[16] The syringaldehyde was separated from the vanillin by the method of Hunter and Hibbert.[17] A total of 400 g. of maple woodmeal was treated to yield 18 g. of syringaldehyde, m. p. 110–112°.

β-(4-Hydroxy-3,5-dimethoxyphenyl)-acrylic Acid (Sinapic Acid).[18]—A mixture of syringaldehyde (11.1 g.), malonic acid (14.5 g.), pyridine (33 cc.) and piperidine (0.7 cc.) was heated together at 80–85° for four hours, cooled, and dilute hydrochloric acid added (125 cc.). The product crystallized out immediately in fine, pale-yellow needles; m. p., 178–183°; yield was 8.2 g. (60%).

β-(4-Hydroxy-3,5-dimethoxyphenyl)-propionic Acid (Hydrosinapic Acid).—Sinapic acid (7.2 g.), ethanol (155 cc.), water (50 cc.) and Raney nickel catalyst (3 g.) were hydrogenated at an initial hydrogen pressure of 2200 lb./sq. in. The charge was heated to 110–115° in fifteen minutes, then allowed to cool for one hour with agitation. Removal of the solvent left a grey-white solid which was recrystallized from water and then from ether–petroleum ether, m. p. 102–103°, yield 6.7 g. (92%). The product crystallized in white needles, readily soluble in ethanol and ether.

Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.4; H, 6.25; OCH_3, 27.5. Found: C, 58.4; H, 6.4; OCH_3, 27.6.

Ethyl Hydrosinapate.—Hydrosinapic acid (5.2 g.) was esterified by the method of Nomura and Hotta.[19] A clear, colorless oil was obtained, b. p. 178–179° (1 mm.), n^{25}D 1.5250; yield was 5.4 g. (93%).

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.4; H, 7.14; OR, 36.6. Found: C, 61.5; H, 7.2; OR, 36.6.

3-(4-Hydroxy-3,5-dimethoxyphenyl)-1-propanol, IV.—To sodium (0.96 g.), in small pieces, was added rapidly with stirring a solution of the ester (1.76 g.) in absolute ethanol (10.6 g.). The mixture was refluxed for four hours, 15 cc. of water added and the refluxing continued for one hour. The ethanol was then removed, the residual solution neutralized with 10% sulfuric acid and extracted with four 10-cc. portions of ether. The latter were combined, extracted with five 5-cc. portions of sodium bicarbonate solution, dried and evaporated to dryness. The residue was recrystallized from ether–petroleum ether, from which, on cooling, fine white needles separated, m. p. 75.5–76.5°; yield was 15–20%. No further change in melting point was found on repeated recrystallization.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.2; H, 7.61; OCH_3, 29.3. Found: C, 62.3; H, 7.8; OCH_3, 29.1.

II. 3-(4-Hydroxy-3-methoxyphenyl)-1-propanol, V.—This was synthesized by the same method as used above, save that vanillin was used as a starting material. The alcohol was a colorless, slightly cloudy oil, b. p. 197° (15 mm.), n^{25}D 1.5545.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.95; H, 7.7; OCH_3, 17.05. Found: C, 65.95; H, 7.95; OCH_3, 17.0.

The **bis-*p*-nitrobenzoate** was prepared by the method of Kawai and Sugiyama,[20] m. p. 119.5–120.5°, yield 30%.

III. Acetate of 3-(4-Hydroxy-3,5-dimethoxyphenyl)-propane.—A sample (0.112 g.) of 3-(4-hydroxy-3,5-dimethoxyphenyl)-propane[17] (b. p. 123–126° (0.1 mm.), n^{25}D 1.5285), glacial acetic acid (0.1 cc.) and acetyl chloride (0.065 cc.) were refluxed for one hour and then poured over ice (2 cc.), whereupon a brown oil separated. The oil and aqueous mixture was extracted with ether, the ether solution dried over sodium sulfate and the solvent removed, leaving a white crystalline solid. Recrystallization from ethanol yielded 0.09 g. of a pure product, m. p. 87–88°.

IV. 4-Ethylcyclohexanol.—Acetovanillone (5 g.), dioxane (60 cc.) and copper–chromium oxide catalyst (3 g.) were hydrogenated for 1.3 hr. at 273–278° at an initial hydrogen pressure of 2930 lb./sq. in. The residual oil was distilled to yield 2.7 g. of a clear colorless oil (b. p. 83–84° (10 mm.), n^{25}D 1.4607) identified as the phenylurethan, m. p. 114–115°.[21]

Summary

1. A new method has been developed for the extraction of lignin from maple wood by a hydrogenation–hydrogenolysis procedure. A separation of this extracted lignin from carbohydrate material has been achieved, and the purified product has been designated as "hydrol" lignin.

2. Hydrogenation studies of hydrol lignin have indicated a marked similarity of behavior to other isolated lignins and to wood under the same conditions of hydrogenation.

3. From hydrol lignin three new propylphenol derivatives have been isolated, *viz.*, 3-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanol, 3-(4-hydroxy-3-methoxyphenyl)-1-propanol and 3-(4-hydroxy-3,5-dimethoxyphenyl)-propane in yields of 8.8, 0.84 and 0.83%, respectively, based on the original Klason lignin. The structural significance of these derivatives to the lignin nucleus rests on the fact that they are the first propylphenol derivatives, isolated from wood or lignin by hydrogenation, in which a terminal —CH_2OH group is present in the side chain.

4. The synthesis and properties of a new compound, 3-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanol, are reported.

CHICAGO, ILLINOIS RECEIVED MAY 19, 1947

---

[16] Creighton, McCarthy and Hibbert, THIS JOURNAL, **63**, 3049 (1941).

[17] Hunter and Hibbert, *ibid.*, **61**, 2190 (1939).

[18] Brand and Westerburg, *Arch. Pharm.*, **269**, 326 (1931).

[19] Nomura and Hotta, *Sci. Repts. Tohoku Imp. Univ., 1st ser.*, **17**, 693 (1928).

[20] Kawai and Sugiyama, *Ber.*, **72B**, 367 (1939).

[21] Adkins, Frank and Bloom, THIS JOURNAL, **63**, 549 (1941).

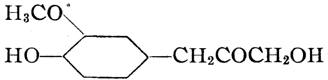
[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LXXXV. Synthesis and Properties of Dimers Related to Lignin[1]

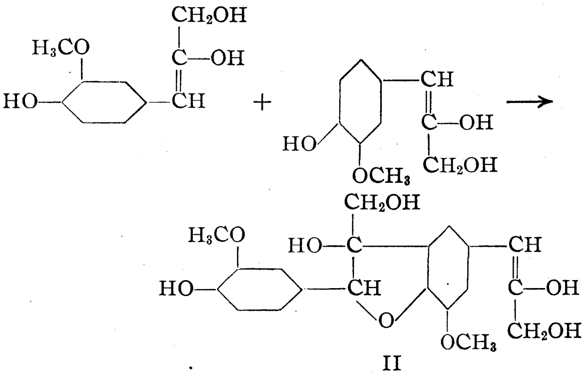
BY SAMUEL B. BAKER,[2] TAYLOR H. EVANS[3] AND HAROLD HIBBERT[4]

A considerable number of previous investigations[5–9] carried out in these laboratories have given clear experimental support to Hibbert's assumption that protolignin consists of a mixture of different substances derived from relatively simple propylphenol units. Although considerable uncertainty still exists regarding the nature of the C_3 side chain and the mode of its linkage in the complex protolignin structure, several experimental facts have been established. The aromatic portion of spruce protolignin is always the guaiacyl (4-hydroxy-3-methoxyphenyl) nucleus,[10] the side chain is an oxygenated radical[7,8,9] without terminal methyl groups[11] and it contains primary hydroxyl groups.[5,6]

According to Hibbert,[12] the experimental results seem to indicate that a large portion of native lignin consists of a polymer or polymers of the dehydrodiisoeugenol type, in which the isoeugenol unit is replaced by β-oxyconiferyl alcohol (I). Dimerization of the enol modification of (I) to yield dehydrodi-(β-oxyconiferyl)-alcohol (II) is highly probable since this has been shown by Erdtman[13] and by Haworth[14] to be typical of the dimeric plant resins or lignins.

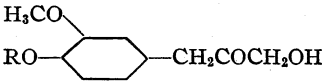


I

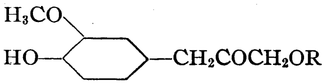


II

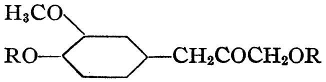
Inasmuch as the ethanolysis reaction indicates that some of the native lignin is present in a much less complex form (water-soluble) than the remainder (water-insoluble fractions),[15] it has been suggested that the ethanolysis products result from the decomposition of the less complex form. Hibbert suggests three general types of relatively simple units that could yield the ethanolysis products. These are assumed to be the glycosides (III), (IV), (V), the hemiketals (VI), (VII) and the ether (VIII).



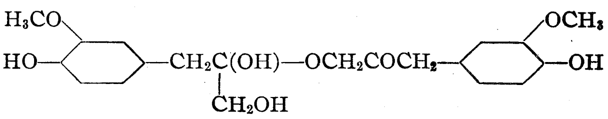
III



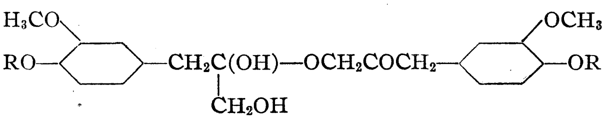
IV



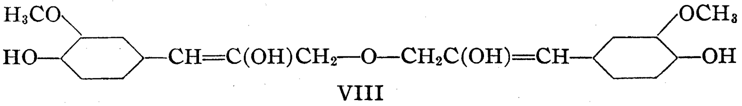
V



VI



VII



VIII

(R is carbohydrate unit)

These (III, IV, V, VI, VII, VIII) could yield β-oxyconiferyl alcohol (I) on ethanolysis and the latter could undergo dismutation and rearrangement[12] to yield the ethyl ethers of (IX) and (XII) and also (X) and (XI), actually obtained by ethanolysis of spruce wood.

---

[1] This paper represents part of a thesis submitted to the Faculty of Graduate Studies and Research, McGill University, by Samuel B. Baker, in partial fulfilment of the requirements for the degree of Doctor of Philosophy, October, 1943.

[2] Present address: Montreal General Hospital, Montreal, Que.

[3] Present address: Dominion Rubber Co. Ltd., Research Laboratories, Guelph, Ont.

[4] Late E. B. Eddy Professor of Chemistry, McGill University.

[5] Godard, McCarthy and Hibbert, THIS JOURNAL, **63**, 3061 (1941).

[6] Cooke, McCarthy and Hibbert, *ibid.*, **63**, 3056 (1941).

[7] Hunter, Cramer and Hibbert, *ibid.*, **61**, 516 (1939).

[8] Brickman, Hawkins and Hibbert, *ibid.*, **62**, 2149 (1940).

[9] Kulka, Hawkins and Hibbert, *ibid.*, **63**, 2371 (1941).

[10] Creighton, Gibbs and Hibbert, *ibid.*, **66**, 32 (1944).

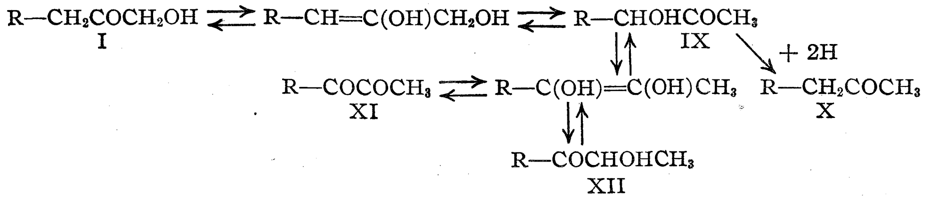
[11] MacGregor, Evans and Hibbert, *ibid.*, **66**, 41 (1944).

[12] Hibbert, *Biochem. Rev.*, **11**, 183 (1942).

[13] Erdtman, *Svensk Papperstidn.*, **44**, 243 (1941); translation in *Pulp and Paper Magazine of Canada*, Feb. (1942).

[14] Haworth, *Nature*, **147**, 255 (1941).

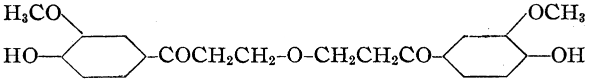
[15] Kulka, Fisher, Baker and Hibbert, THIS JOURNAL, **66**, 39 (1944).

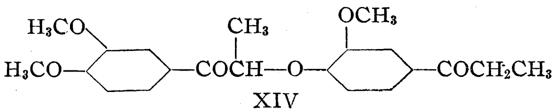


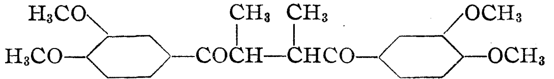
(R is 4-hydroxy-3-methoxyphenyl)

Experimental support for this mechanism recently has been obtained.[16]

It was desirable to synthesize compounds of structures similar to (II) and (VIII) in order to test the validity of Hibbert's[11] suggestions regarding the probable structures of the simple and more complex portions of spruce protolignin. Three dimeric compounds have been synthesized, 2,2′-divanilloyl diethyl ether (XIII), 1-veratroyl-1-(2-methoxy-4-(propanone-1)-phenoxy)-ethane (XIV), and 2,3-diveratroylbutane (XV). The first (XIII) was synthesized by the iodine dehydration[17] of 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone. The second (XIV) was prepared by a Williamson reaction between the sodium phenolate of 1-(4-hydroxy-3-methoxyphenyl)-1-propanone and 2-bromo-1-(3,4-dimethoxyphenyl)-1-propanone. The third (XV) was prepared by means of an acetoacetic ester synthesis.


XIII


XIV


XV

The first dimer (XIII) is characterized by the presence of a dialkyl ether linkage between the two propylphenol units, each of which has a carbonyl group in the γ-position to the ether linkage and adjacent to the ring. The second dimer (XIV) differs from the first (XIII) in that it contains (a) an alkaryl ether linkage and (b) the carbonyl group in the β-position to the ether linkage and adjacent to the ring. The third dimer (XV) is characterized by (a) a carbon–carbon linkage between carbon atoms β- to the ring and (b) carbonyl groups adjacent to the rings.

Each of these dimers (XIII), (XIV), (XV) was heated with 2% ethanolic hydrogen chloride. The first (XIII) yielded about 15% of an amorphous lignin-like product, the balance about 80% being recovered unchanged. Chain fission probably did occur to a small extent and the fission products underwent immediate polymerization. The second (XIV) was unaffected by this treatment; no monomolecular fission products were isolable. The third (XV) treated similarly, with 2% ethanolic hydrogen chloride, gave a high yield (80%) of an amorphous lignin-like product with no indication of chain fission to stable monomolecular units. Hydrogenation[18] of this carbon–carbon linked dimer (XV) did not result in cleavage into monomolecular products. Therefore it may be that polymerization of (XV) during ethanolysis occurred not due to primary cleavage into reactive monomolecular units but due to the inherent reactivity of the 1,4-diketonic grouping.

Experimental

Synthesis of 2,2′-Divanilloyl Diethyl Ether (XIII)

3-Bromo-1-(4-hydroxy-3-methoxyphenyl)-1-propanone. Powdered anhydrous aluminum chloride (10 g.) was suspended in anhydrous carbon disulfide (40 cc.) in a three-necked round-bottomed flask equipped with a mercury-sealed stirrer, a reflux condenser with drying tube and a dropping funnel. The reaction flask was cooled by immersion in ice-water and β-bromopropionyl chloride (13.0 g.) added rapidly to the well-stirred suspension. Veratrole (10.0 g.) was added gradually during one hour with vigorous stirring, then two more 10-g. portions of aluminum chloride were added, the second portion fifteen minutes after the first. The reaction mixture was heated at 50° for one hour, allowed to stand overnight at room temperature and the carbon disulfide decanted. The Perrier complex was decomposed in a mixture of ice and concentrated hydrochloric acid. The product was filtered, washed on the filter with 10% hydrochloric acid and finally with water. The crude, dried product was dissolved in ether and decolorizing charcoal added. The suspension was heated under reflux for one hour, filtered and petroleum ether (30–50°) added until a permanent turbidity was formed. A crystalline product separated from the cooled solution and was recrystallized from ether–petroleum ether yielding 11.1 g. (60%), m. p. 103–104°.

Anal. Calcd. for $C_{10}H_{11}O_3Br$: OCH_3, 11.9; Br, 30.9. Found: OCH_3, 11.8; Br, 30.7.

The product was further characterized by conversion into the known[19] 3-acetoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone.

3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone.—Aqueous sodium hydroxide (1%, 100 cc.) was added to 3-bromo-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (2 g.) in a round-bottomed flask. The reaction mixture was heated at 50° for four hours, cooled and then acidified with dilute hydrochloric acid. The acidified solution was extracted with eight portions of chloroform (60 cc.) and the combined chloroform solutions were dried over anhydrous sodium sulfate. The solvent was removed and the resulting product twice recrystallized from hot benzene (30 cc.) yielding 1.32 g. (88%), m. p. 109–110°. A mixed melting point determination with an authentic sample of 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone showed no depression.

2,2′-Divanilloyl Diethyl Ether (XIII).—3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (3.0 g.) was dissolved in hot anhydrous benzene (25 cc.) in a small Claisen flask fitted with a reflux condenser. A crystal of

---

(16) Fisher, Kulka and Hibbert, THIS JOURNAL, **66**, 598 (1944).

(17) Hibbert, *ibid.*, **37**, 1748 (1915).

(18) Baker and Hibbert, *ibid.*, **70**, 63 (1948).

(19) K. E. West and Hibbert, *ibid.*, **65**, 1170 (1943).

re-sublimed iodine (0.05 g.) was added and the solution was refluxed for one hour on the steam-bath. The benzene was removed by distillation at atmospheric pressure. The resulting product, a viscous oil, was dissolved in hot methanol (5 cc.) and on cooling, crystals separated rapidly. The crude product was recrystallized from anhydrous methanol yield 1.0 g. (36%), m. p. 153–154°.

Anal. Calcd. for $C_{20}H_{22}O_7$: C, 64.17; H, 5.88; OCH_3, 16.6; mol. wt., 374. Found: C, 64.2; H, 5.9; OCH_3, 16.6; Rast mol. wt., 380.

The bis-2,4-dinitrophenylhydrazone was prepared by the usual method.

Anal. Calcd. for $C_{32}H_{30}O_{13}N_8$: C, 52.31; H, 4.08; OCH_3, 8.4. Found: C, 52.4; H, 4.1; OCH_3, 8.4.

Diazomethane Methylation of XIII.—2,2′-Divanilloyl diethyl ether (0.16 g.) was dissolved in benzene and a solution of diazomethane in benzene was added. The solvent was removed after twenty-four hours and the unmethylated portion was removed by washing with 2% alkali. The remaining portion was dissolved in hot ethanol. Crystals separated rapidly when the solution was cooled yielding 0.15 g. (89%), m. p. 139–140°.

Anal. Calcd. for $C_{22}H_{26}O_7$: C, 65.69; H, 6.47; OCH_3, 30.8; mol. wt., 402. Found: C, 65.6; H, 6.6; OCH_3, 30.6; Rast mol. wt., 395.

Oxidation of 2,2′-Diveratroyl Diethyl Ether.—The methylated ether (0.13 g.) was suspended in 3% aqueous sodium hydroxide (50 cc.) in a small three-necked flask fitted with a reflux condenser, stirrer, and a dropping funnel. Aqueous potassium permanganate (9%, 25 cc.) was added dropwise to the hot (100°) stirred alkaline suspension during one hour. The precipitated manganese dioxide was removed by filtration and the clear filtrate acidified with dilute hydrochloric acid. A crystalline substance separated and was recrystallized from methanol–water (3:1) yielding 0.09 g. (77%), m. p. 180–181°. A mixed melting point determination with an authentic sample of veratric acid showed no depression.

Synthesis of 1-Veratroyl-1-[2-methoxy-4-(propanone-1)-phenoxy]-ethane (XIV)

2-Methoxyphenyl Propionate.—A solution of guaiacol (25 g.), pyridine (20 g.) and propionyl chloride (19 g.) was heated on the steam-bath during one hour. The reaction mixture was cooled and then poured into 2% aqueous hydrochloric acid. The aqueous solution was extracted with two portions (50 cc.) of ether and the combined solutions dried over anhydrous sodium sulfate. The solvent was removed and the resulting oil distilled from a Claisen flask at 140–143° (20 mm.) yielding 34.5 g. (95%).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67; OCH_3, 17.2. Found: C, 66.6; H, 6.9; OCH_3, 17.0.

1-(4-Hydroxy-3-methoxyphenyl)-1-propanone.—Powdered anhydrous aluminum chloride (30 g.) was dissolved in anhydrous nitrobenzene (75 cc.) at 100°. The solution was cooled and added to a three-necked round-bottomed flask, equipped with a mercury-sealed stirrer, a reflux condenser with drying tube, and a thermometer. Stirring was started and 2-methoxyphenyl propionate (20 g.) was added rapidly. The reaction mixture was heated at 60° for one hour, then allowed to stand overnight at room temperature. The mixture was filtered with the exclusion of air and moisture and the Perrier complex washed well with a mixture of benzene and ligroin (2:1). The complex was decomposed in ice–hydrochloric acid and the oily layer extracted with chloroform. The chloroform solution was refluxed for one hour with activated charcoal and after filtration the solvent was removed under reduced pressure. The oily product crystallized and it was recrystallized from ether–petroleum ether (30–50°) yielding 13 g. (65%), m. p. 62–63°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67; OCH_3, 17.2. Found: C, 66.6; H, 6.9; OCH_3, 17.2.

1-Veratroyl-1-[2-methoxy-4-(propanone-1)-phenoxy]-ethane.[20]—The sodium phenolate, prepared from sodium (2.0 g.) and 1-(4-hydroxy-3-methoxyphenyl)-1-propanone (14.7 g.) was dissolved in anhydrous ethanol (300 cc.) in a round-bottomed flask. 2-Bromo-1-(3,4-dimethoxyphenyl)-1-propanone[21] (22.3 g.) was added and the solution heated under reflux for four hours. The hot solution was poured into cold water and the microcrystalline precipitate removed by filtration. The crude product was recrystallized twice from methanol yielding 23.8 g. (78%), m. p. 148–149°.

Anal. Calcd. for $C_{21}H_{24}O_6$: C, 67.74; H, 6.45; OCH_3, 25.0; mol. wt., 372. Found: C, 67.7; H, 6.5; OCH_3, 24.9; Rast mol. wt., 387.

The bis-2,4-dinitrophenylhydrazone was prepared by the usual method.

Anal. Calcd. for $C_{33}H_{32}O_{12}N_8$: C, 54.09; H, 4.37; OCH_3, 12.7; mol. wt., 732. Found: C, 54.0; H, 4.4; OCH_3, 12.6; Rast mol. wt., 724.

Synthesis of 2,3-Diveratroylbutane (XV)

Ethyl Veratrate.—The ester was prepared by refluxing during four hours veratric acid (80 g.), anhydrous ethanol (500 cc.) and sulfuric acid (15 cc.). The product was isolated in the usual manner yielding 82 g. (89%) which after one recrystallization from ether–petroleum ether (30–50°) melted sharply at 43.5–44.5°.

Anal. Calcd. for $C_{11}H_{14}O_4$: OCH_3, 44.3. Found: OCH_3, 43.9.

Ethyl Veratroylacetate.—Ethyl veratrate (50 g.) was added to a three-necked flask equipped with a reflux condenser, a dropping funnel and a glycerol-sealed stirrer. Granulated sodium (4 g.) was added, the stirrer started and the mixture heated at 80°. A pasty mass was obtained to which ethyl acetate (15 g.) was added dropwise, and the temperature raised to 90°. An additional quantity of sodium (4 g.) and ethyl acetate (15 g.) was added to the reaction mixture. This addition of sodium and ethyl acetate was continued until a total of 20 g. of sodium and 75 g. of ethyl acetate had been added. Stirring and heating were continued for sixteen hours. The mixture was cooled, added with stirring to ice–hydrochloric acid, and the acidic solution extracted with three portions of ether (250 cc.). The combined ethereal solutions were dried over anhydrous sodium sulfate and the solvent removed. The resulting oil was distilled under reduced pressure. The first fraction, boiling up to 120° (0.01 mm.), consisting mainly of ethyl acetoacetate and ethyl veratrate was discarded. The required product distilled as a viscous oil at 150–160° (0.01 mm.) yielding 24.1 g. (40%).

Anal. Calcd. for $C_{13}H_{16}O_5$: OCH_3, 36.9. Found: OCH_3, 37.3.

Methyl Ethyl Veratroylacetate.—Ethyl veratroylacetate (24 g.) was dissolved in anhydrous benzene (150 cc.) in a three-necked round-bottomed flask equipped with a reflux condenser, dropping funnel, and a glycerol-sealed stirrer. Granulated sodium (2.2 g.) was added in small portions during four hours and the mixture heated with stirring during twelve hours. Methyl iodide (15 g.), dissolved in anhydrous benzene (200 cc.), was added dropwise to the cooled mixture. Stirring was continued until the reaction mixture became transparent. The mixture was heated on the steam-bath during one hour, then cooled and added in a fine stream to cold water (500 cc.). The benzene layer was decanted and the aqueous solution extracted with ether (100 cc.). The combined benzene and ether solutions were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The resulting oil was distilled and the fraction boiling at 155–167° (0.01 mm.) collected yielding 25 g. (98%).

Anal. Calcd. for $C_{14}H_{18}O_5$: OCH_3, 34.9. Found: OCH_3, 34.3.

bis-(Methyl Ethyl Veratroylacetate).—Methyl ethyl veratroylacetate (25 g.) was dissolved in anhydrous benzene (300 cc.) in a three-necked flask equipped with a dropping funnel, a glycerol-sealed stirrer and a reflux con-

---

(20) Kratzl, *Ber.*, **77B**, 717 (1944).

(21) Cramer, Hunter and Hibbert, THIS JOURNAL, **61**, 509 (1939).

denser with a drying tube. The solution was heated on a steam-bath and granulated sodium (2.2 g.) added in small portions during two hours, with vigorous stirring. The reaction mixture became very viscous and another portion of benzene (300 cc.) was added. Iodine (13 g.) dissolved in anhydrous benzene (250 cc.), was added dropwise to the hot, well-stirred mixture during four hours. Stirring was continued for one hour longer and the solution added in a fine stream to water (one liter). The benzene layer was decanted, washed with 5% aqueous sodium thiosulfate (100 cc.) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting oil distilled at 210–216° (0.01 mm.), yielding 23.3 g. (93%).

Anal. Calcd. for $C_{28}H_{34}O_{10}$: OCH_3, 35.1. Found: OCH_3, 34.6.

2,3-Diveratroylbutane (XV).—bis-(Methyl ethyl veratroylacetate) (23 g.) was dissolved in anhydrous ethanol (375 cc.) containing sodium hydroxide (8.5 g.) and the mixture allowed to stand at room temperature during twenty-four hours with occasional stirring. The reaction mixture was cooled and concentrated hydrochloric acid added dropwise until the evolution of carbon dioxide ceased. The mixture was immediately added to cold water (450 cc.), the solution filtered, the oily product dissolved in chloroform–ethanol (1:2, 200 cc.) and charcoal added. The mixture was heated under reflux on the steam-bath during two hours and filtered while hot. The solvent was removed under reduced pressure and the tan-colored crystalline substance which separated was twice recrystallized from hot methanol yielding 8.4 g. (48%), m. p. 189–190°.

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.39; H, 6.76; OCH_3, 32.1; mol. wt., 386. Found: C, 68.3; H, 6.9; OCH_3, 31.9; Rast mol. wt., 395.

The bis-2,4-dinitrophenylhydrazone was prepared by the usual method.

Anal. Calcd. for $C_{34}H_{34}O_{12}N_8$: OCH_3, 16.6. Found: OCH_3, 16.6.

Action of 2% Ethanolic Hydrogen Chloride on XIII.—2,2′-Divanilloyl diethyl ether (1.00 g.) was heated under reflux with 2% ethanolic hydrogen chloride (50 cc.) for forty-eight hours in an atmosphere of carbon dioxide. A small amount (0.15 g.) of an amorphous lignin-like substance which separated was removed by filtration. The filtrate was neutralized with sodium ethylate and the precipitated sodium chloride removed by filtration. The solvent was removed under reduced pressure and the product recrystallized from methanol yielding 0.75 g., m. p. 153–154°. A mixed melting point determination with an authentic sample of XIII showed no depression.

Action of 2% Ethanolic Hydrogen Chloride on XIV.—The effect of 2% ethanolic hydrogen chloride on this dimer (XIV) (1.00 g.) was determined as above. The starting material was recovered unchanged in a yield of 0.91 g.

Action of 2% Ethanolic Hydrogen Chloride on XV.—In this reaction 1.00 g. of dimer (XV) was used and the amorphous product weighed 0.79 g.

Acknowledgment.—The authors gratefully acknowledge the kind financial assistance of the Canadian Pulp and Paper Association and the Spruce Falls Power and Paper Company.

Summary

1. Several propylphenol monomolecular compounds related to lignin progenitors were prepared. Some of these were new compounds, while others were prepared by new and better methods.

2. The synthesis of three dimers from these propylphenol units has been carried out.

3. Ethanolysis of the three dimers did not yield the customary monomolecular fission products, obtained by the ethanolysis of wood. This indicates that these synthetic dimers differ from those materials forming the readily hydrolyzable portion of native lignin.

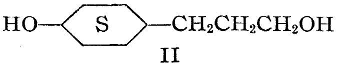
MONTREAL, CANADA RECEIVED APRIL 10, 1947

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

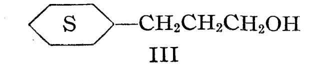
Studies on Lignin and Related Compounds. LXXXVI. Hydrogenation of Dimers Related to Lignin[1]

BY SAMUEL B. BAKER[2] AND HAROLD HIBBERT[3]

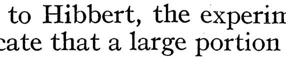
Complete liquefaction of spruce wood has been achieved by means of high-pressure catalytic hydrogenation.[4] The protolignin is converted in part to 4-*n*-propylcyclohexanol (I), 3-(4-hydroxycyclohexyl)-1-propanol (II) and 3-cyclohexyl-1-propanol (III) in yields of 9.9, 5.8 and 12.6%, respectively (based on the Klason lignin content of the wood).[4,5,6] These isolated products (I, II, III) serve to establish the propylphenol units in lignin. Further investigations[7,8] have shown that a relatively high proportion of the cyclohexylpropane units contains oxygen atoms attached to the terminal carbon atoms in the side chains.



I



II



III

According to Hibbert, the experimental results seem to indicate that a large portion of native lig-

---

[1] This paper represents part of a thesis submitted to the Faculty of Graduate Studies and Research, McGill University, by Samuel B. Baker, in partial fulfilment of the requirements for the degree of Doctor of Philosophy, Oct., 1943.

[2] Present address: Montreal General Hospital, Montreal, Que.

[3] Late E. B. Eddy Professor of Chemistry, McGill University.

[4] Godard, McCarthy and Hibbert, THIS JOURNAL, **63**, 3061 (1941).

[5] Bower, Cooke and Hibbert, *ibid.*, **65**, 1192 (1943).

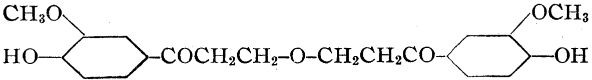
[6] Cooke, McCarthy and Hibbert, *ibid.*, **63**, 3056 (1941).

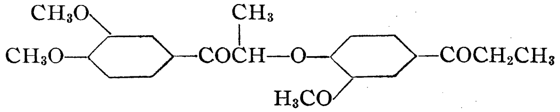
[7] Harris, D'Ianni and Adkins, *ibid.*, **60**, 1467 (1938).

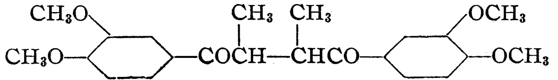
[8] Harris and Adkins, *Paper Trade J.*, **107**, No. 20, 38 (1938).

nin could conceivably consist of complex polymers of the dehydrodiisoeugenol type.[9] This similarity in structure between lignin and the lignans has been noted by Erdtman[10] and Haworth.[11]

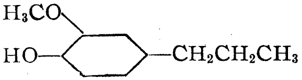
The three dimers, 2,2′-divanilloyl diethyl ether (IV), 1-veratroyl-1-[2-methoxy-4-(propanone-1)-phenoxy]-ethane (V), and 2,3-diveratroylbutane (VI) whose syntheses have been reported previously[9] have been hydrogenated using conditions developed in these Laboratories for the hydrogenation of spruce wood.

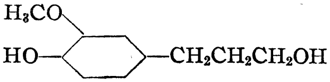

IV

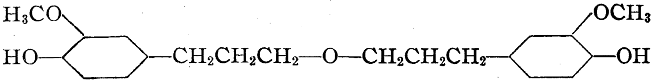

V


VI

Hydrogenation of IV.—Hydrogenation of IV[12] over Raney nickel in aqueous ethanol (1:1), containing 3% alkali, for four hours at 165°, at an initial pressure of 3020 p.s.i., resulted in the hydrogenolysis of the ether linkage to the extent of 60%. Both carbonyl groups were reduced while the aromatic rings remained intact. The remaining 30% consisted of the original dimer in which the only change taking place was that of a reduction of the carbonyl to methylene groups. The products were identified as 4-hydroxy-3-methoxyphenylpropane (VII), 3-(4-hydroxy-3-methoxyphenyl)-1-propanol (VIII) and 2,2′-divanillyl diethyl ether (IX), in yields of 30, 30 and 33%, respectively.


VII

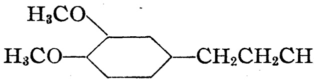

VIII

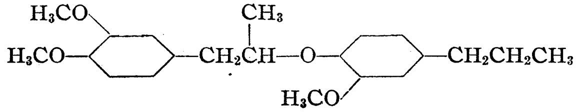

IX

Hydrogenation with the same type of catalyst and medium at 185° for eighteen hours yielded the following cyclohexane derivatives: 4-*n*-propylcyclohexanol (I), and 3-(4-hydroxycyclohexyl)-1-propanol (II), in yields of 46 and 50%, respectively. Evidently chain fission occurred at the ether linkage followed by reduction of the aromatic rings. This type of reaction probably occurs in the hydrogenation of native lignin when spruce and maple woods are hydrogenated.[5,6]

Using copper–chromium oxide as catalyst, hydrogenation of the first dimer (IV) in aqueous ethanol at 150–160° for one hour at an initial pressure of 2980 p.s.i., but in the absence of alkali, gave only one product, 2,2′-divanillyl diethyl ether (IX) in a yield of 95%. Chain fission did not occur under these conditions.

Hydrogen of V.—Treatment[12] of the second dimer (V) under the same conditions using Raney nickel, ethanol–water (1:1), 3% alkali at 165° for four hours and at an initial pressure of 3030 p.s.i. brought about both cleavage of the ether linkage and reduction of the carbonyl groups. The products isolated were 4-hydroxy-3-methoxyphenylpropane (VII), 3,4-dimethoxyphenylpropane (X) and the carbonyl-reduced dimer (XI) in yields of 30% each. The same result was obtained under similar conditions as above but in the absence of alkali.


X


XI

Substitution of copper–chromium oxide catalyst for the Raney nickel, at 150–160° in ethanol for one hour yielded the same products (VII), (X) and (XI) in yields of 40, 40 and 15%, respectively. Hydrogenation of the carbonyl-reduced dimer (XI), under the same conditions of time, temperature and pressure but with copper–chromium oxide catalyst left the product unchanged. The presence of alkali brought about a partial cleavage (15%), the remainder of the saturated dimer (XI) being recovered unchanged. On the other hand, hydrogenation of the latter (XI) over Raney nickel at 160–165° for four hours brought about a cleavage, the reaction products comprising (VII), (X) and (XI) in yields of 25, 25 and 50%, respectively. The presence of the two carbonyl groups appeared to exert a marked effect in the hydrogenation of the dimer over copper–chromium oxide catalyst since cleavage did not occur when the saturated dimer (XI) was hydrogenated, while fission did occur when the unreduced dimer (V) was hydrogenated under the same conditions. When the hydrogenation over Raney nickel was carried out at 185° for eighteen hours, only one product was obtained, namely, 4-*n*-propylcyclohexanol (I) in a yield of 85%. Under these conditions both ether cleavage and reduction of the aromatic rings apparently occurred.

Hydrogenation[12] of VI.—Using Raney nickel catalyst, ethanol–water (1:1), 3% alkali, a

---

[9] Baker, Evans and Hibbert, This Journal, **70**, 60 (1948).

[10] Erdtman, *Svensk Papperstidn.*, **44**, 243 (1941); translation in *Pulp and Paper Magazine of Canada*, Feb. (1942).

[11] Haworth, *Nature*, **147**, 255 (1941).

[12] The authors are indebted to Dr. J. M. Pepper, Research Chemist, Dominion Rubber Company, Ltd., for the hydrogenations reported in this paper.

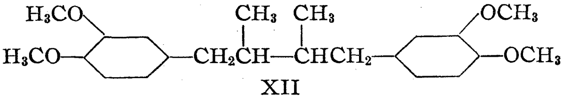
TABLE I

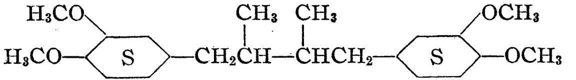
HYDROGENATION OF 2,2′-DIVANILLOYL DIETHYL ETHER

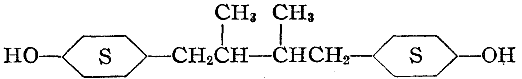
Weight, g.	Solvent, 1:1,100 cc.	Catalyst, g.	NaOH, g.	Time, hours	Temp., °C.	Initial pressure, p.s.i.	Products,[a] g.
1.0	EtOH-H_2O	RaNi 1.0	3.0	4	165	3020	0.85 A
1.0	EtOH-H_2O	RaNi 1.0	3.0	18	185	3000	0.71 B
1.0	EtOH-H_2O	CuCrO 0.5	None	1	150–160	2980	0.88 C

[a] A, B, C refer to Experimental Text.

temperature of 165°, time of four hours, and at an initial hydrogen pressure of 2950 p.s.i., the only reaction product obtained was the dimer with the side chain saturated, namely, 2,3-diveratrylbutane (XII). The same result was obtained using copper–chromium oxide catalyst at 150–160° for one hour. This reduced dimer (XII) when hydrogenated over the latter catalyst at 185–190° for twelve hours underwent reduction of the aromatic rings, but no fission occurred. The product isolated was 2,3-bis-(hexahydroveratryl)-butane (XIII). Substitution of the copper–chromium oxide catalyst in the last reduction by Raney nickel gave, under the same conditions, only the one product, namely, 1,4-bis-(4-hydroxycyclohexyl)-2,3-dimethylbutane (XIV). The latter, on hydrogenation at 225–230° over Raney nickel and at 260 and 280° over copper–chromium oxide catalyst, was recovered unchanged with gasification to the extent of 10, 20 and 38%, respectively.


XII


XIII


XIV

These experimental results apparently substantiate Hibbert's theories regarding the types of linkages found in native lignin. It would appear that a portion of the lignin contains easily cleaved linkages, in all probability, ether linkages. The greater portion of the hydrogenated native lignin consists of a complex mixture of dimeric, trimeric, etc., type of substances since hydrogenolysis of a carbon–carbon linkage does not occur even at 280° over copper–chromium oxide catalyst, it seems that the dimers obtained from the hydrogenation of spruce wood do not arise by the cleavage of more complex polymers.

Experimental

Hydrogenation of IV.—2,2′-Divanilloyl diethyl ether (IV) was hydrogenated in a small Parr bomb of 500-cc. capacity under the various conditions given in Table I.

The product (A) (0.85 g.) obtained in the first hydrogenation was dissolved in ethereal diazomethane solution (200 cc.) and the solution allowed to stand overnight at 0°. The solvent and excess diazomethane were removed under reduced pressure and the resulting product re-methylated to completion, as shown by a negative ferric chloride–phenol test. This methylated product was distilled under reduced pressure yielding two fractions (i) and (ii).

(i) **Low-boiling Fraction.**—Bath temperature at 80–90° (0.1 mm.); yield, 0.51 g. The oily product was analyzed to determine whether cleavage of the dialkyl ether linkage occurred. The methods used were methoxyl and Smith–Bryant[13] hydroxyl determinations.

Anal. Calcd. for cleavage mixture: OH, 4.54; OCH_3, 32.9. Found: OH, 4.5; OCH_3, 32.8.

(ii) **High-boiling Fraction.**—Bath temperature at 150–153° (0.01 mm.); yield, 0.28 g.

Anal. Calcd. for $C_{22}H_{30}O_5$: OCH_3, 33.1. Found: OCH_3, 33.1.

The product (B) from the second hydrogenation of 2,2′-divanilloyl diethyl ether was distilled under reduced pressure yielding the two fractions (i) and (ii).

(i) **First Fraction.**—Bath temperature at 115–119° (15 mm.); yield, 0.31 g. The phenyl urethan of this distillate was prepared (m. p. 127–128°) and a mixed melting point determination with the phenyl urethan of 4-*n*-propylcyclohexanol showed no depression.

(ii) **Second Fraction.**—Bath temperature at 119–123° (0.1 mm.); yield, 0.35 g. The product (0.35 g.) was dissolved in a mixture containing chromic oxide (1.1 g.), glacial acetic acid (10 cc.), water (5.5 cc.) and benzene (20 cc.) in a small Erlenmeyer flask. The reaction mixture was shaken at room temperature during nineteen hours, the benzene layer removed and the dark green acid mixture extracted with three portions (10 cc.) of benzene. The combined benzene solutions were washed once with water (15 cc.) to remove suspended chromic acid, then extracted with four portions (10-cc. each) of sodium carbonate solution (10%). The carbonate solution was cautiously acidified with dilute hydrochloric acid and the milky solution extracted with five portions (10 cc. each) of benzene. The combined benzene solutions were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The yield of the resulting oil was 0.17 g. This oil was dissolved in aqueous ethanol (50%, 1 cc.) and added to a solution consisting of semicarbazide hydrochloride (0.2 g.), potassium acetate (0.25 g.) and water (5 cc.). The solution was heated at 60° for ten minutes and the crystalline product which separated was removed by filtration and recrystallized twice from hot water; yield, 0.09 g., m. p. 200–202°. A mixed melting point determination with an authentic sample of the semicarbazone of 3-(4-cyclohexanone)-1-propanoic acid showed no depression, thereby indicating that the original product, prior to the chromic acid oxidation, was 3-(4-hydroxycyclohexyl)-1-propanol (II).

The copper–chromium oxide catalytic hydrogenation of 2,2′-divanilloyl diethyl ether (1.0 g.) resulted in a product (C) which after complete methylation with diazomethane, was distilled at a bath temperature of 150–154° (0.01 mm.); yield, 0.88 g.

Anal. Calcd. for $C_{22}H_{30}O_5$: OCH_3, 33.1. Found: OCH_3, 33.0.

Hydrogenation of V.—The second dimer (V) was hydrogenated under the various conditions indicated in Table II. The resulting products were isolated by alkaline separation into phenolic and non-phenolic fractions, dis-

---

(13) Smith and Bryant, THIS JOURNAL, **57**, 61 (1935).

TABLE II

HYDROGENATION OF 1-VERATROYL-1-[2-METHOXY-4-(PROPANONE-1)-PHENOXY]-ETHANE[a]

Dimer, g.	Sat. dimer,[b] g.	Charge solvent, cc.	Ra Ni, g.	CuCrO, g.	Time, hours	Total weight, g.	Sat. dimer, g.	Products,[c] g. RCH2-CH2CH3	RCH2-CH2CH3
4.0	..	EtOH–H_2O 1:1, 100	3.5	...	4	3.6	1.1	1.1	1.2
8.2	..	EtOH 150	...	4	1	7.3	1.1	2.9	3.0
...	1.0	EtOH 75	...	0.3	1	0.96	0.96	..	..
...	0.96	EtOH–H_2O 1:1, 100	1.0	...	4	.88	.42	0.23	0.21
1.0	..	EtOH–H_2O 1:1, 100	1.0	...	4	.86	.40	.21	.23
1.0	..	EtOH–H_2O 1:1, 100	1.0	...	1	.91	.59	.12	.10
1.0	..	H_2O 100	1.0	...	4	.92	.40	.23	.21
...	1.0	EtOH–H_2O 1:1, 100	...	0.5	1	.92	.74	.08	.07
1.0	..	EtOH–H_2O 1:1, 100	1.0	...	12	.65	Identified as 4-*n*-propylcyclohexanol 117–120° (15 mm.)		

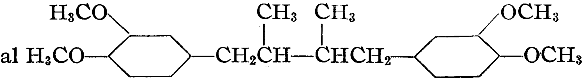
[a] Sodium hydroxide (3 g.) was added to mixture in 1st, 4th, 8th and 9th runs. Pressure was 3000 p.s.i. in each run. Temperature was 150–160° except in the last run, which was 185°. B. p. of sat. dimer was 171–173° (0.01 mm.). B. p. of $RCH_2CH_2CH_3$ was 70–72° (0.01 mm.). B. p. of $R'CH_2CH_2CH_3$ was 83–85° (0.01 mm.). [b] This refers to XI. [c] R and R^1 refer to veratryl and guaiacyl, respectively.

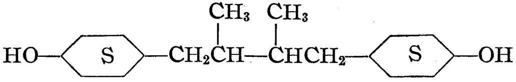
TABLE III

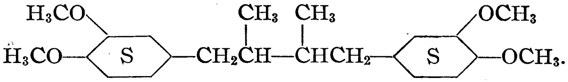
HYDROGENATION OF 2,3-DIVERATROYLBUTANE[a]

Weight, g.	Solvent, cc.	Catalyst, g.	Time, hours	Temp., °C.	Products
5.0 XII	EtOH–H_2O 1:1, 150	RaNi 5	4	165	4.2 g. (91%) distilled[b] at 211–213° (0.02 mm.), m. p. 77–78°. Calcd. for $C_{22}H_{30}O_4$: OCH_3, 34.7; C, 73.74; H, 8.38. Found: OCH_3, 34.6; C, 73.88; H, 8.45.
3.7 Product 1	EtOH–H_2O 1:1, 150	RaNi 3.7	12	185	2.4 g. (83%) distilled[c] at 185–188° (0.01 mm.) Calcd. for $C_{11}H_{34}O_2$: OCH_3, 0.0; OH, 12.0. Found OCH_3, 0.3; OH, 11.8
2.0 Product 2	EtOH–H_2O 1:1, 150	RaNi 2	12	225–230	1.8 g. (90%) distilled[c] at 190–194° (0.02 mm.)
5.0 XII	EtOH 150	CuCrO 2.5	1	150–160	4.3 g. (93%) m. p. 77–78°[b] mixed m. p. with 1, no depression
3.8 Product 4	EtOH 150	CuCrO 1.9	12	185–190	3.3 g. (87%) distilled[d] at 200–205° (0.01 mm.). Calcd. for $C_{22}H_{42}O_4$: OCH_3, 33.6. Found: OCH_3, 33.6
3.3 Product 5	EtOH 100	CuCrO 1.6	12	225–230	2.3 g. (92%) distilled[c] at 180–184° (0.02 mm.)
2.0 Product 6	EtOH 100	CuCrO 1.0	12	260	1.6 g. (80%) distilled[c] at 180–185° (0.01 mm.)
1.3 Product 7	1,4-Dioxane 100	CuCrO 0.65	12	280	0.8 g. (62%) distilled[c] at 194–199° (0.03 mm.)

[a] Sodium hydroxide was added to mixture in 1st, 2nd and 3rd runs. Runs 1, 2, 4, 5 at 3000 p.s.i.; runs 3, 6 at 2450 p.s.i., run 7 at 1800 p.s.i., run 8 at 1650 p.s.i.

[b] Products 1, 4 are identical 

[c] Products 2, 3, 6, 7, 8 are identical 

[d] Product 5 is 

tilled under reduced pressure and finally identified by ultimate analysis. In each case the low-boiling phenolic fractions were shown to be 4-hydroxy-3-methoxyphenylpropane by the formation of the *p*-nitrobenzoate (m. p. 73.5–74.5°). A mixed melting point determination with an authentic sample of the *p*-nitrobenzoate of 4-hydroxy-3-methoxyphenylpropane showed no depression.

The final hydrogenation over Raney nickel resulted in one product only, 4-*n*-propylcyclohexanol. The phenyl urethan (m. p. 127–128°) was prepared and a mixed melting point determination with an authentic sample of the phenyl urethan of 4-*n*-propylcyclohexanol showed no depression.

Hydrogenation of VI.—The third dimer (VI) was hydrogenated and the products rehydrogenated under the various conditions given in Table III. Examination of the products indicated reduction of the carbonyl groups, demethylation, demethoxylation and/or ring reduction. However, cleavage of the carbon-to-carbon linkage in the side chain did not occur even at 280°.

Acknowledgment.—The authors gratefully acknowledge the kind financial assistance of the Canadian Pulp and Paper Association and the Spruce Falls Power and Paper Company.

Summary

1. Three dimeric compounds, containing linkages similar to those in the complex structure of

native lignin, have been hydrogenated under similar conditions to those used in the hydrogenation of spruce wood.

2. The ether-linked dimers cleaved at the ether linkage, yielding products similar to those found in the reaction mixture after hydrogenation of spruce wood.

3. The carbon-to-carbon linked dimer did not yield fission products although nuclear reduction occurred. This apparently substantiates the opinions of Hibbert that dimeric, trimeric, etc., substances obtained by the hydrogenation of wood do not arise through the carbon-to-carbon cleavage of similar but more complex polymers. It would therefore appear that these complex substances exist as such in the wood prior to the hydrogenation reaction.

MONTREAL, CANADA RECEIVED APRIL 10, 1947

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LXXXVII. High Pressure Hydrogenation of Maple Wood[1]

BY JAMES M. PEPPER[2] AND HAROLD HIBBERT[3]

Although abundant evidence is available[4] which points to the now well-recognized essentially aromatic character of native lignin, the actual yield, to date, of identified products, is in no case very large. By means of the ethanolysis procedure[5] all of the identified lignin products obtained from maple wood are *propylphenol* derivatives but amount to only 9.75% of the original lignin (Klason basis).[6] From nitrobenzene oxidation studies[7] much larger amounts of aromatic compounds are obtained, the total mixed aldehydes (vanillin and syringaldehyde) have been isolated in yields of 43% of the lignin, but in this case it must be remembered that these derivatives have only a C_6–C skeleton and as such cannot be used as positive evidence for the presence of a C_6–C–C–C lignin monomer. Much higher yields of C_6–C–C–C compounds have been obtained by means of the high pressure hydrogenation technique[4] but in every such case these have been *propylcyclohexyl* derivatives, and, although it is improbable that these could arise from any source except a propylphenyl unit, it still remained necessary to isolate the *aromatic* C_6–C–C–C units in high yields to justify the several formulas for native lignin that have been proposed.[4,8]

In a previous communication[9] a new technique has been described by which, under greatly milder conditions of hydrogenation and hydrogenolysis, propylphenol lignin derivatives have been isolated and identified. The apparent advantages of such a method include, apart from the value of the results obtained, the use of a starting material containing *all* of the lignin *in situ* and the stabilization, by reduction, of any reactive groups formed during the pressure cook thereby preventing any subsequent polymerization which might otherwise occur. It was thought that if it were possible to remove the entire lignin fraction from the wood by this means greatly increased yields of aromatic lignin products could be obtained. To effect this a detailed study of the conditions of isolation was undertaken and subsequently when it was found possible to isolate all the lignin as a chloroform-soluble product, characterization of this material was commenced in an attempt to increase the yield of aromatic derivatives.

Preliminary Experiments.—A concurrent investigation[9] had shown that for the hydrogenation of maple wood in a neutral medium (ethanol–water (1:1)), the optimum conditions for lignin removal were 165–170° for four hours at an initial pressure of 3000 lb./sq. in. Such a medium, after the cooking procedure, had a *p*H of 5.5, and this slight acidity may have been sufficient to bring about an effective hydrolysis of any existent lignin–carbohydrate complex. This fact initiated a series of experiments[10] to study the effect of *p*H on the lignin removal by this newly developed technique. Complete solution of the lignin was obtained in both acidic and basic media. The extensive use of an acid medium (hydrochloric acid) was not favored for the following reasons: (a) poisoning of the catalyst (Raney nickel) which does not take place in alkali; (b) the tendency toward increased polymerization which is minimized in alkali due to the blocking of the phenolic hydroxyl groups, and (c) the increased tendency toward formation of hydroaromatic derivatives at a lower temperature.[11]

Dioxane was chosen to replace ethanol in the final large-scale hydrogenation experiments in

---

(1) This paper represents part of a thesis submitted to the Graduate Faculty of McGill University by James M. Pepper in partial fulfilment of the requirements for the degree of Doctor of Philosophy, October 1943.

(2) Present address: Department of Chemistry, University of Saskatchewan, Saskatoon, Sask.

(3) Late E. B. Eddy Professor of Industrial and Cellulose Chemistry, McGill University, Montreal, Quebec.

(4) Hibbert, *Ann. Rev. Biochem.*, **11**, 183 (1942).

(5) Hibbert, *et al.*, THIS JOURNAL, **65**, 1176 (1943).

(6) Kulka, Fisher, Baker and Hibbert, *ibid.*, **66**, 39 (1944).

(7) Creighton, McCarthy and Hibbert, *ibid.*, **63**, 312 (1941).

(8) Freudenberg, *Ann. Rev. Biochem.*, **8**, 88–112 (1939).

(9) Brewer, Cooke and Hibbert, THIS JOURNAL, **70**, 57 (1948).

(10) Pepper and Hibbert, unpublished results.

(11) Foresti, *Boll. soc. Eustachiana*, **38**, 19 (1940).

order to prevent any ethoxylation occurring at the elevated temperatures. Duplicate hydrogenation experiments using, on the one hand, a dioxane–water (1:1) solvent and on the other, an ethanol–water (1:1) solvent, showed that in the latter case and not in the former ethoxyl groups (as determined by the method of Cooke and Hibbert)[12] were present to the extent of 5.6%.

Large-scale Hydrogenation Experiments.—In order to obtain the reaction products in amounts sufficient to permit of a detailed study, two 500-g. portions (Series A and B) of extracted wood meal were suspended in dioxane–water (1:1) containing sodium hydroxide (3%) and hydrogenated over Raney nickel catalyst[13] at 173° (initial pressure of hydrogen of 3000 lb./sq. in.) for six hours and the combined products, in each case, treated in the following manner.

After separation of the catalyst and residual wood meal, the filtrate was acidified (congo red) in the presence of chloroform and then thoroughly extracted with chloroform. The residual meal was similarly extracted in a Soxhlet extractor and the two chloroform extracts combined. This process effected an almost complete separation of the extracted lignin from carbohydrate contaminants. From Series A the total chloroform-soluble fraction was distilled from a Claisen flask thus separating it into the fractions: A1, distilling below 150° (bath temperature) (1 mm.); A2, distilling below 250° (1 mm.), and A3, a non-distillable resin. The low-boiling fraction, A1, was divided into water-insoluble (A1x) and water-soluble (A1y) portions and the former (A1x) fractionally distilled through the recently developed spiral screen packed laboratory column[14] (twenty-one theoretical plates) to yield (4-hydroxy-3-methoxyphenyl)-ethane and (4-hydroxy-3,5-dimethoxy-phenyl)-ethane, identified by the preparation of their *p*-nitrobenzoates and comparison with the *p*-nitrobenzoates of authentic samples.

The preparation of Series B was necessary in order to replace the fraction A2 from Series A which was not studied completely. By a treatment similar to that given for Series A, the total chloroform-soluble fraction from Series B, after distillation through a Claisen flask, was divided into four portions according to their boiling ranges: B1, distilling below 180° (bath temperature) (1.2 mm.); B2, at 180–215° (1 mm.); B3, at 215–280° (0.1 mm.) and B4, a non-distillable resin. Distillates B2 and B3 were combined, divided into a water-soluble portion (Bx) and a water-insoluble portion (By) and each of these fractions then fractionally distilled through the spiral screen packed column. From the former portion (Bx) was isolated the crystalline material 2-(4-hydroxy-3,5-dimethoxyphenyl)-ethanol, identified by formation of the phenyl urethan of its 4-methoxy derivative. The fractionation of the latter portion (By) yielded (4-hydroxy-3,5-dimethoxyphenyl)-ethane, and a fraction which crystallized in the condenser, subsequently identified as 2-(4-hydroxy-3,5-dimethoxyphenyl)-ethanol by a mixed melting point determination with the previously identified material.

In order to obtain the maximum amount of the isolated lignin as identified products, all the non-distillable (resin) fractions as well as the distilled fractions which were not identified from the various fractionation procedures were combined and rehydrogenated under the conditions (at 280° for twelve hours, initial pressure 3000 lb./sq. in.) used previously.[15] The object was to convert them, if possible, into the known cyclohexyl derivatives: 4-*n*-propylcyclohexanol, 3-cyclohexyl-1-propanol, 3-(4-hydroxycyclohexyl)-propanol-1 and 4-*n*-propylcyclohexane-diol-1,2. Rehydrogenation of the resins followed by fractional distillation of the product yielded three "flats"[15a] whose empirical analyses and molecular weights showed them to be derivatives of the "dimeric" type. Further study on these fractions was not carried out. Similar retreatment of the unidentified fractions and fractionation of the product yielded a distillation curve showing three "flats" which were identified, by means of their phenylurethans, as 4-ethylcyclohexanol, 4-*n*-propylcyclohexanol and 3-cyclohexyl-1-propanol.

Discussion

Although the entire native lignin has been obtained as a chloroform-soluble material, only a minor part (27.4% on a Klason lignin basis) has been characterized as combined alkylphenolic and alkylcyclohexyl derivatives. However during the various fractionation treatments, a total of 66% (by weight) of the isolated lignin products were distilled through the twenty-one or twenty-eight plate columns[14]: a convincing indication of their relatively simple (low molecular weight) nature and thermal stability. Of the distillable products from 500 g. of maple wood, 45.4 g. of lignin products (42.7% of the Klason lignin) existed either as identifiable "flats" or as crystalline material. A summary of the identified products, from 500 g. of maple wood, their yields, refractive indices and melting points of their characterizing derivatives is given in Table I.

The previously observed more readily extractable syringyl components of the native lignin from maple wood, as compared with those of the guaiacyl type, finds confirmation in these results: the guaiacyl and syringyl components being isolated in a ratio of 1 to 10. Significant, too, is the fact that after removal of the more easily distillable portion of the hydrogenation products,

---

[12] Cooke and Hibbert, *Ind. Eng. Chem., Anal. Ed.*, **15**, 24 (1943).

[13] Mozingo, "Organic Syntheses," **21**, 15 (1941).

[14] Bower and Cooke, *Ind. Eng. Chem., Anal. Ed.*, **15**, 290 (1943).

[15] Bower, Cooke and Hibbert, THIS JOURNAL, **65**, 1192 (1943).

[15a] Several fractionation samples taken in succession and having similar refractive indices.

TABLE I

IDENTIFIED LIGNIN COMPOUNDS OBTAINED FROM MAPLE WOOD (500 G.)

Identified compound	$n^{25}D$	Weight, g.	%age of Klason lignin	M. p. of derivatives, °C.
				p-Nitrobenzoates
(4-Hydroxy-3-methoxyphenyl)-ethane	1.5240	2.3	2.16	98–99[16]
(4-Hydroxy-3,5-dimethoxyphenyl)-ethane	1.5335	16.4	15.38	153.5–154.5
				α-Naphthyl urethan of methylated product
2-(4-Hydroxy-3,5-dimethoxyphenyl)-ethanol	Cryst.	6.6	6.2	132–133
				Phenyl urethan
4-Ethylcyclohexanol	1.4484	1.99	1.87	113.5–114.5
4-*n*-Propylcyclohexanol	1.4620	0.92	0.86	123.5–124.5
3-Cyclohexyl-1-propanol	1.4656	.87	.82	83–84
Recovery		29.13	27.35	

rehydrogenation of the resins at elevated temperatures (280° instead of 173°) yielded products polymeric in type and having the same general characteristics (empirical analyses, refractive indices, boiling points and molecular weights) as those obtained from the analogous spruce resins which are in all probability polymers having the guaiacyl-type nucleus. Also it may be noted that since rehydrogenation of the resins under the conditions used for direct hydrogenation of wood did *not* give any propylcyclohexyl derivatives, the source of these compounds was the more easily isolated aromatic units obtained by the initial milder treatment.

Comparison of these results with those of Brewer, Cooke and Hibbert[9] shows the pronounced and somewhat drastic effect of the alkali (other conditions being similar) in the isolation of C_6–C–C units and not C_6–C–C–C units as was the case with the neutral medium. The isolation of these C_6–C–C units and most especially the 2-(4-hydroxy-3,5-dimethoxyphenyl)-ethanol, would seem to indicate their derivation from a polymeric form in which the side chains of the building units are united through an oxygen linkage in the beta position. The presence of this type of linkage in all plant resins (lignans) has been repeatedly emphasized by Erdtman[17] and Haworth.[18]

Experimental

Preparation of Maple Wood Meal.—Maple wood meal (40-mesh) was extracted continuously with a mixture of ethanol and benzene (4:1) for forty-eight hours, then with ethanol for twenty-four hours, washed overnight with hot water, air-dried for three days and finally dried in a vacuum oven at 50–55° (15 mm.) for thirty-six hours.

Anal. Moisture, 3.5; OCH_3, 5.95; Klason lignin, 20.6.

Hydrogenation of Maple Wood (Series A and B).—Seven portions of solvent extracted maple wood meal together totaling 500 g. (Series A) were hydrogenated in an Aminco hydrogenator (2500 cc. capacity). A typical run is described as follows: wood meal (75.5 g.) was suspended in dioxane–water (1:1) (900 cc.) containing sodium hydroxide (27 g.) and hydrogenated over Raney nickel catalyst (55 g.) (wet with ethanol) at 173° (initial hydrogen pressure, cold, 3000 lb./sq. in.) for six hours. At the end of this time hydrogen absorption had ceased, the total hydrogen used being 0.38 mole per 100 g. of wood. A further seven portions of similar wood meal together weighing 500 g. (Series B) were hydrogenated under the same conditions. For each series the bomb contents were examined initially by the procedure outlined previously. For Series A, from the 500 g. wood meal there was obtained 364 g. of dried pulp and catalyst (equivalent approximately to 130 g. of residual pulp), and a chloroform soluble fraction containing 107.3 g. of hydrogenation products.

Examination of the Hydrogenation Products (Series A).—The total chloroform soluble fraction (107.3 g.) was distilled from a Claisen flask, thus dividing it into three portions; fraction A1 (36.7 g.) distilling below 150° (bath temperature) (1 mm.), fraction A2 (26.5 g.) distilling 150 to 250° (1 mm.) and a non-distillable resin A3 (26.0 g.). Distillate A1 (36.7 g.) was dissolved in chloroform (300 cc.) and extracted successively with five portions of saturated sodium bicarbonate solution giving a bicarbonate- and water-insoluble fraction A1x (25.9 g.) and a bicarbonate-soluble fraction A1y.

Fractional Distillation of Bicarbonate- and Water-Insoluble Fraction A1x.—Fraction A1x (24.6 g.) was fractionated through the Cooke–Bower spiral screen type fractionating column (14) (twenty-one plates). Two distinct "flats" were obtained, one in the $n^{25}D$ 1.5230–1.5251 range and the second in the $n^{25}D$ 1.5323–1.5344 range. Conversion of test samples from the first "flat" into their *p*-nitrobenzoates showed the former to be 4-hydroxy-3-methoxyphenylethane (m. p. of the *p*-nitrobenzoate 98–99°, mixed m. p. with an authentic sample showed no depression).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.0; H, 7.9; OCH_3, 20.4. Found: C, 70.4; H, 7.8; OCH_3, 20.5.

The second "flat" upon similar treatment proved to be 4-hydroxy-3,5-dimethoxyphenylethane (m. p. of the *p*-nitrobenzoate 153.5–154.5°, mixed m. p. with an authentic sample gave no depression).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.9; H, 7.8; OCH_3, 34.1. Found: C, 65.2; H, 7.; OCH_3, 33.6.

Examination of the Hydrogenation Products (Series B).—The total chloroform-soluble fraction (123.1 g.) was distilled from a Claisen flask thus dividing it into four portions; fraction B1 (33.8 g.) distilling below 180° (bath temperature) (1.2 mm.), fraction B2 (23.4 g.) distilling 180 to 215° (1 mm.), fraction B3 (15.2 g.) distilling 215 to 280° (0.1 mm.) and a non-distillable resin B4 (48.6 g.). Distillates B2 and B3 were combined (38.7 g.), dissolved in chloroform (150 cc.) and extracted with water (4 × 30 cc.) and the aqueous extract back-extracted once with chloroform (20 cc.). This yielded a water-soluble fraction Bx (5.0 g.) and a water-insoluble fraction By (33.3 g.).

Fractional Distillation of Water-soluble Fraction Bx.—The water-soluble fraction Bx (5.0 g.) was fractionated through the twenty-one plate column. Distillation was discontinued when a white crystalline material accumulated in the take-off condenser. The combined distillates (2.71 g.) contained no identifiable "flats" but the crude crystalline material (1.15 g.) was partially identified as 2-(4-hydroxy-3,5-dimethoxyphenylethanol (0.82 g.) (see below). The non-distillable resin (0.76 g.) was rehydrogenated (see below).

Fractional Distillation of Water-insoluble Fraction By.—The water-insoluble fraction By (33.3 g.) was fractionated as before (28-plate column). The distillation was discontinued when, as before, a crystalline material accumulated in the condenser. This effected a separation into a distilled portion (17.12 g.), an undistilled portion (14.3 g.) and the residue (crystalline) remaining in the condenser and column (0.94 g.). The fractionation curve of the distilled portion showed one pronounced "flat" in the $n^{25}D$

---

(16) Reported by Reichstein (*Helv. Chim. Acta*, **15**, 1450 (1932)) to be 100°.

(17) Erdtman, *Svensk Papperstidn.*, **44**, 243–253 (1941).

(18) Haworth, *J. Chem. Soc.*, 448 (1942).

1.5320–1.5339 range. Conversion of test samples of this "flat" into their *p*-nitrobenzoates showed this product to be 4-hydroxy-3,5-dimethoxyphenylethane (m. p. of the *p*-nitrobenzoate 153.5–154.5°, mixed m. p. with an authentic sample showed no depression).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.9; H, 7.8; OCH_3, 34.1. Found: C, 65.3; H, 7.8; OCH_3, 33.8.

Isolation and Identification of 2-(4-Hydroxy-3,5-dimethoxyphenyl)-ethanol. Isolation.—The undistilled portion (14.3 g.) of the water-insoluble fraction By was distilled through a "goose-neck,"[19] thus separating it into a distillate (13.0 g.) and a non-distillable resin (1.2 g.). Washing of the distillate, which had become partially crystalline on standing, with ether removed the occluded non-crystalline fraction (8.2 g.) and left a non-ether-soluble crystalline portion (4.8 g.). Added to this was the material obtained from the column holdups in the fractionation of the water-insoluble fraction By (0.94 g.) and in the fractionation of the water-soluble portion Bx (0.82 g.) to give a total recovery of the pure material of 6.6 g. A sample of this crystalline product was recrystallized from ether-petroleum ether and from ethanol–petroleum ether and melted 116–117°.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.6; H, 7.1; OCH_3, 31.1. Found: C, 60.7; H, 6.9; OCH_3, 31.3.

Identification.—2-(4-Hydroxy-3,5-dimethoxyphenyl)-ethanol (0.6 g.) was methylated with diazomethane (three times), the methylated product dissolved in acetone–water (1:1) (20 cc.) and oxidized by boiling for one hour with a 3% solution of potassium permanganate (40 cc.). The reaction mixture was extracted with ether, then acidified and again extracted with ether. The second extract contained 3,4,5-trimethoxy-benzoic acid (0.12 g.); recrystallized from ether–petroleum ether, m. p. 167–168°; no m. p. depression when mixed with an authentic sample of 3,4,5-trimethoxybenzoic acid. This gave strong evidence that the compound had a syringyl type nucleus. 2-(4-Hydroxy-3,5-dimethoxyphenyl)-ethanol (1.0 g.) was methylated (four times) with diazomethane (400% excess). The methylated product was distilled at 220–235° (bath temperature) (0.02 mm.); yield 0.44 g.

Anal. Calcd. for $C_{11}H_{16}O_4$: OCH_3, 43.8. Found: OCH_3, 43.6.

The 2-(3,4,5-trimethoxyphenyl)-ethanol was identified by preparation of the α-naphthyl urethan derivative, m. p. 132–133°; mixed m. p. with an authentic sample showing no depression.

Rehydrogenation of Resins from Claisen and Fractional Distillations of the Hydrogenation Products from Series B.—Part (42.0 g.) of the non-distillable resins (50.5 g.) obtained during the fractionation of the hydrogenation products of Series B were dissolved in dioxane (645 cc.) and hydrogenated over copper chromium oxide (18 g.) at 255° (initial hydrogen pressure, cold, 3000 lb./sq. in.) for six hours. Total hydrogen absorption was 3.4 moles per 100 g. of resin. Half of the product from this hydrogenation (14.9 g.) (4.2% methoxyl) was dissolved in dioxane (200 cc.) and rehydrogenated over copper chromium oxide (6.0 g.) at 280° (initial hydrogen pressure, 3000 lb./sq. in.) for six hours. Total absorption was 1.81 moles per 100 g. starting material.

The colorless, methoxyl-free product (12.5 g.) was fractionated through the previously described column (28-plates) to yield a distillable fraction (9.39 g.) and a non-distillable fraction (2.81 g.). The fractionation curve showed three "flats" in the $n^{25}\mathrm{D}$ 1.4882–1.4900 (I), 1.4909–4910 (II) and 1.4992–1.5007 (III) ranges.

Anal. Found for "flat" I: C, 79.9; H, 11.9; mol. wt. (Rast), 235. II: C, 81.3; H, 12.7; mol. wt. (Rast), 215. III: C, 82.5; H, 12.6; mol. wt. (Rast), 288.

Rehydrogenation of Non-identified Portions from Fractional Distillations of Hydrogenated Products, Series A and B.—All the non-identified portions, representing 7.57 g. from Series A and 16.43 g. from Series B, were combined (24.0 g.), dissolved in dioxane (200 cc.) and rehydrogenated over copper chromium oxide (9.29 g.) at 280–290° (initial hydrogen pressure, 3000 lb./sq. in.) for eighteen hours. The product (10.1 g.) was fractionated through the 28-plate column, yielding a distillable portion (7.63 g.) and a non-distillable resin (2.37 g.). The distillation curve showed three "flats," in the $n^{25}\mathrm{D}$ 1.4582–1.4611, 1.4616–1.4629 and 1.4650–1.4664 ranges. Conversion of test samples from these "flats" into their phenyl urethans showed these products to be 4-ethylcyclohexanol, m. p. of phenyl urethan 113.5–114.5°; 4-*n*-propylcyclohexanol, m. p. of phenyl urethan 124–125°; and 3-cyclohexyl-1-propanol, m. p. of phenyl urethan 83–84°, respectively; mixed melting points with authentic samples of their phenylurethanes showing no depression.

Syntheses of Reference Compounds

(1) **Synthesis of 4-Hydroxy-3-methoxyphenylethane.**—4-Hydroxy-3-methoxyphenyl methyl ketone (10.0 g.) was dissolved in ethanol (100 cc.) and hydrogenated (initial hydrogen pressure, cold, 2950 lb./sq. in.) over Raney nickel (4.0 g.) at 180–190° for thirty-five minutes. The product (7.8 g.) on distillation gave a fraction b. p. 90–100° (15 mm.), $n^{25}\mathrm{D}$ 1.5281, whose *p*-nitrobenzoate derivative, recrystallized from ethanol–water, melted at 98–99°. Reported m. p. of this compound is 100°.[16]

(2) **Synthesis of 4-Hydroxy-3,5-dimethoxyphenylethane.**[20] **A. Preparation of 1-Acetyl-2,6-dimethylpyrogallol.**—2,6-Dimethylpyrogallol (5.0 g.) was dissolved in anhydrous benzene (5.0 cc.) containing anhydrous pyridine (3.3 g.) and acetyl chloride (3.0 g.) added dropwise to the vigorously stirred solution. The mixture was then heated at 60° for two hours, cooled and filtered. Removal of the solvent from the filtrate and distillation of the residual oil at 120–130° (bath temperature) (0.01 mm.) gave the required product: yield, 5.7 g.

Anal. Calcd. for $C_{10}H_{12}O_3$: OCH_3, 31.6. Found: OCH_3, 31.0.

B. Preparation of 4-Hydroxy-3,5-dimethoxyphenyl Methyl Ketone.—1-Acetyl-2,6-dimethylpyrogallol (5.7 g.) and powdered anhydrous aluminum chloride (7.7 g.) were added to nitrobenzene (35 cc.) in a three-necked flask fitted with a mercury-sealed stirrer and a reflux condenser. The solution was stirred for two hours at 2–5°, allowed to stand at room temperature for twenty-two hours and then poured into a mixture of ice (250 g.) and concentrated hydrochloric acid (25 cc.). The resultant product, after solvent removal, was distilled at 160–175° (bath temperature) (0.01 mm.) to yield a crystalline product (0.80 g.); recrystallized from ether, m. p. 121–122°. A mixed m. p. with an authentic sample showed no depression.

C. Reduction of 4-Hydroxy-3,5-dimethoxyacetophenone.—4-Hydroxy-3,5-dimethoxyacetophenone (0.4 g.), zinc amalgam (amalgamated prior to use) (20 g.) and 50% hydrochloric acid (100 cc.) were refluxed for six hours. The resultant product was distilled at 160–170° (bath temperature) (0.02 mm.): yield, 0.17 g.

Anal. Calcd. for $C_{10}H_{14}O_3$: OCH_3, 34.1. Found: OCH_3, 33.8. The *p*-nitrobenzoate derivative of this oil, recrystallized from ethanol–water and ether–petroleum ether, melted at 151–152°.

(3) **Synthesis of 2-(3,4,5-Trimethoxyphenyl)-ethanol.**[21] **A. Preparation of 3,4,5-Trimethoxybenzoyl Chloride.**—Trimethylgallic acid (2.0 g.) and purified thionyl chloride (7 cc.) were heated under reflux in an all-glass apparatus for one hour. The reaction mixture was then transferred to a small Claisen flask and the excess thionyl chloride removed by co-distillation with anhydrous benzene. The resulting product was used directly in the next procedure.

B. Preparation of 3,4,5-Trimethoxyphenyl Diazomethyl Ketone.—The 3,4,5-trimethoxybenzoyl chloride

---

(19) A "goose-neck" consists of a piece of 6 mm. (i. d.) tubing, 12.5-cm. in length bent at the middle to an angle of 60° and connected to the distillation pot through a ground joint.

(20) Synthesized by Samuel B. Baker.

(21) Synthesized by Samuel B. Baker and James M. Pepper.

(see above) was dissolved in benzene and the solution added slowly to an ethereal solution of diazomethane prepared from nitrosomethylurea (7.0 g.) and allowed to stand at 0° for sixteen hours. The solvent, together with the excess diazomethane, were removed under reduced pressure. The crude product (2.1 g.) was used directly in the following procedure.

C. Hydrolysis of 3,4,5-Trimethoxyphenyl Diazomethyl Ketone.—The 3,4,5-trimethoxyphenyl diazomethyl ketone (2.1 g.) (see above) was hydrolyzed by heating at 70° for three hours with aqueous 2% sulfuric acid (100 cc.). The solution, after cooling, was extracted with chloroform, the chloroform solution dried and the solvent removed. The resulting product was recrystallized from ether: yield, 1.5 g., m. p. 77–78°.

Anal. Calcd. for $C_{11}H_{14}O_5$: OCH_3, 41.1. Found: OCH_3, 40.85.

D. Reduction of 3,4,5-Trimethoxyphenyl Hydroxymethyl Ketone.—3,4,5-Trimethoxyphenyl hydroxymethyl ketone (1.0 g.) was dissolved in ethanol (100 cc.) and hydrogenated over copper chromium oxide (0.5 g.) at 150–160° for one hour. The bomb contents were filtered, the filtrate concentrated under reduced pressure and the resulting yellow oil distilled at 220–240° (bath temperature) (0.02 mm.): yield, 0.8 g.

Anal. Calcd. for $C_{11}H_{16}O_4$: OCH_3, 43.8. Found: OCH_3, 43.5.

The α-naphthyl urethan derivative of this oil melted at 131–133°.

Acknowledgment.—The authors wish to thank the National Research Council of Canada for the award of two studentships to one of them (J. M. P.) and also the Canadian Pulp and Paper Association for their kind financial assistance. The authors also wish to thank Dr. R. F. Patterson who so kindly assisted in the lengthy continuous fractionation procedures.

Summary

1. Maple wood meal has been suspended in dioxane containing 3% sodium hydroxide and hydrogenated over Raney nickel catalyst using an initial pressure of 3000 lb./sq. in. and a temperature of 170° and complete conversion of the lignin portion of the wood into chloroform-soluble products has been effected.

2. From the reaction mixture three new lignin aromatic degradation products were isolated: 4-hydroxy-3-methoxyphenylethane, 4-hydroxy-3,5-dimethoxyphenylethane and 2-(4-hydroxy-3,5-dimethoxyphenyl)-ethanol in yields of 2.2, 15.4 and 6.2% (based on the Klason lignin content of the wood), respectively.

3. The syntheses of 4-hydroxy-3-methoxyphenylethane, 4-hydroxy-3,5-dimethoxyphenylethane and 2-(3,4,5-trimethoxyphenyl)-ethanol were accomplished.

4. The isolation of these lignin derivatives thus provides further confirmatory evidence for the essentially aromatic (alkylphenolic) nature of lignin; and for the belief that the lignin of hardwoods is composed of units of both the guaiacyl and syringyl types, compounds containing the latter type being the more readily isolated.

5. The isolation of 2-(4-hydroxy-3,5-dimethoxyphenyl)-ethanol as a lignin degradation product provides some evidence for a carbon–oxygen linkage through the β-carbon atom of the alkyl side chain.

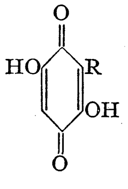
MONTREAL, CANADA RECEIVED APRIL 10, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of Embelin, Rapanone and Related Quinones by Peroxide Alkylation[1]

BY LOUIS F. FIESER AND EARL M. CHAMBERLIN

Embelin, an orange pigment isolated from the berries of the Indian shrub *Embelia ribes*, is of interest because of early reports that the substance, like the fruit from which it is derived, possesses valuable properties as an anthelmintic agent, particularly against tapeworm.[2] Degradative studies of the substance led to varying conclusions[3]; then Hasan and Stedman[4] synthesized 2,5-dihydroxy-3-lauryl-1,4-benzoquinone (II) and an isomer and concluded from the results of their comparisons that embelin is identical with synthetic II. More recently Asano and Yamaguti[5] obtained analytical data pointing to a structure with one less methylene group. The latter investigators synthesized both II and the lower homolog I and found that both quinones have very nearly the same melting point as embelin and give no depression when mixed with the natural pigment. However, they observed that although the three hydroquinone tetraacetates likewise had very similar melting points, the derivative of II gave a definite, slight depression when mixed with the embelin derivative (Hasan and Stedman indeed reported a mixed melting point 1–2° below that of either component). We have not found in the Japanese paper any statement of a comparison of the derivatives of I and of embelin.



I, R = $-(CH_2)_{10}CH_3$
II, R = $-(CH_2)_{11}CH_3$
III, R = $-(CH_2)_{12}CH_3$

---

(1) Based largely upon the doctoral dissertation of Earl M. Chamberlin, May 6, 1946.

(2) Paranjpe and Gokhale, *Arch. intern. pharmacodyn.*, **42**, 212 (1932) [*C. A.*, **27**, 1400 (1933); E. Merck's *Jahresber.*, **20**, 33 (1906)].

(3) Heffter and Feuerstein, *Arch. Pharm.*, **238**, 15 (1900); Kaul, Ray and Dutt, *J. Indian Chem. Soc.*, **6**, 577 (1929); **8**, 231 (1931); Nargund and Bhide, *ibid.*, **8**, 237 (1931).

(4) Hasan and Stedman, *J. Chem. Soc.*, 2112 (1931).

(5) Asano and Yamaguti, *J. Pharm. Soc. Japan*, **60**, 105 (1940 [*C. A.*, **34**, 5069 (1940)].

Asano and Yamaguti[6] further characterized a pigment rapanone isolated (by Kawamura, 1937) from the bark and woody portion of *Rapanea maximowiczii* and assigned to it the structure II on the basis of degradation and synthesis. They synthesized III and the next higher homolog and showed that these quinones likewise give no melting point depressions when mixed with the natural pigment, but that a differentiation can again be made by comparison of the hydroquinone tetraacetates.

We have now synthesized the homologs I, II and III by causing the appropriate diacyl peroxide to decompose in an acetic acid solution containing 2,5-dihydroxybenzoquinone.[7] The yields were low and in the first instance the dialkyl derivative was isolated as a by-product, but small amounts of the pure pigments can be prepared readily by this method. Our comparison of natural embelin with the synthetic substances and their derivatives confirms the conclusion of Asano and Yamaguti[5] that embelin has the structure I (see table).

TABLE I

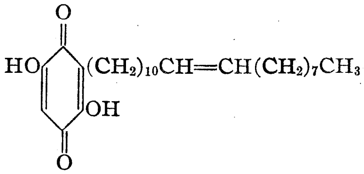
MELTING POINTS, °C.

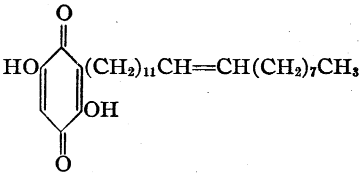
Substance	Hasan and Stedman	Asano and Yamaguti	Fieser and Chamberlin
		Quinones	
Embelin	143	142	142–143
I	...	143–144	145–146
II	143	142	142–143
Embelin + I	...	143–144	.....
Embelin + II	143	142	.....
I + II	...	.....	144–145
		Hydroquinone Tetraacetates	
Embelin	121	123.5	125–126
I	...	124	124.5–125.5
II	121	120	120–121
Embelin + I	...	.....	125–126
Embelin + II	119	118	.....
I + II	...	.....	118–119

The depressions observed with mixtures of homologous hydroquinone tetraacetates are very evident to the experimenter even though they amount to only a degree or two.

Some two years after the synthetic work of this paper had been completed, one of us received from O. Fernandez of Madrid a supply of orange pigment melting at 141–142° that had been extracted from *Oxalis purpurata*, Jacq.[8] Analyses indicate the formula $C_{19}H_{30}O_4$, which is that of rapanone (III), and the color, solubilities, melting point, and formation of a hydroquinone tetraacetate, m. p. 116.5–117.5°, all suggested strongly that the substance is a member of the embelin–rapanone series. Mixtures of the pigment with the quinones I–III melted the same as the components or at intermediate temperatures, which definitely places the substance in this series. The hydroquinone tetraacetate did not depress the melting point of the derivative of synthetic III, whereas mixtures with the derivatives of I and II melted at 110.5–111.5° and 114–115.5°, respectively. From these observations we conclude that the pigment isolated from the Spanish plant is identical with rapanone, III.

The orange-red pigment maesaquinone[9] may be another member of the same or a related series, for it has been characterized as a dihydroxybenzoquinone with a C_{20} side chain (or chains) with one double bond. Fieser and Gates[10] noted that the side chain may be a phytyl group, and as a test of this hypothesis we initially planned to try to synthesize 2,5-dihydroxy-3-dihydrophytyl-1,4-benzoquinone for comparison with dihydromaesaquinone. The required acid intermediate was prepared from dihydrophytol through the bromide and the nitrile and found to be a liquid at ordinary temperatures: $CH_3CH(CH_3)CH_2CH_2[CH_2CH(CH_3)CH_2CH_2]_3COOH$ (homophytanic acid). An acid of the same composition was isolated by Hiramoto as a product of the oxidation of dihydromaesaquinone and stated, without supporting evidence, to be heneicosanoic acid (m. p. 75–76°). Since the acid is a solid, the side chain of the saturated quinone can hardly be the dihydrophytyl group. If the side chain is normal, it is possible that maesaquinone is related to one of two known naturally occurring eicosenoic acids, namely, the Δ^{11}-derivative found in the liquid seed wax of *Californica simmondsia;* hence the structure may be IV. The acid intermediate required for the synthesis of IV was prepared from oleyl alcohol by the steps indicated (X = Br or $SO_2C_6H_4CH_3$-*p*)


IV


V

$$\underset{\text{VI}}{CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2X} \xrightarrow{\text{mal. ester}}$$

$$\underset{\text{VII}}{CH_3(CH_2)_7CH{=}CH(CH_2)_9COOH} \longrightarrow$$

---

(6) Asano and Yamaguti, *J. Pharm. Soc. Japan*, **60**, 585 (1940) [*C. A.*, **36**, 81 (1942)].

(7) Fieser and Oxford, THIS JOURNAL, **64**, 2060 (1942).

(8) Fernandez and Pizarroso, *Farm. nueva* (*Madrid*), **108**, 3 (1946).

(9) Hiramoto, *Proc. Imp. Acad.* (*Tokyo*), **15**, 220 (1939).

(10) Fieser and Gates, THIS JOURNAL, **63**, 2948 (1941).

$$\underset{\text{VIII.}}{\text{methyl ester}} \longrightarrow$$

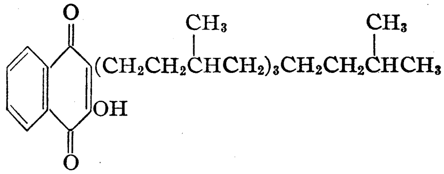
$$\underset{\text{IX}}{CH_3(CH_2)_7CH{=}CH(CH_2)_9CH_2OH} \longrightarrow$$

$$\underset{\text{X}}{\text{bromide}} \longrightarrow \underset{\text{XI}}{\text{nitrile}} \longrightarrow$$

$$\underset{\text{XII}}{CH_3(CH_2)_7CH{=}CH(CH_2)_{10}COOH}$$

Δ^{12}-Heneicosenoic acid (XII) was obtained as a crystalline solid melting at 56–57°. However, in a trial alkylation of 2,5-dihydroxybenzoquinone with the peroxide from erucic acid, the next higher homolog V was produced (along with the dialkyl derivative) with such difficulty and in so low yield (0.3%) that the synthesis of IV has not yet been attempted. The quinone V melts at 112.5–113.5°; maesaquinone melts at 122°.

Because of the interest in naphthoquinone antimalarials in this Laboratory, the intermediate homophytanic acid was utilized for the synthesis of 2-hydroxy-3-dihydrophytyl-1,4-naphthoquinone. The substance was isolated with difficulty by high vacuum distillation as a yellow oil; it possesses no antirespiratory activity.



XIII

Tests of synthetic embelin and rapanone for their effects on dog helminths kindly conducted at the American University at Beirut by Dr. D. A. Berberian and E. Rajm through the courtesy of Dr. S. E. Kerr were negative (method of M. C. Hall).[11]

Experimental

1. 2,5-Dihydroxy-3-undecyl-1,4-benzoquinone (Embelin), I

Peroxide.—Redistilled lauric acid (44.1 g.) was heated with phosphorus trichloride (11 g.) at 50° for one hour, the upper layer was decanted, treated with a current of dry air to remove excess reagent, and the lauroyl chloride distilled; b.p. 138–142° (15 mm.), yield 45.9 g. (95%). A solution of 45 g. of the acid chloride in 100 cc. of 20–40° petroleum ether was added to a mixture of 100 cc. of petroleum ether, cracked ice, and 20 g. of sodium peroxide. The mixture was shaken vigorously for two minutes and then, after the addition of 15 g. more sodium peroxide and more ice, for ten minutes. The mixture was transferred to a separatory funnel, enough diethyl ether was added to keep the dilauroyl peroxide in solution, and the organic layer was separated, washed, dried, and the solvent removed in vacuum at room temperature. The yield of waxy white solid, dried over potassium hydroxide in vacuum, was 35.5 g. (85%).

Alkylation.—A suspension of 11.2 g. of 2,5-dihydroxybenzoquinone[12] and 35.5 g. of dilauroyl peroxide in 550 cc. of acetic acid was warmed to the point where gas began to be evolved (92°), maintained at that temperature for one-half hour and the solution allowed to stand overnight. A crystallizate that separated proved to be the dialkylated derivative (see below); the filtered solution was concentrated to a small volume in vacuum at steam-bath temperature. Some product separated during the evaporation and was collected after cooling and crystallized in turn from alcohol, benzene and acetic acid. **2,5-Dihydroxy-3-undecyl-1,4-benzoquinone** was thus obtained as glistening orange plates, m.p. 145–146°; yield 1.7 g. (7.2%).

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 69.35; H, 9.19. Found: C, 69.53; H, 8.90.

The **hydroquinone tetraacetate** when recrystallized from alcohol melted at 124.5–125.5° (Asano and Yamaguti,[5] 124°).

Anal. Calcd. for $C_{25}H_{36}O_8$: C, 64.70; H, 7.77 Found: C, 64.36, H, 8.21.

2,5-Dihydroxy-3,6-diundecyl-1,4-benzoquinone.—The material that separated from the cooled alkylation mixture was crystallized from alcohol and found to contain unchanged dihydroxybenzoquinone. The dialkyl derivative could be extracted from the mixture with hot benzene, and it separated from the benzene filtrate as orange crystals. Recrystallization from alcohol gave glistening orange plates, m.p. 129–130°.

Anal. Calcd. for $C_{28}H_{48}O_4$: C, 74.95; H, 10.78. Found: C, 74.99; H, 10.84.

Natural embelin was obtained by extracting dried powdered berries of *Embelia Ribes* (22.4 g.) with ether in a Soxhlet apparatus and digesting the extracted product with petroleum ether. The residue (340 mg.) melted at 141–144.5°, and the material crystallized from absolute alcohol formed glistening orange plates, m.p. 142–143° (Heffter and Feuerstein,[3] 142°). The **hydroquinone tetraacetate**[13] melted at 125–126° (A. and Y.,[6] 123.5°). A mixture of the synthetic and natural tetraacetates showed no depression; m.p. 125–126°.

2. 2,5-Dihydroxy-3-dodecyl-1,4-benzoquinone, II

Tridecylic acid was prepared by a known method[14] as follows. Technical lauryl alcohol was distilled through a Widmer column and a fraction boiling at 168–175° (43 mm.) converted according to Kamm and Marvel[15] into the bromide, b.p. 178–180° (48 mm.), in 91% yield. The nitrile (76% yield) boiled at 153–158° (12 mm.), and the acid (97% yield) boiled at 155–160° (3 mm.) and melted at 44.5–45.5°; the melting point is the same as that reported for tridecylic acid prepared by another synthesis.[16] The conversion to the acid chloride (97%) and the crystalline peroxide (65%) was conducted as in the first section, as was the alkylation of 2,5-dihydroxy-1,4-benzoquinone (2 g.). A precipitate separated from the reaction mixture but was removed and not investigated; the filtrate in the course of several days deposited orange crystals of **2,5-dihydroxy-3-dodecyl-1,4-benzoquinone**. Recrystallized from acetic acid, the substance melted at 142–143° (A. and Y.,[5] 142°). The **hydroquinone tetraacetate** melted at 120–121° (A. and Y.,[5] 120°).

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.31; H, 9.24.

3. 2,5-Dihydroxy-3-tridecyl-1,4-benzoquinone (Rapanone), III

Synthesis.—By the procedures described above myristic acid was converted into the chloride (97%) and the

---

(11) Fieser, Leffler and co-workers, papers submitted for publication.

(12) Prepared most conveniently by the procedure of R. G. Jones and Shonle, THIS JOURNAL, **67**, 1034 (1945).

(13) In conducting the reductive acetylation of this and other members of the series with zinc dust, acetic anhydride and triethylamine in the ordinary way, I observed the formation of persistent specks of a sparingly soluble purple substance; the formation of this substance can be avoided by warming the quinone with acetic anhydride and triethylamine until the initially red solution becomes yellow and then adding the zinc dust.—L. F. F.

(14) Ruzicka, M. Stoll and Schinz, *Helv. Chim. Acta*, **11**, 685 (1928).

(15) Kamm and Marvel, "Organic Syntheses," Coll. Vol. I, 2nd ed., 29 (1941).

(16) Levine, *J. Biol. Chem.*, **23**, 71 (1915).

peroxide (crystalline solid, 42%) and the latter (6 g.) used for the alkylation of 2,5-dihydroxybenzoquinone (1.7 g.). The material that precipitated from the reaction mixture was recrystallized in turn from methanol, benzene and 95% alcohol and obtained as glistening golden-orange plates, m.p. 141–142° (A. and Y.,[6] 139–140°). The **hydroquinone tetraacetate** melted at 116–117° (A. and Y.,[6] 118°).

From *Oxalis Purpurata*, **Jacq.**—The material as supplied by O. Fernandez was in the form of orange crystals melting at 141–142°. Three further crystallizations from toluene gave lustrous orange plates of the same melting point.

Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 71.07, 70.86; H, 9.64, 9.43.

A mixture of this substance with the synthetic rapanone described above melted at 141–142°; a mixture with synthetic embelin melted at an intermediate temperature: 142–144°.

The **hydroquinone tetraacetate** formed small colorless needles, m.p. 116.5–117.5°.

Anal. Calcd. for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19. Found: C, 66.13; H, 8.33.

A mixture of this substance and the corresponding derivative of synthetic rapanone melted at 116–117°; the melt readily solidified and remelted at the same temperature.

4. Experiments with Unsaturated Acids

Alkylation of 2,5-Dihydroxybenzoquinone with Dierucoyl Peroxide.—A mixture of 10.9 g. of erucic acid and 8.3 g. of purified thionyl chloride was allowed to stand overnight and then heated on the steam-bath for one-half hour. The excess reagent was removed by evaporation in vacuum with dry benzene and the erucoyl chloride was then distilled by the "unobstructed path" technique of Hickman[17] at a bath temperature of 180–190° (0.08 mm.); the yield of colorless product was 9.4 g. (81%). The peroxide was prepared from 8 g. of the acid chloride as in the other instances but was not isolated from the ether–petroleum ether solution; titration of an aliquot indicated a yield of 56% of peroxide. The solution was then run slowly into a solution at 65° of 0.89 g. of the benzoquinone in 70 cc. of acetic acid and at the rate of evaporation of the low-boiling solvents. The reaction mixture was then refluxed for one-half hour and allowed to stand overnight, when an orange precipitate containing the disubstituted product had separated (see below). The mother liquor was evaporated in vacuum and the residue extracted with petroleum ether. The extract was evaporated in a stream of dry air to a point where a small amount of oily dark solid separated and this was removed by centrifugation. After considerable further processing, the clarified petroleum ether solution, when cooled in Dry Ice, yielded a solid product, and this on spontaneous evaporation of an acetone solution afforded orange crystals of **2,5-dihydroxy-3-(Δ^{12}-heneicosenyl)-1,4-benzoquinone (V)**, m.p. 109–114°. When recrystallized from alcohol–water and from absolute alcohol the substance was obtained in glistening orange plates, m.p. 112.5–113.5°; the yield was only 8 mg. (0.3%).

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.98; H, 10.39.

Purification of the less soluble reaction product that separated from the reaction mixture by repeated slow evaporation of a petroleum ether solution afforded 15 mg. (0.6%) of **2,5-dihydroxy-3,5-di-(Δ^{12}-heneicosenyl)-1,4-benzoquinone**, m.p. 84–85°.

Anal. Calcd. for $C_{48}H_{84}O_4$: C, 79.38; H, 11.80. Found: C, 79.43; H, 11.85.

Δ^{12}-Heneicosenoic Acid, XII

Oleyl alcohol was prepared according to Reid and Cockerille[18] except that methyl oleate was employed for reduction with sodium and butyl alcohol; the yield from 1333 g. of methyl oleate, b.p. 140–145° (0.3 mm.) of twice distilled, colorless oleyl alcohol, b.p. 132–142° (0.2 mm.) was 804 g. (67%).

The preparation of **oleyl bromide** by the method of Deatherage and Olcott[19] proved tedious because of the troublesome emulsions encountered, and in batches of 1 mole each the yield was never better than 43% of colorless, fractionated product, b. p. 175–178° (0.6 mm.).

Oleyl *p*-toluenesulfonate was investigated as a possible alternate intermediate and was obtained readily by the method of Tabern and Volwiler[20] by interaction of the alcohol and acid chloride in pyridine and benzene; the crude product was obtained in 94% yield as an oil that failed to crystallize and that decomposed on attempted distillation, but it could be employed satisfactorily in place of the bromide in the malonic acid synthesis.

Methyl Δ^{11}-eicosenoate (VIII) was the next intermediate isolated in a pure form. Oleylmalonic ester proved to be undistillable at 0.1 mm. but on saponification afforded a solid dibasic acid; this was decarboxylated at 160–180° and the product esterified with methanol and sulfuric acid. After an initial rough distillation, the ester was fractionated through a Vigreux column and obtained as a colorless liquid boiling at 164–174 (0.02 mm.). The yield from 100.8 g. of oleyl bromide was 52 g. (53.5%), which represents an over-all yield from oleyl alcohol of 23%. The over-all yield from 588 g. of oleyl alcohol through the tosylate was 189 g. (26%).

Anal. Calcd. for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42. Found: C, 77.76; H, 12.27.

A sample of free **Δ^{11}-eicosenoic acid** (VII) obtained by hydrolysis of the ester, purified through the lead salt, and crystallized from acetone melted at 49–51° (Bodenstein,[21] m.p. 50°).

Butyl Δ^{11}-eicosenate was prepared from 20 g. of the acid, 300 cc. of *n*-butyl alcohol and 4 g. of acetyl chloride at room temperature.[22] After six days the ester was recovered and distilled, b.p. 190–193° at 0.7 mm. (11.5 g.).

Anal. Calcd. for $C_{24}H_{46}O_2$: C, 78.62; H, 12.65. Found: C, 78.70; H, 12.80.

Δ^{11}-Eicosenyl alcohol (IX) was prepared by reduction of 188 g. of methyl Δ^{11}-eicosenate with sodium (66 g.) and *n*-butyl alcohol (1200 cc.) in the usual manner; the yield was 77.3 g. (45%); b.p. 134–146° (0.1 mm.), m.p. 25–26°.

Anal. Calcd. for $C_{20}H_{40}O$: C, 81.01; H, 13.60. Found: C, 80.88, 81.23; H, 13.89, 13.73.

Δ^{12}-Heneicosenoic Acid (XII) A. Through the Bromide.—Δ^{11}-Eicosenyl bromide was obtained by the action of phosphorus tribromide on the alcohol (50 g.) and distilled: b.p. 175–180° (0.7 mm.), yield 27.7 g. (46%). The product was refluxed for thirty hours in 300 cc. of alcohol with 10.7 g. of potassium cyanide dissolved in the minimum amount of water; 120 cc. of 50% sodium hydroxide was then added and refluxing continued for twelve hours. The bulk of the alcohol was distilled, the mixture diluted with water and the white curd of soap collected. The soap was digested with hot acetone and heated with hydrochloric acid until a clear oily layer formed, and the free acid was taken up in ether and the solution clarified with charcoal and evaporated. The residue (dried in vacuum) was a white crystalline solid, m.p. 56–57°; yield 5.5 g. (22% from the bromide, 10% from the alcohol).

B. Through the Tosylate.—The crude tosylate (15.2 g.) from 10 g. of Δ^{11}-eicosenyl alcohol was converted through the nitrile to the acid exactly as in (a) and afforded 5.0 g. of crude acid (46% from the alcohol).

For purification, boiling solutions of 5 g. of the crude acid and 3.5 g. of lead acetate trihydrate, each in 25 cc. of alcohol, were mixed and the lead salt that crystallized was recrystallized from 70 cc. of alcohol and then shaken with

---

[17] Hickman, *Chem. Rev.*, **34**, 51 (1944).

[18] Reid and co-workers, "Organic Syntheses," Coll. Vol. II, 468 (1943).

[19] Deatherage and Olcott, This Journal, **61**, 630 (1939).

[20] Tabern and Volwiler, *ibid.*, **56**, 1139 (1934).

[21] Bodenstein, *Ber.*, **27**, 3403 (1894).

[22] Method of Freudenberg, *ibid.*, **74**, 100 (1941).

ether and dilute sulfuric acid. The acid recovered from the ether layer on recrystallization from acetone afforded 0.2 g. of pure acid, m.p. 56–57°.

Anal. Calcd. for $C_{21}H_{40}O_2$: C, 77.72; H, 12.43; mol. wt., 324. Found: C, 77.54; H, 12.61; neut. equiv., 322.

5. 2-Hydroxy-3-dihydrophytyl-1,4-naphthoquinone, XIII

Dihydrophytyl Bromide.—Commercial phytol was shaken with catalyst and redistilled and the product (101 g.) was hydrogenated[23] in absolute alcohol (200 cc.) in the presence of Adams catalyst (0.5 g.) and gave 101 g. of **dihydrophytol**, b.p. 157–159° (0.8 mm.). This was converted to the bromide with phosphorus tribromide (92 g.) in carbon tetrachloride (30 cc.) according to Deatherage and Olcott[19] and the product extracted with ligroin. The solution was washed with saturated calcium chloride solution and with 30% methanol, dried and evaporated, and the bromide distilled. The yield of colorless liquid, b.p. 154–156° (0.1 mm.), was 68.3 g. (55%).

Anal. Calcd. for $C_{20}H_{41}Br$: C, 66.46; H, 11.43. Found: C, 66.67; H, 11.52.

Homophytanic Acid (4,8,12,16-Tetramethylheptadecanoic Acid).—Dihydrophytyl bromide (68g.) was refluxed with 15.5 g. of potassium cyanide in 625 cc. of alcohol for twenty-four hours, a solution of 25 g. of sodium hydroxide in 200 cc. of alcohol was added and refluxing continued for another thirty hours. The solution was concentrated to a small volume on the steam-bath, acidified and extracted with ether. For purification, the crude acid (58 g.) was converted to the acid chloride with thionyl chloride (44 g.) and the product refluxed with methanol (500 cc.); the **methyl ester** when twice distilled was a colorless liquid (44.5 g.), b.p. 145–147° (0.1 mm.).

Anal. Calcd. for $C_{22}H_{42}O_2$: C, 77.58; H, 13.02. Found: C, 77.90; H, 13.17.

A solution of the pure ester (44.5 g.) in 300 cc. of methanol was refluxed with 35 g. of potassium hydroxide in 200 cc. of 45% methanol for sixteen hours and the solution was concentrated on the steam-bath to the point of frothing, acidified and diluted. Extraction with ether and distillation afforded 35.2 g. (57% from the bromide) of acid as a clear liquid b.p. 184–188° (1.2 mm.).

Anal. Calcd. for $C_{21}H_{42}O_2$: C, 77.24; H, 12.96. Found: C, 77.48; H, 13.04.

Peroxide.—The acid (10 g.) was converted to the acid chloride with purified thionyl chloride and the excess reagent removed by evaporation in vacuum with benzene. Distillation by the Hickman technique[17] gave 9.9 g. (93%) of the acid chloride, b.p. 150–155° (0.08 mm.). The acid chloride was treated with sodium peroxide, petroleum ether and ice, as above, and the peroxide collected in dried petroleum ether solution and titrated: yield 60%.

Alkylation.—The alkylation was conducted by running the solution of the peroxide into a solution of hydroxynaphthoquinone in acetic acid maintained at 65°. In one experiment the peroxide from 24 g. of acid chloride was caused to react with 3.6 g. of hydroxynaphthoquinone and the material recovered by evaporation of the acetic acid solution in vacuum and the residue was digested with several portions of 70–90° ligroin. The combined extract was cooled in Dry Ice, filtered from hydroxynaphthoquinone and evaporated. The residue was a reddish oil weighing 15.8 g. This was then processed by a procedure used with success for the isolation of vitamin K_1,[24] namely, by extraction of the hydroquinone from petroleum ether with Claisen alkali and oxidation with silver oxide. A small amount (50 mg.) of a viscous red oil was obtained of composition not far from that of the expected product (C, 78.38; H, 11.55).

In a second experiment the crude material resulting from the alkylation of 1 g. of hydroxynaphthoquinone was distilled in high vacuum. At a pressure of 5×10^{-5} mm., 2.63 g. of light yellow oil distilled at a bath temperature of 100°, and then 0.63 g. (24%) of a dark reddish oil distilled at 140–150° that appeared to be substantially pure **2-hydroxy-3-dihydrophytyl-1,4-naphthoquinone**. The substance did not crystallize when an acetone solution was chilled in Dry Ice, but the oil itself solidified in the ice box to waxy orange plates that melted at room temperature.

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.24; H, 10.20. Found: C, 79.52; H, 10.54.

The **hydroquinone triacetate** was obtained by crystallization from alcohol as a waxy white solid melting at 79–80°.

Anal. Calcd. for $C_{36}H_{54}O_6$: C, 74.19; H, 9.34. Found: C, 74.40; H, 9.54.

Summary

1. The peroxide alkylation reaction has been applied to the synthesis of the 3-undecyl (I), 3-dodecyl (II) and 3-tridecyl (III) derivatives of 2,5-dihydroxy-1,4-benzoquinone. A comparison with natural embelin confirms the structure I assigned to the pigment by Asano and Yamaguti.

2. A pigment isolated by Fernandez from a plant in Spain has been found identical with synthetic rapanone, III.

3. A structure is suggested for maesaquinone on the basis of certain model experiments.

4. The synthesis of 2-hydroxy-3-dihydrophytyl-1,4-naphthoquinone is described.

CAMBRIDGE, MASSACHUSETTS RECEIVED MAY 23, 1947

---

(23) Willstätter and A. Stoll, "Untersuchungen über Chlorophyll," 312 (1913).

(24) Fieser, THIS JOURNAL, **61**, 3467 (1939).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF J. T. BAKER CHEMICAL CO.]

Some Isomers of Amidone and Related Compounds

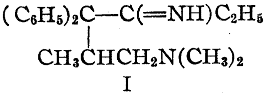
BY NELSON R. EASTON, JOHN H. GARDNER, MARY L. EVANICK AND JOSEPH R. STEVENS

In a recent Communication to the Editor[1] from this Laboratory, it was stated that 4-dimethylamino-2,2-diphenyl-3-methylbutanenitrile, the lower melting nitrile formed in the original Amidone synthesis,[2] reacts with ethylmagnesium bromide to give a ketimine (I), salts of which are readily isolated in a pure state. This ketimine hydrolyzes with difficulty to the corresponding ketone (II), which has been given the trivial name, Isoamidone II. After the ketimine had been boiled with 20% hydrochloric acid for five hours, some unreacted ketimine was isolated from the crude mixture in the form of its sesquioxalate. Its identity was confirmed by the preparation of the dipicrate.

On working up the product obtained from the reaction of ethylmagnesium bromide with the crude mixture prepared by the condensation of diphenylacetonitrile and 1-dimethylamino-2-chloropropane, another isomer of Amidone, designated as Isoamidone I, has been found in addition to Amidone and Isoamidone II ketimine. The details of this work are now described in the Experimental Part of this paper. The structure of Isoamidone I has not yet been determined, but is being studied at the present time.

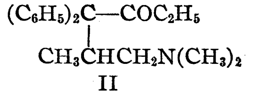
In this connection, 7-dimethylamino-4,4-diphenyl-3-heptanone (III) was prepared and characterized as the hydrochloride, picrate and methiodide. All of these salts were markedly different from the corresponding salts of Isoamidone I. Also, the ketimine of III was isolated as the picrate.

As further members of this series of compounds, the acetyl ketimine related to Amidone has been prepared as the base (IV) and hydrochloride. The acetyl ketimine (V) related to Isoamidone II was found to be an oil which was converted into the hydrochloride without purification. Also, the dipicrate of Amidone ketimine has been prepared.



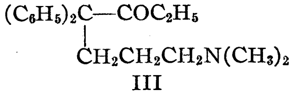
$$\begin{array}{l}(C_6H_5)_2C\text{—}C(=NH)C_2H_5\\ \qquad\;\; |\\ \quad CH_3CHCH_2N(CH_3)_2\end{array}$$

I



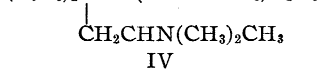
$$\begin{array}{l}(C_6H_5)_2C\text{—}COC_2H_5\\ \qquad\;\; |\\ \quad CH_3CHCH_2N(CH_3)_2\end{array}$$

II



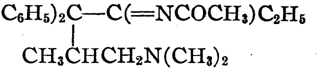
$$\begin{array}{l}(C_6H_5)_2C\text{—}COC_2H_5\\ \qquad\;\; |\\ \qquad CH_2CH_2CH_2N(CH_3)_2\end{array}$$

III



$$\begin{array}{l}(C_6H_5)_2C\text{—}C(=NCOCH_3)C_2H_5\\ \qquad\;\; |\\ \qquad CH_2CHN(CH_3)_2CH_3\end{array}$$

IV



$$\begin{array}{l}(C_6H_5)_2C\text{—}C(=NCOCH_3)C_2H_5\\ \qquad\;\; |\\ \quad CH_3CHCH_2N(CH_3)_2\end{array}$$

V

Experimental

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanoneimine (I).—To an ethereal solution of ethylmagnesium bromide prepared from 26.4 g. (1.08 moles) of magnesium turnings and 132 g. (1.21 moles) of ethyl bromide in 180 ml. of ether, there was added during a half hour, with stirring, a solution of 150 g. (0.53 mole) of 4-dimethylamino-2,2-diphenyl-3-methylbutanenitrile[2] in 150 ml. of xylene. The mixture was heated on a water-bath for three hours. The mixture was then poured into a solution of 170 ml. of concentrated hydrochloric acid in 300 ml. of water. A vigorous reaction resulted, evaporating the xylene and ether. The acid solution was made alkaline with 50% sodium hydroxide. Celite 503 was added and the mixture filtered. Both the precipitate and filtrate were extracted with ether. The ether solution was dried over magnesium sulfate, filtered and evaporated to dryness, leaving 147 g. of the crude ketimine as an oily residue.

For the preparation of the sesquioxalate, the oil was treated with an equal weight of oxalic acid dissolved in alcohol. On cooling and scratching, the sesquioxalate crystallized. After crystallization from a mixture of alcohol and ether, it melted at 145–146°.

Anal. Calcd. for $2C_{21}H_{28}N_2 \cdot 3H_2C_2O_4$: C, 64.99; H, 7.05; N, 6.32; $H_2C_2O_4$, 30.45. Found: C, 65.15; H, 6.96; N, 6.36; $H_2C_2O_4$, 30.50.

The dihydrochloride was prepared by treating an alcoholic solution of the ketimine with the theoretical amount of 30% alcoholic hydrogen chloride. On standing, an oil separated which eventually crystallized. After crystallization from a mixture of alcohol and ether, the white crystals melted at 200–202° dec.

Anal. Calcd. for $C_{21}H_{28}N_2 \cdot 2HCl$: C, 66.13; H, 7.93; N, 7.35; Cl, 18.59. Found: C, 66.00; H, 7.75; N, 7.30; Cl, 18.43.

For the preparation of the dipicrate, the oily ketimine was dissolved in alcohol and a hot alcoholic solution of picric acid was added. The mixture was heated on the steam-bath and crystals formed. The solid material was separated and recrystallized successively from acetone, acetone containing a little picric acid and from ethyl acetate. The yellow product melted at 140–141°, and could be converted into a more stable form, m. p. 166.5–168° by crushing on a porous plate or by boiling for some time in alcohol. *Anal.* Calcd. for $C_{21}H_{28}N_2 \cdot 2C_6H_3O_7N_3$: C, 51.69; H, 4.47; N, 14.62. Found: C, 51.65, 51.75; H, 4.54, 4.38; N, 14.41, 14.58.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone [Isoamidone II (II)] Oxalate.—A solution of 17.4 g. of the ketimine dihydrochloride in 150 ml. of 20% hydrochloric acid was refluxed for five hours, cooled and made alkaline with 50% sodium hydroxide. After cooling, it was extracted twice with ether. The ether solution was concentrated to about 50 ml. and a solution of 17.5 g. of oxalic acid in 75 ml. of alcohol was added. On cooling and scratching, crystals were deposited. After crystallization from a mixture of acetone and alcohol, the yield was 9.7 g. (47%), m. p. 163–164°.

Anal. Calcd. for $2C_{21}H_{27}ON \cdot 3H_2C_2O_4$: C, 64.86; H, 6.76; N, 3.15; $H_2C_2O_4$, 30.41; neut. equiv., 148. Found: C, 65.2; H, 6.66; N, 3.43, 3.39; $H_2C_2O_4$, 30.40; neut. equiv., 149.

On diluting the original mother liquor with ether to complete precipitation, an oil was deposited which slowly

---

[1] N. R. Easton, J. H. Gardner and J. R. Stevens, THIS JOURNAL, **69**, 976 (1947).

[2] Office of the Publication Board, Department of Commerce, Report PB 981, p. 96; E. M. Schultz, C. M. Robb and J. M. Sprague, THIS JOURNAL, **69**, 188 (1947); W. R. Brode and M. W. Hill, *ibid.*, **69**, 724 (1947).

crystallized on standing in the refrigerator. The liquid was decanted and the residue recrystallized twice from a mixture of acetone and alcohol, giving white crystals, m. p. 145–146°. A mixed melting point with Isoamidone II ketimine sesquioxalate showed no depression. For confirmation, the base from 0.5 g. of the oxalate was dissolved in 5 ml. of alcohol and treated with a solution of 0.5 g. of picric acid in 8 ml. of alcohol. The picrate came down as an oil. The alcoholic mother liquor was decanted and the oil was dissolved in about 75 ml. of hot alcohol. On cooling, the picrate formed yellow crystals, m. p. 166–167°, mixed with Isoamidone II ketimine dipicrate, m. p. 167–169°.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone [Isoamidone II Base (II)].—An aqueous solution of 7.8 g. of Isoamidone II oxalate was made alkaline with sodium hydroxide. The base was extracted with ether and the ether extract was dried over potassium carbonate. The ether was distilled. The residue was dried by heating in a water aspirator vacuum on a steam-bath and distilled in vacuum. The yield was 3.9 g. (72%) of a clear, slightly yellow, very viscous liquid, b. p. 215° under 12 mm.

Anal. Calcd. for $C_{21}H_{27}ON$: C, 81.55; H, 8.74; N, 4.53. Found: C, 81.50; H, 8.90; N, 4.54, 4.52.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone [Isoamidone II (II)] Hydrochloride, Picrate and Methiodide.—For the preparation of the hydrochloride, 16 g. of the oxalate was converted to the base as above. The crude base was treated with 8 ml. of 20% hydrochloric acid in an evaporating dish and the mixture was evaporated to dryness on a steam-bath, and finally dried at 70° in a vacuum oven. The yield of crude product was 12.5 g., m. p. 187–188°, after softening at 139°. After crystallization from isopropyl alcohol, there were obtained 5.7 g. of white crystals, m. p. 145–149°, rising to m. p. 190–193° after drying in a vacuum at 100°. Working up the mother liquors gave an additional 4.3 g. of the same m. p. after drying. The total yield was 10.0 g. (80%).

Anal. Calcd. for $C_{21}H_{27}ON{\cdot}HCl$: C, 72.92; H, 8.16; N, 4.05; Cl, 10.25. Found: C, 72.90; H, 8.13; N, 4.02, 4.01; Cl, 10.20.

The picrate was prepared by treating a solution of 0.4 g. of the base in 2 ml. of alcohol with a solution of 0.6 g. of picric acid in 5 ml. of hot alcohol. The solution was cooled and the yellow crystals were filtered out and after recrystallization from alcohol, the yield was 0.45 g. (64.5%), m. p. 149–150°.

Anal. Calcd. for $C_{21}H_{27}ON{\cdot}C_6H_3O_7N_3$: C, 60.21; H, 5.62; N, 10.40. Found: C, 59.95; H, 5.54; N, 10.55, 10.52.

For the preparation of the methiodide, the base from 2 g. of the oxalate was dissolved in ether. The ether solution was dried over magnesium sulfate, filtered and an excess of methyl iodide was added. On standing crystals, m. p. 263–264°, unchanged by recrystallization from methanol, separated.

Anal. Calcd. for $C_{22}H_{30}ONI$: C, 58.54; H, 6.70; N, 3.10; I, 28.11. Found: C, 58.45; H, 6.78; N, 3.06; I, 28.25, 28.35.

Isolation of Isoamidone I.—Diphenylacetonitrile (213.5 g.) was condensed with 133 g. of 1-dimethylamino-2-chloropropane by the procedure described in the Report PB 981.[2] The crude mixture of nitriles was treated with ethylmagnesium bromide and the resulting complex decomposed as described in the Report. The three layers which formed were separated. The middle layer was made alkaline with 50% sodium hydroxide and extracted with ether. The ether extract was dried over magnesium sulfate and concentrated to a thick oil. The oil was dissolved in absolute alcohol and the calculated amount of absolute alcoholic hydrogen chloride was added. Amidone hydrochloride crystallized and was recrystallized from absolute alcohol. The yield was 54 g., m. p. 229–231°.

The mother liquor was concentrated, neutralized with 50% sodium hydroxide and extracted with ether. The ether extract was dried over magnesium sulfate and evaporated to dryness, leaving an oil. An equal weight of oxalic acid dissolved in alcohol was added to the oil. On adding anhydrous ether and scratching, 13 g. of Isoamidone I oxalate, m. p. 158–160°, crystallized. A sample for analysis was recrystallized from acetone, with no change in melting point.

Anal. Calcd. for $C_{21}H_{27}ON{\cdot}H_2C_2O_4$: C, 69.15; H, 7.32. Found: C, 69.20; H, 7.06.

The base was liberated by the addition of sodium hydroxide to an aqueous solution of the oxalate and was extracted with ether. The ether solution was washed with water and dilute ammonium hydroxide and dried over magnesium sulfate. The ether was distilled and the residue dried by heating under reduced pressure.

Anal. Calcd. for $C_{21}H_{27}ON$: C, 81.50; H, 8.80; N, 4.53. Found: C, 81.34; H, 8.84; N, 4.76, 4.73.

A sample, when distilled under 3 mm. pressure, boiled at 164–167°.

The hydrochloride was prepared by the addition of alcoholic hydrogen chloride and anhydrous ether to the base. After crystallization from acetone, it melted at 172–173°.

Anal. Calcd. for $C_{21}H_{27}ON{\cdot}HCl$: C, 72.92; H, 8.16; N, 4.05; Cl, 10.25. Found: C, 73.05; H, 8.21; N, 4.25, 4.22; Cl, 10.25.

The methiodide was prepared by adding methyl iodide to an ethereal solution of the crude base. After crystallization from a mixture of acetone and di-isopropyl ether, it melted at 195–196°.

Anal. Calcd. for $C_{22}H_{30}ONI$: C, 58.53; H, 6.70; I, 28.11. Found: C, 58.65; H, 6.85; I, 28.40, 28.50.

For the preparation of the picrate, a sample of the base liberated from the hydrochloride was dissolved in alcohol and treated with a solution of an equal weight of picric acid in alcohol. After crystallization twice from alcohol and drying in vacuum at 77°, it melted at 131–133°.

Anal. Calcd. for $C_{21}H_{27}ON{\cdot}C_6H_3O_7N_3$: C, 60.21; H, 5.62; N, 10.40. Found: C, 60.05; H, 5.54; N, 10.61, 10.62.

For the isolation of Isoamidone II ketimine, the bottom layer from the decomposition of the original complex was neutralized with 50% sodium hydroxide and extracted with ether. The ether extract was dried over magnesium sulfate and evaporated to dryness. The residue was dissolved in alcohol and absolute alcoholic hydrogen chloride was added. After adding anhydrous ether and scratching, 12 g. of crystals, m. p. 195–200°, separated. A sample was recrystallized from absolute alcohol and then melted at 200–202°. A mixture with an authentic sample of Isoamidone II ketimine dihydrochloride melted at 199–201°.

To determine whether Isoamidone I might be a molecular compound between Amidone and Isoamidone II, the melting point ranges of several mixtures of the hydrochlorides of the last two compounds were determined. Each mixture melted over a wide range with an upper limit of 190° or higher and the melting range of no mixture approached that of Isoamidone I hydrochloride. The data are shown in Table I.

TABLE I

Hydrochlorides of Amidone, %	 Isoamidone II, %	Softened, °C.	Completely melted, °C.
76	24	175	218
55	45	176	211
28	72	145	190

A mixture made up of approximately equal amounts of the hydrochlorides of Amidone and Isoamidone II was dissolved in alcohol and precipitated by the addition of ether. The resulting granular precipitate softened at 157° and was completely melted at 200°.

5-Dimethylamino-2,2-diphenylpentanenitrile.—To a well-stirred suspension of 9 g. of sodamide in 50 ml. of dry benzene, warmed to 45–50°, there was added, during a fifteen-minute period, 39 g. of diphenylacetonitrile. The temperature of the reaction mixture was maintained at 40–45° for one and one-half hours. The mixture was cooled to 20–25° and 25 g. of 3-dimethylaminopropyl chloride was added during thirty minutes. The mixture was refluxed for five hours. After standing overnight, the mixture was poured into water. The water layer was separated and discarded. The benzene layer was extracted with 20% hydrochloric acid. The acid layer was neutralized with 10% sodium hydroxide and extracted with ethyl ether. The ether solution was dried over magnesium sulfate, filtered and evaporated to dryness. The product was recrystallized from petroleum ether and from Skellysolve C. The yield of white crystals melting at 64–65° was 19.4 g.

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.95, 81.90; H, 7.82, 7.98; N, 10.09, 10.02.

7-Dimethylamino-4,4-diphenyl-3-heptanone (III) Hydrochloride, Picrate and Methiodide.—A solution of 25.4 g. of 5-dimethylamino-2,2-diphenylpentanenitrile in 20 ml. of xylene was added to a Grignard reagent prepared from 4.4 g. of magnesium and 22 g. of ethyl bromide in 20 ml. of ether. The reaction mixture was heated on a steam-bath for five and one-half hours. After standing overnight, it was poured into a solution of 40 ml. of concentrated hydrochloric acid in 100 ml. of water. Two layers were formed. The water layer was separated, made alkaline with 10% sodium hydroxide and extracted with ether. The ether solution was dried over magnesium sulfate, filtered and evaporated to dryness, leaving 28 g. of an oil.

A small portion of the oil was converted into a picrate, m. p. 181–182°, in the usual way. Analysis showed it to be the dipicrate of the ketimine.

Anal. Calcd. for $C_{21}H_{28}N_2 \cdot 2C_6H_3O_7N_3$: C, 51.69; H, 4.47; N, 14.62. Found: C, 51.50; H, 4.59; N, 14.50, 14.51.

The remaining oil was boiled with concd. hydrochloric acid for five hours. The mixture was cooled, made alkaline with 10% sodium hydroxide and extracted with ether. After being dried over magnesium sulfate, the ether solution was treated with dry hydrogen chloride. The oil which separated gradually crystallized. The solid was dissolved in ethyl acetate, treated with Nuchar C, filtered and the resulting solution was cooled. The white crystals which separated melted at 139–140°.

Anal. Calcd. for $C_{21}H_{27}ON \cdot HCl$: C, 72.92; H, 8.16; N, 4.05. Found: C, 73.00; H, 8.30; N, 4.06.

The picrate was prepared by treating the base liberated from the hydrochloride with picric acid in alcohol. After crystallizing from the same solvent, it melted at 118–119°.

Anal. Calcd. for $C_{21}H_{27}ON \cdot C_6H_3O_7N_3$: C, 60.21; H, 5.62; N, 10.40. Found: C, 60.30; H, 5.85; N, 10.32.

The methiodide was prepared by treating the base with methyl iodide in ether. After crystallizing from methanol, it melted at 250–252°.

Anal. Calcd. for $C_{22}H_{30}ONI$: C, 58.54; H, 6.70; N, 3.10; I, 28.11. Found: C, 58.25; H, 6.98; N, 3.16; I, 28.55.

6-Dimethylamino-4,4-diphenyl-3-heptanone-acetylimine (IV).—4-Dimethylamino-2,2-diphenylpentanenitrile was treated with ethylmagnesium bromide according to the procedure for the preparation of Amidone by the original method.[2] The resulting mixture was poured into acetic anhydride with cooling in an ice-bath. Ethyl alcohol was added and most of the solid precipitate dissolved. The mixture was concentrated under reduced pressure and the residue dissolved in water. After making alkaline with sodium hydroxide, the base was extracted with ether. The ether solution was dried over magnesium sulfate and evaporated to dryness. The residue crystallized on standing and was recrystallized from Skellysolve C, m. p. 130–131°.

Anal. Calcd. for $C_{23}H_{30}ON_2$: C, 78.82; H, 8.63; N, 7.99. Found: C, 78.90; H, 8.70; N, 8.08.

The hydrochloride was prepared by passing dry hydrogen chloride into a solution of the base in di-isopropyl ether. After recrystallizing from acetone, it melted at 219–221°.

Anal. Calcd. for $C_{23}H_{30}ON_2 \cdot HCl$: C, 71.38; H, 8.08; N, 7.24; Cl, 9.16. Found: C, 71.30; H, 8.17; N, 7.23; Cl, 9.14.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone-acetylimine (V) Hydrochloride.—A mixture of 25 g. of the ketimine and 50 g. of acetic anhydride was heated on the steam-bath for about three hours, and then concentrated under reduced pressure. The residue was dissolved in water and the solution made alkaline with sodium hydroxide. The base was extracted with ether, the ether solution dried over magnesium sulfate and evaporated to dryness. On attempting to prepare the oxalate in the usual way, an oil which did not crystallize was formed. The base was regenerated and converted into the hydrochloride by adding an alcoholic solution of hydrogen chloride and then ether. The hydrochloride crystallized on scratching; m. p. 213–215°.

Anal. Calcd. for $C_{23}H_{30}ON \cdot HCl$: C, 71.38; H, 8.08; N, 7.24; Cl, 9.16. Found: C, 71.45; H, 8.12; N, 7.23, 7.23; Cl, 9.15.

6-Dimethylamino-4,4-diphenyl-3-heptanoneimine (Amidone Ketimine) Dipicrate.—Ethylmagnesium bromide was brought into reaction with 4-dimethylamino-2,2-diphenylpentanenitrile as in the original preparation of Amidone.[2] On completion of the reaction, the reaction mixture was poured into a mixture of ice and 30% acetic acid. After neutralization with 10% sodium hydroxide, the mixture was extracted with ether. The ether solution was dried over magnesium sulfate, filtered and concentrated. A portion of the residue was dissolved in alcohol and treated with an alcoholic solution of picric acid. The solid which precipitated was recrystallized from a mixture of ethyl acetate and acetone. The yellow product melted at 182–184°.

Anal. Calcd. for $C_{21}H_{28}N_2 \cdot 2C_6H_3O_7N_3$: C, 51.69; H, 4.47; N, 14.62. Found: C, 51.60; H, 4.28; N, 14.68, 14.65.

Acknowledgment.—We are indebted to Dr. V. B. Fish of this Laboratory for the analyses reported in this paper.

Summary

1. Three isomers of Amidone have been described.

2. Four ketimine derivatives related to Amidone have been prepared.

PHILLIPSBURG, N. J. RECEIVED MAY 8, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTH TEXAS STATE COLLEGE]

Thiophene Analogs of DDT

BY PRICE TRUITT, MARJORIE MATTISON[1] AND EUGENE RICHARDSON[1]

Since thiophene very often yields compounds that are analogous to benzene derivatives in general physiological properties,[2] it was decided to prepare a number of compounds derived from thiophene and halogenated thiophenes that would be analogous to DDT, 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl)-ethane.[3]

1,1,1-Trichloro-2,2-bis-(thienyl)-ethane had been previously prepared by the action of phosphorus pentoxide on a mixture of thiophene and chloral, and in a similar fashion 1,1,1-tribromo-2,2-bis-(thienyl)-ethane has been prepared from bromal and thiophene with sulfuric acid as a condensing agent.[4] However, it seemed desirable to again prepare these compounds and test their insecticidal properties along with the new compounds.

In our hands, the use of sulfuric acid with thiophene and substituted thiophene without a diluent gave very little of the desired product and a large amount of orange-colored material which was soluble in alkali.

The use of phosphorus pentoxide was very unsatisfactory since the material became very lumpy and difficult to stir. However, when acetic acid was used as a diluent with sulfuric acid,[5] the amount of sulfonation was materially reduced, and the desired products obtained. None of the above methods was satisfactory for the preparation of 1,1,1-tribromo-2,2-bis-(thienyl)-ethane.

Experimental

Thiophene used in this work was obtained from Socony-Vacuum and was used without further purification.

2-Chlorothiophene.—This compound was prepared by the action of sulfuryl chloride on thiophene in ether with aluminum chloride as a catalyst according to the directions of Thol and Eberhard.[6] 200 g. of thiophene gave 145 g. of 2-chlorothiophene, b. p. 127–128°, n^{20}D 1.5510.

2-Bromothiophene.—This compound was donated by Michigan Chemical Corporation, St. Louis, Michigan, and was used without further purification.

2-Iodothiophene.—This compound was prepared according to the procedure given in "Organic Syntheses."[7]

2-Methylthiophene.—This compound was donated by Socony–Vacuum and was used without further purification.

Chloral.—This compound was donated by Westvaco Chlorine Products Company, New York, N. Y.

1,1,1-Trichloro-2,2-bis-(chlorothienyl)-ethane.—To a well-stirred mixture of 34.0 g. (0.29 mole) chlorothiophene and 14.7 g. (0.1 mole) of chloral in 150 ml. of glacial acetic acid, 67 g. of concentrated sulfuric acid were added dropwise over a period of one hour. The temperature was kept below 5° during addition, and the reaction mixture was stirred in an ice-bath for several hours. The reaction mixture was neutralized with 10% potassium hydroxide solution, and the crystals which separated were filtered. The product was recrystallized from 95% ethanol, and when pure melted at 63.7–63.8°.

Anal. Calcd. for $C_{10}H_5S_2Cl_5$: Cl, 48.38. Found: Cl, 48.21.

1,1-Dichloro-2,2-bis-(chlorothienyl)-ethylene.—A solution of 6.73 g. of 1,1,1-trichloro-2,2-bis-(chlorothienyl)-ethane and 3.2 g. of potassium hydroxide in 100 ml. of ethanol was refluxed for two hours. Some of the alcohol was removed *in vacuo*, and the remainder of the alcoholic solution was poured over ice. The oil which separated was extracted with ether. The ethereal solution was dried over sodium sulfate. The ether was removed under reduced pressure, and the residue was distilled *in vacuo*. The product boiled at 208–210° (6 mm.), n^{21}D 1.6833.

Anal. Calcd. for $C_{10}H_4S_2Cl_4$: Cl, 42.97. Found: Cl, 42.64.

1,1,1-Trichloro-2,2-bis-(bromothienyl)-ethane.—To a well-stirred mixture of 24 g. (0.15 mole) of bromothiophene and 8.85 g. (0.06 mole) of chloral in 150 ml. of glacial acetic acid, 54 g. of fuming sulfuric acid were added dropwise over a period of two hours. The temperature was kept below 15° during addition, but the reaction was heated to 55° after addition was complete and was stirred for twenty-four hours. The product mixture was poured into ice-water, and the organic fraction which separated as an oil was extracted with ether. The ether solution was washed with water, bicarbonate solution, and dried over anhydrous calcium chloride. The ether was evaporated, and the crude crystalline product obtained. The product was recrystallized from a mixture of petroleum ether and *n*-hexane, and when pure melted at 93.7°.

Anal. Calcd. for $C_{10}H_5S_2Cl_3Br_2$: Cl, 23.35; Br, 35.09; Found: Cl, 23.32; Br, 35.03.

1,1,1-Trichloro-2,2-bis-(iodothienyl)-ethane.—To a well-stirred mixture of 63.8 g. (0.31 mole) iodothiophene and 19.1 g. (0.13 mole) of chloral in 50 ml. of glacial acetic acid, 100 g. of concentrated sulfuric acid was added dropwise over a period of two hours. The temperature was kept below 20° during addition, and the reaction mixture was stirred in an ice-bath for two hours and at room temperature for twenty-four hours. The product mixture was poured into ice-water, and the organic fraction, a black oily mass, was extracted with ether. The ether solution was washed with water, bicarbonate solution, and dried over sodium sulfate. The ether was evaporated, and petroleum ether was added to the residue. The mixture was cooled overnight, and the brown crystals which separated were filtered and washed with *n*-hexane. The crude product was recrystallized from *n*-hexane and when pure melted at 94.8–95.1°.

Anal. Calcd. for $C_{10}H_5S_2Cl_3I_2$: Cl, 19.36; I, 46.20. Found: Cl, 19.36; I, 46.27.

1,1,1-Trichloro-2,2-bis-(methylthienyl)-ethane.—To a well-stirred mixture of 75 g. (0.75 mole) of 2-methylthiophene and 49.5 g. (0.30 mole) of chloral hydrate in 100 ml. of glacial acetic acid, 184 g. of concentrated sulfuric acid were added dropwise with stirring while the temperature was kept at 15°. The reaction mixture was stirred at room temperature for twenty-four hours. The product mixture was poured into ice water, and the aqueous layer decanted. The crystalline product was dissolved in ether. The ether solution was washed with water, bicarbonate solution, and dried over anhydrous calcium chloride. The ether was evaporated, and the product recrystallized from an alcohol–acetone mixture. When pure it melted at 72.2°.

---

[1] The work described in this paper was carried out under a grant from the Graduate School, North Texas State College, Denton, Texas.

[2] Steinkopf and Ohse, *Ann.*, **437**, 14 (1933).

[3] Zeidler, *Ber.*, **7**, 1180 (1874).

[4] Peter, *ibid.*, **17**, 1345 (1884).

[5] Cristol and Haller, THIS JOURNAL, **68**, 140 (1946).

[6] Thol and Eberhard, *Ber.*, **26**, 2947 (1893).

[7] Blatt, "Organic Syntheses," Coll. Vol. II, p. 357.

Anal. Calcd. for $C_{12}H_{11}S_2Cl_3$: Cl, 32.70. Found: Cl, 32.26.

Discussion of Results

1,1,1-Trichloro-2,2-bis-(thienyl)-ethane was previously reported melting at 76.0°. Using the same procedure in preparation of this compound, we obtained a compound, when pure, melting at 78.4°.[8] However, analysis of this product proves it to be the desired product.

Attempts to determine the structure of 1,1,1-trichloro-2,2-bis-(chlorothienyl)-ethane were carried out by the method of Cristol and Haller.[9]

This method failed to give the product anticipated. Treatment of 1,1-dichloro-2,2-bis-(chlorothienyl)-ethylene with chromic oxide in boiling glacial acetic acid gave a yellow oil which failed to crystallize. Since the bis-chlorothienyl ketone was expected to be a solid, it was concluded the susceptibility of the thiophene nucleus to oxidation led to decomposition.

When the olefin was refluxed with alkaline and neutral potassium permanganate, the original product was recovered. Hydrolysis of the olefin with barium hydroxide[10] in ethylene glycol gave a neutral oil and a trace of acidic material. The yield of neutral product was insufficient for characterization, but a qualitative test showed the presence of sulfur and a trace of halogen. A halogen analysis indicated approximately 1.0% chlorine. Evidently the chlorine in the thiophene nucleus was removed by barium hydroxide as well as that attached to the ethylenic chain. No definite structure has been assigned to these compounds, but on the basis of analysis and the known high reactivity of the 2,5-positions of thiophene, it is suspected that the thiophene nucleus is joined at the 5-position.

Laboratory tests of the insecticidal properties indicate that 1,1,1-trichloro-2,2-bis-(chlorothienyl)-ethane is the most effective compound against cockroaches; however, the derivatives of 2-bromothiophene and 2-iodothiophene show some activity. The derivative of 2-methylthiophene shows no insecticidal activities. 1-Trichloro-2,2-bis-(chlorothienyl)-ethane seems to be as active as DDT against cockroaches.

Summary

A series of thiophene analogs of DDT have been prepared. The ones not previously reported are: 1-trichloro-2,2-bis-(chlorothienyl)-ethane, 1-dichloro-2,2-bis-(chlorothienyl)-ethylene, 1-trichloro-2,2-bis-(bromothienyl)-ethane, 1-trichloro-2,2-bis-(iodothienyl)-ethane, 1-trichloro-2,2-bis-(methylthienyl)-ethane.

AMES, IOWA RECEIVED AUGUST 7, 1947

---

[8] Peter, ref. 4, p. 1345.

[9] Cristol and Haller, ref. 5, p. 140.

[10] Cristol, Soloway and Haller, THIS JOURNAL, **69**, 510 (1947).

[CONTRIBUTION FROM THE LABORATORIES OF PHYSICAL AND PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF WISCONSIN]

Biophysical Studies of Blood Plasma Proteins. VII. Separation of γ-Globulin from the Sera of Various Animals[1]

BY J. CHARLES NICHOL AND H. F. DEUTSCH

The separation of the components of biological tissues and fluids by ethanol fractionation as carried out by Cohn, *et al.*,[2] is directed to the isolation and recovery of all recognizable entities of the system in question. Often, however, in the interests of expediting the recovery or of increasing the yield of a given component it may be desirable to separate such an entity with immediate (but not necessarily eventual) disregard for other constituents. The antibodies of various animal species immunized to different antigens are known to possess the gross physical–chemical characteristics of the γ-globulins and to separate from solution with them. The scientific and technical importance of these antibody-rich fractions is the incentive which has led us to the development of a simple and effective procedure for removal of the normal γ-globulins from the sera of human beings and of the goat, dog, rabbit, rat, chicken and guinea pig.

It is found that in the individual species the chemical treatment may vary somewhat, but in all cases there is an initial and important step in which the antibody-rich γ-globulins are precipitated from a diluted serum which may be followed by a purification treatment to remove certain small amounts of contaminant β-globulins. In this way the γ-globulins are obtained in relatively pure form. The methods used involve variations in ethanol and salt concentrations and *p*H such as were used previously in studies on human γ-globulin.[3,4,5]

The general scheme, based in part upon our previous work,[3,4] consists in diluting one volume of serum with three volumes of water, adjusting the

---

[1] This work was supported in part by grants from Eli Lilly and Company, the Wisconsin Alumni Research Foundation, and the U. S. Public Health Service.

[2] (a) E. J. Cohn, J. A. Luetscher, Jr., J. L. Oncley, S. H. Armstrong, Jr., and B. D. Davis, THIS JOURNAL, **62**, 3396 (1940); (b) E. J. Cohn, L. E. Strong, W. L. Hughes, D. J. Mulford, J. N. Ashworth, M. Melin and H. L. Taylor, *ibid.*, **68**, 459 (1946).

[3] H. F. Deutsch, L. J. Gosting, R. A. Alberty and J. W. Williams, *J. Biol. Chem.*, **164**, 109 (1946).

[4] H. F. Deutsch, R. A. Alberty and L. J. Gosting, *ibid.*, **165**, 21 (1946).

[5] J. L. Oncley, M. Melin, D. A. Richert, J. W. Cameron and P. M. Gross, Jr., in press.

*p*H to 7.6–7.7, and adding 50% ethanol to give a final ethanol concentration of 20%. Temperatures are maintained to within one degree of the freezing point at all times. The precipitate which forms (ppt. A) contains most of the serum γ-globulins in admixture with some β-globulins. After removal by centrifugation, this precipitate is suspended in cold distilled water at a concentration of 0.5–1.0% and the suspension is adjusted to a *p*H ranging from 5.0 to 5.2. Various concentrations of ethanol and salt are used at this point, depending upon the species from which the original serum was obtained, to effect removal of the β-globulin (ppt. B), while maintaining the major portion of the γ-globulins in solution. The ppt. A from all the sera which were studied contains two families of γ-globulins, γ_1- and γ_2-globulins in our nomenclature.[4]

To effect the separation of the globulin of higher electrophoretic mobility (γ_1) when it was not removed entirely in ppt. B, the supernatant in this precipitation is brought to *p*H 5.6–6.0, the ethanol concentration to 10% and the ionic strength to 0.01, giving ppt. C-1. This precipitate consists predominantly of γ_1-globulin, along with some γ_2-globulin. The proteins remaining in solution at this point are essentially pure γ_2-globulins. Supernatants to ppt. B or ppt. C-1 are adjusted to *p*H 7.2–7.4 and the ethanol concentration is brought to 25% to effect precipitation. The γ_2-globulins, ppt. C-2, obtained in this manner are removed by centrifugation, suspended in distilled water, frozen and dried *in vacuo*.

A general scheme for the fractionation of an animal serum for γ_2-globulin is shown in Fig. 1. The conditions found suitable for that step of the fractionation process involving the separation of the beta from the gamma globulins for the various sera are shown in Table I. In the case of dog and rat sera it was necessary to introduce an additional step at *p*H 5.6–6.0 to remove γ_1-globulin (ppt. C-1) prior to the precipitation of the γ_2-globulin (ppt. C-2). An alternative procedure designed to remove γ_1-globulins with ppt. B is to raise the alcohol concentration above the values shown in Table I for the rat and dog systems.

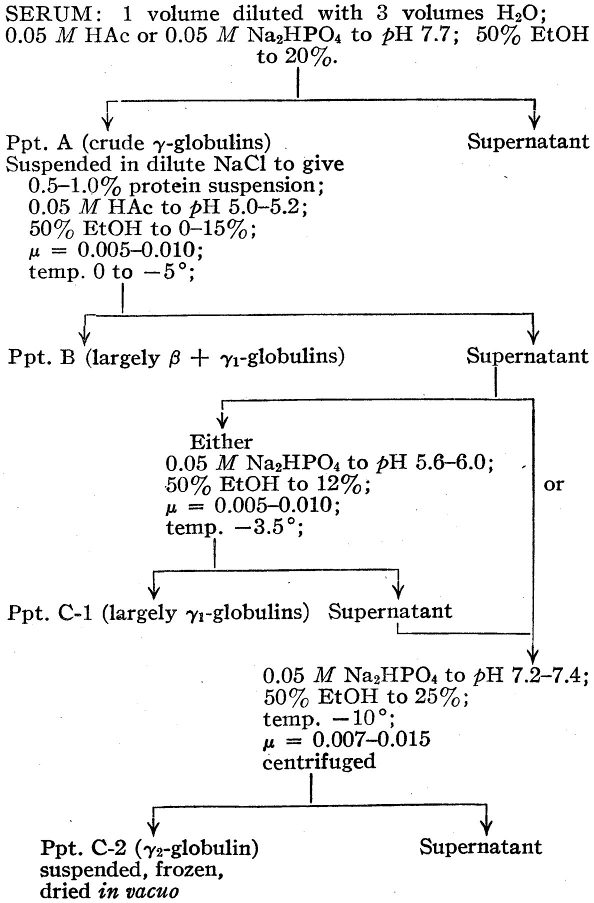


Fig. 1.—Fractionation scheme for isolation of γ_2-globulin from animal sera.

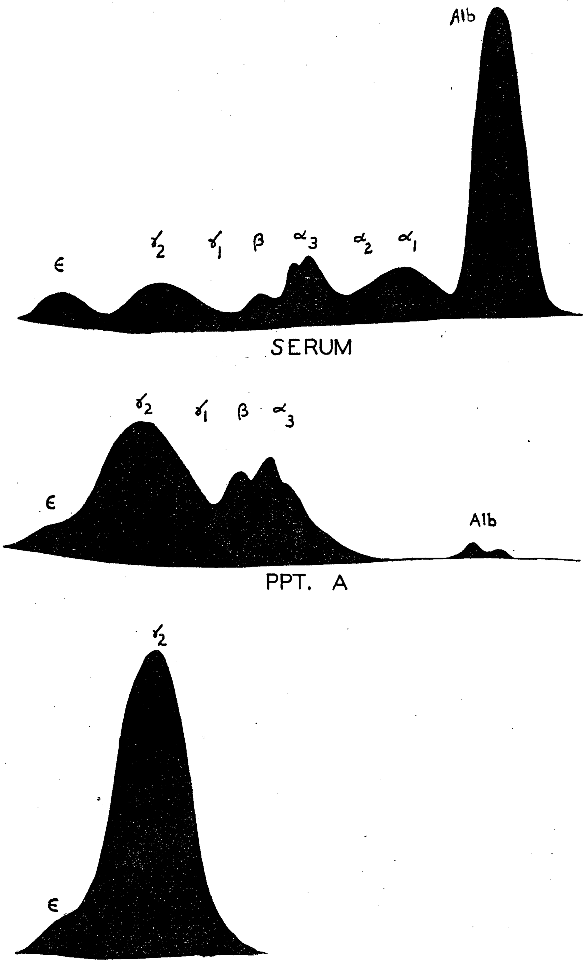


Fig. 2.—Descending electrophoretic patterns showing the course of fractionation of goat serum. Electrophoretic experiments were performed using barbiturate–citrate buffer, μ = 0.088, *p*H 8.6; duration of experiments 7800 sec. at potential gradient of 8.5 volts per cm.

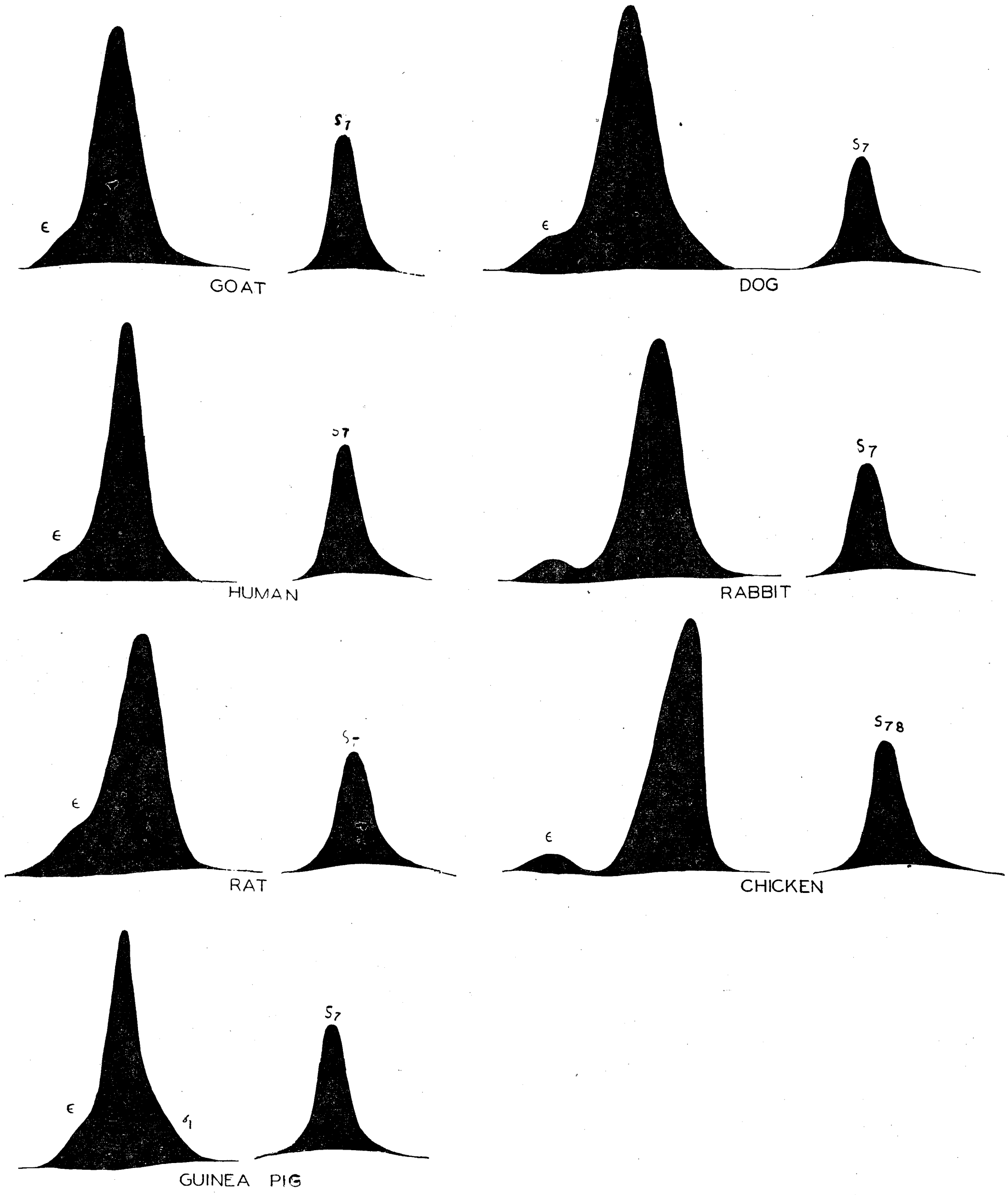


Fig. 3.—Descending electrophoretic patterns and sedimentation pictures of the γ_2-globulin of various animals (electrophoretic diagrams on left). Electrophoretic experiments were performed using barbiturate buffer, $\mu = 0.1$, pH 8.6 at a potential gradient of 6.5 volts per cm.; duration of experiments in seconds, goat 7800; human 8400; dog 11,000; rabbit 12,000; rat 7200; chicken 7800; and guinea pig 7200. Sedimentation pictures were taken after sixty minutes in the ultracentrifuge at 50,400 r. p. m.

However, by carrying out the precipitation step C-1 (Fig. 1) one can also obtain concentrates of γ_1-globulins whereas by the above procedure they are carried down into a precipitate consisting largely of β-globulins.

The electrophoretic patterns following the course of the fractionation of goat serum as outlined in Fig. 1 are shown in Fig. 2.

The fractionations were evaluated in terms of yield (recovery) and electrophoretic "purity" of product. The latter analyses were carried out in a pH 8.6 diethylbarbiturate buffer of ionic strength 0.1 at a constant potential gradient of approximately 6.5 volts per cm. The duration of experiments was from 7200 to 12000 seconds. Mobilities were determined by using the center of the initial boundary as the reference point.

Sedimentation analyses were carried out with γ-globulin solution in the high-velocity oil-turbine ultracentrifuge at 50,400 r.p.m., using a

TABLE I

CONDITIONS USED FOR THE SECOND PRECIPITATION STEP (PPT. B)

Serum	pH	Ethanol concentration, vol.%	Ionic strength, μ
Goat	5.2	0	0.01
Human	5.1	15	.01
Dog[a]	5.2	6	.005
Rabbit	5.2	10	.01
Rat[a]	5.0	10	.01
Chicken	5.0	10	.01
Guinea pig	5.1	15	.01

[a] Supernatants contain γ_1-globulins which were removed by step C.

schlieren method to record the position of the boundaries as a function of time.

Diffusion studies performed in this Laboratory by Polson[6] with solutions of our rabbit γ_2-globulin gave normal scale line displacement-distance curves to give $D_{20\text{w}} = 4.1 \times 10^{-7}$ sq. cm./sec. The method of moments was used in the computation. From this value and our sedimentation constant $s_{20\text{w}} = 7.05\ S$ a molecular weight of 160,000 is calculated. It is of interest that this value is in agreement with data of Kabat[7] for immune rabbit globulin.

The γ_2-globulins of the various animals are quite similar as regards their electrophoretic and sedimentation behavior (Table II, Fig. 3). However, it is apparent that chicken γ-globulin deviates somewhat in its properties, because it can be seen from Fig. 3 that two closely related electrophoretic components are present. The average mobility of this fraction is considerably higher than that of the γ_2-globulins of the other species studied. The sedimentation experiments show a single, somewhat broadened, peak but the sedimentation constant is somewhat higher than that of the other γ_2-globulins and heterogeneity is indicated. This fraction is free of lipid and was designated as a γ_2-globulin since it represented the component of lowest electrophoretic mobility in chicken serum. We have found this protein fraction to contain antibody.

Except as just noted, all γ_2-globulins sedimented as relatively homogeneous proteins with $s_{20\text{w}} = 7S$. Ppt. B of dog serum, consisting largely of γ_1-globulin, contained a component of high molecular weight ($s_{20\text{w}} = 18S$). γ_1-Globulins from other species were not separated from the main γ-globulin fraction for study, although electrophoretic analyses of the various fractions indicated their presence. From the point of view of their physical properties, the several animal γ_2-globulins appear to be quite similar to those found in human plasma. In addition, the γ_1-globulin of the dog shows similar molecular and electrokinetic behavior as compared to that of the corresponding fraction in human plasma.

TABLE II

PHYSICAL CONSTANTS AND YIELDS OF γ_2-GLOBULIN

Serum	$-U \times 10^5$ cm.^{2} volt^{-1} sec.$^{-1}$ [a]	% Component of sedimentation constant $s_{20\text{w}} = 7S$	γ_2-Globulin recovered per 100 ml. serum, g.	γ_2-Globulin in product, % (electrophoresis)	% Yield of γ_2-globulin[b]
Goat	1.5	99	0.65	98	60–65
Human	1.3	93	.5	98	60–70[c]
Dog	1.2	95	.25	98	55–60
Rabbit	1.7	95	1.0	98	70–75
Rat	1.8	95	0.45	98	50–55
Chicken	2.6	92[d]	.6	95	(30–35)[e]
Guinea pig	1.1	98	.3	80	75–70

[a] Mobilities measured from center of the initial boundary. [b] Based on per cent. of γ_2-globulin in original serum as determined by electrophoresis. [c] Source material was old reconstituted dried plasma. [d] $s_{20\text{w}} = 7.8$ for the chicken γ_2-globulin. [e] Electrophoretic pattern suggests the presence of two closely related proteins. Lipoproteins having the same electrophoretic mobility as those of the gamma globulins in chicken sera make it impossible to give an exact estimate of the γ-globulin yield.

After being shell-frozen and dried, the final products (γ_2-globulins) of the fractionation are recovered as white powders which are readily soluble in 0.15 M sodium chloride to give clear and stable solutions. Cruder products which are contaminated with γ_1- and β-globulins may give solutions showing considerable amounts of suspended material and turbidity.

Acknowledgments.—The authors wish to acknowledge the many helpful suggestions of Dr. J. W. Williams during the course of these investigations. The valuable technical assistance of Mr. E. M. Hanson and Mrs. Alice McGilvery is gratefully recognized.

Summary

A method for the separation of γ_2-globulins from normal animal sera has been developed. It has been applied successfully to human, goat, dog, rabbit, guinea pig, rat and chicken sera.

MADISON, WISCONSIN RECEIVED NOVEMBER 12, 1946

---

(6) A. Polson, personal communication.

(7) E. A. Kabat, *J. Exptl. Med.*, **69**, 108 (1939).

[Contribution from the Laboratories of Physical and Physiological Chemistry, University of Wisconsin]

Biophysical Studies of Blood Plasma Proteins. VIII. Separation and Properties of the γ-Globulins of the Sera of Normal Cows[1]

By E. L. Hess and H. F. Deutsch

By applying the latest methods of Cohn, *et al.*,[2] for the separation of γ-globulins from human plasma, two immune globulins have been fractionated from the plasma of hyperimmunized cows by Smith.[3] Prior to this time Cohn and associates[4] had described the fractionation of the bovine plasma proteins by equilibration across membranes with ethanol–water mixtures of controlled *p*H, ionic strength and temperature. Work in this Laboratory on the recovery of the γ-globulins of animal sera indicates that increased yields and sharper fractionations may be obtained by determining methods more or less specific for the removal of a given component in the plasma of a particular species of animal.[5] There has been evolved what is believed to be the optimum *combination* of conditions for the separation and recovery of the γ-globulins of normal bovine sera. Under these conditions two closely related γ-globulin fractions differing in electrophoretic mobility and in solubility have been separated in good yield from normal bovine serum.[5a] The conditions of separation, yield, and some of the physical properties of these normal bovine serum γ-globulins constitute the subject of this report.

Fractionation Studies

Pooled sera of Holstein cows served as a source of starting material. The experimental conditions used to separate the γ-globulins in crude form are consistent with those previously reported.[5] In this way there was obtained a fraction of composition 85% γ-globulins and 15% β-globulins. The electrophoretic patterns in Figure 1 follow the course of the fractionation. Figures 1A and 1B represent the serum and the first crude fraction (hereafter called precipitate A), respectively. The conditions necessary to precipitate the beta globulins from precipitate A, while maintaining the major portion of the γ-globulins in solution, were then studied in detail. These experiments were carried out on 1-g. samples of precipitate A. As shown in Fig. 2, the conditions *p*H 4.95 ($\pm$0.05), $\mu = 0.01$, and ethanol concentration = zero, represented suitable conditions for this separation. The γ-globulin resulting after the removal of β-globulin is indicated by the electrophoretic pattern shown in Fig. 1C.

This γ-globulin fraction (Fig. 1C) which is heterogeneous on electrophoresis, was separated into two sub-fractions in a manner similar to that employed previously in the analogous system of human γ-globulin.[6] The effect of variation of ethanol concentration at *p*H 5.65 ($\pm$0.05) was first studied on 2-g. samples of precipitate C since the γ-globulins of higher electrophoretic mobility should be isoelectric near this *p*H. The effect of *p*H variation in the sub-fractionation of the γ-globulins was likewise investigated, starting with 2-g. samples of precipitate C, with the results shown in Fig. 3. A *p*H of 5.8 and an ethanol concentration of 10% was selected as suitable for a separation of the γ_1- and γ_2-globulins.

The effect of variation of ionic strength, at *p*H 5.80 ($\pm$0.05) and 10% ethanol concentration was then studied, with the result shown in Fig. 4. The electrophoretic patterns of the γ_1- and γ_2-globulin sub-fractions obtained by precipitating the γ_1 fraction at *p*H 5.8 ($\pm$0.05) ethanol concentration of 10%, and $\mu = 0.01$, under which conditions approximately equal amounts of γ_1- and γ_2-globulins result, are shown in Fig. 1 for precipitates C-1 and C-2, respectively.

The complete fractionation procedure, with yield data for the gamma globulins, is indicated schematically in Fig. 5.

Characterization Studies

Diffusion and Sedimentation.—Diffusion studies of Kahn and Polson,[7] which were carried out in this Laboratory, indicate the same diffusion constant for both γ_1- and γ_2 fractions (precipitates C-1 and C-2), giving $D_{20\mathrm{w}} = 4.1 \times 10^{-7}$ sq. cm./sec. at a protein concentration of 1%. The normalized curves indicate traces of polydispersity.

The two fractions were analyzed in the standard Svedberg oil turbine ultracentrifuge for their molecular mass spectra. Observations of the change of position of the boundaries were made by using a schlieren optical system. Within the limits of experimental error, the same sedimentation content is observed for the γ_1- and γ_2-globulin sub-fractions. At a protein concentration of 1%

---

[1] This work was supported in part by grants from the Wisconsin Alumni Research Foundation, and the U. S. Public Health Service.

[2] (a) E. J. Cohn, L. E. Strong, W. L. Hughes, Jr., D. J. Mulford, J. N. Ashworth, M. Melin and H. L. Taylor, This Journal, **68**, 459 (1946); (b) J. L. Oncley, M. Melin, D. A. Richert, J. W. Cameron and P. M. Gross, Jr., in press.

[3] E. L. Smith, *J. Biol. Chem.*, **164**, 345 (1946).

[4] E. J. Cohn, J. A. Luetscher, J. L. Oncley, S. H. Armstrong, Jr., and B. D. Davis, This Journal, **62**, 3396 (1940).

[5] J. C. Nichol and H. F. Deutsch, *ibid.*, **70**, 80 (1948).

[5a] In accordance with our terminology for the immune globulins of humans, we have called the fraction of higher electrophoretic mobility, γ_1-globulins, and the fraction of lower mobility, γ_2-globulins. Thus the γ_1-globulin fraction is comparable to the "T" component of Smith[3].

[6] H. F. Deutsch, R. A. Alberty and L. J. Gosting, *J. Biol. Chem.*, **165**, 21 (1946).

[7] D. S. Kahn and A. Polson, *J. Phys. Coll. Chem.*, **51**, 816 (1947).

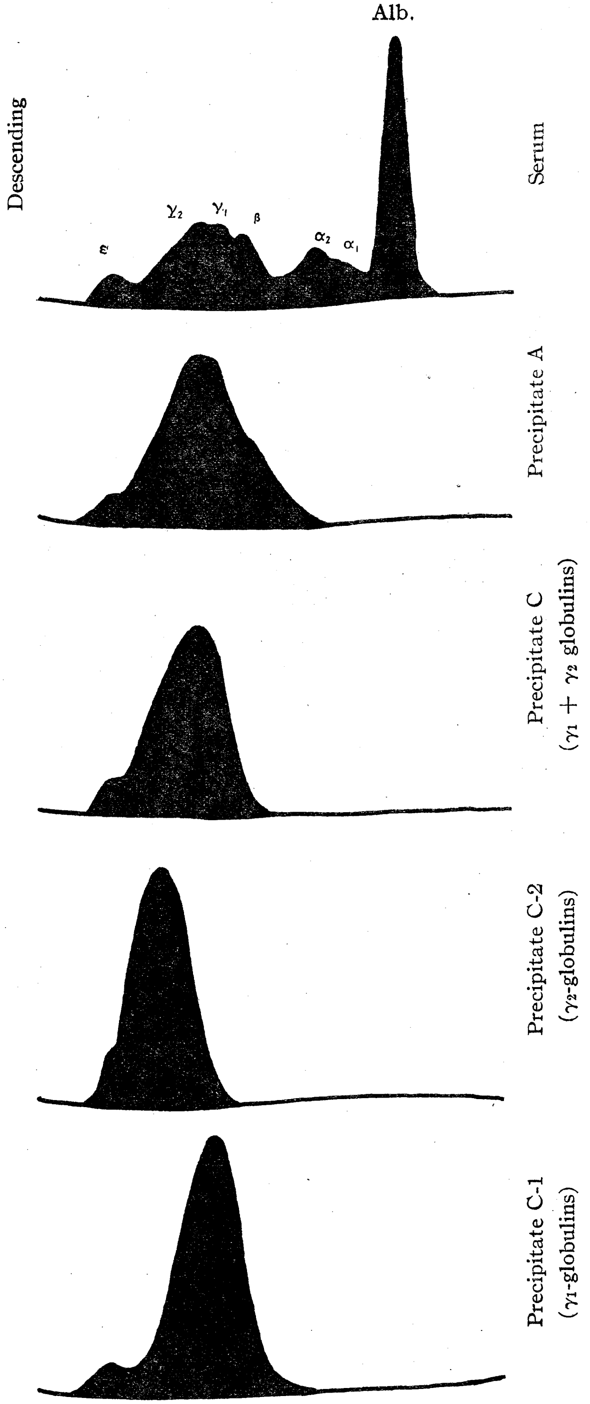


Fig. 1.—Electrophoretic patterns of bovine serum fractions in barbiturate–citrate buffer: μ, 0.088; pH, 8.6 after 120 minutes at 8.5 volts/cm.; concentration of protein 3%.

the sedimentation constant is $s_{20w} = 7.4S$. The sedimentation diagrams themselves are shown in Figs. 6B and 6D. An analysis of Fig. 6B indicates the presence of approximately 4% of heavier constituents with $s_{20w} \cong 9S$ (but no component with $s_{20w} = 20S$) in the γ_1-globulin sub-fraction. An examination of Fig. 6D shows that all the γ_2-

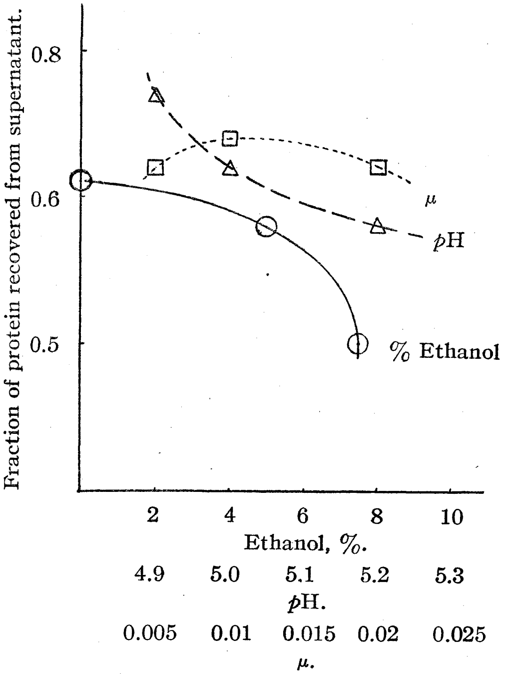


Fig. 2.—The effect of variation of per cent. ethanol, pH and ionic strength in the separation of β- and γ-globulins: ⊙, % ethanol at pH 5.1, μ = 0.0065; △, pH at μ = 0.0065, ethanol none; ⊡, ionic strength at pH 5.1, ethanol none. Protein concentration in all cases is 0.25%.

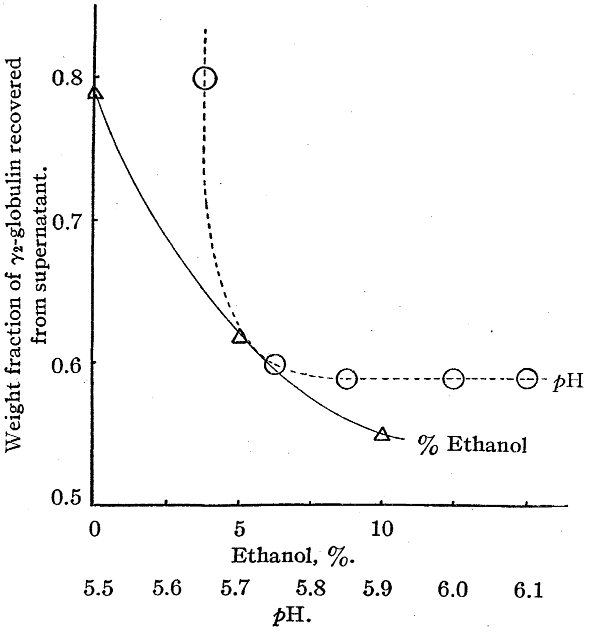


Fig. 3.—The effect of variation of ethanol concentration and pH in the subfractionation of γ-globulins: ⊙, pH variable with % ethanol = 0, μ = 0.008; △, ethanol variable, pH 5.65 ± 0.05, μ = 0.008. Concentration of protein is 0.5% in all cases.

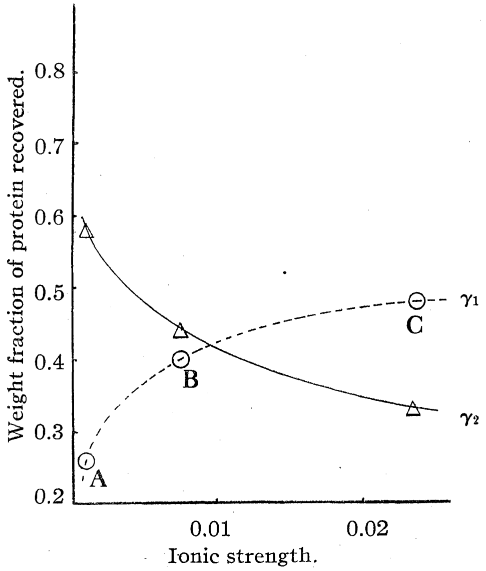


Fig. 4.—The effect of ionic strength on the yield of gamma one and gamma two globulins at *p*H 5.80 ± 0.05 and ethanol concentration = 10%; ⊙, weight fraction of γ_1-globulin precipitated; △, weight fraction of γ_2-globulin that can be obtained from the supernatant.

globulins have sedimentation constant $s_{20w} = 7.4S$ within the limits of experimental error.

In order to apply a criterion of homogeneity to the sedimentation diagrams an apparent diffusion constant was calculated from the sedimentation diagram 6B. An apparent diffusion constant of $D_{20w} = 5.4 \times 10^{-7}$ sq. cm./sec. was obtained, indicating that, as regards sedimentation behavior, the γ_1 sub-fraction is essentially monodisperse. Similar analysis applied to the sedimentation diagram for the γ_2-globulin leads one to the same conclusion.

The γ_1- and γ_2-globulins have a molecular weight of approximately 175,000 based upon the sedimentation velocity and independent diffusion measurements. The frictional ratio $f/f_0 = 1.4$ may be computed from diffusion data. This molecular weight agrees well with values which have been previously reported for some animal serum globulins.[3,8,9,10]

Electrophoresis.—The electrophoretic mobilities of the γ_1- and γ_2-globulin fractions were observed in a buffer system at a *p*H of 8.6 with the aid of the conventional Tiselius assembly. The medium was either a veronal buffer at $\mu = 0.1$ or a veronal–citrate buffer at $\mu = 0.088$. The veronal system was used when mobilities were measured. The patterns for the two gamma globulins are shown in Figs. 6A and 6C. The mobility of the γ_1-globulin fraction under these conditions is 2.1×10^{-5} sq. cm./sec./volt, the same value as that reported for the "T" component by Smith. The mobility of the γ_2-globulin fraction as observed, 1.25×10^{-5} sq. cm./sec./volt, is slightly higher than that reported by Smith for his component which corresponds. Mobilities were determined from the rate of movement of the maximum ordinate, which involves negligible error because of the essential symmetry of the refractive index gradient.[11]

An apparent diffusion constant $D_{20w} = 245 \times 10^{-7}$ sq. cm./sec. was calculated from the electrophoretic pattern for γ_1-globulin (by using the diagram, Fig. 6A). A value $D_{20w} = 135 \times 10^{-7}$ sq. cm./sec. was obtained for γ_2-globulin by using Fig. 6C. These apparent diffusion constant data indicate boundary spreading of far greater magnitude than can be attributed to normal diffusion. In these studies, the ascending and descending patterns were virtually mirror images of one another. A reversal of the current and a calculation of the diffusion constant, after the spreading due to electrophoretic inhomogeneity had been eliminated, gave an apparent value for the diffusion constant of $D_{20w} = 11 \times 10^{-7}$ sq. cm./sec. for the γ_2-globulins. These data indicate that although there is some irreversible boundary spreading, the major part of the spreading is reversible and therefore most probably due to electrical inhomogeneity. The γ_1-globulin fraction is less homogeneous than the γ_2-globulin fraction.

The reversible boundary spread exhibited by the gamma globulin sub-fractions is similar to that observed by Sharp, Cooper and Neurath[7] for pseudoglobulin from horse serum. As a measure of heterogeneity Sharp, Taylor, Beard and Beard[12] have proposed a heterogeneity constant $H = \Delta\sigma/E\Delta t$ where $\Delta\sigma$ is the change in the standard deviation σ during the time interval Δt, and E is the potential gradient. An average value of $H = 5 \times 10^{-6}$ sq. cm./sec./volt was computed for γ_2-globulins from electrophoretic patterns obtained in veronal buffer at $\mu = 0.1$, *p*H = 8.6, which is slightly lower than the heterogeneity values obtained by Sharp, Hebb, Taylor and Beard[13] for pseudoglobulin from horse serum. Quite possibly a whole series of γ-globulins varying only slightly in their chemical and physical behavior is present in the serum of normal animals. In studies of hyperimmune bovine plasma, which are now in progress, we hope to obtain more information concerning this matter.

By reference to Fig. 1C it will be seen that there is no real resolution of the γ_1- and γ_2-globulins in veronal–citrate buffer of $\mu = 0.088$ and *p*H 8.6. Consequently, it is impossible to estimate from the pattern in the conventional way the relative amounts of the two families of γ-globulins which are present. However, a study was made of the electrophoretic behavior in the same buffer solution of synthetic mixtures of the γ_1- and γ_2-globu-

---

[8] Sharp, Cooper and Neurath, *J. Biol. Chem.*, **142**, 203 (1942).

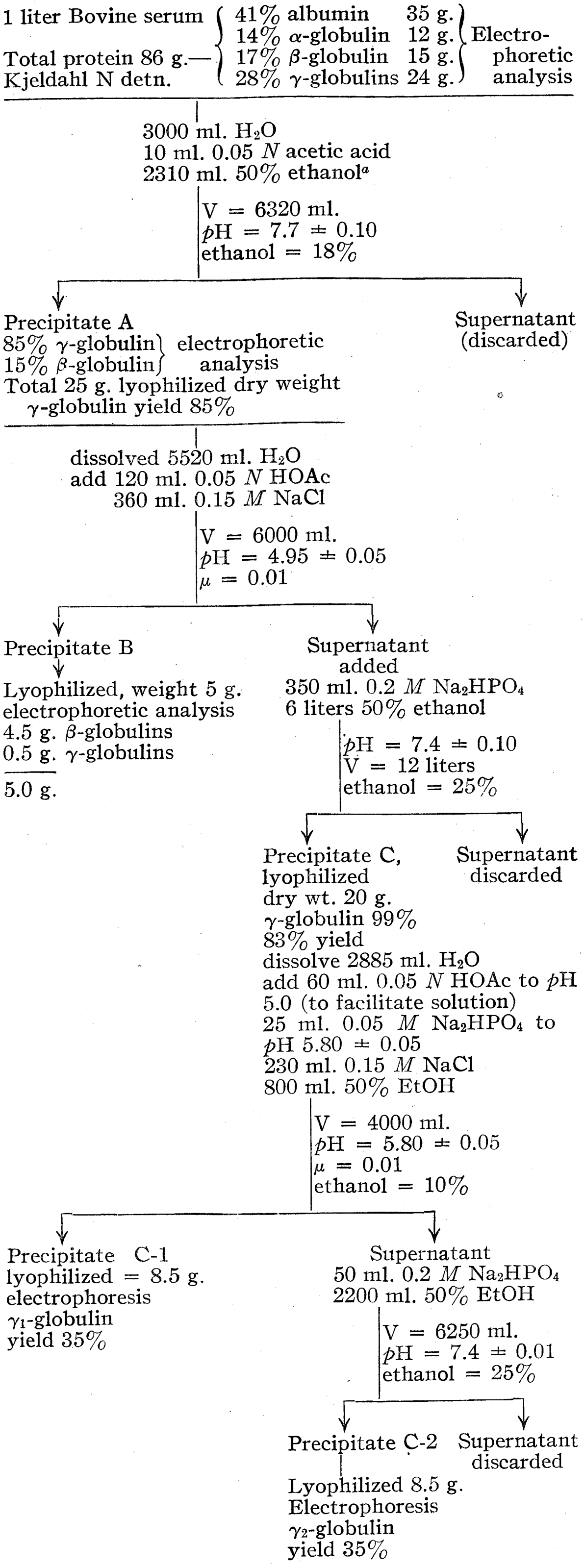
[9] Tiselius, *Biochem. J.*, **31**, 1464 (1937).

[10] Kabat, *J. Exptl. Med.*, **69**, 108 (1939).

[11] Longsworth, *Ann. New York Acad. Sci.*, **41**, 267 (1941).

[12] Sharp, Taylor, Beard and Beard, *J. Biol. Chem.*, **142**, 193 (1942).

[13] Sharp, Hebb, Taylor and Beard, *ibid.*, **142**, 217 (1942).



1 liter Bovine serum
Total protein 86 g.—Kjeldahl N detn.
41% albumin 35 g.
14% α-globulin 12 g.
17% β-globulin 15 g.
28% γ-globulins 24 g.
Electrophoretic analysis

3000 ml. H_2O
10 ml. 0.05 N acetic acid
2310 ml. 50% ethanol[a]
V = 6320 ml.
$pH = 7.7 \pm 0.10$
ethanol = 18%

Precipitate A
85% γ-globulin
15% β-globulin
electrophoretic analysis
Total 25 g. lyophilized dry weight
γ-globulin yield 85%

Supernatant (discarded)

dissolved 5520 ml. H_2O
add 120 ml. 0.05 N HOAc
360 ml. 0.15 M NaCl
V = 6000 ml.
$pH = 4.95 \pm 0.05$
$\mu = 0.01$

Precipitate B
Lyophilized, weight 5 g.
electrophoretic analysis
4.5 g. β-globulins
0.5 g. γ-globulins
5.0 g.

Supernatant added
350 ml. 0.2 M Na_2HPO_4
6 liters 50% ethanol
$pH = 7.4 \pm 0.10$
V = 12 liters
ethanol = 25%

Precipitate C, lyophilized
dry wt. 20 g.
γ-globulin 99%
83% yield
dissolve 2885 ml. H_2O
add 60 ml. 0.05 N HOAc to pH 5.0 (to facilitate solution)
25 ml. 0.05 M Na_2HPO_4 to pH 5.80 ± 0.05
230 ml. 0.15 M NaCl
800 ml. 50% EtOH
V = 4000 ml.
$pH = 5.80 \pm 0.05$
$\mu = 0.01$
ethanol = 10%

Supernatant discarded

Precipitate C-1
lyophilized = 8.5 g.
electrophoresis
γ_1-globulin
yield 35%

Supernatant
50 ml. 0.2 M Na_2HPO_4
2200 ml. 50% EtOH
V = 6250 ml.
$pH = 7.4 \pm 0.01$
ethanol = 25%

Precipitate C-2
Lyophilized 8.5 g.
Electrophoresis
γ_2-globulin
yield 35%

Supernatant discarded

Total yield $\gamma_1 + \gamma_2$ = 17 g. = 70% of γ globulins in starting material.

Fig. 5.—Schematic fractionation procedure bovine serum.

lins. It was observed that in these mixtures a single peak (corresponding to Fig. 1C) appeared, and that a linear relationship was obtained when the average mobility was plotted against the weight fraction of the γ_1-globulin present in the mixture.

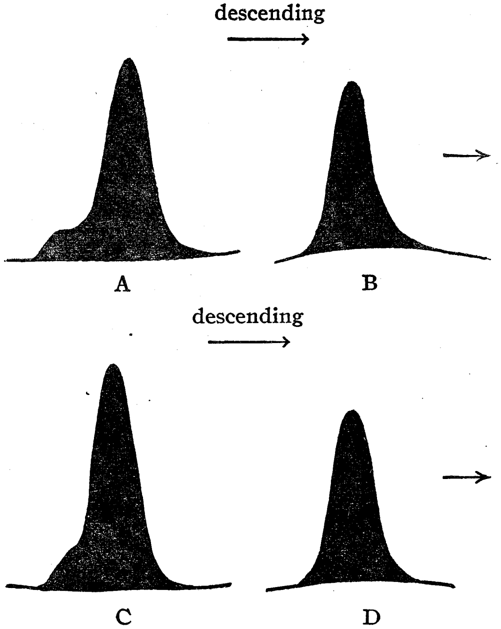


Fig. 6.—Electrophoretic and sedimentation patterns of γ_1- and γ_2-globulins: A, γ_1-globulins in μ = 0.1 veronal buffer, pH 8.6, 120 minutes at 6.25 volts/cm., conc. prot. 3%; B, sedimentation velocity diagram of γ_1-globulins 74 minutes at 50,400 r. p. m. in 0.15 M sodium chloride; C, γ_2-globulins μ = 0.1 veronal buffer, pH 8.6, 120 minutes at 6.45 volts/cm., 3% concn.; D, sedimentation velocity diagram of γ_2-globulins after 87 minutes at 50,400 r. p. m. in 0.15 M sodium chloride.

Discussion

There has been described a method for the recovery, with subsequent separation into two fractions, of the γ-globulin constituents of bovine serum. The application of these procedures is important in that a considerable increase in yield of the proteins concerned with antibody production results. At the same time, "purity" of the fractions, as judged by electrophoretic analysis has not been sacrificed. Comparison may be made with the experiments of Smith[3] whose yields of the γ-globulins were approximately one-half those obtained in our experiments, in spite of the fact that hyperimmune serum was available to him and not to us.

In the earlier publications[3,6] the starting material has been the Fraction II + III of the Cohn framework.[2a] In the present instance the γ-

---

[a] Fifty per cent. by volume ethanol–water mixture prepared at room temperature. All ethanol additions were made at the freezing point of the solution to which the ethanol was added. The fifty per cent. ethanol was cooled to its freezing point before adding it to the solution.

globulins are precipitated directly from the blood serum for such later purification or separation into sub-fractions as may be desired. The important differences in conditions of separation are the immediate adjustment of the serum to *p*H 7.7 and the use of a considerably greater dilution of the serum as fractionation begins. The new conditions serve several very useful purposes. The sharpness of cleavage between β- and γ-globulins is markedly increased. The removal of the gamma globulin is simple and direct. Tendencies toward denaturation are reduced. Actual yields of γ-globulin are now in excess of 85%.

As a result of the work described in this report and in the companion article[5] it may be predicted that practical and economical ethanol fractionation methods for the removal of antibody from hyperimmune sera will be soon in operation.

Acknowledgments.—The authors wish to thank Dr. J. W. Williams and Dr. Gerson Kegeles for their many helpful suggestions during the course of this work. It is a pleasure as well to thank Mr. E. M. Hanson and Mrs. Alice McGilvery for their technical assistance.

Summary

A procedure for the fractionation of bovine serum, which recovers approximately 85% of the gamma globulins in normal serum, has been outlined. These γ-globulins can be further separated into fractions with varying electrophoretic mobilities. The γ_1 and γ_2 sub-fractions are essentially monodisperse as regards molecular kinetic behavior, but there are marked indications of electrophoretic inhomogeneity.

MADISON, WISCONSIN RECEIVED NOVEMBER 12, 1946

[CONTRIBUTION FROM THE EMERYVILLE LABORATORIES OF SHELL DEVELOPMENT COMPANY]

Decompositions of Di-*t*-Alkyl Peroxides. I. Kinetics

BY JOHN H. RALEY, FREDERICK F. RUST AND WILLIAM E. VAUGHAN

The di-*t*-alkyl peroxides have been reported, almost simultaneously by Milas and Surgenor[1] and George and Walsh,[2] to undergo clean-cut decompositions in the vapor phase to ketone and hydrocarbon which, for the di-*t*-butyl compound, can be represented by

$$(CH_3)_3COOC(CH_3)_3 \xrightarrow{k_1} 2(CH_3)_3CO \quad (1)$$

$$(CH_3)_3CO \longrightarrow (CH_3)_2CO + CH_3 \quad (2)$$

$$CH_3 + CH_3 \longrightarrow C_2H_6 \quad (3)$$

During the past few years we have investigated the preparation and properties of these compounds in some detail,[3] and in this paper we present the results of a kinetic study of the pyrolyses of the di-*t*-butyl and di-*t*-amyl derivatives. The reactions of the free radicals produced in these decompositions with various compounds are reported in a following paper.[4]

In the studies of Milas and co-workers the vaporous peroxides were decomposed in the presence of a large amount of glass surface. Under such conditions, reactions of the alkyl radicals are essentially limited to combinations with one another and, in the case of di-*t*-butyl peroxide, ethane and acetone are the sole products. However, if the decompositions are carried out in a large diameter, unpacked vessel, interaction of the alkyl radicals and the ketone becomes important. Thus, methyl, ethyl and higher ketones and methane can also be formed

$$CH_3 + CH_3COCH_3 \longrightarrow CH_4 + CH_3COCH_2 \quad (4)$$

$$CH_3 + CH_3COCH_2 \longrightarrow CH_3COCH_2CH_3 \quad (5)$$

In the kinetic experiments to be described the fraction of released methyl radicals which reacts substitutively (5–10%) is dependent on the acetone concentration as well as the surface. Somewhat higher values (20%) are observed if the decomposition proceeds to completion or if acetone is added.

The reality of the *t*-butoxy radical is demonstrated by the formation of *t*-butyl alcohol when the decomposition is carried out in isopropylbenzene solution. The solvent is converted to 2,3-dimethyl-2,3-diphenylbutane.[5]

Experimental

1. **Materials.**—The di-*t*-butyl peroxide[3] ($n^{20}D$ 1.3890), redistilled under high vacuum, assayed at least 98% (reduction by hydriodic acid[3]) and gave negative tests for *t*-butyl alcohol and hydroperoxide. Steam-distilled di-*t*-amyl peroxide[3] was treated with bromine and vacuum distilled to remove olefin. The resultant material ($n^{20}D$ 1.4086) was also redistilled on the high vacuum line. The nitrogen, oxygen and propylene were taken directly from commercial cylinders and the carbon dioxide sublimed from Dry Ice. Nitric oxide was prepared according to the method of Noyes.[6]

2. **Rate Measurements.**—The apparatus used for all rate measurements is shown in Figs. 1 and 2. The temperature of the oil-bath was measured by a thermometer which was calibrated in position by comparison with a platinum resistance thermometer. The accuracy of the temperature readings is estimated as 0.04°. The quartz spiral gage[7] and leads from the reaction vessel were heated electrically to prevent condensation. The degassed liquid

---

[1] Milas and Surgenor, THIS JOURNAL, **68**, 205, 643 (1946).

[2] George and Walsh, *Trans. Faraday Soc.*, **42**, 94 (1946); based on data supplied by Asiatic Petroleum Company.

[3] Vaughan and Rust, U. S. 2,403,771, July 9, 1946; *cf.* also earlier patents.

[4] Rust, Seubold and Vaughan, THIS JOURNAL, **70**, 95 (1948).

[5] Kharasch, McBay and Urry (*J. Org. Chem.*, **10**, 401 (1945)) have previously demonstrated this free radical coupling reaction using acetyl peroxide.

[6] Noyes, THIS JOURNAL, **47**, 2170 (1925).

[7] Vaughan, *Rev. Sci. Instruments*, **18**, 192 (1947).

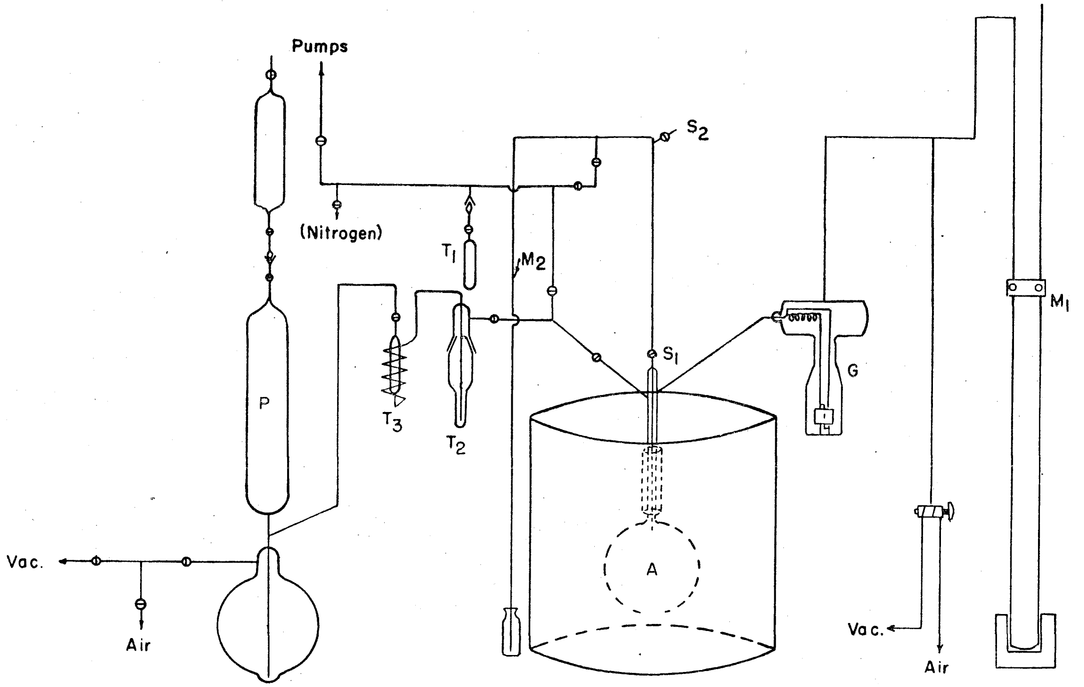


Fig. 1.—Apparatus for peroxide decompositions. Legend (see text): A, reaction vessel; G, quartz spiral pressure gage; M_1, gage manometer (equipped with vernier); M_2, input manometer; P, Toepler pump; S_1, input stopcock for peroxide and nitrogen; S_2, stopcock for admitting di-*t*-amyl peroxide; T_1, storage trap for di-*t*-butyl peroxide; T_2, T_3, product condensing traps.

peroxide was admitted to the capillary above S_1 (either by distillation or through S_2) and nitrogen added, the pressure of which was registered by M_2. The nitrogen served to force the peroxide into the reaction vessel when S_1 was opened. The pressure increase during the decomposition was followed by using the gage as a null point instrument in conjunction with M_1. The reaction was halted by freezing the vapors into T_2 and pumping the residual gases into a sample bulb for analysis with a mass spectrometer. Ketone was determined by adding an excess of hydroxylamine hydrochloride solution to the contents of T_2 and titrating the liberated acid.

3. **Flow Experiments.**—The technique for these experiments is described in the following paper.[4] In the subsequent paragraphs "cc./min." refers to cc. of vapor (N.T.P.) per minute.

Ketone Products of Di-*t*-butyl Peroxide.—Di-*t*-butyl peroxide (165 cc./min.) and nitrogen (25 cc./min.) were passed through the unpacked Pyrex tube at 225°. The liquid product was collected in a Dry Ice-cooled trap and fractionated. The distillation cuts obtained were (1) 56° (acetone), (2) 79° (methyl ethyl ketone), (3) higher boiling carbonylic compounds.

TABLE I

KETONE PRODUCTS FORM DI-*t*-BUTYL PEROXIDE

Ketone	Cc./min. N. T. P.	$n^{20}D$ Found	$n^{20}D$ Lit.	Deriv.	M. p., °C. Deriv.	M. p., °C. Mixed
Acetone	274	1.3589	1.3589	....	..	...
Methyl ethyl	21	1.3790	1.3788	*p*-Nitrophenylhydrazone	128[a]	128

[a] Literature value (Huntress and Mulliken, "Identification of Pure Organic Compounds") was 128–129°.

Di-*t*-butyl Peroxide and Nitric Oxide.—A mixture of the peroxide (67 cc./min.), nitric oxide (175 cc./min.), and nitrogen (50 cc./min.) was passed through the tube at 225° for one hundred and forty minutes, the liquid product being collected in ether cooled with Dry Ice. Distillation (after addition of Cellosolve to furnish a high boiling residue) gave a fraction of b. p. 83–85° which was collected in ether. Treatment of one third of the distillate with hydrogen chloride gas according to the method of Dunston and Bossi[8] yielded one gram of the hydrochloride [m. p. 136–137°, lit.[8] 136°; % Cl (Volhard) 20.8, calcd. for $(CH_2NOH)_3{\cdot}HCl$, 20.66]. A second portion of the distillate was converted to the benzoate derivative [m. p. 168–168.5° (decomp.), lit.[8] 168.5° (decomp.); % N (Dumas) 9.29, 9.30; % C 64.40, 64.67; % H 4.80, 5.02; theory 9.39, 64.42, 4.73, respectively]. Characteristic behaviors of formaldoxime—condensation to a white, insoluble solid upon standing, and violet coloration with cupric sulfate–potassium hydroxide solution—were also observed with the crude product.

Decomposition of Di-*t*-amyl Peroxide.—Di-*t*-amyl peroxide and nitrogen (*ca.* 100 cc./min. of each) were passed through the tube at 235°. The liquid product contained 87–88% acetone, 4–5% methyl ethyl ketone (aqueous azeotrope, b. p. 73°), and higher boiling ketones. The gaseous products, separated by low temperature distillation, were as in Table II.

TABLE II

GASEOUS DECOMPOSITION PRODUCTS OF DI-*t*-AMYL PEROXIDE

Gas	Cc./min.
n-C_4H_{10}	66.6
C_2H_6	19.5
C_3H_8	5.9
C_2H_4	5.2
CH_4	4.3
C_4H_8	1.4

4. **Di-*t*-butyl Peroxide and Isopropylbenzene (liquid phase).**—A solution of di-*t*-butyl peroxide (0.27 mole) and

---

[8] W. R. Dunston and A. L. Bossi, *J. Chem. Soc.*, **73**, 353 (1898).

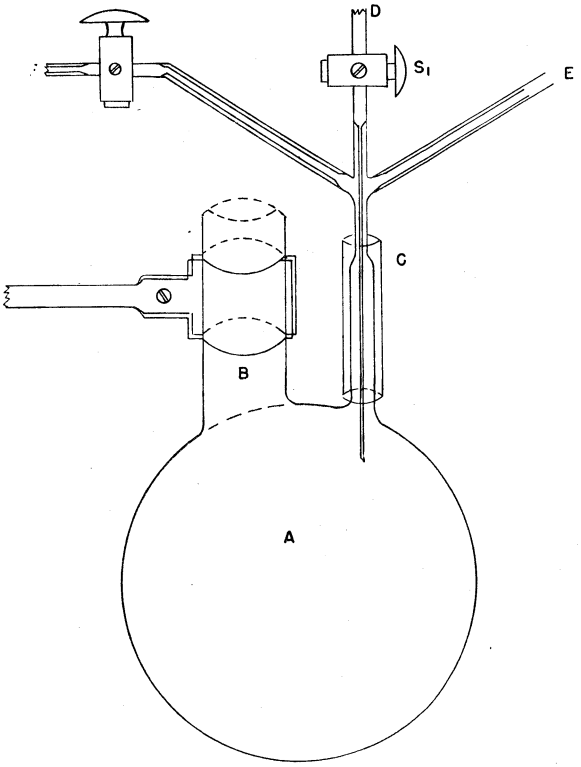


Fig. 2.—Reaction vessel for peroxide decompositions. Legend (see text): A, 500 cc. bulb; B, butt-sealed, heavy wall tube for clamping; C, copper sheath, partially immersed in oil-bath, for heating inlet line; D, inlet for liquid peroxide; E, lead to gage; F, lead to Toepler pump.

isopropylbenzene (1.44 moles) was heated in an oil-bath at 130° for thirty hours. The following products were obtained: *t*-butyl alcohol (0.24 mole), methane (0.06 mole), 2,3-dimethyl-2,3-diphenylbutane (0.07 mole) (C, 90.65; H, 9.3; mol. wt., 242; theory C, 90.75; H, 9.25; mol. wt., 238).

Decomposition of Di-*t*-butyl Peroxide

Kinetic Order.—If the pyrolysis follows the over-all stoichiometries

$$(CH_3)_3COOC(CH_3)_3 \longrightarrow 2(CH_3)_2CO + C_2H_6 \quad (6)$$

or

$$\longrightarrow CH_3COCH_3 + CH_3COC_2H_5 + CH_4$$

the peroxide pressure, $(A - x)$, is related to P, the total pressure, by

$$(A - x) = A - (P - P_0)/2 \quad (7)^9$$

where P_0 is the initial total pressure, obtained by a short extrapolation. The initial peroxide pressure, A, is obtained from

$$A = P_0 - P_{N_2} \quad (8)$$

where P_{N_2} is the nitrogen pressure, obtained by analysis of the product gases. log $(A - x)$ as a function of time is illustrated in Fig. 3 from which it is clear that, at least in the first 30–40%, the decomposition follows a first order expression. Data for typical runs are given in Table III. As the reaction approaches completion, a slight curvature is noticeable (Fig. 4) and upon complete decomposition, the total pressure of the products is found to be slightly less than three times the initial peroxide pressure. If the experimental ratio (2.88) is used to calculate values for $(A - x)$, adherence to the first order expression is indicated for virtually the entire reaction.[10] We have preferred, however, to use equation (7) since during the early stages of the reaction, where all rate measurements were made, the discrepancy between assumed and observed stoichiometries is within experimental error (Table IV). The initial rate constant calculated in this manner is essentially independent of pressure over the range 50–380 mm. (Table V).

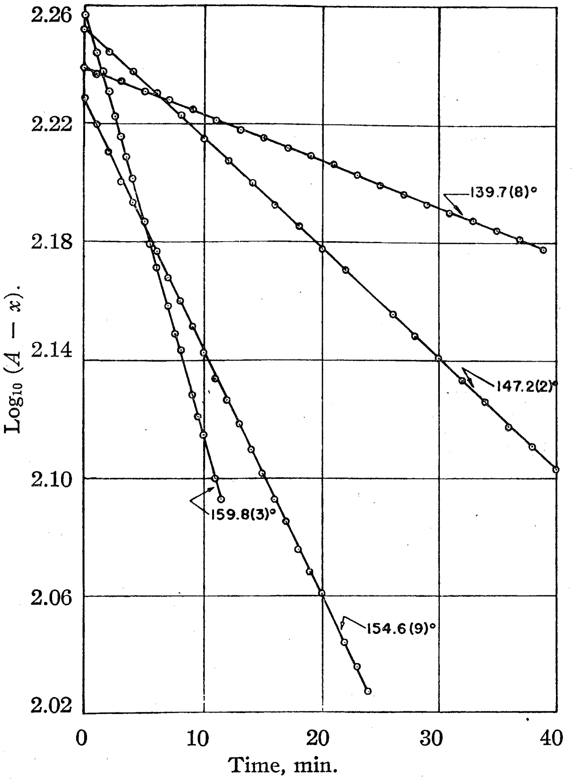


Fig. 3.—Decomposition of di-*t*-butyl peroxide, 140–160°.

Homogeneity.—Although the fate of methyl radicals produced during the reaction is modified by the surface of the confining vessel, the decomposition itself is apparently homogeneous. As shown in Table VI, the rate constant is not affected by the presence of Pyrex rod packing (2 mm. diameter) sufficient to produce an elevenfold change in surface–volume ratio of the vessel.

Tests for a Chain Reaction.—A number of well recognized chain inhibiting reagents have

---

[9] Since the higher ketones are also probably formed by substitutive methylation, their production should not alter the pressure change during decomposition.

[10] It should be mentioned that the apparent decrease in rate is not traceable to interaction with reaction products since addition of a spent mixture does not influence the decomposition of a fresh peroxide charge.

TABLE III

DECOMPOSITION OF DI-*t*-BUTYL PEROXIDE—TYPICAL RUNS

Temperature, 154.6(9)°				Temperature, 147.2(2)°			
Time, min.	Total press., mm.	$(A - x)$, mm.	$k \times 10^4$[a] (sec.$^{-1}$)	Time, min.	Total press., mm.	$(A - x)$, mm.	$k \times 10^4$[b] sec.$^{-1}$
0	173.5	169.3		0	182.6	179.5	
2	187.3	162.4		2	190.5	175.5	
3	193.4	159.3	3.38	6	201.7	169.9	
5	205.3	153.4	3.17	10	213.6	164.0	
6	211.3	150.4	3.20	14	224.3	158.6	
8	222.9	144.6	3.28	18	235.0	153.3	
9	228.6	141.7	3.31	20	240.4	150.6	1.46
11	239.8	136.1	3.37	22	245.4	148.1	1.41
12	244.4	133.8	3.19	26	255.6	143.0	1.44
14	254.5	128.8	3.06	30	265.2	138.2	1.43
15	259.2	126.4	3.16	34	274.4	133.6	1.43
17	268.7	121.7	3.15	38	283.3	129.1	1.43
18	273.9	119.1	3.31	40	288.0	126.8	1.43
20	282.0	115.0	3.15	42	292.0	124.8	1.43
21	286.8	112.6	3.12	46	300.2	120.7	1.41
			Av. 3.22 ± 0.08				Av. 1.43 ± 0.01

[a] Calculated for successive three-minute intervals. [b] Calculated for successive twenty minutes intervals.

TABLE IV

DECOMPOSITION OF DI-*t*-BUTYL PEROXIDE. RATE CONSTANTS AND YIELDS

Temp., °C.	Peroxide press., (mm.)	$k \times 10^4$, sec.$^{-1}$	Product yields,[a] %			
			Ketone	Ethane	Methane	Total paraffin
139.7(8)	163	0.589 ± 0.007	99			
	163	.620 ± .008	97	88	11	99
	173	.596 ± .007				
		Mean 0.60				
147.2(2)	180	1.43 ± 0.01				
154.6(9)	168	3.22 ± .18	97			
	169	3.22 ± .08	97			
		Mean 3.22				
159.8(3)	181	5.53 ± 0.16	105	103	6	109

[a] The yields are based on the amount of peroxide decomposed, as calculated from the total pressure increase by equation (7).

TABLE V

DECOMPOSITION OF DI-*t*-BUTYL PEROXIDE. EFFECT OF INITIAL PRESSURE ON INITIAL RATE CONSTANT

Temperature, 147.2(2)°

Initial peroxide press., mm.	$k \times 10^4$, sec.$^{-1}$
51.6	1.38 ± 0.0
66.3	1.33 ± .02
167	1.40 ± .02
179 + 190 mm. N_2	1.49 ± .02
180	1.43 ± .01
386	1.48 ± .01
	Mean 1.41

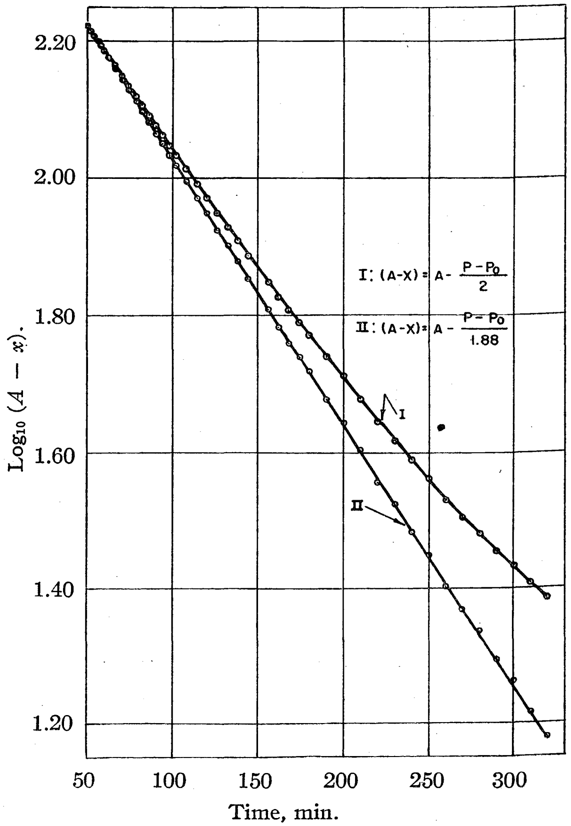


Fig. 4.—Decomposition of di-*t*-butyl peroxide, *ca.* 90% completion, temperature 147.2(2)°.

been added in attempts to detect chain processes in the di-*t*-butyl peroxide decomposition. In the first of these tests the peroxide and additive were passed through a heated tube[4] and the unreacted peroxide collected and measured. From the results, summarized in Table VII, it is clear that neither nitric oxide nor propylene appreciably affects the decomposition velocity. That methyl radicals react readily under the experimental conditions with both additives is shown by the isolation of products derivable only from these sources. The formation of formaldoxime has been postulated previously[11] but apparently this is the first report of its isolation from a methyl radical–

---

(11) For example, see Taylor and Bender, *J. Chem. Phys.*, **9**, 761 (1941); Forsyth, *Trans. Faraday Soc.*, **37**, 312 (1941).

TABLE VI

DECOMPOSITION OF DI-*t*-BUTYL PEROXIDE. EFFECT OF REACTOR SURFACE: VOLUME RATIO

Temperature, 147.2(2)°; peroxide pressure, 170–215 mm.

Vessel	S/V, cm.$^{-1}$	$k \times 10^4$, sec.$^{-1}$	Product yields, % Ketone	Ethane	Methane	Total paraffin
Unpacked	0.61	1.41 ± 0.01[a]	99[b]	..	..	99+[b]
Packed	2.07	1.42 ± .01	103	94	6	100
Packed	6.96	1.49 ± .02	102	90	13	103

[a] Average of four runs. [b] Estimated from the data of Table IV.

nitric oxide combination. Formaldoxime is probably further attacked by methyl radicals since when an excess of peroxide is used, a complex product is obtained. The reaction products with propylene are discussed in detail in the succeeding paper.[4]

TABLE VII

DECOMPOSITION OF DI-*t*-BUTYL PEROXIDE. EFFECT OF CHAIN INHIBITORS

Temperature, 209–210°; flow rates, 100 cc./min. (N.T.P.), peroxide, 200 cc./min. (N.T.P.), additive; residence time, 2.5–2.6 minutes.

Additive	Peroxide dec., %	Product
Nitrogen	95	....
Nitric oxide	94	Formaldoxime
Propylene	95	C_4H_8, C_4H_{10}, C_5H_{12}, etc.

In a closed system oxygen causes a slight acceleration in the rate of pressure increase, but apparently the velocity of decomposition is not affected since the production of ketone is virtually unchanged (Table VIII).

TABLE VIII

DECOMPOSITION OF DI-*t*-BUTYL PEROXIDE. EFFECT OF OXYGEN

Temperature, 147.2(2)°; reaction time, 47 min.

Peroxide, mm.	Oxygen, mm.	Oxygen consumed, mm.	Ketone produced, mm. Found	Calcd.[a]
170.1	41.4	37.2	113	112

[a] Assuming the rate constant (1.41×10^{-4} sec.$^{-1}$) at this temperature for an oxygen-free system.

It should be noted that the major gaseous oxidation product of methyl radicals at this temperature is carbon monoxide, in contrast to the formaldehyde and methanol reported for the reaction at 0°.[12] A test for aldehyde with Schiff reagent on the liquid product was negative.

Mechanism and Activation Energy.—A summary of all data presented above leads to the conclusion that the decomposition of di-*t*-butyl peroxide is a homogeneous, first order, nonchain process. The suggested mechanism (equations (1), (2) and (3)) yields the rate equation

$$-\frac{d[(CH_3)_3COOC(CH_3)_3]}{dt} = \frac{d[C_2H_6]}{dt} = \frac{{}^1/_2 d[(CH_3)_2CO]}{dt} = k_1[(CH_3)_3COOC(CH_3)_3]$$

from which it is seen that k_1 and the experimentally determined rate constant should be identical. In support of this, the calculated energy of activation, E_1, for (1) is in close agreement with the experimental value. Since (1) is postulated as a unimolecular dissociation reaction, E_1 may be taken equal to the energy of dissociation.[13] The latter value has been calculated from the heat of combustion of the peroxide and other thermochemical data.[14]

The combustion heats for the peroxide and *t*-butyl alcohol lead to the equation

$$\underset{1282.6}{C_4H_9O_2C_4H_9(g)} + \underset{68.4}{H_2(g)} \longrightarrow \underset{2(640.7)}{2C_4H_9OH(g)}; \quad \Delta H_{298} = -69.6; \ \Delta E = \Delta H.$$

$$D_{O-O} \text{ (in peroxide)} = 2D_{O-H} - D_{H-H} - 69.6$$

The value of D_{O-H} in *t*-butyl alcohol is computed from

$$\underset{686.3}{C_4H_{10}(g)} + {}^1/_2O_2(g) \longrightarrow \underset{640.7}{C_4H_9OH(g)}; \quad \Delta H_{298} = -45{,}6; \ \Delta E = -45.3.$$

$$D_{O-H} = D_{C-H} + {}^1/_2 D_{O-O} \text{ (in oxygen)} - D_{C-O} + 45.3 = 105.2 \text{ kcal./mole}$$

Hence $E_1 = D_{O-O}$ (in peroxide) = 39 kcal./mole.[15]

The data of Table IV, plotted in the conventional manner in Fig. 5, yield an experimental activation energy of 39.1 ± 0.5 kcal./mole.

Calculation of the pre-exponential factor gives, for the rate constant $k = 3.2 \times 10^{16}(e^{-39{,}100/RT})$.

The entropy of activation is the abnormally high[16] value + 14.5 E.U. at 160°.

Decomposition of Di-*t*-amyl Peroxide

Milas and Surgenor[1] have shown that the decomposition of di-*t*-amyl peroxide over glass wool yields, mainly, *n*-butane and acetone with small amounts of ethane, propane and methyl ethyl ke-

---

(12) Bates and Spence, THIS JOURNAL, **53**, 1689 (1931); also *Trans. Faraday Soc.*, **27**, 468 (1931).

(13) Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., New York, N. Y., 1941.

(14) (a) Data from this Laboratory: Di-*t*-butyl peroxide: heat of combustion = 1273 kcal./mole for (1) 25°; heat of vaporization = 9.6 kcal./mole. *t*-Butyl alcohol: heat of combustion = 629.4 kcal./mole for (s) 25°; heat of fusion = 1.6 kcal./mole; heat of vaporization = 9.7 kcal./mole; (b) Rossini, *J. Research Natl. Bur. Standards*, **15**, 357 (1935): Isobutane; heat of combustion = 686.3 kcal./mole for (g) 25°; (c) Baughan and Polanyi, *Trans. Faraday Soc.*, **39**, 19 (1943): D_{C-O} in *t*-butyl alcohol = 85.0 kcal./mole. D_{C-H} in isobutane (for the *t*-hydrogen) = 86.0 kcal./mole; (d) W. A. Noyes, Jr., and P. A. Leighton, "The Photochemistry of Gases," Reinhold Publishing Corp., New York, N. Y., 1941, pp. 134–135: D_{H-H} in hydrogen = 4.454 e. v./mole. D_{O-O} in oxygen (normal atoms) = 5.11 e. v./mole.

(15) Pauling ("The Nature of the Chemical Bond," Cornell University Press (1939)) estimated D_{O-O} in hydrogen peroxide as 34.9 kcal./mole while Skinner (*Trans. Faraday Soc.*, **41**, 645–662 (1945)) gives the much higher value 52 kcal./mole. However, recently Glockler and Matlack, (*J. Chem. Phys.*, **14**, 504 (1946)) using methods similar to those of Skinner, reported that the latter's value is much too high and that 34.9 is the better figure.

(16) For example, the activation entropies for the decomposition of nitrogen pentoxide and dimethyl ether are, respectively, −2.5 and +2.5 E. U.

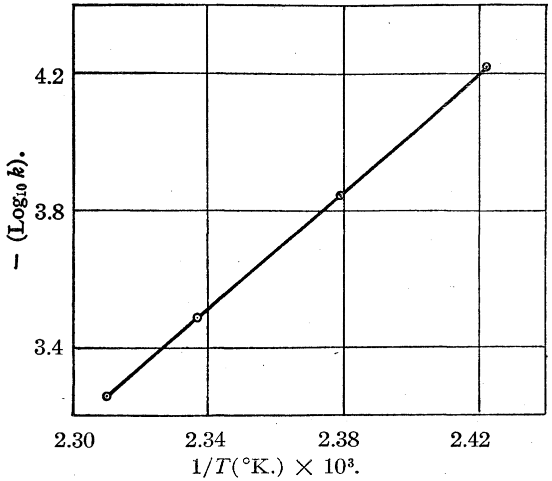


Fig. 5.—Decomposition of di-*t*-butyl peroxide, effect of temperature.

tone. With a larger bore, unpacked tube we find, in addition, small amounts of ethylene, methane and unidentified higher ketones. These additional products are attributed to free radical processes in the gas phase, the ethylene (and perhaps some methane) being ascribed to disproportionation reactions and the rest to alkyl radical attack on the primary ketone products.

Kinetic Order.—Since all products except ethylene are derivable from processes which should give rise to a three-fold pressure increase, the instantaneous values of the di-*t*-amyl peroxide pressure were also calculated from equation (7). A typical experiment is illustrated in Table IX and the summarized data for the decomposition at 132–150° are given in Table X and Fig. 6. (As before, the rate constants and ketone yields were computed from measurements taken during the first third of the reaction. No hydrocarbon yields are given because of difficulty in recovering the butane quantitatively.)

TABLE IX

DECOMPOSITION OF DI-*t*-AMYL PEROXIDE—TYPICAL RUN

Temperature, 142.2(4) °

Time, min.	Total press., mm.	$A - x$, mm.	$k \times 10^4$,[a] sec.$^{-1}$
0	165.6	157.4	
2	173.5	153.4	
4	182.8	148.8	
6	190.8	144.8	
8	198.3	141.0	
10	205.7	137.3	2.28
12	212.4	134.0	2.25
14	218.8	130.8	2.15
16	225.9	127.2	2.16
18	232.8	123.8	2.17
20	238.1	121.1	2.09
22	244.6	117.9	2.14
24	250.6	114.9	2.16
26	256.2	112.1	2.11
28	261.6	109.4	2.06
30	267.4	106.5	2.14
			Av. 2.15 ± 0.04

[a] Calculated for ten-minute intervals.

TABLE X

DECOMPOSITION OF DI-*t*-AMYL PEROXIDE. RATE CONSTANTS AND YIELDS

($A - x$) calculated from equation (7); peroxide pressure, 150–70 mm.

Temp., °C.	Rate constant $k \times 10^4$, sec.$^{-1}$	Ketone yield,[a] %
132.2(2)	0.721 ± 0.15	97
	.759 ± .14	95
	.683 ± .13	98
	Mean 0.72	97
136.7(4)	1.15 ± 0.02	95
142.2(4)	2.11 ± 0.04	
	2.15 ± .04	
	2.38 ± .17 (?)	96
	2.20 ± .04	
	2.18 ± .07	99
	Mean of four 2.16	97
149.7(3)	4.69 ± 0.09	106
	4.96 ± .09	92
	Mean 4.8	99

[a] See footnote [a], Table IV.

However, with this peroxide the rate constant is not pressure independent, regardless of whether it is calculated by use of equation (7) or the empirical equation

$$A - x = A - \frac{P - P_0}{n - 1} \qquad (8)$$

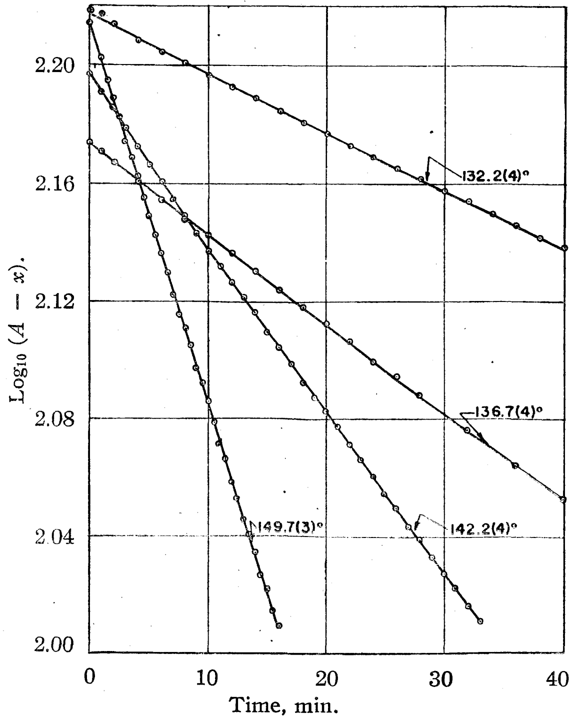


Fig. 6.—Decomposition of di-*t*-amyl peroxide, 130–150°.

where n is the observed ratio of final to initial pressure. The values of n, obtained by completely decomposing the peroxide at *ca.* 150°, are given in Table XI, together with the rate "constants" calculated therefrom.

TABLE XI

DECOMPOSITION OF DI-*t*-AMYL PEROXIDE. EFFECT OF INITIAL PRESSURE

Temp., °C.	Peroxide press., mm.	$k \times 10^4$, sec.$^{-1}$	
136.7(4)	46.6	1.06	
	149.2	1.15	
	339	1.34	
	352	1.34	
142.4(4)	155	2.16	
	360	2.41	
149.7(3)	41.1	5.02	4.43 for $n = 3.19$
	55.0	4.93	4.56 for $n = 3.12$
	155	5.04	4.84 for $n = 3.06$
	184 + 257 CO_2	5.12	
	339	5.61	

Furthermore, in the higher pressure runs, a definite falling off of the rate is noticeable before the decomposition is 30% complete. These results probably indicate that the principal mode of decomposition is first order but that a higher order process is also occurring.

Homogeneity.—No appreciable difference in rate was observed when the pyrolysis was carried out in the packed vessel (Table XII). It is concluded, therefore, that the decomposition takes place only in the gas phase.

Activation Energy.—Since the decomposition of di-*t*-amyl peroxide is not strictly first order, the over-all activation energy, 37 kg.-cal./mole (Fig. 7), does not represent the energy requirements of any single process. Presumably, however, a closer approximation to the activation energy for scission of the oxygen–oxygen bond could be obtained from low pressure data where effects of higher order processes would be minimized. Extrapolation to zero pressure of the values (for $n = 3$) in Table XI yields $E = 41$ kcal./mole. Hence, it is probable that the true value of E_1 is between 37 and 41 kcal./mole.

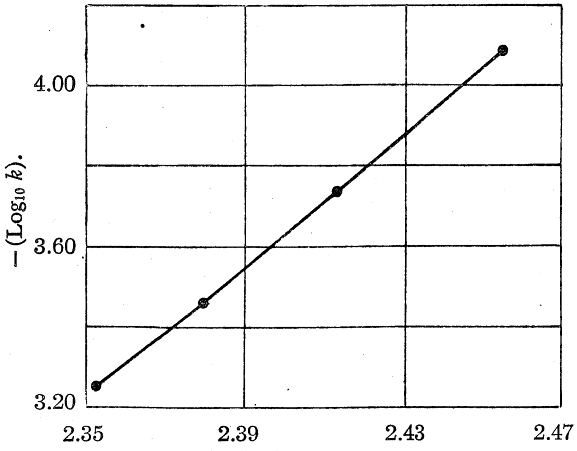


Fig. 7.—Decomposition of di-*t*-amyl peroxide, effect of temperature.

TABLE XII

DECOMPOSITION OF DI-*t*-AMYL PEROXIDE. EFFECT OF REACTOR SURFACE:VOLUME RATIO

Temperature, 142.2(4)°; pressure, 150–170 mm.

Vessel	S/V, cm.$^{-1}$	Initial rate constant $k \times 10^4$, sec.$^{-1}$	Ketone yield, %
Unpacked	0.61	2.16 ± 0.03	97
Packed	7.0	2.14 ± .02	101

Acknowledgment.—The authors wish to thank Messrs. F. H. Seubold and E. R. Bell for their assistance in performing the flow experiments. They also are indebted to Dr. D. P. Stevenson of the Physics Department and to Messrs. W. R. Keeler and V. Lantz of the Analytical Department of this Company for supplying the mass spectrometric and calorimetric data.

Summary

1. The vapor phase decomposition of di-*t*-butyl peroxide at 140–160° is a homogeneous, first order, non-chain reaction, the rate constant for which is given by $k = 3.2 \times 10^{16}(e^{-39{,}100/RT})$. The rate-determining step is the scission of the oxygen–oxygen bond and the experimental activation energy closely approximates the calculated strength of this bond.

2. The decomposition proceeds through the formation of *t*-butoxy and methyl radicals. The primary reaction product of the latter and nitric oxide has been identified as formaldoxime.

3. The principal decomposition products are ethane and acetone. However, some methyl radicals react with acetone to yield methane and methyl ethyl and higher ketones. A small fraction of the peroxide may decompose in another manner.

4. The pyrolysis of di-*t*-amyl peroxide at 130–150° is a homogeneous, approximately first order reaction. The over-all activation energy is 37 kcal./mole and that for the initial step is estimated as 37–41 kcal./mole. The predominant products are n-butane and acetone, but methane, ethane, ethylene, propane and methyl ethyl and higher ketones are also found in small amounts. All products can be accounted for by the intermediate formation of *t*-amyloxy, ethyl and methyl radicals.

EMERYVILLE, CALIFORNIA RECEIVED[17] JULY 31, 1947

---

[17] Original manuscript received September 26, 1946.

[CONTRIBUTION FROM THE EMERYVILLE LABORATORIES OF SHELL DEVELOPMENT COMPANY]

Decompositions of Di-*t*-Alkyl Peroxides. II. Reactions of the Resultant Free Radicals

BY FREDERICK F. RUST, FRANK H. SEUBOLD AND WILLIAM E. VAUGHAN

In the previous paper[1] evidence was presented that free methyl radicals derived from decomposing di-*t*-butyl peroxide reacted with and converted a part of the acetone—also a product of the decomposition—to methyl ethyl ketone and higher ketones. The inclusion of other compounds with the decomposing di-*t*-butyl and di-*t*-amyl peroxides has now made possible a study of other gas phase reactions of free methyl and free ethyl in the temperature region of 200–235°. Although possibilities for organic syntheses will suggest themselves—such as the addition of two methyl or ethyl groups to a double bond or the replacement of hydrogen atoms by methyls, it is not the intent of the present paper to present optimum conditions for such syntheses. Instead, it is hoped that the present study will demonstrate the usefulness of the di-*t*-alkyl peroxides as tools in the study of free radical phenomena. The fate of the various peroxide-derived free radicals in different hydrocarbon atmospheres is revealed by the components which have been separated from fairly complex reaction mixtures.

Thus, the abstraction of a hydrogen atom from a molecule by methyl and the combination of the resulting radical with another methyl is shown by the formation of ethylbenzene from toluene and triptane from 2,3-dimethylbutane.

$$(CH_3)_3COOC(CH_3)_3 \longrightarrow [2(CH_3)_3CO-] \longrightarrow 2CH_3 + 2CH_3COCH_3 \qquad (1)$$

$$RH + CH_3 \longrightarrow CH_4 + R \qquad (2)$$

$$R + CH_3 \longrightarrow RCH_3 \qquad (3)$$

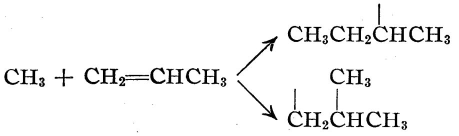
When olefins become the objects of radical attack the transformations are more complex, but the results are in general agreement with current concepts of chain initiation, transfer, and termination in polymerization reactions. Thus, as suggested by other workers,[2] *methyl addition to ethylene* gives a propyl radical which adds to other ethylene molecules unless or until the chain is terminated by collision with another methyl.

$$CH_3 + nC_2H_4 \longrightarrow CH_3(C_2H_4)_n \qquad (4)$$

$$CH_3(C_2H_4)_n + CH_3 \longrightarrow CH_3(C_2H_4)_nCH_3 \qquad (5)$$

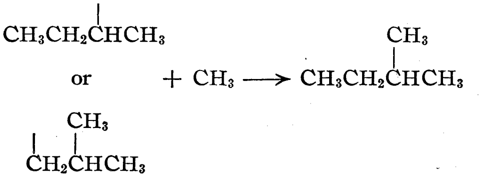
At these low temperatures, however, the polymerization is relatively uncomplicated by disproportionation reactions. *n*-Butane, *n*-hexane and *n*-octane were isolated and no odd carbon-numbered hydrocarbons or unsaturates were found.

The reaction of *methyl and propylene* has been more extensively studied. Addition of free methyl to the double bond



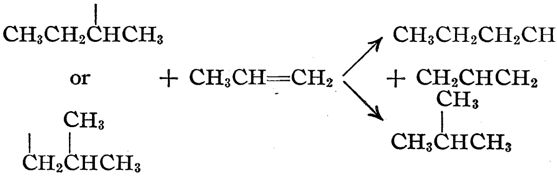
$$CH_3 + CH_2{=}CHCH_3 \begin{array}{l} \nearrow CH_3CH_2\overset{|}{C}HCH_3 \\ \searrow \overset{|}{C}H_2\overset{\overset{CH_3}{|}}{C}HCH_3 \end{array} \qquad (6)$$

is followed either by (a) combination with another methyl to give isopentane



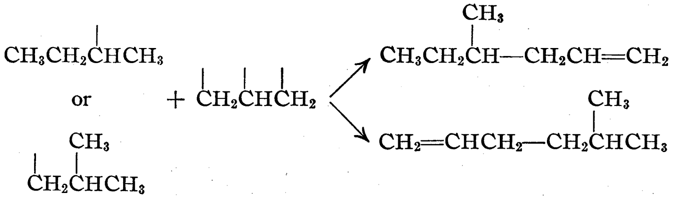
$$\begin{array}{c} CH_3CH_2\overset{|}{C}HCH_3 \\ \text{or} \\ \overset{|}{C}H_2\overset{\overset{CH_3}{|}}{C}HCH_3 \end{array} + CH_3 \longrightarrow CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_3 \qquad (7)$$

(b) abstraction of a hydrogen atom from propylene to yield butanes



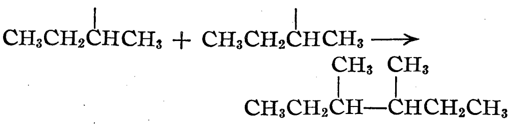
$$\begin{array}{c} CH_3CH_2\overset{|}{C}HCH_3 \\ \text{or} \\ \overset{|}{C}H_2\overset{\overset{CH_3}{|}}{C}HCH_3 \end{array} + CH_3CH{=}CH_2 \begin{array}{l} \nearrow CH_3CH_2CH_2CH_3 \\ \quad + CH_2CHCH_2 \\ \searrow CH_3\overset{\overset{CH_3}{|}}{C}HCH_3 \end{array} \qquad (8)$$

(c) combination with allyl to form a heptene

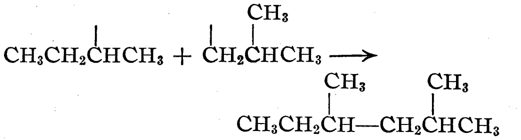


$$\begin{array}{c} CH_3CH_2\overset{|}{C}HCH_3 \\ \text{or} \\ \overset{|}{C}H_2\overset{\overset{CH_3}{|}}{C}HCH_3 \end{array} + \overset{|}{C}H_2\overset{|}{C}H\overset{|}{C}H_2 \begin{array}{l} \nearrow CH_3CH_2\overset{\overset{CH_3}{|}}{C}H{-}CH_2CH{=}CH_2 \\ \searrow CH_2{=}CHCH_2{-}CH_2\overset{\overset{CH_3}{|}}{C}HCH_3 \end{array} \qquad (9)$$

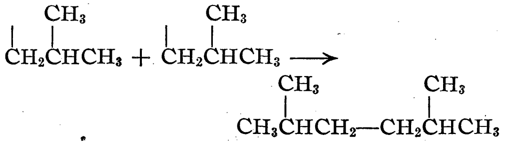
(d) addition to other radicals to form, for example, octanes



$$CH_3CH_2\overset{|}{C}HCH_3 + CH_3CH_2\overset{|}{C}HCH_3 \longrightarrow CH_3CH_2\overset{\overset{CH_3}{|}}{C}H{-}\overset{\overset{CH_3}{|}}{C}HCH_2CH_3 \qquad 10)$$



$$CH_3CH_2\overset{|}{C}HCH_3 + \overset{|}{C}H_2\overset{\overset{CH_3}{|}}{C}HCH_3 \longrightarrow CH_3CH_2\overset{\overset{CH_3}{|}}{C}H{-}CH_2\overset{\overset{CH_3}{|}}{C}HCH_3 \qquad (11)$$



$$\overset{|}{C}H_2\overset{\overset{CH_3}{|}}{C}HCH_3 + \overset{|}{C}H_2\overset{\overset{CH_3}{|}}{C}HCH_3 \longrightarrow CH_3\overset{\overset{CH_3}{|}}{C}HCH_2{-}CH_2\overset{\overset{CH_3}{|}}{C}HCH_3 \qquad (12)$$

(e) addition to propylene in a manner analogous

---

[1] Raley, Rust and Vaughan, THIS JOURNAL, **70**, 88 (1948).

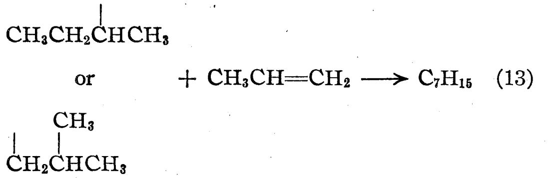
[2] Steacie, "Atomic and Free Radical Reactions," Reinhold Publishing Corp., 1946.

TABLE I

ISOLATED PRODUCTS FROM REACTION OF METHYL WITH 2-BUTENE AND ISOBUTENE, 235°

Products from 2-butene	Products from isobutene	Mechanism of formation, equation
$CH_3\overset{CH_3}{\overset{\vert}{C}}H\overset{H}{\overset{\vert}{C}}HCH_3$	$(CH_3)_2\overset{H}{\overset{\vert}{C}}CH_2—CH_3$	6 and 8
$CH_3—CH_2CH{=}CHCH_3$	$CH_2{=}C(CH_3)CH_2—CH_3$	14 and 15
$CH_3\overset{CH_3}{\overset{\vert}{C}}{=}CHCH_3$	$(CH_3)_2C{=}CH—CH_3$	14 and 15
$CH_3\overset{CH_3}{\overset{\vert}{C}}H\overset{CH_3}{\overset{\vert}{C}}HCH_3$	$(CH_3)_2\overset{CH_3}{\overset{\vert}{C}}CH_2—CH_3$	6 and 7
Nonenes	Nonenes	6 and 9
$CH_3\overset{CH_3}{\overset{\vert}{C}}HCH(CH_3)—(CH_3)CH\overset{CH_3}{\overset{\vert}{C}}HCH_3$	Decanes	6 and 10
Higher boiling	Higher boiling	....

to the addition of methyl with eventual formation of octanes and higher products



$$CH_3CH_2\overset{\vert}{C}HCH_3 \text{ or } \overset{\vert}{C}H_2\overset{CH_3}{\overset{\vert}{C}}HCH_3 + CH_3CH{=}CH_2 \longrightarrow C_7H_{15} \quad (13)$$

When methyl abstracts a hydrogen atom from propylene

$$CH_3 + CH_3CH{=}CH_2 \longrightarrow CH_4 + CH_2CHCH_2 \quad (14)$$

the resulting allyl can be found in the C_7 olefin (equation 9) or as butene.

$$CH_3 + CH_2CHCH_2 \longrightarrow CH_3CH_2CH{=}CH_2 \quad (15)$$

Each of these hydrocarbons has been identified in the reaction products and, perhaps equally important, no others of different carbon structure have been found.

Evidence for initial addition of methyl to either end of the propylene double bond is indicated by the presence of both normal and isobutane among the reaction products (equation 8). That ethyl behaves similarly is shown by isolation of *n*- and isopentane from the reaction of propylene and di-*t*-amyl peroxide (*cf.* Beeck and Rust[3]).

One unexplained phenomenon is the shift in the double bond of the olefinic products which probably occurs at the time of formation. Thus, both 1- and 2-butene are found and, although a terminal double bond would be predicted for the heptenes, actually a shift to an internal position has occurred in a part of the product. The expected carbon structure is, however, borne out by infrared analysis of the hydrogenated C_7 fraction.

The attack of methyl on 2-butene or isobutylene gives the products which would be predicted from the analogous reactions of methyl with propylene. These products are listed in Table I, together with references to the equations representing the mode of formation of the analogous compounds derived from propylene. Thus, 2,3-dimethylbutane which is derived by dimethylation of the double bond of 2-butene is analogous to isopentane which is formed by dimethylation of the propylene double bond. The mechanism is illustrated by equations 6 and 7. The exaggerated bonds shown in the table are the ones newly formed as a consequence of radical attack.

When di-*t*-amyl peroxide is decomposed at 235°, the products prove that ethyl radicals are released and when propylene is mixed with the decomposing peroxide, the expected compounds are formed. 3-Methylhexane, from the addition of two ethyl groups to the double bond; iso- and normal pentane, from internal and external addition, respectively, of ethyl radical to the double bonds (equation 6 and 8); and straight chain pentenes, from the replacement of a hydrogen atom by an ethyl group (equation 14 and 15), have all been isolated.

Effect of Surface

Extensive investigation by previous workers[2] has provided ample evidence for the combination of methyl radicals at the wall. So important is this wall effect that virtually no olefin could be involved in reactions with methyl if 15-mm. Pyrex tubing were used as the reactor. Successful results were obtained in 70-mm.-tubes. The obvious implication is that methyl addition to double bonds and methane formation by hydrogen abstraction are largely gas phase reactions. The conditions of combination for larger radicals are not suggested by the present work.

Materials and Procedure

The ethylene was a product of the Ohio Chemical Company and assayed 99.5%. Propylene was prepared by dehydration of isopropyl alcohol and, after being purified by distillation, analyzed 98.2%, the remainder being air and saturates. The 2-butene was analyzed by infrared absorption to be as follows: 1-butene, 5.5%; 2-butene, 94.2%; butadiene, 0.2%; and *n*-butane, 0.1%. The isobutene was a refinery product which analyzed 99.7%. The liquid hydrocarbons were all carefully distilled and checked for purity by refractive indices.

---

[3] Beeck and Rust, *J. Chem. Phys.*, **9**, 480 (1941).

The di-*t*-butyl and di-*t*-amyl peroxides were synthesized in accordance with the procedures given by Vaughan and Rust.[4] The di-*t*-butyl peroxide had an index $n^{20}\mathrm{D}$ 1.3890 and was 98+% pure. The di-*t*-amyl peroxide distilled at 54.5–55° at 17–18 mm.; its refractive index was $n^{20}\mathrm{D}$ 1.4083.

In general, experiments were conducted by metering the gaseous hydrocarbons or carrier nitrogen through flowmeters and the liquid peroxide through a rotameter. The peroxide was vaporized and mixed with the gaseous materials in a glass tubular coil surrounded usually by boiling water. The reaction mixture then passed directly into the top of the reactor tube (1250 cc., 70 mm. i.d.), which was heated by a thermostated oil-bath. The liquid product was collected in a water wash-bottle and an ice-cooled trap while the effluent gas was passed into an aspirator bottle. The gases and vapors were analyzed by low temperature distillation except where otherwise specified.

Experimental

Toluene and Di-*t*-butyl Peroxide. 2,3-Dimethylbutane and Di-*t*-butyl Peroxide.—Mixtures of hydrocarbon and peroxide in a molar ratio of 2:1 were metered into the reaction system at a rate calculated to give a total vapor flow of 300 cc./minute[5] N.T.P. Carrier nitrogen (50 cc./minute) was added. The reaction temperature was 235°.

From toluene, ethylbenzene (b. p. 136°, $n^{20}\mathrm{D}$ 1.4937) was produced in a 6.25% yield based on the input peroxide. Higher boiling product, 50% greater in amount than the ethylbenzene, was also collected; this material had a molecular weight of 199 which compares with 182 for diphenylethane.

Under comparable conditions triptane was produced from the dimethylbutane in a yield of 7.7%. The analysis of the triptane fraction was made by infrared absorption. Higher boiling products in comparable volume were not investigated.

Ethylene and Di-*t*-butyl Peroxide.—Experiments were carried out as follows: A mixture of ethylene plus peroxide was introduced at a rate of 200 cc./min. vapor volume into a Pyrex tube heated to 225 or 235°. Ratios of ethylene to peroxide between 1:1 and 9:1 were used. The data are given in Table II.

TABLE II

REACTION OF DI-*t*-BUTYL PEROXIDE AND ETHYLENE

Temp., °C.	210	225	225	225	225	235
Ratio C_2H_4:peroxide	1:1	1:1	2:1	4:1	9:1	9:1
% Peroxide reacted	56.8	89.6	94.2	80.4	59.2	63.5
% Reacted peroxide converted to						
Ethane	66.9	82.3	68.2	62.1	40.7	61.6
n-Butane	9.7	6.8	14.2	15.1	28.8	13.6
n-Hexane	4.4	1.6	4.6	13.4	10.2	16.0
n-Octane	...	...	...	...	...	4.0

In every case higher boiling products were produced but the amounts were too small to permit identification. The hexane had a boiling point of 69° and $n^{20}\mathrm{D}$ 1.3750 (lit.[6] 68.7° and 1.3750). Respective values for the octane isolated are b. p. 124.2° and $n^{20}\mathrm{D}$ 1.3986 (lit., 125.6° and 1.3976). The above estimates of conversions are based on the actual amounts of materials isolated and on the amount of decomposed peroxide as given by the ketone formed. Unreacted peroxide in the high boiling fractions was removed by boiling with concentrated hydrogen iodide in acetic acid; the resulting iodine was destroyed with thiosulfate solution and the alkyl iodides with alcoholic potassium hydroxide. The residue was then washed and fractionated.

Propylene and Di-*t*-butyl Peroxide.—Propylene and di-*t*-butyl peroxide vapor reacted at 235° with input flow rates of propylene and peroxide of 200 cc./min. and 100 cc./min. The effluent vapors, after passing through a water bubbler and ice-cooled trap, were collected in an aspirator bottle and later fractionated by low temperature distillation. The gaseous fractions were analyzed subsequently in an Orsat-type apparatus with the exception of the C_4 cut which was analyzed by infrared spectrophotometry. The composition of these light fractions is shown in Table III.

TABLE III

Product	Per cent.
Propylene	60.6
Methane	13.7
Ethane	9.8
Isopentane	6.3
n-Butane	2.4
1-Butene	2.0
2-Butene	0.8
Isobutane	0.4
Others	4.0

The liquid product was washed with water and hydroxylamine to remove as much ketone as possible and then fractionated. Besides the low boiling cuts (C_5) this distillation showed fractions in the C_7, C_8 and C_9 ranges and a very substantial amount of still higher boiling material. The 107 to 113.5° cut after washing with concentrated sulfuric acid and distilling, had a refractive index of $n^{20}\mathrm{D}$ 1.3970. According to infrared analysis this fraction was *ca.* 95% 2,4-dimethylhexane, and 5% 2,5-dimethylhexane. These two octanes have reported boiling points of 109.8 and 109.3° and indices $n^{20}\mathrm{D}$ 1.3958 and 1.3929, respectively. The 113.5 to 119.5° fraction had an index $n^{20}\mathrm{D}$ 1.4044 before and after washing with concentrated sulfuric acid. Infrared analysis showed it to be 98% 3,4-dimethylhexane (lit. b. p. 117.85°, $n^{20}\mathrm{D}$ 1.40436). The next higher fraction boiling around 135° appears to be a nonane, but has not been identified. Figure 1 is a line diagram of the infrared absorption spectra of the heptene and octane fractions.

In order to determine the carbon skeleton of the small heptene fraction, propylene and peroxide were passed through the reactor at 235° for twenty-five hours. The resulting product, after being washed free of acetone, was hydrogenated at 80° in isopropyl alcohol with Ruffert nickel. The product was filtered, water-washed, dried

TABLE IV

YIELD OF HIGHER HYDROCARBONS DERIVED FROM PROPYLENE (BASED ON INPUT PEROXIDE)

Product	Per cent.
n-Butane	4.5
1- and 2-butene	5.0
Isobutane	<1.0
Isopentane	20.0
Heptenes	0.5
3,4-Dimethyloctane	2.0
2,4-Dimethyloctane	1.5
2,5-Dimethyloctane	<0.1

---

(4) Vaughan and Rust, U. S. Patent 2,403,771.

(5) Hereinafter, "cc./min." means cc. vapor/minute N.T.P.

(6) The literature values for the physical constants for the hydrocarbons cited herein are taken from M. P. Doss, "Physical Constants of the Principal Hydrocarbons," The Texas Company, New York, N. Y., 1942.

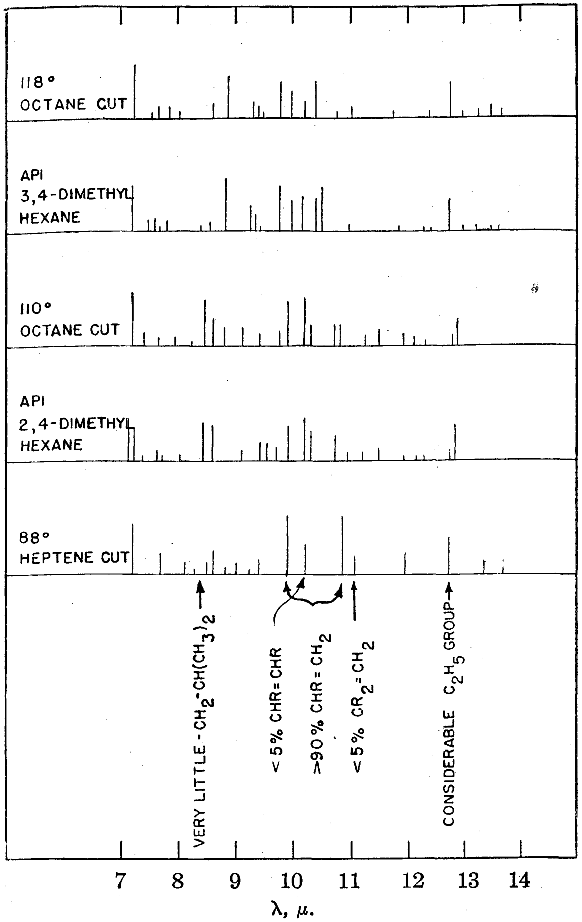


Fig. 1.—Infrared spectra of di-*t*-butyl peroxide–propylene reaction products.

and fractionated. The heptane fraction was separated and by infrared analysis was found to be 85–95% 3-methylhexane and 5–15% 2-methylhexane. The yields of some products are given in Table IV.

2-Butene and Di-*t*-butyl Peroxide.—Di-*t*-butyl peroxide (100 cc./min.) and 2-butene (200 cc./min.) were mixed and passed into the reactor at 235°. Analysis of the effluent gaseous products gave

	Per cent.
Butenes	60.0
Methane	17.5
Ethane	9.3
Pentenes	4.2
Isopentane	1.2
Other	7.8

The fraction containing dimethylbutane was washed with water and concentrated sulfuric acid to remove acetone and olefins. The material was then distilled and found to have an index $n^{20}D$ 1.3750 and a boiling point of 58.2° (lit., 1.3749 and 57.99°). The dibromide derivative was prepared (2,3-dibromo-2,3-dimethylbutane); this had a melting point of 163–164°, and a mixed melting point of 163.5–164.0°.

The higher boiling product was carefully water-washed and then steam distilled. The hydrocarbons were separated from the water in the distillate and refractionated. The material that boiled between 128 and 142° had a molecular weight (by vapor density) of 122.6 to 122.7, and a molecular weight on the basis of bromine number of 126; the molecular weight of nonene is 126. A narrow boiling fraction between 153.5 and 155.0° had a molecular weight of 139, while the theoretical value for decane is 142. Based on the probable reaction mechanism this decane must be the heretofore unreported 2,3,4,5-tetramethylhexane. The boiling point, as given by the distillation flat, was 155° and the index, $n^{20}D$, 1.426. A substantial amount of still higher boiling material remained. The yields are given in Table V.

TABLE V

YIELD OF HIGHER HYDROCARBONS DERIVED FROM 2-BUTENE (BASED ON INPUT PEROXIDE)

Product	Per cent.
Pentenes	10.0
Isopentane	3.5
Dimethylbutane	8.0
Nonenes	2.0
Decane	1.5

Isobutene and Di-*t*-butyl Peroxide.—Isobutene (200 cc./min.) and di-*t*-butyl peroxide (100 cc./min.) were passed into the reactor at 235°. The reaction products were analyzed essentially as described for propylene and 2-butene. Dimethylation of the double bond gives neohexane. The boiling point of the isolated fraction was 49–50° and its index $n^{20}D$ 1.3686 (lit., 49.7° and 1.3686, respectively). However, the principal products are *t*-amylenes. The predicted compound would be $CH_2{=}\overset{CH_3}{\overset{|}{C}}CH_2CH_3$ but the usual accompanying isomerization, in this case to trimethylethylene, seems to be rapid. Infrared analysis of the amylene fraction shows 60% 2-methyl-1-butene and 40% trimethylethylene. Isopentane is formed in an appreciable quantity ($n^{20}D$ 1.3530, b. p. 28.0°; lit., $n^{20}D$ 1.3540, b. p. 27.9°).

The low temperature distillation of the gaseous effluent gave results as follows

	Per cent.
Isobutene	56.0
Methane	21.3
Ethane	8.0
t-Pentenes	5.1
Isopentane	4.7
Others	4.9

A fraction boiling in the nonene range, 128–136°, had a molecular weight of 121.5 and bromine number of 115.5; for nonene the molecular weight and theoretical bromine number are both 126.

A fraction distilling between 162 and 172° was found to have a molecular weight of 141 and a bromine number of 2.6, which compares well with 142 and zero for decane. By analogy with propylene the decanes expected and probably present are 2,2,4,4-, 2,2,5,5- and 3,3,4,4-tetramethylhexanes. Inclusion of additional isobutene units in the reaction chain gives higher molecular weight hydrocarbons. Yields are shown in Table VI.

TABLE VI

YIELD OF HIGHER HYDROCARBONS DERIVED FROM ISOBUTENE (BASED ON INPUT PEROXIDE)

Product	Per cent.
t-Amylenes	8.5
Isopentane	7.5
Neohexane	6.0
Nonenes	2.0
Decanes	2.0

Propylene and Di-*t*-amyl Peroxide.—Propylene 200 cc./min. and di-*t*-amyl peroxide vapor 100 cc./min. were passed through the reactor at 235°. The effluent gaseous products of the reaction were found to be as follows

	Per cent.
Propylene	61.3
n-Butane	17.3
Ethane	8.5
Ethylene	2.0
Propane	2.0
Straight chain pentenes	1.3
n-Pentane	1.1
Methane	0.9
Isopentane	0.7
Others	4.9

The liquid products collected were water-washed and fractionated. Cut I (20–54°) was water-washed to remove some acetone and analyzed by infrared absorption. Its hydrocarbon composition was 50% isopentane, 25% *n*-pentane, 10% 1-pentene and 5% each of 2-pentene, 2-methyl-1-butene and 2-methyl-2-butene. The 54–57° fraction was almost entirely acetone, and the very small amount of water-insoluble organic material (b. p. 70–71°) was not analyzed further. A small intermediate fraction (57–91°) was washed with hydroxylamine hydrochloride solution and dried; infrared analysis showed 5% of a 1-olefin, 60% 3-methylhexane and 30% 2-methylhexane. The remaining 5% was ketone which was not completely removed by water-washing. Cut IV (b. p. 91–94) was washed with concentrated sulfuric acid with virtually no change in volume or the refractive index of 1.3890. Infrared analysis identified the material as 3-methylhexane and a vapor density measurement gave the molecular weight as 100 (theory 100.2). The decane fraction (153–161°) after being washed with concentrated sulfuric acid and 6 *N* sodium hydroxide analyzed as follows: carbon 84.4%, hydrogen 15.4%, mol. wt. 149; calcd., 84.5, 15.5 and 142, respectively.

TABLE VII

YIELD OF HIGHER HYDROCARBONS DERIVED FROM PROPYLENE (BASED ON DI-*t*-AMYL PEROXIDE)

Product	Per cent.
Amylenes	2.7
n-Pentane	2.5
Isopentane	1.6
3-Methylhexane	8.0
Nonenes and decanes	3.0

Acknowledgment.—The authors are indebted to the members of the Spectroscopic Department of This Company, and in particular to Dr. R. S. Rasmussen, for the infrared analyses.

Summary

1. The di-*t*-alkyl peroxides are especially useful tools for the study of free radical processes.

2. Some of the products from the interaction of free methyl and ethyl with various saturated and unsaturated hydrocarbons have been isolated and identified. Mechanisms of formation of these compounds are suggested.

EMERYVILLE, CALIFORNIA RECEIVED[7] JULY 19, 1947

---

[7] Original manuscript received September 26, 1946.

[CONTRIBUTION FROM THE INSTITUTE FOR ATOMIC RESEARCH AND DEPARTMENT OF CHEMISTRY OF THE IOWA STATE COLLEGE]

The Structures of the Carbides, Nitrides and Oxides of Uranium[1]

BY R. E. RUNDLE, N. C. BAENZIGER, A. S. WILSON AND R. A. MCDONALD

Introduction

The systems uranium–carbon, uranium–nitrogen and uranium–oxygen have been given thorough X-ray study in the course of work carried out for the Metallurgical Project. In this paper this work will be summarized rather briefly, giving pertinent structural information and necessary details concerning the methods used in carrying out the work.

In general, little discussion of the structures will be presented here. The nature of the metal-like monocarbide, mononitride and monoxide are discussed elsewhere along with other similar compounds.[2] Since the structures of nearly all the phases examined have been simple, parameterless structures of types described thoroughly in "Strukturbericht," it has seemed unnecessary to present lengthy accounts of the structural determinations, together with tables of calculated and observed intensities. In every case not otherwise indicated a careful comparison of observed and calculated intensities for the assigned structure has been made.

Though this paper is intended primarily as a summary of X-ray structures, many of the compounds whose structures are reported here were discovered and their compositions first obtained either solely by X-ray study or jointly with chemical investigations. It seems well to point out, therefore, that X-ray study of the carbides, nitrides and oxides of uranium has required extensive revision of formulas in these systems. The monocarbide and the mononitride were discovered, with chemical and metallographic aid, by X-ray diffraction; the monoxide was found solely by X-ray diffraction. Not a single nitride of uranium had been assigned a correct formula before these X-ray studies were made.[3] Even among the higher oxides new phases were found, and the relationships among the higher oxides

---

[1] Paper No. 7 of the Institute for Atomic Research. Work done under contract W-7405 eng-92, Manhattan Project, U. S. Corps of Engineers. F. H. Spedding, Project Director. A review of this work will be published in Div. VIII, Manhattan Project Technical Series.

[2] R. Rundle, "A New Interpretation of Interstitial Compounds," submitted for publication in *Acta Crystallographica*.

[3] Gmelin's "Handbuch der anorganischen Chemie," system Number 55, Verlag Chemie, Berlin, 1936, p. 107 ff.

and nitrides turned out to be more complex than hitherto suspected.

Most of the compounds reported here are prepared by the reaction of solids to form solid products which are difficult to handle chemically. The fact that X-ray study has required extensive revision of formulas in the systems provides an example of the serious errors which can arise in the interpretation of solid–solid reactions by purely chemical examination.

The authors do not wish to imply that unaided X-ray study is a substitute for unaided chemical study. The authors have had the full coöperation of metallographic, inorganic and analytical chemists in preparing and determining the compositions of the compounds reported here. Indeed, much of this work originated with metallographic or inorganic studies of uranium systems.

It must be pointed out that determination of compositions of phases involving light elements and uranium is generally possible only in the case of relatively simple structures. It is, of course, nearly impossible to locate light elements in the presence of uranium, particularly in structures involving parameters. Consequently, even in those cases where X-ray study gave a clear indication of composition, confirmation by analytical chemists was sought.

Uranium Carbides

Uranium Monocarbide.[4]—The lowest carbide of uranium is the monocarbide, UC. Dendritic material of this composition can be separated even from uranium metal of very low carbon content by dissolving the metal preferentially with dilute acids. X-Ray diagrams of dendritic material were identical with diagrams of material prepared from metal and carbon at the stoichiometric ratio, UC. Other methods of preparation are described below.

Uranium monocarbide is face-centered cubic, $a = 4.951 \pm 0.001$ Å., with four "molecules" per unit cell. The X-ray density is, then, 13.63 g./cc.

The possible structures are the sodium chloride- and zinc-blende-types, which differ only in the positions of the carbon atoms. Although relative to uranium the X-ray scattering power of carbon is very slight, it appears possible to differentiate between these two structures by examining the pair of reflections (331) and (420). These reflections have the same multiplicity factor and are separated by only three degrees on X-ray diagrams made with CuKα radiation. The intensity factors dependent upon scattering angle only may, therefore, be considered essentially identical, particularly in the neighborhood $2\theta = 90°$, where these reflections occur.

For the sodium chloride-type structure the structure factors for (331) and (420) are $(4f_u - 4f_c)$ and $(4f_u + 4f_c)$, respectively, where f represents the atom form factor. For the zinkblende-type structure the corresponding structure factors are $(4f_u - 4if_c)$ and $(4f_u - 4f_c)$. For the sodium chloride-type structure $I_{(420)} > I_{(331)}$ by about 14%, while for the zinkblende-type structure, $I_{(331)} > I_{(420)}$ by about 7%. (The values of the atom form factor used in these calculations, $f_u = 54.3$, $f_c = 1.8$, are those for uranium and carbon atoms. Actually this is the most unfavorable case, since there may be some transfer of electrons from the electropositive to the electronegative element. Similar intensity comparisons have been made for uranium mononitride and monoxide, where the intensity ratios are greater, due to larger scattering of nitrogen and oxygen.) On X-ray powder diagrams made using cylindrical, well-powdered samples (420) was clearly more intense than (331). Other intensity comparisons, while not as critical as the above, also support the sodium chloride-type structure.

Range of Composition of the Monocarbide Phase.—Precise values of the lattice constant of the monocarbide have been obtained for samples containing excess carbon and for others containing excess metal. In a large group of samples of various compositions, lattice constants ranging from 4.947 to 4.951 Å. have been observed, but these varied at random and were in no way related to composition. Dendritic samples, which probably contain all the oxygen and nitrogen impurities of the metal, have spacings of about 4.948 Å. The isomorphous monoxide and mononitride of uranium are known to have smaller lattice constants than the carbide (see below). We presume, therefore, that the composition of the monocarbide is quite definite in the absence of nitrogen and oxygen, and that the largest spacing observed, 4.951 Å., represents the best value of the lattice constant of the monocarbide. The solubility of both carbon and uranium in the monocarbide is negligible at room temperature.

Solubility of Nitrogen and Oxygen in the Monocarbide.—A striking example of the interchange of nitrogen atoms for carbon atoms in the uranium monocarbide lattice is shown by by the following experiment. Mr. P. Chiotti of this Laboratory has heated uranium monocarbide and uranium mononitride at 1950° for fifteen minutes. Precision X-ray diagrams of the sample showed that the spacing of the uranium monocarbide had changed from $a = 4.947$ to 4.921 Å., and that of uranium mononitride from 4.883 to 4.917 Å. After longer heating the sample would undoubtedly come to equilibrium with just one spacing of approximately 4.92 Å.

Similar experiments with the isomorphous uranium monoxide are more difficult to carry out since uranium monoxide cannot be prepared in pure form. However, in systems in which oxygen was the principle contaminant, the monocarbide spacing was considerably lowered.

In the case of mononitride and monocarbide, complete solid miscibility has been demonstrated.

---

[4] Mostly from Metallurgical Project Report CT-686, May (1943).

It appears likely that monoxide and monocarbide are also completely miscible. In view of the very similar lattice spacings of carbide (4.951), oxide (4.91) and nitride (4.880) this is not surprising.

Uranium Sesquicarbide.[5]—U_2C_3 is the next phase of higher carbon content. This phase, which exists only at very high temperatures, has resisted all attempts to quench it to room temperature. Samples of the composition U_2C_3 quenched from well above 2000° are two-phase, uranium monocarbide and uranium dicarbide, as shown by powder diagrams and by microscopic examination. The microscopic and X-ray investigations do indicate, however, that at very high temperatures (probably above 2000°) uranium sesquicarbide must indeed exist. At the composition U_2C_3 what appear superficially to be single crystals are formed in the melt. At room temperature these "single crystals" give broad but definite, single-crystal X-ray reflections, but the reflections are due to both uranium monocarbide and dicarbide arranged so that their crystal axes are mutually parallel to the main edges of the apparently single crystal. Microscopic examination reveals a Widmanstatten structure. Quite apparently the sesquicarbide forms at high temperatures but decomposes to the mono- and dicarbides at lower temperatures.

Uranium Dicarbide.—Uranium dicarbide is the only carbide whose X-ray structure had been reported previously in the literature.[6] Its structure then was established as isomorphous with calcium dicarbide. Since purer uranium was available to this laboratory than to earlier workers, the lattice constants of the dicarbide were re-examined.

The lattice constants of the body-centered, tetragonal dicarbide vary with the previous heat treatment of the sample; all samples which were cooled slowly to room temperature had lattice constants independent of carbon content, a = 3.517 ± 0.001 Å., c = 5.987 ± 0.001 Å. Samples which contained an excess of carbon (about 10–11 weight per cent. carbon) and which were quenched from 2400 and 2700° had much smaller lattice constants: a = 3.504 ± 0.001 Å., c = 5.951 ± 0.001 Å. and a = 3.507 ± 0.001 Å., c = 5.962 ± 0.001 Å. for samples quenched from the two temperatures. X-Ray diagrams of the samples allowed to cool slowly to room temperature contained maxima of the monocarbide and carbon as well as that of uranium dicarbide. The lattice constants of the dicarbide had increased to that for slowly cooled samples.

Apparently carbon dissolves in the dicarbide at higher temperatures and may be maintained in solution by quenching. Samples which are not quenched not only precipitate carbon, but also apparently yield monocarbide and more carbon through decomposition of the dicarbide at some intermediate temperature. Unlike the sesquicarbide, however, the dicarbide is easily quenched.

The decrease in lattice constants with increased carbon solubility may be explained in several ways. Either an uranium atom is occasionally replaced by a carbon atom or C_2 group, or the structure containing excess carbon must be thought of as a uranium dicarbide lattice deficient in uranium, allowing cell dimensions to shrink slightly.

Previously the carbon positions in uranium dicarbide had been assumed to be like those in calcium carbide. Because of the different chemical properties of calcium and uranium dicarbides, it does not appear that the uranium dicarbide can be regarded as a salt of acetylene. Accordingly, we have tried to see if anything can be said about the carbon positions from intensity considerations.

Reflections differing only in carbon contributions and close enough together to be compared with reliability are rare for powder diagrams of uranium dicarbide. However, reflections (204) and (310) meet these requirements. M. von Stackelberg has discussed the possible structures,[7] and we have considered these for uranium dicarbide.

With U at 000 and $\frac{1}{2}\frac{1}{2}\frac{1}{2}$ there are five possible sets of body-centered positions for the carbon atoms. These are

A $000, \frac{1}{2}\frac{1}{2}\frac{1}{2} + 00z, 00\bar{z}$
B $000, \frac{1}{2}\frac{1}{2}\frac{1}{2} + 0\frac{1}{2}z, \frac{1}{2}0\bar{z}$
C $000, \frac{1}{2}\frac{1}{2}\frac{1}{2} + 0\frac{1}{2}0, \frac{1}{2}00$
D $000, \frac{1}{2}\frac{1}{2}\frac{1}{2} + 0\frac{1}{2}\frac{1}{4}, \frac{1}{2}0\frac{1}{4}$
E $000, \frac{1}{2}\frac{1}{2}\frac{1}{2} + 0\frac{1}{2}z, \frac{1}{2}0z$

Structures A and B permit C_2 groups. A is the calcium carbide structure, and B is related to the zinkblende structure, with C_2 groups parallel to the c axis replacing a monatomic ion.

If C_2 groups with a C–C distance equal to that in acetylene are assumed, then z in structures A and B becomes approximately 0.4 and 0.15, respectively. One then finds that for structure A, $I_{(204)}/I_{(310)} = 26/34$, while for B, $I_{(204)}/I_{(310)} = 26/26$. (Atom form factors were chosen in the same manner as for the monocarbide.) On powder diagrams (310) is clearly more intense than (204), so that if there are C_2 groups, the calcium carbide-type structure must be chosen.

Structures C and D make $I_{(204)} > I_{(310)}$ and can be eliminated Structure E with $z = 1/8$ or $3/8$ is satisfactory as far as the intensity comparisons are concerned, but it does not seem to be a reasonable structure, in that there are four carbon atoms bonded very closely to uranium at about 1.90 Å. This bond is shorter than the sum of the covalent radii of uranium and carbon (2.17 Å.). Moreover, all four carbons would lie on one side of uranium, with no good bonds on the other side. We consider that these intensity considerations, while fragmentary, support C_2 groups and the calcium carbide-type structure for uranium dicarbide.

---

(5) Largely from Metallurgical Project Report CT-751A, June (1943).

(6) G. Hägg, *ibid.*, **B12**, 12 (1931).

(7) M. v. Stackelberg, *ibid.*, **B9**, 437 (1930).

Uranium Nitrides

Uranium Mononitride.[8]—Uranium mononitride, UN, is the lowest nitride of uranium. Its face-centered cubic lattice constant is $a = 4.880$ Å.; its X-ray density, $\rho = 14.32$ g./cc. It is entirely isomorphous with uranium monocarbide. Here again a comparison of the intensities of reflections (420) and (331) shows (420) as the stronger reflection, indicating the sodium chloride-type structure.

Uranium mononitride heated with uranium to high temperatures does not change its lattice constant beyond the limit of error. If the mononitride is treated with more nitrogen, a second phase with the composition U_2N_3 appears, but the lattice constant of the mononitride remains unchanged. Thus, the solubility of either nitrogen or uranium in the mononitride is vanishingly small.

Uranium Sesquinitride.[8]—Uranium sesquinitride, U_2N_3, is body-centered cubic, $a = 10.678 \pm 0.005$ Å., $Z = 16$, $\rho = 11.24$ g./cc. The structure of this phase is isomorphous with manganese sesquioxide (Type $D5_3$ in the "Strukturbericht" designation). The location of the uranium atoms requires one parameter, which has been found to be -0.018 at the ideal composition.[9] Nitrogen positions presumably are similar to those of oxygen in manganese sesquioxide. Since the structure is a well known type, the structure determination will not be reproduced here, nor will atomic positions be listed.

The lattice constant of uranium sesquinitride has been studied as a function of composition by heating uranium sesquinitride with uranium mononitride and uranium. Detectable changes in the constant cannot be produced on the low nitrogen side of the composition U_2N_3, so the phase must not exist below this ideal composition.

Uranium Dinitride and the Phase Between the Sesquinitride and Dinitride.[8]—The sesquinitride structure is very similar to the fluorite-type structure. Indeed, if the weak reflections from uranium sesquinitride were ignored a face-centered cubic pseudo-lattice, $a = 5.339$ Å. (half the true lattice constant), could be chosen. This is nearly identical with that of the dinitride which has the fluorite structure.

The sesquinitride structure is essentially a distorted fluorite-type structure with nitrogen missing in a regular way from the lattice.[10] As nitrogen is added to the sesquinitride the distortion in the structure from that of the fluorite-type decreases and the system remains one phase. This is shown by the gradual decrease in intensity of the weak lines of the uranium sesquinitride structure, corresponding to a change of the uranium parameter from -0.018 toward zero.

At a nitrogen pressure of one atmosphere the maximum obtainable nitrogen–uranium ratio seems to be about 1.75, which probably accounts for the fact that U_4N_7 and other unusual formulas for uranium nitrides have been reported in the literature. Compositions in this range at ordinary pressures are determined by the pressure and temperature of preparation of the nitride, and, since the system remains one phase throughout the region from uranium sesquinitride to dinitride, only the extreme ends of the phase need be considered as distinct compounds.

In the one-phase region between uranium sesquinitride and dinitride the lattice constant decreases with increasing nitrogen content, at least up to the composition $UN_{1.75}$. At $UN_{1.5}$, $a = 10.678 \pm 0.005$ Å., while at $UN_{1.75}$, $a = 10.580 \pm 0.005$ Å. At $UN_{1.75}$ the maxima requiring the doubled unit are just barely visible. Presumably this decrease in lattice constant is due to a shift toward a more closely packed structure as the distortion, occasioned by nitrogen missing from the fluorite-type structure, is removed.

Samples prepared at high nitrogen pressures (126 atm. nitrogen) in the composition range UN to UN_2 are two-phase, consisting of UN and UN_2. Here the UN_2 phase has the ideal fluorite structure and a lattice constant, $a = 5.31 \pm 0.01$ Å. Apparently at high pressures U_2N_3 disproportionates into the mono- and dinitrides. This is to be expected from the change in volume in the reaction

$$U_2N_3 = UN + UN_2$$

The unit volume of U_2N_3 is 1217.5 Å.^{3} and the corresponding volume for UN plus UN_2 is 1057 Å.^{3} The volume decrease is thus about 13%.

It is to be noted, however, that between $UN_{1.75}$ and UN_2 the lattice expands, since at $UN_{1.75}$ the lattice constant is 10.58 ± 0.01 Å. and twice the lattice constant of UN_2 is 10.62 ± 0.02 Å. Pure UN_2 seems to be difficult to prepare, as most samples of nitrides prepared at high pressures contained some UN, but in a few cases the UN_2 phase was pure, at least to the extent that UN reflections could no longer be detected on X-ray diagrams.

Uranium Oxides

Uranium Monoxide.[11]—Uranium monoxide is face-centered cubic, $a = 4.92 \pm 0.02$ Å. with the sodium chloride-type structure. (The evidence for the sodium chloride structure is again the comparison of reflections (331) and (420).) Since uranium monoxide has never been prepared in any quantity and is known only from X-ray data, it seems necessary to describe its preparation and the nature of the evidence for the compound.

The monoxide was discovered during attempts to make X-ray diagrams of uranium metal in the beta and gamma temperature ranges. The diagrams, in almost all cases, consisted chiefly of a

---

[8] From Metallurgical Project Reports CT-686, May (1943) and CC-1524, March (1944).

[9] Parameter as listed in "Strukturbericht," Vol. II, 38 (1937).

[10] For a more complete description of the relation between these structures see "Strukturbericht," ref. 9.

[11] Metallurgical Project Reports CN-1495, April (1944), and CC-1984, Dec. (1944). British workers found this oxide independently at a later date.

face-centered cubic phase, a = 49.1 Å. The metal had been previously cleaned, and was contained in carefully evacuated, quartz capillaries which had been cleaned up with a zirconium getter. The metal was kept away from the quartz with columbium metal spacers. The chief contaminant in these samples was known to be oxygen.

Later it was found that a uranium metal surface which has become badly discolored due to "oxidation" continues to give a powder diagram characteristic of the metal until heated. The gold or even black coating disappears on heating, producing a metallic-looking surface somewhat whiter in appearance than uranium itself. The surface after heating produces an X-ray diagram of a face-centered cubic phase, a = 4.91 Å. The chief impurity in the surface is oxygen, though small amounts of nitrogen and carbon also are present.

Attempts to prepare the monoxide by heating UO_2 or a higher oxide with metal have usually been disappointing. Generally the high temperature necessary has caused considerable contamination by carbon (from graphite heating elements in some cases). Where carbon and nitrogen have been very carefully excluded little or no reaction has resulted. In cases of considerable carbon contamination the face-centered phase was produced. In these instances oxygen was the chief light element of the UX phase. Though it seems probable that carbon is necessary only to promote the reaction of a higher oxide with uranium to form UO, the possibility cannot be excluded that some UC or UN must be present for the phase to form. It may be possible that UO should be described as a UX phase, where X is carbon, nitrogen and oxygen, but that the amount of oxygen in the phase can be made to predominate.

Due to the fact that UO has never been prepared with great purity, the spacing is not known precisely. The spacing lies between that of the carbide and the nitride. Spacings between 4.93 and 4.91 Å. have been observed. Since carbon contamination has generally exceeded nitrogen contamination, the lower spacing is probably more nearly correct.

Uranium Dioxide.—Uranium dioxide has been investigated by many early workers in the field of X-ray diffraction.[12] Various values of the cubic spacing have been reported, so it was thought well to check the values with a sample of the very pure oxide available on this project. The lattice constant of such a sample is a = 5.4581 ± 0.0005 Å.

Subsequent investigation showed that a wide variation in spacing is possible due to solubility in uranium dioxide. When the oxide is heated with uranium above 2000°, as in making the monoxide, the dioxide spacing is increased to a = 5.4610 ± 0.0007 Å. Presumably in this region uranium is introduced into the vacant set of cubic interstices in the uranium dioxide structure. As one increases the oxygen content by heating uranium dioxide with U_3O_8 in a sealed quartz system, the lattice constant of the dioxide decreases in magnitude, finally reaching a = 5.4297 ± 0.0008 Å. as a limit. A new phase appears in a sample of composition $UO_{2.3}$, so the limit of the solubility region must lie between $UO_{2.2}$ and $UO_{2.3}$.

Uranium dioxide has the fluorite structure. This may be considered as a simple cubic lattice of oxygen ions with U^{+4} ions in one half of the cubic interstices. If the oxygen ion lattice remains fixed but U^{+4} ions are occasionally missing at random from the lattice, the oxygen lattice would be allowed to shrink slightly giving the lower lattice constants. If the density is calculated on this assumption, using $UO_{2.25}$ as the limiting composition, the density would change from 10.96 g./cc. for pure uranium dioxide to 10.04 g./cc. for $UO_{2.25}$.

Biltz and Müller have examined the uranium–oxygen system and have found a discontinuity in both vapor pressure and molecular volume at $UO_{2.25}$ in agreement with the X-ray data.[13] They have reported an increase in densities with composition in this region for samples prepared above 1000° and a decrease in density for samples prepared below 1000°. The reliability of these observations is open to question since by a different choice of their densities, the opposite trend may be shown. Moreover, their experimental value for the density of UO_2 is 10.73 to 10.82 g./cc., well below the calculated X-ray density, and the highest density reported in the whole region above uranium dioxide (with one exception) is less than the calculated X-ray density of uranium dioxide. Since densities measured by liquid displacement methods are subject to errors due to micro cracks and fissures, the data of Biltz and Müller cannot finally decide the type of solubility.

It is difficult to reconcile the decrease in lattice constant with the type of solubility requiring the introduction of additional oxygen ions into an already close-packed arrangement of oxygen ions. Accordingly, we feel that the solubility is due to the absence of U^{+4} ions rather than the presence of interstitial oxygen ions. Calculating the density on the alternative assumption that oxygen ions are being introduced into interstices in the UO_2 structure, the density would increase to 11.30 g./cc.

Higher Uranium Oxides.[14]—The oxides U_2O_5, U_3O_8, several forms of UO_3 and a hydrate of UO_4 are known. W. H. Zachariasen first examined the structures of U_3O_8, UO_3 and the hydrated UO_4. These will, presumably, be reported by him.

Biltz and Müller found that a one phase area extended from UO_3 to $UO_{2.62}$. X-Ray diagrams

---

(12) V. Goldschmit and L. Thomassen, *Videnskaps Selskapets Skrifter, I. Mat.-Naturw. Klasse Kristiania*, 2 (1923); A. van Arkel, *Physica*, **4**, 286 (1924); A. Schoep and V. Billiet, *Bull. soc. geol. Belg.*, **58**, 198 (1935).

(13) W. Biltz and H. Müller, *Z. anorg. Chem.*, **163**, 257 (1927).

(14) Largely from Metallurgical Project Report CC-1980, Nov. (1944).

of the samples in this range show that this one phase area is based on the "ideal" UO_3 phase. U_3O_8 has been shown to be very similar to UO_3 by W. H. Zachariasen; this has been confirmed by our data. Our X-ray evidence also indicates that this one phase area may extend to the composition $UO_{2.5}$.

X-Ray diagrams of an equimolar mixture of U_3O_8 and UO_2 were made both before and after heating to 1100°. Before heating the sample the uranium dioxide maxima were the strongest maxima in the diagram due to the higher symmetry of the phase. After heating the sample the $UO_{2.25}$ maxima, although present, were weak and the U_3O_8 maxima had shifted in position and intensity. By examination of known mixtures of U_3O_8 and UO_2 it was possible to estimate the relative amounts of the phases present in the $UO_{2.5}$ sample. The upper bound on the lower limit of the composition of the UO_3-like phase was found to be $UO_{2.52}$.

By chance single crystals of $UO_{2.5}$ have been obtained by thermal decomposition of UO_2Cl_2. Powder diagrams of these needles were identical with those of $UO_{2.5}$ as described above. A detailed structure of U_2O_5 will be given later. However, the unit cell can be reported as orthorhombic, $a = 8.27 \pm 0.02$ Å., $b = 31.65 \pm 0.1$ Å., $c = 6.72 \pm 0.02$ Å., with 16 U_2O_5 per unit cell. There is a pseudo cell with $a = 4.135$ Å., $b = 3.956$ Å., $c = 6.72$ Å. The X-ray density is 8.35 g./cc.

Experimental

Methods.—X-Ray diagrams were made using Debye–Scherrer powder cameras of 5.73 and 5 cm. radius with the exception of the oxide samples in the composition range uranium dioxide to trioxide. These diagrams were obtained using an unsymmetrical self-focusing powder camera of 10 cm. radius manufactured by the Wyland Company. This camera gave very high dispersion and was ideally suited for the examination of the complex phases between uranium dioxide and trioxide. Nickel filtered CuK radiation was used in all but precision diagrams. Precision diagrams were prepared using a symmetrical self-focusing, back-reflection camera manufactured by the Wyland Co. Unfiltered CuK radiation and the mixed radiations of a copper–nickel alloy target were used to obtain more lines in the back reflection region. The data were evaluated using Cohen's method. The limit of error, when reported, is the standard error as determined from the measurement of one film.

X-Ray densities were calculated according to the suggestion of Jette and Foote using the formula $\rho = 1.65023\ MN/V$, where M is the molecular weight, N is the number of molecules per unit cell, and V is the volume of the unit cell calculated in terms of Siegbahn wave lengths.[15]

Preparation of Samples.—Most of the samples were prepared by other members of the Ames laboratory of the Manhattan Project. The general methods of preparation are given below.

Uranium Carbides.—Messrs. A. Daane, A. Snow, P. Chiotti and H. Carter prepared the carbide samples. The carbides were prepared by the direct reaction of appropriate amounts of uranium or uranium oxide and carbon in graphite crucibles at elevated temperatures obtained by induction heating. Samples were subsequently analyzed for carbon, since some carbon was dissolved from the crucibles. A. Tevebaugh separated uranium monocarbide dendrites from uranium by using dilute hydrochloric acid containing some hydrogen peroxide.

Metallographic study of the uranium carbon system by the above members of the Ames metallographic group is reported elsewhere. The metallographic reports contain additional information on the uranium–carbon system.[16]

Uranium Nitrides.—A. Newton prepared most of the nitride samples except those at high pressure. A. Daane first prepared uranium mononitride by the thermal decomposition of higher nitrides of uranium in a vacuum. It may also be prepared by heating uranium and the higher nitrides at elevated temperatures, the reduction of higher nitrides with hydrogen, the direct reaction of ammonia or nitrogen with uranium hydride and the direct reaction of nitrogen and uranium. Higher nitrides were prepared by the direct reaction of either nitrogen or ammonia with the hydride or the metal and by the reduction of still higher nitrides with hydrogen. The dinitride was prepared only at high pressures (about 126 atm.) of nitrogen on uranium metal. W. Tucker and P. Figard prepared the high pressure samples.

Chemical investigation of the uranium–nitrogen system has been reported by the above members of the Ames inorganic group.[17]

Uranium Oxides.—P. Chiotti, R. Raeuchle and J. Warf prepared the uranium–oxygen samples in the composition ranges between uranium and uranium dioxide by heating to over 2000° powdered metal and oxide which had been pressed into a billet. Samples of higher oxygen content than the dioxide were prepared by heating to about 1100° calculated amounts of UO_2 plus U_3O_8 or U_3O_8 plus UO_3 in sealed evacuated quartz capillaries. R. Raeuchle prepared the first U_2O_5. O. Johnson prepared single crystals of U_2O_5 by thermal decomposition of UO_2Cl_2 at 900°. The UO_2, U_3O_8, and UO_3 used were the pure materials available on the Manhattan Project.

Acknowledgments.—The authors wish to acknowledge gratefully the help of the above members of the Metallurgical Project, together with the analytical group at Ames.

Summary

1. Uranium monocarbide is face-centered cubic, $a = 4.951$ Å., and has the sodium chloride-type structure. Uranium dicarbide is body-centered tetragonal, $a = 3.517$ Å., $c = 5.987$ Å., and has the calcium carbide structure. Carbon is soluble in the dicarbide at high temperatures, and the dicarbide decomposes into the monocarbide and carbon at intermediate temperatures. Uranium sesquicarbide probably exists at temperatures above 2000°. It does not exist at room temperature.

2. Uranium mononitride is face-centered cubic, $a = 4.880$ Å., and has the sodium chloride-type structure. Uranium sesquinitride is body-centered cubic, $a = 10.678$ Å., and has the manganese sesquioxide structure. The uranium sesquinitride structure gradually changes toward the ideal dinitride structure in a one phase region extending to the composition $UN_{1.75}$. High pressure is needed to form the dinitride which is face-centered cubic, $a = 5.31$ Å., and has the fluorite structure.

3. Uranium monoxide is face-centered cubic, $a = 4.92$ Å., and has the sodium chloride-type

---

(15) Jette and F. Foote, *Phys. Rev.*, **58**, 81 (1940).

(16) The uranium–carbon system will be reviewed in Div. VIII and Div. IV of the Manhattan Project Technical Series.

(17) Work to be reviewed in Div. VIII of the Manhattan Project Technical Series.

structure. It is very difficult to prepare free from carbon or nitrogen. Uranium dioxide has the fluorite structure, a = 5.4581 Å. Oxygen is soluble in the fluorite structure up to approximately the composition $UO_{2.25}$ at which point the lattice constant is a = 5.4297 Å. U_2O_5 is orthorhombic, a = 8.27 Å., b = 31.65 Å., c = 6.72 Å. The structure is related to those of U_3O_8 and UO_3. A one phase region exists from U_2O_5 to UO_3 in which the various structures continuously transform from one to another.

AMES, IOWA RECEIVED MAY 3, 1947

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL CHEMISTRY, COUNCIL FOR SCIENTIFIC & INDUSTRIAL RESEARCH]

Basic Fluorides of Aluminum

BY J. M. COWLEY AND T. R. SCOTT

Introduction

The readiness with which aluminum and fluorine form complex ions in solution has been demonstrated by Brosset,[1] who determined the proportions of ions of the type AlF_n (where n = 1 to 6) in dilute solutions at constant activity. In solutions containing both aluminum fluoride and sulfate, the complex cations AlF^{2+} and $AlF_2{}^+$ appear to predominate, and the former may well be present in the salt $AlF_3 \cdot Al_2(SO_4)_3$ or $(AlF)SO_4$, discovered by Ehret and Frere.[2] Various Russian workers, *e.g.*, Nikolaev,[3] have described the preparation of aluminum fluosulfate, $(AlF_2)_2SO_4$ or $4AlF_3 \cdot Al_2(SO_4)_3$, although Ehret and Frere found no evidence for the formation of this compound in the system AlF_3–$Al_2(SO_4)_3$–H_2O at 25°. It is thus conceivable that aluminum might form hydroxy- (or oxy-) fluorides having the compositions $AlF(OH)_2$ and $AlF_2(OH)$: methods for the preparation of the latter compound (or the oxyfluoride $(AlF_2)_2O$) have indeed been given in several Russian patents.[4,5] Apart from the work of Schober and Thilo,[6] who described the diffraction pattern of $Al_7O_{10}F$ (prepared by the thermal hydrolysis of aluminum fluoride), no X-ray diffraction studies of these compounds have been made. The present paper describes the preparation of basic fluorides with compositions varying within the limits AlF_3 and $Al(OH)_3$, and gives details of their crystallographic structures.

Experimental

The basic fluorides may be precipitated from solutions of aluminum fluosulfate by treatment with ammonia[3] or by hydrolysis at temperatures ranging from 100–180°.[4] Aluminum fluonitrate solution may also be neutralized with calcium carbonate, leaving calcium nitrate in solution and precipitating basic aluminum fluoride.[5] Solutions of aluminum fluoride undergo slight hydrolysis on boiling, but the precipitate is very gelatinous and difficult to manipulate. While it is probable that hydrolysis at 150–200° would produce basic fluorides in better yield and in more satisfactory physical form, suitable corrosion-resistant equipment for this method was not available.

For the present study, samples were prepared by the addition of ammonia to solutions of aluminum sulfate containing varied proportions of aluminum fluoride. The aluminum sulfate was of A.R. grade, while solutions of aluminum fluoride were prepared by dissolving Laboratory Reagent grade aluminum metal in A.R. hydrofluoric acid. The general reaction was

$$6NH_4OH + Al_2(SO_4)_3 + xAlF_3 \longrightarrow 3(NH_4)_2SO_4 + Al_{2+x}(OH)_6F_{3x}$$

where x was varied from 0.4 to 14.0. Nikolaev[3] used this method for the production of AlF_2OH and his directions for the use of 20% more than the theoretical quantity of ammonia and for subsequent boiling of the gelatinous suspension of basic fluoride were carefully followed. (With a greater excess of ammonia, the fluorine content of the basic fluoride is considerably reduced.) After boiling for two hours, the suspensions were filtered and the basic fluorides thoroughly washed with water. The products were dried at 130°, again washed with water to remove entrained ammonium sulfate, and dried for a further four to six hours at 130°. No sulfate could be detected in the final products, though in all instances combined ammonia was present. Attempts to prepare uncontaminated basic fluorides by other methods were no more successful. The compound obtained by hydrolysis of aluminum fluosulfate solution at 100° contained 5% of sulfate, and it is highly probable that the treatment of aluminum fluonitrate with calcium carbonate would also yield an impure product. A further sample was obtained by adding ammonia to molar aluminum fluoride solution until the pH reached 6.4, and consisted of a mixture of almost equal parts by weight of aluminum basic fluoride and ammonium tetrafluoaluminate.

All specimens were analyzed for aluminum, fluorine, silica and ammonia, the oxygen content being calculated from the atomic ratio Al:F and the water content being obtained by difference. Aluminum was precipitated and weighed as the hydroxyquinolate, after fusion of the sample with potassium pyrosulfate or digestion with concentrated sulfuric acid. Fluorine was determined by the Willard–Winter distillation followed by titration of an aliquot of the distillate with thorium nitrate solution. Silica was estimated by a distillation method[7] devised by one of the authors.

X-Ray diffraction patterns were obtained from all samples with the 14.3 cm. powder-camera of the General Electric XRD unit, using filtered cobalt Kα radiation. The powder was packed into a wedge using a dilute solution of collodion in amyl acetate as binder and rocked through an angle of 20° during the exposure. To obtain the relative intensities of the lines, a key pattern, that from sample 4 (Table II), was microphotometered and used as an intensity standard. In the powder-wedge method, the reflections at small angles are weakened by absorption. The extent of this effect was estimated by comparison of the intensities of the key pattern with those given by a fine cylindrical sample, and the appropriate correction was made to the observed intensities of the diffraction lines.

---

[1] Brosset, "Electro-chemical and X-Ray Crystallographic Investigation of Complex Aluminum Fluorides," Stockholm, 1942.

[2] Ehret and Frere, THIS JOURNAL, **67**, 64 (1945).

[3] Nikolaev, *J. Chem. Ind. U. S. S. R.*, **14**, 1087 (1937).

[4] Kashcheev and Lazarev, Russian Patent 46,256 (Mar. 31, 1936).

[5] Morozov and Ivanov, Russian Patent 53,812 (Sept. 30, 1938).

[6] Schober and Thilo, *Ber.*, **73B**, 1219 (1940).

[7] Scott, *J. Council Sci. Ind. Research* (Australia), **19**, 103 (1946).

Results

Composition of Basic Fluorides.—Empirical formulas for the compounds prepared are given in Table I. It is interesting to compare the formula of sample 6 with the compound $Al_2OF_4 \cdot 3.5H_2O$ (*i. e.*, $Al(OH)F_2 \cdot 1.25H_2O$) described by Kashcheev and Lazarev.[4] The samples contained silica (0.2–1.8%) and ammonium hexafluoaluminate (2.3–7.3%) as impurities, but neither of these was found to produce lines in the X-ray powder photographs. With "amorphous" ammonium hexafluoaluminate, it is quite possible that the diffuse lines caused by 7% of the material would not be apparent in the diffraction patterns.

TABLE I

COMPOSITION OF BASIC FLUORIDES

Sample no.	Al	Empirical formula[a] OH	F	H_2O	Percentage of ammonium hexafluo-aluminate
1	1	2.60	0.40	0.25	2.3
2	1	2.30	.70	.31	4.1
3	1	1.98	1.02	.58	7.0
4	1	1.35	1.65	1.09	6.0
5	1	1.25	1.75	1.14	7.2
6	1	1.04	1.96	0.90	7.3
7	1	0.93	2.07	0.91	4.4

[a] Corrected for presence of $(NH_4)_3AlF_6$.

Ammonium hexafluoaluminate was distinguished by the fact that at 300°, in air, it decomposes almost completely to aluminum fluoride and volatile ammonium fluoride. By contrast, ammonium tetrafluoaluminate is relatively stable and retains the greater part of its ammonia until higher temperatures are reached. The latter compound was identified by its diffraction pattern in the precipitate obtained by the treatment of aluminum fluoride solution with ammonia, but was only present in minor quantities, if at all, in the samples listed in Table I. It is noteworthy that the ammonium hexafluoaluminate inferred to be present could not be removed from the basic fluorides by leaching with water, despite its appreciable solubility (0.76 at 25°). Nevertheless, the ignition behavior of the contaminated oxyfluorides, with respect to their ammonia contents, was so closely parallel to that of ammonium hexafluoaluminate, that no doubt is felt as to the presence of the latter compound.

Although only a small excess of ammonia was used in the preparation of the basic fluorides, a portion of the fluorine was lost by reactions of the type $NH_4OH + AlF_2OH \rightarrow NH_4F + AlF(OH)_2$. When the atomic ratio F:Al did not exceed 2:1 in the solutions used, the ratio in the resulting basic fluorides was, on the average, about 10% smaller, but increase of the ratio beyond 2:1 did not result in a proportional increase in the basic fluoride obtained. Sample 7, for example, with a F:Al ratio of 2.07:1, was prepared from solution of aluminum sulfate and fluoride in which the ratio was 2.63:1, and the former ratio was not exceeded even in basic fluorides prepared from aluminum fluoride solutions alone.

X-Ray Diffraction Studies.—Except for sample 1, all samples gave the same line-pattern, and in no case were any lines due to aluminum oxides, fluorides or any other impurities observed. Sample 1 gave only diffuse haloes such as are obtained from "amorphous" aluminum hydroxide. These diffuse haloes were present faintly with the line-patterns from 2 and 3. Samples 4 and 5 gave good patterns of sharp lines. For 6 and 7 the lines were broadened, indicating smaller crystal size.

The pattern from no. 4 was measured and analyzed in detail. The lattice spacings and intensities are set out in Table II. Spacings agree with those for a cubic structure with unit cell dimension $a_0 = 9.829 \pm 0.010$ Å. The missing reflections indicate the space group $O_h^7 - Fd3m$.

TABLE II

LATTICE PLANE SPACINGS AND INTENSITIES FROM HYDROXYFLUORIDE PATTERNS

Re-flec-tion	Dried at 130°[a] $d_{obs.}$	d_{calcd}	$Int._{obs.}$	$Int_{calcd.}$	Dehydrated at 500°[b] $Int_{obs.}$	$Int._{calcd.}$
111	5.70	5.67	460	490	680	750
220	...	3.48	...	...	31	27
311	2.979	2.964	220	203	105	113
222	2.841	2.837	100	100	100	100
400	2.460	2.457	26	20	9	7
331	2.258	2.255	21	20	8	5
422	2.009	2.006	44	46	74	86
333 511	1.893	1.892	92	106	80	93
440	1.737	1.737	110	110	71	85
531	1.661	1.661	33	30	37	51
620	1.553	1.554	26	26	17	14
533	1.498	1.499	40	42	26	31
622	1.480	1.482	42	42	32	42
444	1.417	1.418	9	8	7	12
711 551	1.375	1.376	51	44	41	70
731 553	1.277	1.279	45	58	30	42
800	1.227	1.228	13	17		
733	1.201	1.201	2	3		
822 660	1.158	1.158	31	28		
662	1.127	1.127	17	22		
840	1.099	1.099	14	15		
911	1.079	1.079	10	8		
753						
664	1.047	1.048	9	14		
931	1.031	1.030	20	37		

[a] Sample 4, containing 6 molecules of water per unit cell.

[b] Sample 6, containing no molecules of water per unit cell after dehydration.

The measured density is 2.25. Assuming that only one third of the water is in the lattice, this gives 16 $AlX_3 \cdot 6H_2O$ per unit cell, where X may be (OH) or F. (The remaining water is less firmly held and is apparently absorbed physically.)

This group may be fitted into the unit cell as follows

$48X$ in $O_h^7(f)$, general position $(u00)$
16 Al in $O_h^7(c)$, general position $(\frac{1}{8}\frac{1}{8}\frac{1}{8})$
$6H_2O$ in $O_h^7(b)$, general position $(\frac{1}{2}\frac{1}{2}\frac{1}{2})$

the six molecules of water being distributed among the eight sites.

Agreement between calculated and observed intensities is obtained for $u = 3/16$. With this value of u, the hydroxyl and fluorine ions lie at the corners of regular octahedra with aluminum ions arranged tetrahedrally, as centers, and form part of a hexagonal close-packed lattice. Each hydroxyl or fluorine ion is shared by two octahedra. The water molecules lie at the mid-points of the edges, at the body center, and at the centers of the unfilled segments of the unit cube (Fig. 1). This arrangement gives the distances between neighboring atoms as

Al—F, O_{OH}	1.84 Å.
F, O_{OH}—F, O_{OH}	2.61 Å.
F, O_{OH}—O_{H_2O}	3.07 Å.

These values are consistent with those for similar groups in other compounds. The observed intensities and those calculated for this structure are compared in Table II. Intensities calculated for more or less than six molecules of water in the lattice give less satisfactory agreement. The intensity of the *222* line does not vary with the number of water molecules present, and has been taken as the standard for the comparison of intensities.

The line patterns from the other samples had the same relative intensities, but the unit cell dimension was found to vary. Corresponding to the progressive replacement of hydroxyl by fluorine ions, which have smaller ionic radius, the lattice constant decreased regularly with increasing fluorine content as shown in Table III.

TABLE III

VARIATION OF LATTICE CONSTANT WITH FLUORINE CONTENT

Sample	Ratio F:Al	Lattice constant	
1	0.40	..	Diffuse haloes only
2	0.70	9.85	Diffuse haloes present
3	1.02	9.84	Diffuse haloes present
4	1.65	9.83	
5	1.75	9.81	
6	1.96	9.77	Lines broader
7	2.07	9.77	Lines broader

Effect of Ignition on Basic Fluorides.—Samples were weighed into platinum crucibles and heated for three hours in an electric furnace at temperatures ranging from 200 to 600°. Material ignited at 300° or more was gritty and hygroscopic, sample 6 regaining more than half the weight lost at 300°, when exposed to the air for three days. The hygroscopicity was less marked in samples ignited at 500–600°.

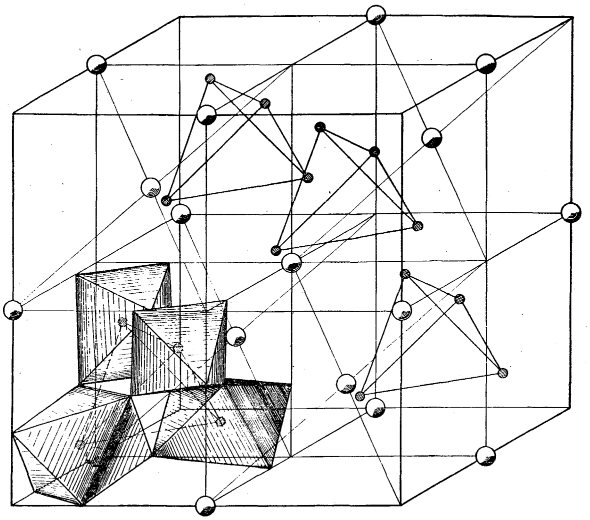


Fig. 1.—Unit cell of aluminum hydroxyfluoride containing 16 $Al(F,OH)_3 \cdot 6H_2O$: ●, aluminum; ◒, water (only 6 of the 8 sites per unit cell shown are occupied by water molecules); fluorine or hydroxyl ions occupy the corners of the octahedra surrounding the aluminium ions, as shown in only one octant of the unit cube.

At 600°, the basic fluoride pattern of sample 6 was replaced by lines due to fluorides and oxides of aluminum. Ignition at 300, 400 and 500° gave basic fluoride patterns showing a progressive decrease in lattice constant (Table IV) and a progressive variation in relative intensities of the lines. In particular the *220* line became visible and increased in intensity. The observed intensity variations follow closely those of the intensities calculated for the removal of the six water molecules from the lattice. The observed intensities for sample 6 heated to 500° are compared in Table II with those calculated for a structure in which no water molecules remain. The number of molecules of water remaining, corresponding to the intensity distribution at each stage of the heating, is given in the third column of Table IV.

TABLE IV

PROPERTIES OF IGNITED BASIC FLUORIDES

Sample	Lattice constant	Molecules of water/ unit cell	Ignition loss Calcd., %	Ignition loss Actual %
3 unheated	9.84	6		
3 heated 400°	9.65	0	14.7	28.9
6 unheated	9.77	6		
6 heated 300°	9.72	5	14.6	19.6
6 heated 400°	9.65	2	18.0	23.7
6 heated 500°	9.63	0	20.2	25.5

Discussion

In the introductory remarks, it was stated that aluminum might form either the hydroxyfluorides $AlF(OH)_2$ and $AlF_2(OH)$, or the corresponding oxyfluorides AlFO and $(AlF_2)_2O$, when solutions containing the complex cations AlF^{++} and AlF_2^+ were treated with ammonia. X-Ray diffraction studies support this view, but the ionic radii of fluorine and hydroxyl ions are so similar that the same crystal structure serves for the range of composition from $AlF(OH)_2$ to AlF_2OH. The small decrease in lattice constant, as the proportion of fluorine increases, is not only incompatible with an oxyfluoride structure but also shows that the samples do not merely consist of mixtures of aluminum hydroxide or fluoride with a single hydroxyfluoride of constant composition. Assuming that the ionic radii of the oxygen and fluorine ions in the hydroxyfluoride structure are in the same ratio as those given by Pauling[8] for a sodium chloride-type structure, the decrease in unit cell dimension is calculated as 0.7% for a change in composition from $AlF(OH)_2$ to $AlF_2(OH)$. The observed decrease of 0.8% is in good agreement with this figure. (The ionic radius of hydroxyl ion is only slightly greater than that of oxygen ion.[9])

It is improbable that cations containing more fluorine than AlF_2^+, or less than AlF^{++}, exist in solution to any important extent, and the range of hydroxyfluoride compositions is consequently confined to the limits given above. Despite numerous attempts to prepare samples with a F:Al ratio significantly greater than 2:1, the highest value obtained was 2.07:1 (sample 7) and this is almost certainly due to the presence of small quantities of aluminum fluoride. Samples 1 and 2 contain a smaller proportion of fluorine than $AlF(OH)_2$, but are contaminated with considerable amounts of aluminum hydroxide, the presence of which is revealed not only by the X-ray diffraction data (Table III) but also by the much smaller water content of these samples when compared with purer basic fluorides (nos. 4–7).

Dehydration of the hydroxyfluorides might be expected to yield oxyfluorides which would obviously differ in structure with variation in their fluorine content. Samples 3 and 6 were chosen for investigation because simple dehydration would produce AlFO and $(AlF_2)_2O$, respectively, but, even at 500°, the hydroxyfluoride structure was retained. At higher temperatures, decomposition to aluminum fluoride and oxide occurred and no evidence was obtained for the formation of distinct oxyfluoride structures. It is of interest to note that fluorine may be completely removed from ignited hydroxyfluorides by the Willard–Winter distillation, using 55% sulfuric acid, but that, once decomposition has occurred, only a small fraction of the fluorine can be released by this method.

The loss of weight of hydroxyfluorides was found to increase smoothly with temperature up to 500° and no distinction could be made between loss of loosely-combined water, crystal water (*i. e.*, 6 moles per unit cell) and water derived from the conversion of hydroxyl to oxygen ions. The latter process might be expected to result in the formation of oxyfluorides, but the hydroxyfluoride structure was retained in sample 3 when slightly more than 50% of the hydroxyl groups were thus decomposed. Table IV shows the actual ignition losses at various temperatures, compared with the losses calculated on the basis that hydroxyl ions were undisturbed and that crystal water was lost in amounts determined from the change in intensities of the lines of the diffraction patterns. It is evident that conversion of hydroxyl to oxygen ions must occur simultaneously with loss of crystal water at all temperatures from 300–500°. This would not have any great effect upon the X-ray line intensities.

Two factors combine to increase the calculated ignition losses given in Table IV. As with most hydrated fluorides, thermal hydrolysis occurs during ignition, resulting in loss of hydrogen fluoride instead of water, but it is unlikely that more than 10% of the fluorine is lost in this fashion, even at 500°. The corresponding increase in the calculated ignition loss is 1 to 2%. The second factor depends on the presence of aluminum hydroxide in samples 1, 2 and 3, as demonstrated by the diffraction patterns. Assuming that this contaminant is present to the extent of 25% and decomposes to γ-Al_2O_3 at 400°, the calculated ignition loss of sample 3 would be increased by a further 8%. Consideration of these two factors makes it possible to substitute a figure of 24% for that of 14.7% for the calculated ignition loss of sample 3 at 400° as given in Table IV. This brings the behavior of sample 3 more into line with that of sample 6, but still requires the destruction of at least 50% of the hydroxyl groups.

In the hydroxyfluoride structure derived above it was shown that the hydroxyl or fluorine ions formed regular octahedra about the aluminum ions. In both the fluoride and hydroxide there is a similar arrangement of ions except that the octahedra in these two cases are distorted. It may be concluded that the value of the radius of the negative ion which allows the six negative ions to surround the aluminum ion so that they just touch each other, lies between the values for the hydroxyl and fluorine ions. Thus groups of four hydroxyl and two fluorine, or two hydroxyl and four fluorine could be fitted about aluminum ions to give very nearly regular octahedra, whereas groups of either six fluorine or six hydroxyl would lead to deformation of the octahedra.

From the Al–F distance of 1.84 Å., the ionic radii are found to be 0.54 Å. for Al^{3+} and 1.30 Å. for the negative ions. This value for Al^{3+} lies between the values 0.57 Å., given by Goldschmidt,[10] and 0.50 Å., given by Pauling,[8] for coördination number 6. For oxygen and fluorine ions with the same coördination number, Goldschmidt gave 1.32 and 1.33 Å., and Pauling 1.40 and 1.36 Å., respectively, for the ionic radii.

---

[8] Pauling, THIS JOURNAL, **49**, 765 (1927).

[9] W. H. and W. L. Bragg, "The Crystalline State," G. Bell and Sons, London, 1933, p. 122.

[10] Goldschmidt, *Trans. Faraday Soc.*, **25**, 253 (1929).

The above value for the negative ions is lower than these, as would be expected from the lower value of the coördination number occurring in this structure.

Conclusions

The treatment of mixed solutions of aluminum fluoride and sulfate with ammonia produces hydroxyfluorides falling within the range of composition $AlF(OH)_2$ to $AlF_2(OH)$. These compounds are cubic with space group O_h^7-Fd3m. The lattice constant decreases with increasing fluorine content from 9.85 to 9.77 Å. The unit cell contains sixteen formula-groups plus six water molecules.

The hydroxyfluoride structure is stable up to 500°, the gradual loss of water being reflected by a corresponding contraction of the lattice. The remarkable stability of the lattice is demonstrated by the retention of the structure despite the destruction of more than half the hydroxyl groups at high temperatures. At 600°, the hydroxyfluoride structure is no longer evident. No oxyfluorides are formed, the hydroxyfluorides decomposing directly to aluminum oxide and fluoride.

MELBOURNE, AUSTRALIA RECEIVED MARCH 24, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

The Aqueous Ionization Constants of Inorganic Oxygen Acids

BY JOHN E. RICCI

It is presumably possible to determine independently the formulas, structures and aqueous ionization constants of inorganic acids. The data so obtained may then be correlated either empirically or on the basis of theories of molecular structure and of the process of ionization in solution, in which case the results of the comparison may serve as a test of the theories. A remarkably successful correlation has been obtained by Kossiakoff and Harker, in a paper on "The Calculation of Ionization Constants of Inorganic Oxygen Acids from their Structures,"[1] and the results have been interpreted as supporting the mechanism proposed as the basis of the calculation.[2] The purpose of this paper is to examine critically the treatment and results of Kossiakoff and Harker, and to determine which of their assumptions are supported by their calculations.

Kossiakoff and Harker assume (1) that the ionization constant of an oxygen acid is defined by the free energy of transfer of a proton from a hydroxyl group to the surrounding water structure, and (2) that this energy, in electrostatic terms, depends on (a) the formal charge of the central atom of the acid, (b) the number of non-hydroxyl oxygen atoms in the acid ion available for attachment of a proton, (c) the number of equivalent hydrogens available for "dissociation," and (d) the structure of the acid as determined by crystallographic data on its salts.[3]

We shall see that the first and main assumption is not effectively tested by the treatment of Kossiakoff and Harker, and that the test of 2(c) and 2(d) is entirely inconclusive, but that the assumptions 2(a) and 2(b) are effective and lead to very enlightening empirical correlations.

I. Calculations of Kossiakoff and Harker

The general expression used by Kossiakoff and Harker for the free energy change fixing a particular ionization constant is

$$\Delta F = \sum W_i - C + RT \ln n_O/n_H \qquad (1)$$

Here C is a solvent constant, n_O is the number of equivalent non-hydroxyl oxygens in the ion being formed, n_H is the number of equivalent (transferable) hydrogens in the acid, and W_i is the electrostatic energy of a single transfer. Furthermore

$$W_i = \sum_j \frac{m_j e}{\epsilon}\left(\frac{1}{r_j} - \frac{1}{r_j'}\right) \qquad (2)$$

in which $r_j' - r_j$ is the displacement of the proton relative to the j'th atom of the solute particle, whose formal charge is m_j; e is the charge of the electron and ϵ the dielectric constant of the medium. The formal charge of an atom is its group number in the periodic table minus the number of electrons in its valence shell, a shared pair being counted as one.

For the evaluation of C, Kossiakoff and Harker chose K_1 of orthophosphoric acid H_3PO_4(pK_1 = 2.1, ΔF = 2.9) as reference; from structural data they calculated ΣW_i = 46.1. For this calculation, the first term of ΣW_i, or the term for the first transfer, from hydroxyl to adjacent water molecule, was taken as

$$W_1 = \frac{e^2}{\epsilon}\left[\left(\frac{1}{R} - \frac{1}{R'}\right) - \left(\frac{1}{\rho} - \frac{1}{\rho'}\right) + \left(\frac{1}{d} - \frac{1}{d'}\right)\right] \qquad (3)$$

in which $R' - R$ is the absolute displacement of the proton (R being the original O—H distance), ρ'-ρ its displacement relative to the central atom, phosphorus (with m = +1), and d'-d its displace-

---

[1] A. Kossiakoff and D. Harker, THIS JOURNAL, **60**, 2047 (1938).

[2] For a discussion of their method and results, see O. K. Rice, "Electronic Structure and Chemical Binding," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 429–438.

[3] "Structure" refers not to the formula but to the physical quantities of bond angles and interatomic distances. A formula such as $Ge(OH)_4$, graphical or otherwise, is the result of chemical and analytical reasoning, independent of the physical determination of the structure of the substance.

ment relative to each (here only 1) non-hydroxyl oxygen (with $m = -1$) of the acid.

The distances R and R' are assumed to be constant for all oxygen acids in water, in all subsequent calculations. It will therefore be useful at this point to re-write equation (3) in the form

$$W_1 = W_0 + mf(\rho) + nf(\mathrm{d}) \qquad (4)$$

in which m is the formal charge of the central atom and n the number of non-hydroxyl oxygens of the acid. In the case of orthophosphoric acid, the values of these terms were

$$W_1 = 52.4 - 12.4 + 4.9 = 44.9 \text{ kcal.} \qquad (5)$$

The remaining terms of ΣW_i amounted to only 1.2, giving $\Sigma W_i = 46.1$. Now with $RT \ln n_0/n_\mathrm{H} = -0.2$, $C = 46.1 - 2.9 - 0.2 = 43.0$ kcal. This value of C was then used in equation (1) to calculate the twenty-six other ionization constants, for acids with "non-resonating" structures (this excludes those of the first row elements: B,C,N). For the purpose of the calculation, the authors furthermore pointed out that since the difference, $\Sigma W_i - W_1$, ($\cong 1.2$ for orthophosphoric acid) is expected to be equally small and nearly constant for all the other acids to be considered, this quantity may be combined with the constant C, so that C_1 (to be used with W_1 alone) $= C - 1.2 = 41.9$. In other words, instead of equation (1) we may write, with negligible error

$$\Delta F = W_1 - C_1 + RT \ln n_0/n_\mathrm{H} \qquad (6)$$

The over-all average deviation between observed and calculated log K, for these twenty-six calculations, was 0.89.[4] According to Kossiakoff and Harker, "The quantities calculated represent differences between large numbers (presumably meaning ΣW_i and C, or W_1 and C_1), making the resulting agreement all the more encouraging." The agreement is then taken as supporting the assumptions involved in calculating ΣW_i and through it C, and specifically the electrostatic theory of the work of separating a proton from the hydroxyl group to the first water molecule through the immediate distance R'-R.[5]

II. Criticism and Discussion

Since R and R' are assumed to be the same for all oxygen acids in water, and since C_1 is a solvent constant, then writing k for $W_0 - C_1$, and combining (4) and (6), we have

$$\Delta F = k + mf(\rho) + nf(\mathrm{d}) + RT \ln n_0/n_\mathrm{H} \qquad (7)$$

With orthophosphoric acid as reference (*i.e.*, using its K_1), k has the value 10.5. The calculation of the other twenty-six ionization constants then involves this reference constant k, or the constant difference $W_0 - C_1$, but never the supposed actual values of W_0 and C_1 separately. For the purpose of the calculation of the other twenty-six constants it was in fact not necessary at all to derive or state separate values of the quantities $W_0 - C$. The actual "solvent constant" is the difference $W_0 - C$, and at no point do the subsequent calculations and comparisons test the separate values of W_0 and C. The whole set of calculations is then practically, if not completely, independent of the assumptions concerning the distances R and R', once it is assumed that W_0 and C are constants for all oxygen acids in water. Perhaps it should be pointed out, too, that even if the comparisons had succeeded in verifying the separate values of W_0 and C, the result would probably be equally explainable either as a transfer of proton from solute to solvent (according to the modern or Brönsted picture) or as a transfer of hydroxyl from solvent to solute, (as suggested some time ago by Werner[6]), giving rise in either case to a negative solute ion.

Furthermore, W_0 is by far the largest term in equations (4) and (5). When it is realized that the difference between the two largest quantities of equation (6), namely, $W_0 - C_1$, is a constant in all the calculations, the final agreement between calculated and observed ionization constants is perhaps no longer very impressive. The over-all agreement is nevertheless sufficient to suggest that at least the difference, $W_0 - C_1$, has been verified, as a fundamental constant for oxygen acids in water. But even this conclusion may be questioned. As a purely mathematical problem, it would seem that the best determination of the solvent constant, k (or $W_0 - C_1$), from equation (7), would be through the known first ionization constant (and hence ΔF) of what may be called a "true ortho-acid," for which both m and $n = 0$.[7] For an acid of this class, with the formula H_aMO_a, in other words, we have

$$k = (W_0 - C_1) = \Delta F + RT \ln \mathrm{a} \qquad (8)$$

presumably requiring no information about structure, but only knowledge of its formula. In the list of acids considered by Kossiakoff and Harker, hypochlorous acid is the only acid believed beforehand to be a true ortho-acid; it gives $k = 10.0$,[8] in close agreement with the value 10.5 from ortho phosphoric acid. Three other acids, of doubtful formula beforehand, are classified as true ortho-acids on the basis of the calculated constants; these are H_3AsO_3, H_4GeO_4 and H_6TeO_6. But these give $k = 13.3$, 12.7 and 11.0, respectively.

---

(4) Based on observed values as listed in ref. 2 itself; relative to values listed below (Table I), the deviation is hardly changed, being 0.91.

(5) In ref. 2, O. K. Rice states that the calculations give a "remarkable check" and discusses the "reasonableness" of the value of C (and hence by implication, of W_0 and of the distances R and R') given by the method.

(6) Alfred Werner's ideas on this subject, in "Neuere Anschauungen auf dem Gebiete der anorganischen Chemie," and *Z. anorg. Chem.*, **3**, 267 (1893), and **15**, 1 (1897), are rarely mentioned. They are presented (but with disapproval) in P. Walden's book, "Salts, Acids and Bases," McGraw-Hill Book Company, New York, N. Y., 1929, p. 118–120.

(7) A true ortho-acid has the formula $M(OH)_a$, or H_aMO_a; as a result the formal charge on the central atom is always zero, and n, the number of non-hydroxyl oxygens, is also zero.

(8) Ionization constants used in the present discussion are listed below, in Table I, where sources are also stated.

Hypobromous and hypoiodous acids, not mentioned by Kossiakoff and Harker, give $k = 12.0$ and 15.2, respectively. Altogether this is a rather large range for what is presumably a fundamental constant not involving the functions $f(\rho)$ and $f(d)$ of equation (7) at all for its determination; this is so even if we disregard hypoiodous acid, here and later, because of the uncertainty about its ionization constant.[9]

It must be noted clearly that in the case of true ortho-acids, the calculation of Kossiakoff and Harker does not involve their structures at all. Despite the title of their paper, the calculations for HClO, H_3AsO_3, H_4GeO_4 and H_6TeO_6, as ortho-acids, involved nothing more than their written formulas.[10] If the fundamental assumptions for the application of equation (7) are correct, and $W_0 - C_1$ is a constant, then according to equation (8) all these ortho-acids should have values of K_1 identical except for the small differences due to the term $-RT \ln a$. The actual great variation, even in so close a series as the hypohalous acids, which should on this basis have identical ionization constants, suggests that the equation is overlooking some fundamental difference in the properties (perhaps in what may be called the property of "acidity," or the electronegativity) of the central atom. The nature of the central atom, M, presumably affects the calculation through the effect on the M–O distances (and the angles between the oxygens) in the structure of the acid, and hence through the second and third terms of equation (7). But even this effect is assumed to disappear entirely in the ortho-acids, since there is no formal charge on either the M or the oxygens of the acid. While the calculated K_1 for H_4GeO_4, in other words, agrees with the observed value, the identical value would be calculated for any other acid of the general formula H_4MO_4 or H_aMO_a, which is probably not to be expected in reality.

One may of course attribute the variation among these ortho-acids to incorrect assignment of their formulas in some cases, although this is hardly likely for hypobromous acid (and hypoiodous acid). Moreover, the agreement for the four ortho-acids in Kossiakoff and Harker's list already involves a choice of formula for all but hypochlorous acid, to give the agreement.

This insensitivity to the nature of the central atom in the case of true ortho-acids suggests that an equation like (7) is essentially only a semi-empirical equation concerned with the relative effects of the formal charge on the central atom (m) and of the number of oxygens, in a given series of acids. Most of the examples in Kossiakoff and Harker's list are acids with $m = 1$. For higher values of m the strengths become so high that reliable data are not in general available. At any rate there are hardly two acids in the list with $m > 1$, having formulas and structures similar enough for a clear check on the effect of the secondary variables (n and $f(d)$). Of the twenty-seven acids: four are ortho ($m = 0$); seventeen are the molecules and ions of seven acids with $m = +1$ and n varying from 1 to 3 depending on the charge on the acid; four are the molecule and ions of $H_4P_2O_7$, a special case with two central atoms each having $m = 1$; and the remaining two are HIO_3 ($m = 2$, $n = 2$) and the bisulfate ion ($m = 2$, $n = 3$).

Now the remarkable thing, despite "the wide variation found in the ionization constants of acids" noted by Kossiakoff and Harker, is the striking simplicity and repetition of the values for the inorganic oxygen acids in water; this simplicity or grouping becomes apparent when the acids are classified according to their values of m and n. The actual pK's are then seen to be grouped in such a way as to suggest a (rough) linear dependence upon m and n without detailed dependence upon the structure (angles, M–O distances, etc.) of the acid. Nor is there, in fact, any systematic correlation between the deviations found by Kossiakoff and Harker (between observed and calculated constants) and relative changes of structure, to suggest, within the precision of the comparison, any dependence upon this structure (see Table II, below). This may be entirely the fault of the inaccuracy and uncertainty of the observed values. But the fact remains that we may assume the functions, $f(\rho)$ and $f(d)$, of equation (7) to be constants for all the acids, and still obtain as good an over-all average agreement between calculated and observed constants, as was obtained by the laborious calculations of Kossiakoff and Harker. The precision of their comparison is so low, for example, (and with no trend) that the average error is greater than the average value of the term, $RT \ln n_O/n_H$, so that even the sign of this particular effect is not being tested.

Assuming then that (whatever the length and angles of the M–O bonds) the effect of the formal charge, m, of the central atom is uniform and constant, and similarly that the effect of each non-hydroxyl oxygen is also constant, and incorporating in the constant k the term $RT \ln n_O/n_H$, we may test the following empirical expression

$$pK = 8.0 - m(9.0) + n(4.0) \qquad (9)$$

Here K is the acid ionization constant of the species H_aMO_b, whatever its net or total charge; m is the formal charge of M; $n = b - a$. The equation has been used to calculate not only the ionization constants of the twenty-seven species listed by Kossiakoff and Harker, but nine more in addition: $HGeO_3^-$ (or $H_3GeO_4^-$), $H_4IO_6^-$, H_3PO_2, $HSeO_4^-$, HBrO, $H_2S_2O_4$, $HS_2O_4^-$, $H_2P_2O_6^=$, $HP_2O_6^≡$. In applying equation (9) the acids

---

[9] See W. M. Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1938, p. 57.

[10] The calculated values of ΔF for HClO, H_3AsO_3, H_4GeO_4, H_6TeO_6, were 10.7, 10.1, 9.9, 9.6; corrected for the statistical factors of 0, −0.6, −0.8, −1.1, respectively, these are all 10.7. The M–O distances listed in Kossiakoff and Harker's paper for these acids (1.59, 1.66, 1.97 and 1.54 Å., respectively) do not enter the calculation at all.

$H_4P_2O_7$, $H_2S_2O_4$ and $H_4P_2O_6$, with $m = +1$ for each of the two central atoms, are treated as though the central complex were a single atom with $m = +2$. Phosphorous acid (dibasic) and hypophosphoric acid (monobasic) are treated as $H_2(PH)O_3$ and $H(PH_2)O_2$, respectively, the central complex having in each case the formal charge of $+1$. These assignments of total formal charge will be found to be in accord with the definition of formal charge already given. For the twenty-seven constants of Kossiakoff and Harker's list, the average deviation between observed and calculated values of log K (according to equation 9), is 0.93, while for the entire thirty-six constants the average deviation is 0.91.[11] Since this is as good as the result of the application of equation (1), using the structure of the acids, the implication is that either the data (ionization constants and structural information) or the assumptions required in the application of equation (1) are not fine enough for a significant test of the assumptions themselves.

It has already been pointed out that the first term of this equation, here the empirical constant 8.0, corresponding to $W_0 - C_1$, was likewise essentially an empirical constant in Kossiakoff and Harker's treatment. Their treatment, however, does apparently succeed in calculating the coefficients of the m and n terms of this expression, as determined, presumably, by the structural data. But since the resulting agreement was not better than that obtained through equation (9), it may be concluded that the theory can predict the rough value of these coefficients but not their detailed dependence upon structure, and that the most that may be deduced is a roughly constant dependence merely on the values of the parameters m and n.

III. Similarity of Ionization Constants for Inorganic Oxygen Acids

Equation (9), although tested indiscriminately on all the thirty-six available (and presumably dependable) ionization constants, is of course not to be suggested as an actual formula for the ionization constant of any oxygen acid in water. It is useful primarily because it suggests certain regularities in the values of the ionization constants. According to such a formula the values of the ionization constants of oxygen acids should fall into groups represented by the various possible combinations of m and n. These classes are listed in Table I, which shows the individual acids and their ionization constants, falling in various classifications.

TABLE I

CLASSIFICATION OF THE CONSTANTS[a]

Class	Example	pK_1	pK_2	pK_3	pK_4
$m = 0$		$(n = 0)$	$(n = 1)$		
	H_4GeO_4	8.6	12.7		
	H_3AsO_3	9.2			
	H_6TeO_6	(6.2; 8.8)[b]	10.4[c]		
	$HClO$	7.2			
	$HBrO$	8.7			
	(HIO)	(11.0)			
$m = 1$		$(n = 1)$	$(n = 2)$	$(n = 3)$	
	H_3PO_4	2.1	7.2	12.0	
	H_3PO_3	1.8	6.2		
	H_3PO_2	2.0			
	H_3AsO_4	2.3	7.0	13.0	
	H_2SO_3	1.9	7.0		
	H_2SeO_3	2.6[d]	8.3[d]		
	H_2TeO_3	2.7	8.0		
	$HClO_2$	2.0			
	H_5IO_6	1.6	6.0		
$m = 2$		$(n = 2)$	$(n = 3)$	$(n = 4)$	$(n = 5)$
	H_2SO_4		1.9		
	H_2SeO_4		2.0		
	HIO_3	0.8[e]			
	$H_4P_2O_7$[f]	.9	2.0	6.7	9.4
	$H_4P_2O_6$[g]	(2.2)[g]	(2.8)	7.3	10.0
	$H_2S_2O_4$	0.3	2.5		

[a] With the exceptions noted, these values are taken from Latimer, ref. 9. [b] D. M. Yost and H. Russell, "Systematic Inorganic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1944, p. 351. The value 6.2, from Blanc, *J. chim. phys.*, 18, 28 (1920); the value 8.8, from Rosenhaim and Janders, *Kolloid Z.*, 22, 23 (1918). [c] From Blanc, referred to in [b]. [d] Yost and Russell, p. 331. [e] Ricci and Naidich, THIS JOURNAL, 61, 3268 (1939). [f] Yost and Russell, p. 228. [g] Yost and Russell, p. 206. The first and second constants of $H_4P_2O_6$, like that of HIO, were not included in testing equation 9. About hypophosphoric acid, Yost and Russell state (p. 207) that the data are unsatisfactory, and that "no definite statement about the ionization constants K_1 and K_2 can be safely made yet."

The group with $m = 1$ is the most complete and most uniform. The un-ionized forms of these acids are all assigned the formula $H_aMO_{(a+1)}$, and all have approximately the same values of the ionization constants, given by the expression, $pK = 2.1 + (n - 1)(4.9)$, with $n = 1, 2, 3$ for K_1, K_2, K_3, respectively. In other words, the experimental values of the pK's for this class, if they are significant, show a surprising independence from structural characteristics, despite a range, in fact, of M–O distance, from 1.50–1.54 for H_2SO_3, H_3PO_4, H_3PO_3, $HClO_2$, through 1.66 for H_3AsO_4, 1.73 for H_2SeO_3, 1.84 for H_2TeO_3 to 1.93 Å. for H_5IO_6.[12] The calculations of Kossiakoff and Harker, involving the structures, do not even reproduce the order of the slight differences between each acid and the reference acid, orthophosphoric acid; this is shown in Table II. (The acids listed

TABLE II

COMPARISON WITH H_3PO_4

Acid	($pK_1 = 2.1$) Obs.	($pK_1 = 2.1$) Calcd., K. and H.	($pK_2 = 7.2$) Obs.	($pK_2 = 7.2$) Calcd., K. and H.
H_3PO_3	−0.3	+0.2	−0.7	−0.5
H_3AsO_4	+ .2	+ .4	− .2	−1.0
H_2SO_3	− .2	+ .2	− .4	− .2
H_2SeO_3	+ .4	+ .8	+1.0	− .9
H_2TeO_3	+ .5	+1.0	+ .7	− .9
$HClO_2$	− .1	+0.5		
H_5IO_6	− .5	+ .8		

---

(11) In terms of root mean square deviation, or $\sqrt{\Sigma\Delta^2/N}$, the deviation is 1.03 in the calculations of Kossiakoff and Harker's paper (relative to their own listed observed values, and 1.11 relative to the observed values listed here in Table I (26 constants). For the 36 constants tested through equation 9, the root mean square deviation is 1.16.

(12) Quoted from ref. 1.

with $m = 2$ are not so comparable among themselves; they furthermore involve much more uncertainty both as to structures and as to values of ionization constants.)

The similarities in Table I are both surprising and instructive. The acids here listed in the class $m = 1$, for example, are usually considered as unrelated, and if related, they are usually thought of as having widely different ionization constants, for the reason that they have never (to the writer's knowledge)[13] been grouped together in this fashion to bring out both the uniformity of their strengths and the similarity of constitution underlying this uniformity. The similarity is simply that the formal charge on the central atom is the same, and this seems to be the controlling factor for the aqueous ionization constant despite the variety of the elements represented, of their oxidation states and of the (analytical) formulas of the acids. The similarity of the first ionization constants of H_3PO_4, H_3PO_3 and H_3PO_2 has been noted by Yost and Russell (Table I, ref. [b], p. 193), who remark that these are "unlike other series of acids (H_2SO_3, H_2SO_4, for example)." But H_2SO_4 (with $m = 2$, $n = 2$) and H_2SO_3 (with $m = 1$, $n = 1$) would not be expected to have similar values of K_1 at all, while the three phosphorus acids would, from this point of view, which may therefore be a useful one for correlation and systematization in general.

At any rate there may be a significant suggestion in the simplicity and uniformity of the ionization constants as arranged in Table I, that whatever the process of ionization may be in water solution, it is much less dependent upon the structure and constitution of the acid—as these are currently pictured, at least—than one would have expected. One wonders to what extent our ideas of these "structures" may be at fault, being possibly preconceived upon the assumption that the structure of the acid is the same as that of its salt, an apparently necessary consequence of the customary but arbitrary definition that an "acid" is something which "dissociates" in water solution to "give off" a proton; that an oxygen acid, in other words, is of necessity a hydrogen compound to begin with, whether we use the Arrhenius or the thermodynamically equivalent Brönsted point of view.

It is possible that a concept of ionization through coördination, more or less as originally suggested by Werner,[6] amounting to capture of hydroxyl ion and capture of proton as the acid and base ionization processes, respectively, might be developed, in which the emphasis would be laid upon the coördination requirements of the actual solute itself (SO_3) and not upon the structure of its ion ($SO_4^{=}$ or HSO_4^-) in its salts, as the determining factor for the ionization constant.

Summary

Critical examination of theoretical calculations of the aqueous ionization constants of inorganic oxygen acids shows that the treatment does not constitute a test of the fundamental assumption of a proton transfer from solute to solvent. An empirical correlation and grouping of these ionization constants based on the formal charge of the central atom and the number of non-hydroxyl oxygens in the acid, is presented. This grouping, apparently independent of the supposed "structures" of the acids, may indicate the need of a different picture of the process of ionization.

NEW YORK, N. Y. RECEIVED JANUARY 18, 194

[13] The referee examining this paper kindly brought to the author's attention a book entitled "General Chemistry," by Linus Pauling (Edward Bros., Inc., Ann Arbor, Michigan, 1944), presenting a classification of ionization constants, based on coördination, which is in several respects similar to that in Table I.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NANKING]

The Influence of Dipolar Ions on the Solubility of Some Sparingly Soluble Salts

BY FANG-HSUIN LEE AND LI-KWON LUH

The interionic attraction theory applied to dipolar ions and real ions in solution has been formulated by Scatchard and Kirkwood.[1,2] This theory has been supported chiefly by experiments of Cohn.[3] Although much work has been done in finding the effect of varying the concentration of salts on the activity of amino acids, only few experiments have been done on influence of amino acids on the activity of salts. Solubility, f. p. and e. m. f. were the method chiefly used for the latter purpose. Among the amino acids glycine was the one most commonly used. The salts studied by previous workers are $NaCl$,[4,5] KCl,[6] $TlCl$,[4,7] $CaCl_2$,[4] $AgIO_3$,[8] $TlIO_3$,[9] $Ba(BrO_3)_2$,[8] $ZnCl_2$,[4] $Ca(IO_3)_2$[8] and $Pb(IO_3)_2$.[8]

According to Kirkwood, the solubility, S, of a sparingly soluble salt is related to the molality, m, of amino acid by the simplified experimental equation

$$\log S/S_0 = K(Z_+ \cdot Z_-/2)m \qquad (1)$$

---

[1] J. G. Kirkwood, *J. Chem. Phys.*, **2**, 351 (1934); *Chem. Rev.*, **19**, 275 (1936).

[2] G. Scatchard and J. G. Kirkwood, *Physik.*, 2, **33**, 297 (1932).

[3] E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides." Reinhold Publishing Corp., New York, N. Y., 1943.

[4] N. R. Joseph, *J. Biol. Chem.*, **111**, 489 (1935).

[5] G. Scatchard and S. S. Prentiss, THIS JOURNAL, **56**, 1486 and 2314 (1934).

[6] R. M. Roberts and Kirkwood, *ibid.*, **63**, 1373 (1941).

[7] C. F. Failey, *ibid.*, **54**, 576 (1932).

[8] R. M. Keefer, H. C. Reiber and C. S. Bisson, *ibid.*, **62**, 2951 (1940); **63**, 689 (1941).

[9] C. F. Failey, *ibid.*, **55**, 4374 (1933).

where Z_+ and Z_- are the valences of the ions and K is a constant which is a function of radius of the dipolar ion and the sum of the mean radius of real ions and that of the dipolar ion. Although K varies to some degree from salt to salt, the slope of (log S) against m of salts of different valence types should bear approximately a relation with their valence. The above-mentioned list indicates that the salts are limited to 1-1 and 2-1 types only. In this present work, study was extended to 2-2 type salt with 1-1 type salt as reference. Thallium chloride and calcium sulfate were thus chosen and their solubilities determined in presence of glycine ranging from 0-1 molal.

Experimental

As to the chemicals used in this experiment, glycine was from Paul Lewis Laboratories and calcium sulfate from Merck Co. Thallium chloride was prepared from pure thallium sulfate. They were recrystallized twice.

For each solubility determination, a glycine solution of a certain known concentration was prepared. The solution was put in a Pyrex container to which an excess of salt was added. The solutions were shaken mechanically for six hours in a thermostat kept at 25.0 ± 0.1°. It has been found that saturation was reached during the time. The solution was then analyzed gravimetrically.

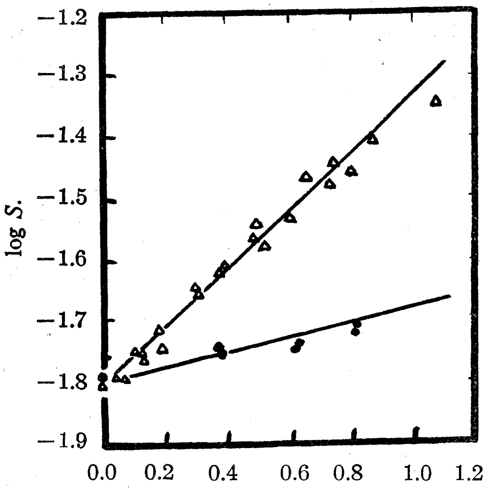


Fig. 1.—△, $CaSO_4$; ⊙, TlCl.

Results

TABLE I

I. Solubility of Thallium Chloride

Glycine, m	Solubility of TlCl (m)	− log S
0.0000	0.01594	1.798
.3619	.01798	1.745
.3849	.01777	1.750
.6060	.01788	1.748
.6169	.01820	1.740
.7978	.01913	1.718
.8008	.01953	1.709

II. Solubility of Calcium Sulfate

	Solubility of $CaSO_4$ (m)	
0.0000	0.01570	1.804
.0418	.01628	1.788
.0608	.01627	1.786
.1260	.01788	1.748
.1282	.01740	1.759
.1880	.01825	1.739
.3089	.02245	1.649
.3778	.02434	1.614
.4835	.02761	1.559
.5048	.02950	1.531
.6514	.03442	1.463
.7423	.03605	1.443
.8634	.03970	1.401
.0873	.04580	1.339
.1046	.01810	1.742
.1809	.01957	1.708
.2996	.02307	1.637
.3929	.02497	1.603
.5246	.02642	1.578
.6012	.02969	1.527
.7225	.03350	1.475
.7990	.03516	1.454

Discussion

The results collected in Table I are plotted in Fig. 1. It is seen that log S bears a linear relationship with m up to 1 m. The slope, $(\log S/S_0)/m$, represents $K(Z_+ \cdot Z_-/2)$ in the equation (1). These are 0.11 and 0.47 for thallium chloride and calcium sulfate, respectively. The constant K calculated from these values comes out to be 0.22 and 0.24 in the respective order. Although values of K in the literature vary somewhat in a considerable range, our values of K for thallium chloride and calcium sulfate (0.22 and 0.24) check very closely to that of thallium chloride by e. m. f. method (0.22) and of sodium chloride by both e. m. f. and f. p. methods (0.24).

Acknowledgment.—The authors are very grateful to Mrs. Dorothy M. Needham of the British Council Cultural Scientific Office for her interest in this work and kindness in supplying the chemicals during the war period while these experiments were performed. They wish also to express their thanks to Professor J. G. Kirkwood for discussing this problem.

Summary

1. The solubilities, S, of thallium chloride and calcium sulfate in glycine ranging from 0–1 m have been determined at 25°.

2. The slope of $(\log S)/m$ for thallium chloride and calcium sulfate are 0.11 and 0.47 bearing out an approximate ratio, 1:4, as required by theoretical equation.

NANKING, CHINA RECEIVED APRIL 1, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

The Structures of the Hydrides of Boron. VIII. Decaborane

BY GLORIA SILBIGER AND S. H. BAUER

In this paper we shall present an analysis of old and new electron diffraction data obtained on several hydrides of boron. The visual procedure will be used. Since the validity of the method has been questioned in the particular case of the hydrides of boron, we wish to state at the outset that although the various subjective factors have been discussed by several investigators,[1] differences of opinion regarding the "interpretations" of detailed features still remain. In any special case, judgment of these details ultimately lies with the individual. However, it is generally agreed that no spurious peaks or shoulders appear visually unless there are definite inflections in the computed curve.

Since it is so often overlooked, one other point needs emphasis. In equation (1) for the diffraction pattern produced by an assembly of atoms, atom form factors (which are a measure of their relative scattering power) and the distances between atomic centers appear. Were the data of high precision, sufficient to resolve these parameters perfectly, the deduced values would be uniquely interpretable, in most cases, in terms of a molecular structure. Unfortunately, that is far from being the case. Hence a statement to the effect that a model is excluded by the data means that within the limits of error imposed by the visual procedure, that particular location of atoms and closely similar configurations are excluded. To eliminate a given structure (wherein only the connexity between atoms is specified) one must eliminate individually models covering the entire range of interatomic distances and bond angles which seem at all plausible.

Decaborane

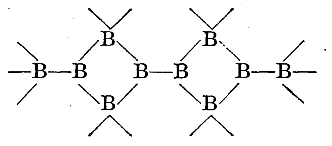
Decaborane, $B_{10}H_{14}$, is one of the most stable of the hydrides of boron. It is a colorless, well-crystallized solid at room temperature, and is formed as a product of decomposition of various boranes standing at room or elevated temperatures. It can be heated for considerable periods at 150° without observable change, but decomposition becomes noticeable at 170°.

A variety of structures have been proposed for decaborane. Möller[2] (1931) concluded from X-ray diffraction studies of single crystals that the space group is V_h^{21} with 8 molecules of $B_{10}H_{14}$ in the unit of dimensions

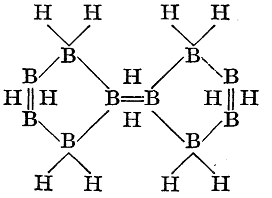
$$a = 14.46\ \text{Å}.;\qquad b = 20.85\ \text{Å}.;\qquad c = 5.69\ \text{Å}.$$

Assuming that in the solid the molecules are undissociated and similar in structure, he concludes that each molecule must have a minimum symmetry at C_2 or C_s. Möller states that C_i is also possible. However, if C_i is a minimum symmetry, the molecule must actually possess C_{2v} which is much higher than the minimum requirement of the space group. Much less reliable appear his conclusions that sub-units containing two molecules, with the dimensions $10.43 \times 7.23 \times 5.69$ Å. and possessing the symmetry V, C_{2h} or C_{2v}, are present in the crystal. Formally, it is possible to arrange the eight $B_{10}H_{14}$ units in four groups of two, each pair being disposed about a point in the lattice in such a manner that this pair exhibits the symmetry V, C_{2h} or C_{2v}. However, Möller's conclusion that these pairs are contiguous and that the envelope circumscribing each pair is a rhombohedron with the dimensions 7.23, 10.43 and 5.69 Å. is unwarranted. If the latter is accepted, $B_{10}H_{14}$ must have a naphthalene-like or similar type of structure.

On the basis of the analogy in chemical stability of decaborane with the pentaborane B_5H_9 Pauling and Bauer[3] (1936) suggested the configuration for the former



In extending his theory of the "protonated double bond" to the various higher hydrides of boron, Pitzer[4] (1945) suggested the structure



In this Laboratory we diffracted electrons on the vapor of decaborane in the hope of eliminating some of the possibilities which have been suggested. In this we were only partly successful.

This electron diffraction study was performed on the equivalent of 8 cc. (STP) of the material, kindly furnished to us by Professor A. B. Burg, to whom we wish to express our sincerest appreciation. The sample, contaminated with mercury, was distilled under vacuum (all joints of the magnetic breaker kind) into a high temperature nozzle. Some fluffy brown material was left in the tube after distillation. The photographs were ob-

---

[1] (a) L. Pauling and L. O. Brockway, *J. Chem. Phys.*, **2**, 867 (1934); (b) L. R. Maxwell, S. B. Hendricks and V. M. Mosley, *J. Chem. Phys.*, **3**, 699 (1935); (c) V. Schomaker, private communication.

[2] H. Moller, *Z. Krist.*, **76**, 500 (1931).

[3] S. H. Bauer and L. Pauling, THIS JOURNAL, **58**, 2408 (1936).

[4] K. S. Pitzer, *ibid.*, **76**, 1136 (1945).

tained with the sample tube at 104–115° and the nozzle at 110–120°; these were recorded on Eastman Commercial plates. The intensity and s values estimated by the usual visual procedures are shown in Table I. Although not shown in the table, slight shoulders were observed to the right of the fourth maximum, and to the left of the sixth maximum.

TABLE I

Max.	Min.	I	s_0	Model J $s_{\text{calcd.}}/s_{\text{obs.}}$
2		10	2.693	(1.040)
	2	− 8	3.752	(0.973)
3		25	4.879	1.025
	3	−15	6.254	0.999
4		10	7.200	1.035
	4	− 5	9.612	1.028
5		3	11.234	1.006
	5	− 2	12.846	1.012
6		1	15.314	1.010

Final B-B$_{\text{av}}$, 1.80 ± 0.03 Å. Average 1.016
B-H$_{\text{av}}$, 1.29 ± 0.04 Å. Average deviation 0.011

Figure 1 shows the radial distribution curve calculated after Walter and Beach.[5] The maxima at 1.28 and 1.78 Å. are very likely due to the B–H and B–B bonded distance, respectively, while the one at 2.88 Å. can be attributed to the distance between boron atoms separated by another boron atom as in a chain or ring; the ratio (2.88/1.78) corresponds to a B–B–B bond angle of 108°. Due to the sharpness and intensity of the peak at 2.88 Å., we are able to eliminate models which do not have tetrahedrally bonded $_{\text{B}}\diagup^{\text{B}}\diagdown_{\text{B}}$ atoms or those which do not contain a pentagon structure with angles of 108°. Therefore the configuration including two-four membered rings of boron suggested by Bauer and Pauling[3] is eliminated. For the same reason we were able to eliminate the planar hexagon configurations proposed by Nekrasov[6] and later by Pitzer[4] as an alternate possibility. All other models considered involved enough angles near 108° to necessitate the computation of diffracted intensity curves. The following structures were considered

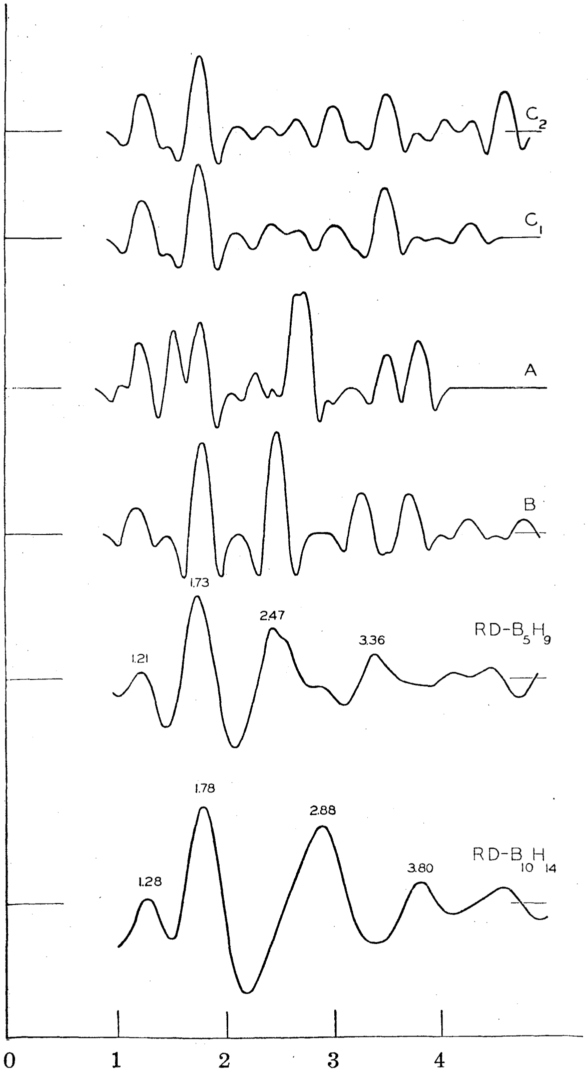
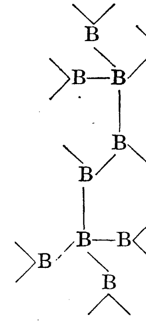


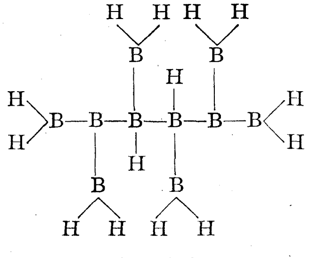
Fig. 1.—Radial distribution curves for B_5H_9 and $B_{10}H_{14}$. R. D. B_5H_9 and R. D. $B_{10}H_{14}$ were computed from diffraction data; A, B, C_1 and C_2 are "synthetic" for B_5H_9.

A. Branched chain



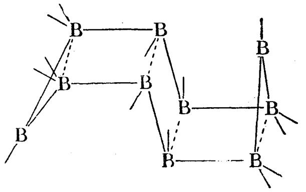
BH = 1.28 Å.
BB = 1.78 A.
All ∠'s 109°30′

B. Branched chain



BH = 1.28 A.
BB = 1.78 Å.
All ∠'s 109°30′

C. Ten membered ring



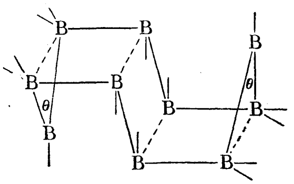
BH = 1.28 Å.
BB = 1.78 Å.
All ∠'s 109°30′

---

[5] J. Walter and J. Y. Beach, *J. Chem. Phys.*, **8**, 601 (1940).

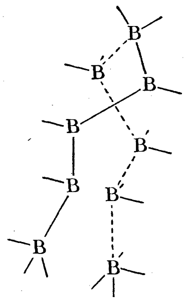
[6] B. V. Nekrasov, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 1021 (1940); **10**, 1156 (1940).

D. Ten membered ring

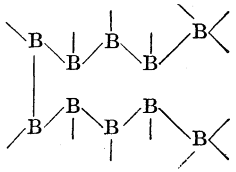


BH = 1.28 Å.
BB = 1.78 Å.
θ = 120°
All other ∠'s = 109°30′

E. Folded chain



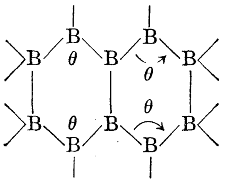
Top view



side view

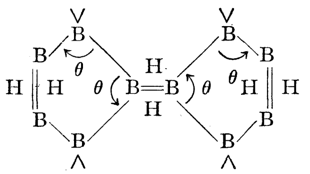
BH = 1.28 Å.
BB = 1.78 Å.
All ∠'s 109°30′

F. Puckered hexagons

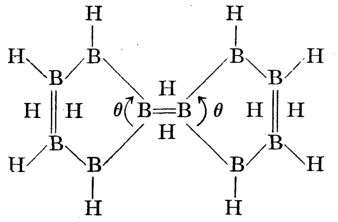


BH = 1.28 Å.
BB = 1.78 Å.
θ = 120°
All other ∠'s 109°30′

G_1. G_2. }Bridge pentagons

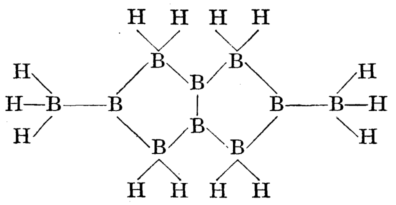


G_1 BH bridge = 1.39 Å.
BH = 1.18 Å.
B=B = 1.76 Å.
B—B = 1.82 Å.
θ = 107°



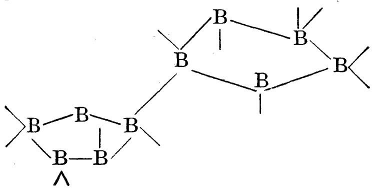
G_2 BH bridge = 1.39 Å.
BH = 1.25 Å.
B=B = 1.76 Å.
BB = 1.82 Å.
θ = 110°

H. Coplanar pentagons



BH = 1.28 Å.
BB = 1.78 Å.
∠'s in ring 108°
all others tetrahedral

J. Pentagons in parallel planes



BH = 1.28 Å.
BB = 1.78 Å.
regular pentagons
all other ∠'s 109°30′

In selecting the above models, we considered as many diverse types as we could picture; we assumed interatomic distances and disposed the hydrogen atoms in such a manner as to get "synthetic" R.D. curves which agree best with the

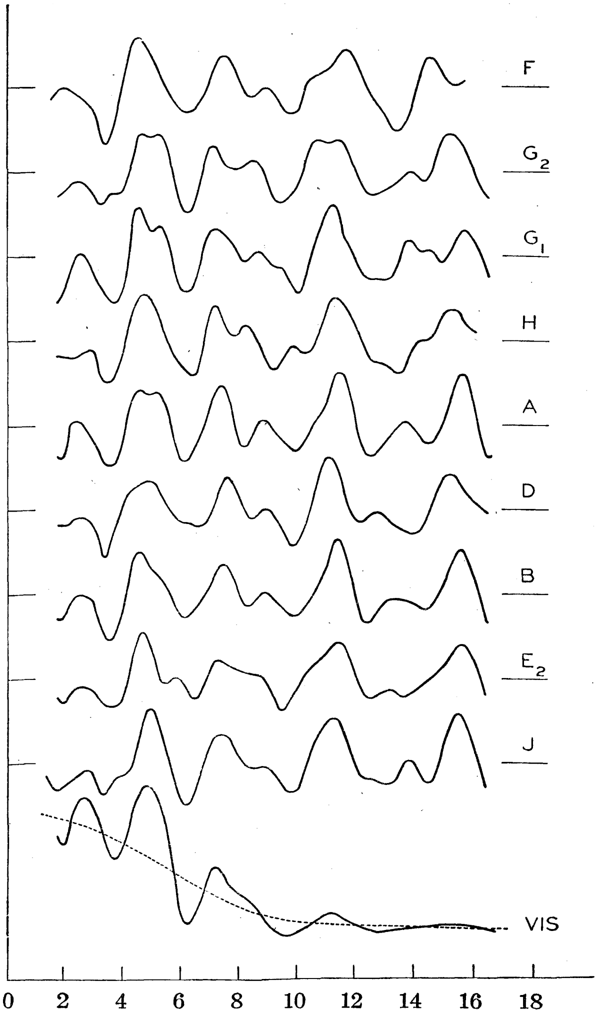


Fig. 2.—Intensity curves for $B_{10}H_{14}$.

R.D. computed from the data. After comparing the visually estimated diffraction pattern with those computed from the models (Fig. 2) using the equation

$$I(s) = \sum_{i}{}' \sum_{j}{}' (Z-F)_i (Z-F)_j \frac{\sin l_{ij}s}{l_{ij}s}{}^{7} \qquad (1)$$

we divided the group into three classes,

DEFINITELY ELIMINATED: A, F, G_1, G_2 and H
POSSIBLE: J, B, C, D and E
MOST PROBABLE: J

It is clear that G_1 and G_2 are eliminated because of the assymmetry introduced in the pentagons by the protonated double bonds. Of the structures considered "possible," we have been able to group only J, C, and D in pairs about a point so that each pair exhibits a symmetry V, C_{2h} or C_{2v} (Fig. 3). Apparently the bent chains, B and E, do not permit such symmetrical arrangements. The planar pentagon configurations (G_1, G_2, H) which were eliminated on the basis of the electron diffraction data could also be arranged to form a unit with V, C_{2h} or C_{2v} symmetry. Finally, although a coplanar pentagon configuration similar to J was not considered, it would fit the X-ray data and probably the E.D. data as well as does model J.

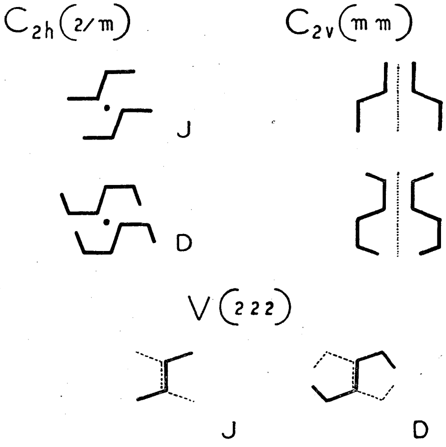
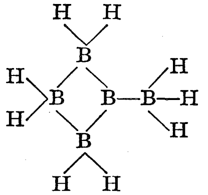


Fig. 3.—Arrangement of two molecules of the J and D configurations for decaborane so as to satisfy the symmetries suggested by Möller: C_{2h} (2/m)-plane of symmetry in plane of page; C_{2v} (m m)-planes of symmetry in plane of page and perpendicular to page at the dotted lines; V(222)-dotted line in plane parallel to that of page.

A careful study of the X-ray data and computations leading to a Fourier projection should permit the elimination of those structures at present considered possible. Were larger amounts of decaborane available for this investigation so that more fully developed electron diffraction photographs could be obtained, a definite structure assignment might have resulted.

Pentaborane, B_5H_9

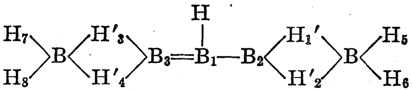
Since hydrogen bridge structures[4,8] were not considered in the original electron diffraction study of B_5H_9,[3] we reconsidered these data with the view of testing the acceptability of a bridge type configuration. The radial distribution curve, recalculated after the method of Walter and Beach[5] (Fig. 1), shows a slightly different ratio of BH/BB distances than was presented in the original report. The slight shift in maxima suggests an increase in the length of the BH distance and permits an even better match between the Bauer–Pauling structure (B, Fig. 1) and the observed data.



BB = 1.76 Å.
BH = 1.17 Å.

Maxima appeared at 1.21, 1.73 and 2.47 Å. These we interpreted as being due to the BH, BB and the $\overset{\diagup \mathrm{B} \diagdown}{\mathrm{B} \leftarrow\!\!\rightarrow \mathrm{B}}$ interactions in the ring, respectively. Because of the intensity of the peak at 2.47 Å. it cannot be assigned to BH interactions only. Since the combination 1.73 and 2.47 Å. leads to a BBB angle of approximately 90°, no model without this 90° angle can be made to agree with the observed pattern. The two suggested models, involving hydrogen bridges contain no BBB angles of 90°. The synthetic R.D. patterns C_1 and C_2 (Fig. 1) were calculated following the suggestion of Longuet-Higgins and Bell.

C_1.



$B_1B_2 = B_1B_3 = 1.70$ Å.
$BH = 1.18$
$BH' = 1.24$
$B_3B_4 = 1.76$

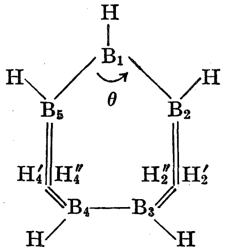
Due to resonance, B_1B_2 equals B_1B_3; H'_1, H'_2, H'_3 and H'_4 determine a plane perpendicular to the plane of H_5, H_6, H_7 and H_8; C_2 is identical with C_1 except that $\angle B_2B_1B_3 = \angle HB_1B_2 = \angle HB_1B_3 = 120°$. As can be seen from a comparison of the synthetic and calculated radial distribution curves, there is no way of varying bond distances or angles for C_1 or C_2 to obtain a suitable fit, since there is no way of obtaining a sufficiently high maximum at 2.47 Å. Thus this bridge structure is definitely eliminated.

---

(7) This equation, rather than $\sum Z_i Z_j \frac{\sin l_{ij}s}{l_{ij}s}$ was used because in taking the photographs a stop was inserted to remove the main beam about 1 cm. from the nozzle. This served not only to clear up the inner region of the photographs, but also acted as a selective mask for small angles, so that the pattern was in effect multiplied by some low power of s. Equation (1) satisfactorily accounts for this change.

(8) (a) H. C. Longuet-Higgins and R. P. Bell, *J. Chem. Soc.*, 250 (1943); (b) *Proc. Roy. Soc.* (*London*), **A183**, 357 (1944–1945).

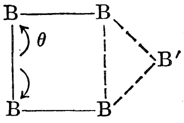
When Pitzer first presented the protonated double bond structures he claimed that the following angles and bond lengths for B_5H_9 fitted the electron diffraction data.



$B_3B_4 = 1.70$ Å.
$B_1B_2 = B_1B_5 = 1.50$ Å.
$B_2B_3 = B_4B_5 = 1.75$ Å.
BH (protonated double bond) = 1.25 Å.
BH = 1.10 Å.
$\theta = 113°$

H_2' and H_2'' (also H_4' and H_4'') were placed 0.86 Å. above and below the plane of the B atoms and displaced outward from the line B_2B_3 (B_4B_5) by 0.25 Å.

That appeared doubtful, since there are no BBB angles of approximately 90° in this configuration. There are other discrepancies in the R.D. curve (A, Fig. 1) which argue against it. Nevertheless, we calculated intensity curves using the distances and angles proposed (Fig. 4A). This should be compared with the curve computed for the methylene cyclobutane model (Fig. 4B) and with the visually estimated pattern. Since the relative intensities and shapes of the maxima are as important as their positions, the curve computed assuming the protonated double bond structure is definitely eliminated.

It is worthwhile to emphasize that for this compound it is the location of the boron atoms and not of the hydrogen atoms which determine the essential features of the pattern. Thus the intensity curves computed for models of the type  wherein BB = 1.76 Å.; B–H = 1.17 Å.; and $90 < \theta < 100°$, will be generally satisfactory. The characteristic features are not specially sensitive to the location of atom B'; and one really cannot specify the type of bonding suggested by the - - - links. This is evident from inspection of the curves plotted in Fig. 5, ref. 3.

Diborane

A recently reported infrared study of diborane[9] argues very strongly in favor of the bridge structure, whereas the original electron diffraction data[10] were interpreted to favor the ethane type configuration. Since that conclusion depends on whether a faint inner ring is present or absent in the region of $s = 3$, the electron diffraction work is being repeated, employing an apparatus with a rotating sector, with the hope of obtaining objective microphotometer traces of the pattern.

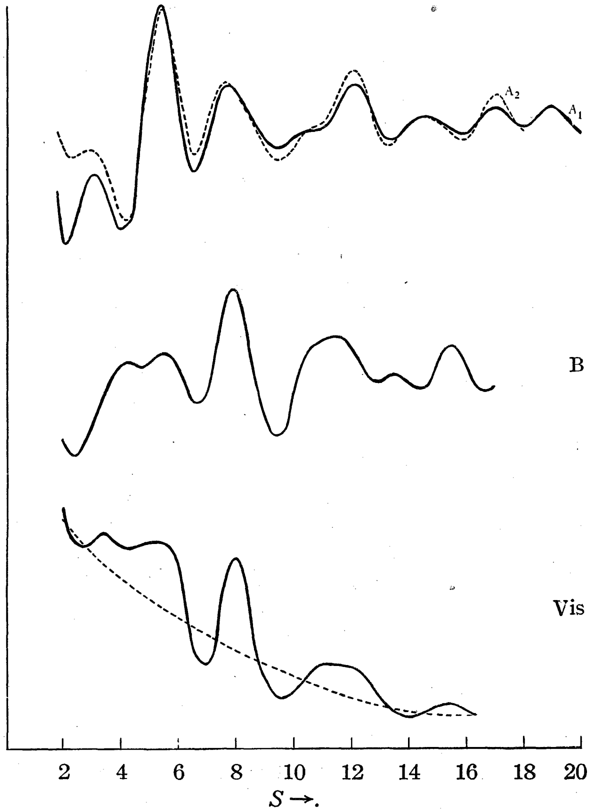


Fig. 4.—Intensity curves for B_5H_9: A_1 was computed using $\Sigma Z_iZ_j \sin(sl_{ij}/sl_{ij})$ for Pitzer's model; A_2 was computed using eq. (1) for the same model; B methylene cyclobutane model, and visual curve from reference 3.

Summary

New electron diffraction data on decaborane are reported. Using the visual procedure we found that

$$B\text{—}B_{av.} = 1.80 \pm 0.03 \text{ Å.}$$
$$B\text{—}H_{av.} = 1.29 \pm 0.04 \text{ Å.}$$
$$\angle B\text{—}B\text{—}B\ 109 \pm 3°$$

Although a unique structure assignment is not possible, the data can best be interpreted on the assumption that $B_{10}H_{14}$ consists of two symmetrical pentagons held together by a B–B bond. Furthermore, we consider the data sufficient to eliminate the H-bridge type configurations which were tested.

Previously published electron diffraction data on B_5H_9 were reviewed, and it is demonstrated that Pitzer's model for this compound is definitely not acceptable.

NOTE ADDED IN PROOF.—I am grateful to Drs. Kasper, Lucht and Harker for kindly communicating to me the conclusion which they reached regarding the structure of decaborane, based on their X-ray diffraction studies of single crystals. Due to its unexpected form, their configuration had not been considered in the above electron diffraction study. It may be obtained by folding model H along the B–B bond shared by the two pentagons upward until the angle between the planes is about 75°; then by bending each of the terminal boron atoms downward until its bond makes an angle of about 50° with the plane of the ring; finally, by redistributing some of the hydrogen atoms. Preliminary computations indicate that this model could be brought into excellent agreement with the electron diffraction data.—S. H. BAUER.

ITHACA, N. Y. RECEIVED DECEMBER 26, 1947

---

[9] W. C. Price, *J. Chem. Phys.*, **15**, 614 (1947).

[10] S. H. Bauer, THIS JOURNAL, **59**, 1096 (1937).

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

Carbonyl Chloride. Entropy. Heat Capacity. Vapor Pressure. Heats of Fusion and Vaporization. Comments on Solid Sulfur Dioxide Structure

BY W. F. GIAUQUE AND W. M. JONES

This paper presents the results of a calorimetric investigation of carbonyl chloride covering the range from 15° K. to its boiling point. A comparison of the entropy calculated from molecular data with the entropy change obtained from the $\int_0^T C_p \, d\ln T$ leads to the conclusion that the planar phosgene molecule shows a nearly complete lack of discrimination between the positions of oxygen and chlorine in the crystal lattice.

Apparatus and Method.—The measurements were made in a vacuum calorimeter which has the laboratory designation Gold Calorimeter IV. A description has been given by Kemp and Giauque,[1] and a more detailed description of this type of calorimeter has been given by Giauque and Egan.[2] One calorie was taken equal to 4.1833 international joules.

The measurements on carbonyl chloride were made immediately after an investigation on nitromethane[3] and temperature scale comparisons presented in that connection apply to the present work. After the completion of all of the heat capacity and heat of fusion measurements, the resistance thermometer was broken due to a very unusual expansion of phosgene which occurred in the region extending some 25° below its melting point. A discussion of this expansion will be given below. A new resistance thermometer was installed prior to the measurements of the vapor pressure and heat of vaporization.

Preparation and Purity of Carbonyl Chloride.—About 500 cc. of Kahlbaum phosgene was fractionated in a vacuum jacketed column filled with glass helices for a length of approximately 75 cm. About three-fourths of the material was discarded. The sample employed weighed 185.5194 g. *in vacuo*, corresponding to 1.87537 moles. The molecular weight was taken as 98.924.

The change of melting point with the fraction melted was used to estimate the liquid soluble–solid insoluble impurity as 7 moles in 100,000 moles.

TABLE I

HEAT CAPACITY OF CARBONYL CHLORIDE. OBSERVED VALUES

0°C. = 273.10°K.

T, °K.	ΔT, °K.	C_p cal. deg.$^{-1}$ mole^{-1}	Ser.
14.80	0.371	1.62	I
15.98	1.509	1.95	I
17.86	1.798	2.69	I
20.43	1.960	3.59	I
23.99	3.590	4.58	I
28.28	4.947	5.63	I
32.94	4.265	6.74	I
38.01	5.673	7.72	I
43.30	4.863	8.47	I
48.48	5.310	9.14	I
53.77	5.222	9.79	I
58.59	4.449	10.26	I
63.98	6.187	10.72	I
70.51	6.827	11.27	I
77.04	5.984	11.74	I
82.81	5.562	12.12	I
89.06	6.924	12.48	I
95.74	6.423	12.92	I
101.90	5.845	13.26	I
108.48	6.592	13.68	I
114.89	6.185	14.12	I
121.43	5.609	14.42*	I
126.91	5.313	14.83*	I
132.91	3.559	15.00*	I
136.65	3.842	15.39*	I
140.68	4.092	15.89*	I
144.36	Melting point		
148.38	4.006	24.98	II
152.68	4.505	24.81	II
157.51	4.967	24.64	II
163.06	5.980	24.46	II
169.34	6.402	24.32	II
175.74	6.252	24.20	II
182.01	6.107	24.14	II
188.20	5.985	23.99	II
194.89	5.856	23.88	II
200.94	5.750	23.79	II
206.89	5.636	23.78	III
207.10	5.628	23.74	II
211.86	5.522	23.77	II
217.74	5.946	23.77	II
224.10	6.369	23.78	II
230.59	6.217	23.77	II
236.90	6.007	23.86	II
243.39	6.467	23.92	II
250.11	6.328	23.94	II
256.59	5.627	23.99	II
262.76	6.065	24.00	II
269.21	5.955	24.00	II
274.89	4.275	24.09	II
279.40	3.664	24.03	II

* Temperature rise obtained with thermocouple.

The Heat Capacity of Carbonyl Chloride.—The heat capacity of the solid and liquid were measured in the usual manner except that the abnormal expansion of carbonyl chloride in the region below the melting point made it im-

---

[1] Kemp and Giauque, THIS JOURNAL, **59**, 79 (1937).

[2] Giauque and Egan, *J. Chem. Phys.*, **5**, 45 (1937).

[3] Jones and Giauque, THIS JOURNAL, **69**, 983 (1947).

practicable to use the resistance thermometer-heater as a thermometer in this region. The heat capacity results are given in Table I. The five points immediately below the melting point are marked with asterisks because the temperature rise was obtained by means of the standard thermocouple on account of the thermometer strain mentioned above. These five points are of decreased accuracy and may be in error by as much as 1%.

The values given in Table II were obtained from a smooth curve through the data. They are believed to be accurate to 0.2% except at 20° K. where the error may be 1% and at 15° K. where it may be 5%.

TABLE II

HEAT CAPACITY OF CARBONYL CHLORIDE. VALUES TAKEN FROM SMOOTH CURVES THROUGH THE DATA

0°C. = 273.10°K.

T, °K.	C_p, cal. deg.$^{-1}$ mole^{-1}	T, °K.	C_p, cal. deg.$^{-1}$ mole^{-1}
15	1.67	150	24.91
20	3.46	160	24.56
30	6.05	170	24.31
40	8.02	180	24.11
50	9.33	190	23.95
60	10.39	200	23.83
70	11.23	210	23.77
80	11.93	220	23.77
90	12.57	230	23.81
100	13.18	240	23.87
110	13.77	250	23.94
120	14.35	260	23.99
130	14.93	270	24.04
140	15.51	280	24.09

When the vapor pressure became appreciable the liquid heat capacity values were corrected for the small amount of vaporization. The liquid densities used in computing the gas space above the liquid in the calorimeter were obtained from the I.C.T.[4]

TABLE III

MELTING POINT OF CARBONYL CHLORIDE

0°C. = 273.10°K.

Date and time	% Melted	T, °K., resistance thermometer	T, °K., thermocouple
11/1/42	Heated into		
12:45 a.m.	melting point		
2:45 a.m.	3	145.272	145.27
3:45 a.m.	3	145.272	145.27
4:00 a.m.	Supplied heat		
5:00 a.m.	10	145.332	145.33
6:00 a.m.	10	145.330	145.32
7:00 a.m.	10	145.329	145.32
7:15 a.m.	Supplied heat		
9:00 a.m.	25	145.339	145.34
9:45 a.m.	25	145.338	145.34
10:00 a.m.	Supplied heat		
11:30 a.m.	40	145.338	145.35
11/2/42			
12:30 p.m.	40	145.337	145.34

Accepted value 145.34 ± 0.05° K.

The Melting Point of Carbonyl Chloride.—The equilibrium melting point temperature was observed as a function of the fraction of the phosgene melted. A summary of the observations is given in Table III. The strain in the resistance thermometer which developed in the region below the melting point disappeared as soon as the melting point was reached, as might be expected.

Heat of Fusion of Carbonyl Chloride.—The data relating to the two determinations of the heat of fusion of carbonyl chloride are given in Table IV. The measurements were started somewhat below the melting point and ended somewhat above, and a correction for $\int C_p dT$ was applied.

TABLE IV

HEAT OF FUSION OF CARBONYL CHLORIDE

Melting point, 145.34°K.

Temperature interval, °K.	Corrected heat input	Pre-melting	Cal./mole $\int C_p dT$	ΔH fusion
144.360–146.263	1405.4	3.2	38.6	1370.0
143.046–147.110	1450.6	1.3	80.4	1371.5

Mean 1371 ± 2

Vapor Pressure of Carbonyl Chloride.—The vapor pressure was measured by means of a mercury manometer, 1.6 cm. i. d., which could be attached to the glass line leading to the calorimeter. After each determination, the calorimeter was shut off from the manometer. The material in the manometer and connecting lines was then condensed, and the lines were pumped out. This was done as a precaution against error which would result if some phosgene reacted with the mercury, although a preliminary experiment did not detect this reaction.

The data of Cawood and Patterson[5] were used for correcting for capillary depression. The standard acceleration of gravity was taken as 980.665

TABLE V

VAPOR PRESSURE OF CARBONYL CHLORIDE

Boiling point 280.66°K.; 0°C. = 273.10°K.

T, °K.	P, obs. int. cm.	$P_{\text{obs.}} - P_{\text{calcd.}}$	$T_{\text{obs.}} - T_{\text{calcd.}}$
215.481	2.475	+0.002	−0.012
221.449	3.732	− .002	+ .009
227.317	5.467	+ .003	− .009
233.743	8.075	− .011	+ .024
240.968	12.212	+ .003	− .005
247.573	17.388	+ .024	− .028
255.322	25.550	− .002	+ .002
264.013	38.188	.000	.000
272.147	54.128	+ .002	− .001
277.048	66.007	− .002	+ .001
281.103	77.312	+ .004	− .001

dP/PdT = 0.038443 deg.$^{-1}$ at 280.66°K.

---

[4] "International Critical Tables," McGraw-Hill Book Co., New York, N. Y., 1926.

[5] Cawood and Patterson, *Trans. Faraday Soc.*, **29**, 522 (1933).

cm. sec.$^{-2}$, and the local value[6] used was 979.973 cm. sec.$^{-2}$.

The vapor pressure observations have been represented by the following equation for the range 215 to 281° K.

$$\log_{10}P_{(\text{int. cm.})} = -(1690.3/T) + 9.68020 - 0.0078981T + 0.0000055847T^2$$

A summary of the observations including a comparison with the above equation is given in Table V. The above equation gives the boiling point as 280.66° K.

Table VI gives a comparison of the melting and boiling points with those of other observers.

TABLE VI

MELTING AND BOILING POINTS OF CARBONYL CHLORIDE

Melting point, °K.	Boiling point, °K.	Observer
	281.3	Beckmann[7] (1907)
155.1		Erdmann[8] (1908)
	280.79	Savoia Paternò and Mazzucchelli[9] (1920)
	281.5	Nikitin[10] (1920)
147.1		Atkinson, Heycock, and Pope[11] (1920)
	280.74	Germann and Taylor[12] (1926)
145.34 ± 0.05	280.66 ± 0.05	This research

Heat of Vaporization of Carbonyl Chloride.—The heat of vaporization of carbonyl chloride was measured directly by adding heat to the calorimeter and removing the gas at constant pressure. By means of a capillary system the pressure could be held at approximately one atmosphere while the gas was condensed in small weighed bulbs by cooling them with liquid air. Heat capacity corrections were made to take into account the small difference in the initial and final temperatures which were measured before and after energy input. Corrections were also applied for heat leak and for the evaporation required to fill the space previously occupied by evaporated liquid.

The heat of vaporization was also calculated from the vapor pressure data by means of the equation $\mathrm{d}P/\mathrm{d}T = \Delta H/T\Delta V$ and Berthelot's equation of state.

$$\Delta H = \frac{RT^2 \mathrm{d}\ln P}{\mathrm{d}T}\left[1 - \frac{9\,PT_c}{128\,P_cT}\left(1 - \frac{6\,T_c^2}{T^2}\right) - \frac{PV_{\text{liq.}}}{RT}\right]$$

The critical constants were taken from Germann and Taylor[12]: $T_c = 455°$ K. and $P_c = 56$ atm. The molal volume of the liquid at the boiling point was taken at 69.2 cc. from the "I.C.T." The use of Berthelot's equation introduced a correction of 192 cal. mole^{-1} for gas imperfection.

The heat of vaporization data are summarized in Table VII.

TABLE VII

HEAT OF VAPORIZATION OF CARBONYL CHLORIDE AT ITS BOILING POINT 280.66°K.

Moles vaporized	Time of energy input, minutes	ΔH vaporization cal. mole^{-1}
0.15098	40	5831
.15261	40	5834
.15916	40	5836
.13241	35	5825
		Mean 5832 ± 6
From the vapor pressure equation assuming a Berthelot gas		5825

The value for the heat of vaporization obtained from the vapor pressure data agrees very well with the direct determinations but can be given no weight in comparison with these more reliable values. However the agreement is evidence in support of the use of Berthelot's equation in correcting for the effect of gas imperfection on the entropy of the carbonyl chloride gas as will be done below.

The Entropy of Carbonyl Chloride.—The calculation of the entropy of carbonyl chloride from the calorimetric measurements is summarized in Table VIII.

TABLE VIII

CALCULATION OF THE ENTROPY OF CARBONYL CHLORIDE FROM THE CALORIMETRIC MEASUREMENTS

	Calories per degree per mole
0–15° K., extrapolation	0.64
15–145.34° K., graphical	19.78
Fusion, 1371/145.34	9.43
145.34–280.66° K., graphical	15.87
Vaporization, 5832/280.66	20.78
	66.50 ± 0.15
Correction for gas imperfection	0.13
S (ideal gas at 280.66° K.) − S (solid at 0° K.) =	66.63

The structure of the carbonyl chloride molecule has been determined by Brockway, Beach and Pauling[13] by electron diffraction measurements. They give the following results; C–O = 1.28 × 10^{-8} cm., C–Cl = 1.68 × 10^{-8} cm. and the Cl–C–Cl angle = 117°. From these values the moments of inertia may be calculated as 105.4 × 10^{-40}, 240.1 × 10^{-40} and 345.5 × 10^{-40} g. cm.^{2}.

The spectrum of phosgene has been investigated by Marton[14] (infrared), Henri and Howell[15] (ultraviolet), Dadieu and Kohlrausch[16] (Raman),

---

(6) Landolt, Börnstein and Roth, "Physik. chem. Tabellen," Verlag Julius Springer, Berlin, 1923.

(7) Beckmann, *Z. anorg. Chem.*, **55**, 370 (1907).

(8) Erdmann, *Ann.*, **362**, 148 (1908).

(9) Paternò and Mazzucchelli, *Gazz. chim. ital.*, **50**, I, 30 (1920).

(10) Nikitin, *J. Russ. Phys.-Chem. Soc.*, **52**, 235 (1920).

(11) Atkinson, Heycock and Pope, *J. Chem. Soc.*, **117**, 1410 (1920).

(12) Germann and Taylor, THIS JOURNAL, **48**, 1154 (1926).

(13) Brockway, Beach and Pauling, *ibid.*, **57**, 2693 (1935).

(14) Marton, *Z. physik. Chem.*, **117**, 97 (1925).

(15) Henri and Howell, *Proc. Roy. Soc.* (*London*), **128A**, 190 (1930).

(16) Dadieu and Kohlrausch, *Ber.*, **139**, 717 (1930).

Ananthakrishnan[17] (Raman), Bailey and Hale[18] (infrared).

The most important work is that of Ananthakrishnan since the polarization estimates on his Raman lines are important in assigning the observed frequencies to the several modes of motion. Only five of the six fundamental frequencies were observed in the Raman spectrum, although all were expected. Thompson[19] has reviewed the data and compared it with that on thiophosgene which he has measured, and in which case he found all six fundamental frequencies. As the two phosgenes are very similar he was able to make a good estimate of the unobserved nonplanar deformation frequency as 230 cm.$^{-1}$. Thompson estimates that the error involved in the uncertainty of his choice would be less than 0.1 cal. deg.$^{-1}$ mole^{-1} in a statistical entropy calculation. The fundamentals are given by Thompson as 1827, 845, 570, 444, 302 and (230) cm.$^{-1}$. The symmetry number of the molecule is two.

The calculation of the entropy of carbonyl chloride gas from molecular data is given below. The physical constants used are taken from the "I.C.T." The calculations are in essential agreement with results derived from equations given by Thompson.[19]

	280.66° K.	298.10° K.
S translation	39.39	39.69
S rotation	24.45	24.63
S vibration	4.42	4.81
S ideal gas, 1 atmos. cal. deg.$^{-1}$ mole^{-1}	68.26	69.13

$$S \text{ (molecular data)} - \int_0^{280.66} C_p \,\mathrm{d}\ln T = 68.26 - 66.63 = 1.63$$

The only appreciable uncertainty in the above calculation is the 230 cm.$^{-1}$ frequency. In order to eliminate the discrepancy it would be necessary to assume a value of about 900 cm.$^{-1}$ instead of 230 cm.$^{-1}$. Not only does this appear unreasonable but the polarization analysis of Ananthakrishnan[17] appears to eliminate possible reassignment of the observed frequencies so as to permit the inclusion of a 900 cm.$^{-1}$ value with the five observed frequencies.

We believe that the explanation of the discrepancy lies in the random orientation of the carbonyl chloride molecules in the crystal lattice. This planar molecule does not differ greatly from an equilateral triangle, with the carbon atom off center, and despite its appreciable electric moment it appears necessary to assume that the oxygen can occupy any of three positions. Complete randomness in this respect would correspond to R ln3 = 2.18 cal. deg.$^{-1}$ mole^{-1} of residual entropy, instead of the value 1.63 given above, but some approach to order has been noted in cases of random orientation in CO and NNO and it is reasonable to assume that some regularity may be attained in the present case.

We have mentioned the abnormal expansion which occurred in solid phosgene in the region below its melting point and it seems probable that this is related to the partial attainment of molecular orientation equilibrium in the solid.

In the some two score condensed gases which have been investigated in this Laboratory with similar calorimeters the only one we can recall which caused a disturbance of this kind was sulfur dioxide. To quote from Giauque and Stephenson[20]: "At 175° K., about 20° below the melting point of sulfur dioxide, the resistance thermometer began to give slightly high values, and just below the melting point the abnormal increase in resistance reached 0.1% of the total resistance. As soon as a portion of the sulfur dioxide was melted, the resistance returned to its normal value. No completely satisfactory explanation of this stretching effect can be offered; none of the many other condensed gases investigated in this calorimeter have caused such a disturbance."

It would seem to be more than a coincidence that the above behavior should occur in these two molecules, since, among all those investigated, only sulfur dioxide like carbonyl chloride is a triangular molecule with elements of the first and second rows of the periodic system at the apexes of the triangle. Accordingly we suggest that when carbonyl chloride and sulfur dioxide are first solidified the amount of random orientation present at the freezing point is reduced by subsequent cooling. This causes dimensional changes in the solid which are not reversed in macroscopic detail when the substance is slowly warmed, thus producing the strain observed in the calorimeter.

In the case of sulfur dioxide the electron diffraction investigation of Schomaker and Stevenson[21] combined with the entropy measurements of Giauque and Stephenson[20] make it certain that perfect order is attained at low temperatures. However the characteristics of sulfur dioxide in the region below its melting point give some basis for the suspicion that it has disorder of the molecular orientation type.

The sulfur dioxide molecule is too far from an equilateral triangle to make it appear probable that simple orientation of the triangle would be the explanation in this case. The crystal structure of sulfur dioxide is unknown; however, it is of interest to speculate about a type of plausible crystalline arrangement which would be in accord with the experimental observations.

If adjacent sulfur dioxide molecules are paired, with their molecular planes 90° apart, and with the O–O sides of the triangles together, the two sulfur and four oxygen atoms would approximate a sphere. If the oxygen atoms were at the corners of a square there would be three orientation

---

[17] Ananthakrishnan, *Proc. Ind. Acad.*, **5A**, 285 (1937).

[18] Bailey and Hale, *Phil. Mag.*, **25**, 98 (1938).

[19] Thompson, *Trans. Faraday Soc.*, **37**, 251 (1941).

[20] Giauque and Stephenson, THIS JOURNAL, **60**, 1389 (1938).

[21] Schomaker and Stevenson, *ibid.*, **62**, 1270 (1940).

positions exchanging oxygen and sulfur atoms for each pair of sulfur dioxide molecules. It is also of interest that, if the oxygen atoms in such an arrangement were located on a staggered square, which is more probable, orientation disorder could result due to rotation of oxygen atoms alone with two possibilities per pair of sulfur dioxide molecules. It is also possible that both types of disorder could occur simultaneously.

In any of the above cases it is reasonable, not only that a good deal of orientation disorder should be present at the freezing point, but also that potential barriers between the several positions should be small enough to permit the attainment of perfect order as the solid is cooled, as was shown by the entropy determination.

It is obviously of interest to have a crystal structure investigation of solid sulfur dioxide. The observations should be made on the solid cooled to at least the temperature liquid air since, if the above explanation of the abnormal expansion of solid sulfur dioxide is correct, disorder near the freezing point may complicate structural observations.

It is not our intention to place too much emphasis on the particular structure suggested to explain possible random orientation in solid sulfur dioxide but rather to illustrate the possiblity of orientation disorder in such a substance.

Kemp and Giauque[22] found very slow thermal equilibrium in their measurements on carbonyl sulfide. In the 75° interval below the melting point, 134.31° K., it took about ten times the usual period to obtain temperature equilibrium after an energy input. The entropy calculations show that the substance attains perfect order at very low temperatures but they expressed the opinion that random orientation of the sulfur and oxygen ends of the molecule characterizes thermodynamic equilibrium at the higher temperatures. The difficulty of such a molecular rotation within the solid was believed to be responsible for the slow thermal equilibrium.

In the case of carbonyl chloride it is probable that a somewhat greater approach to order would be possible with excessively slow cooling, extending over months or years, but the attainment of order in cases of this type often involves coöperation of molecules sufficiently to make the rate drop off rather sharply with temperature. The phenomenon is much the same as the decrease in entropy, and thus the increased order, which accompanies the annealing of a glass. A glass must be annealed above a rather definite temperature or the process will not occur at an appreciable rate. The entropy associated with structural randomness, corresponding to thermodynamic equilibrium in the annealing region of a system, which is non-crystalline in certain respects, will remain when the substance is cooled to very low temperatures.

The solids of carbon monoxide, nitric oxide, nitrous oxide, water and evidently carbonyl chloride, are those known to remain amorphous or glass-like with respect to molecular orientation within their semi-crystalline frameworks, even when considerable time is allowed for thermal equilibrium.

The molecule thiocarbonyl chloride is so nearly an equilateral triangle, with the carbon atom near the center, that it seems safe to predict that it would have a residual entropy of $R \ln 3$ and the same situation should exist with carbonyl fluoride.

Summary

The heat capacity of solid and liquid carbonyl chloride (phosgene) has been determined from 15 to 280° K.

The melting point is 145.34° K. (0° C. = 273.10° K.). The heat of fusion is 1371 cal. mole^{-1}.

The vapor pressure of liquid carbonyl chloride has been measured from 215 to 281° K. The data are represented by the equation, $\log_{10} P_{(\text{int cm.})} = -(1690.3/T) + 9.68020 - 0.0078981T + 5.5847 \times 10^{-6}T^2$.

The boiling point is 280.66° K., and the heat of vaporization at this temperature is 5832 cal. mole^{-1}.

The calorimetric measurements have been used to calculate the increase in entropy between 0° and 280.66° K. as 66.63 cal. deg.$^{-1}$ mole^{-1}.

A calculation of the entropy of carbonyl chloride gas at 280.66° K. from molecular data leads to a value of 68.26 cal. deg.$^{-1}$ mole^{-1}.

The 1.63 cal. deg.$^{-1}$ mole^{-1} discrepancy between the above results is interpreted as due to random orientation of the planar triangular carbonyl chloride molecule in the solid at low temperatures. The maximum value for this effect would be $R \ln 3 = 2.18$ cal. deg.$^{-1}$ mole^{-1} so that some approach to order is indicated.

The entropy of carbonyl chloride is calculated from molecular data to be 69.13 cal. deg.$^{-1}$ mole^{-1} at 298.1° K. and this value, which does not include the entropy due to nuclear spin or the isotope effect, is the most reliable value to use in thermodynamic calculations.

A comparison of the similar anomalous behavior of carbonyl chloride and sulfur dioxide, in the region below their melting points, leads us to infer that sulfur dioxide also has some random orientation in the solid although the data on this substance indicate that it becomes perfectly ordered at very low temperatures. These two molecules each have atoms of the first and second rows of the periodic system at the apexes of their triangular structures.

BERKELEY, CALIFORNIA RECEIVED JUNE 18, 1947

---

[22] Kemp and Giauque, THIS JOURNAL, **59**, 79 (1937).

[Contribution from the Frick Chemical Laboratory, Princeton University]

The Dielectric Polarization and Molecular Association of Hydrogen Fluoride Vapor[1]

By Richard A. Oriani and Charles P. Smyth

The polymerization or molecular association of hydrogen fluoride has been known for a long time. Simons and Hildebrand[2] analyzed the data[3] of Thorpe and Hambly on its vapor density and concluded that the gaseous substance was composed mainly of cyclic hexamers $(HF)_6$. A very careful redetermination of vapor densities led Long, Hildebrand and Morrell[4] also to the conclusion that the data could be represented by an equilibrium existing between the monomer and the cyclic hexamer, except at low pressures, where there was some indication of lower polymers. Fredenhagen[5] also made vapor density measurements, and concluded that forms other than H_2F_2 existed and also that the theory that only HF and $(HF)_6$ existed was untenable. His data were further analyzed by Briegleb,[6,7] who assumed an equilibrium distribution of polymers according to the equation $HF + (HF)_n \rightleftarrows (HF)_{n+1}$, and calculated that the dimer had the largest energy of association, but that values of n up to 8 were significant. Briegleb considered the configurations of the polymers to be chains in which adjacent HF units were anti-parallel to one another (Fig. 1B). The electron diffraction data of Bauer, Beach and Simons[8] indicated that under the conditions obtaining in their experiments at least, the principal configuration existing in gaseous hydrogen fluoride was a chain-like arrangement in which the fluorines occupied the corners of a zig-zag structure, with the hydrogens lying on a line connecting two consecutive fluorines and with a chain angle of about 140° as in Fig. 1C. The same structure with a chain of almost infinite length and angles of 135° was indicated by the X-ray analysis of solid hydrogen fluoride.[9] On the other hand, Pauling[10] calculated that, for a degree of polymerization of 6 or more, the cyclic polymer would be more stable than its chain analog by virtue of the additional bond, that the partial covalent character of the hydrogen bonds tended to stabilize bond angles of about 110 or 120° for fluorine, and that as a consequence the cyclic hexamer was somewhat more stable than other polymers.

Because of the large difference in dipole moment to be expected between a cyclic structure and a zig-zag chain, it has been considered advisable to investigate the molecular association of hydrogen fluoride by measurement of the dielectric polarization of the vapor as a function of temperature and pressure. A preliminary note describing work along these lines has already been published.[11]

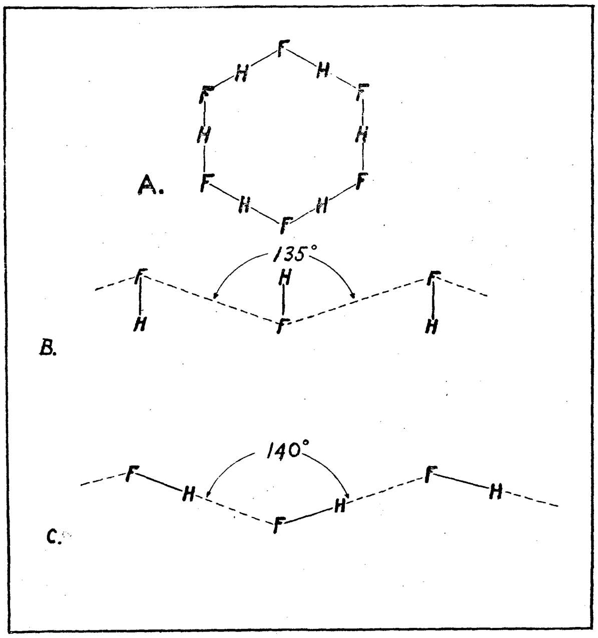


Fig. 1.—A, cyclic hexamer with zero dipole moment; B, linear model with consecutively antiparallel HF molecules; dipole moment either zero or 1.91; C, linear model deduced from electron diffraction data; dipole moment increases with chain length.

Apparatus and Method of Measurement

While the electrical measuring circuit has been previously described,[12] no account has been published of the cell and vacuum system, which were identical, except for some minor modifications, with the apparatus employed by Hannay and Smyth[13] in the determination of the dipole moment of unassociated hydrogen fluoride. The cell was constructed of three concentric nickel cylinders, of which the outer and the inner were silver-soldered to the same nickel disc, while the middle one was insulated from the other two by a gasket of "Teflon."[14] Electrical contact was made to the middle cylinder by a nickel rod passing through a bushing tightly packed with "Teflon." The capacitance of the empty cell was 250 micromicro-

---

[1] Presented before the Physical and Inorganic Division at the 112th meeting of the American Chemical Society, New York City, N. Y., September 16–19, 1947.

[2] Simons and Hildebrand, This Journal, **46**, 2183 (1924).

[3] Thorpe and Hambly, *J. Chem. Soc.*, **55**, 163 (1889).

[4] Long, Hildebrand and Morrell, This Journal, **65**, 182 (1943).

[5] Fredenhagen, *Z. anorg. allgem. Chem.*, **218**, 161 (1934).

[6] Briegleb, *Z. physik. Chem.*, **51B**, 9 (1941).

[7] Briegleb, *Naturwissenschaften*, **29**, 420 (1941).

[8] Bauer, Beach and Simons, This Journal, **61**, 19 (1939).

[9] Geunther, Holm and Strunz, *Z. physik. Chem.*, **B43**, 229 (1939).

[10] Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1945, p. 298.

[11] Benesi and Smyth, *J. Chem. Phys.*, **15**, 337 (1947).

[12] Hurdis and Smyth, This Journal, **64**, 2829 (1942).

[13] Hannay and Smyth, *ibid.*, **68**, 171 (1946).

[14] Renfrew and Lewis, *Ind. Eng. Chem.*, **38**, 870 (1946).

farads, exclusive of lead capacitance; this latter was determined separately and was checked by measurements of the dielectric constant of air. The apparatus for handling the hydrogen fluoride was constructed of copper tubing and nickel with silver-soldered joints, except for the "Kerotest" valves, the brass bodies of which gave some trouble because of jamming due to corrosion. Two valved containers were provided for the purification of the hydrogen fluoride by distillation from one to the other, and for the storage of the purified material. A Bourdon gage, calibrated with air against a mercury manometer and readable to 1 mm., was used to measure the pressure. A commercial tank of hydrogen fluoride from the Matheson Company, East Rutherford, N. J., was permanently connected to the system, as was also a tank of fluorine. The leads to the cell were suitably shielded, and the cell was immersed in a thermostated oil-bath able to hold the temperature constant within 0.02°. The temperature was read by a calibrated platinum resistance thermometer immersed in the bath. The gas system was connected to an oil vacuum pump through a long tube filled with soda-lime. In order to prevent the occurrence of corrosion during the course of a measurement, the system was given a prolonged exposure to fluorine from the attached cylinder, and the fluorination was repeated whenever the inside of the system had been exposed to the atmosphere. The importance of this operation may be gaged by the observation that, when the system was inadequately conditioned, a gas pressure slightly larger than one atmosphere was developed over a period of time apparently by reaction of hydrogen fluoride with the metal.

In order to purify the hydrogen fluoride, a quantity was distilled from the commercial tank into a reservoir by chilling the latter (b. p. of hydrogen fluoride, 19.4°). This material was then distilled back and forth from one reservoir to the other by alternately chilling and warming the containers. After each distillation the apparatus was evacuated, while the condensate was chilled with liquid nitrogen. At least one of these distillations was performed through an atmosphere of fluorine to aid in the removal of moisture. The procedure was repeated until the vapor pressure of the hydrogen fluoride at 0° was close to the literature value of 357 mm.[15] (358.2 mm.[16]). In these purifications, the vapor pressure at 0° always decreased as the purification proceeded to assume values from 354 to 356 mm. Another criterion of purity was the consistency and reproducibility of the dielectric measurements in the low pressure regions at all the temperatures studied, and their agreement with the results of Hannay and Smyth.[13]

In order to carry out a determination of polarization, the system was evacuated of the fluorine left in it, and flushed out repeatedly with hydrogen fluoride. After another evacuation, and after the cell had attained temperature equilibrium, simultaneous readings of pressure and capacitance were made after admittance of successive small portions of hydrogen fluoride, and also after successive withdrawals of the vapor by recondensation into the storage container. Enough time had to be allowed before making readings after each admission or withdrawal of hydrogen fluoride to permit adsorption of the vapor to attain equilibrium. Adsorption was evidenced in a lag in the attainment of constant capacitance and pressure readings at the higher pressures when the temperature was not far above the boiling point. Repeated measurements of capacitance and pressure as functions of time showed that, in typical experiments where adsorption was a maximum when the pressure was raised to 700 mm., the adsorbed layer raised the capacitance by about 50 scale divisions while the total increase of capacitance produced by the hydrogen fluoride was about 1600 scale divisions. The maximum error thereby produced in the dipole moment value, which is proportional to the square root of the capacitance, was, therefore, about 1.6%.

It was believed that the treatment of the hydrogen fluoride with fluorine had removed any last traces of moisture. As moisture has been supposed to affect the association of hydrogen fluoride materially, a considerable quantity of water vapor was introduced into the cell after the completion of the measurements reported in Tables I and II. A very slight apparent increase in the dipole moment at low pressures was observed and, at higher pressures, adsorption or condensation of the water so affected the capacity measurement as to render the experiment valueless. Indeed, the slight increase in apparent moment at low pressures was probably the effect of adsorption.

Experimental Results

The molar polarizations P were computed from the condenser readings C by the relation

$$P = \frac{RT}{3p} \cdot \frac{C - C_0}{fC'_0} \qquad (1)$$

in which f is a condenser calibration factor, C_0 is the condenser reading at zero pressure, C'_0 is the vacuum capacitance in micromicrofarads, R is the gas constant per mole, T is the absolute temperature, and p is the pressure in mm. The dipole moments were computed by the Debye equation

$$\mu = 0.01281\,[(P - MR_\mathrm{D})T]^{1/2} \qquad (2)$$

in which MR_D, the molar refraction, was taken[17] as 2.0.

Table I gives the values of the polarization P in cu. cm. per mole and of the dipole moments in e.s.u. × cm. for the linear portions of the capacitance–pressure isothermal curves, that is, for

---

(15) "International Critical Tables," McGraw-Hill Book Company, Inc., New York, N. Y., 1926.

(16) Claussen and Hildebrand, THIS JOURNAL, **56**, 1820 (1934).

(17) Smyth, "Dielectric Constant and Molecular Structure," The Chemical Catalog Co., Inc., New York, N. Y., 1931, p. 149.

TABLE I

POLARIZATION AND DIPOLE MOMENT VALUES OF UNASSOCIATED HYDROGEN FLUORIDE

t, °C.	P	μ ($\times 10^{18}$)
23.10	76.5	1.90
25.20	77.0	1.91
26.00	74.4	1.89
31.30	77.3	1.93
38.05	75.6	1.93
38.50	74.2	1.91
48.35	72.4	1.92
59.7	68.35	1.91

Mean value of moment = 1.91 ± 0.01

the low pressure ranges where the association of the hydrogen fluoride is negligible and the polarization independent of pressure. The mean value found for the moment is identical with that previously reported.[13] Figure 2 shows the polarization isothermals as functions of pressure, the temperature in °C. being given beside each curve, and Table II lists the polarization values from which the curves were constructed, as well as the dipole moments calculated by means of equation (2). The values at 26.00 and 38.05° are so close to those at 25.20 and 38.50° that they have been omitted.

TABLE II

DEPENDENCE OF POLARIZATION AND AVERAGE DIPOLE MOMENT ON PRESSURE AND TEMPERATURE

Polarization, cu. cm./mole

Pressure	23.10°	25.20°	31.30°	38.50°	48.35°	59.70°
0	76.0	77.0	77.4	74.1	72.4	68.4
50	77.0	77.6	76.9	74.3	72.4	68.4
100	76.5	77.0	77.6	74.7	72.4	68.4
150	77.8	76.6	77.0	74.1	72.4	68.4
200	80.5	78.5	78.0	74.0	72.4	68.4
250	85.0	80.5	79.5	74.1	72.4	68.4
300	91.1	82.7	81.4	74.2	72.4	68.4
350	97.6	85.7	83.8	76.0	72.4	68.4
400	104.3	90.1	86.4	78.0	72.4	68.4
450	110.6	94.6	89.1	80.2	72.4	68.4
500	117.1	99.6	91.5	82.7	72.4	68.4
550	125.0	104.8	95.9	85.4	73.5	68.4
600	135.7	111.3	98.9	88.2	74.6	68.4
650	149.8	127.8	101.0	91.2	76.0	68.4
700	170.9	150.7	104.6	94.2	77.3	68.4
730	198.0	...	...	..	..	68.4
740	....	163.3	...	96.6	78.2	68.4
750	...	...	107.2	..	..	68.4

DIPOLE MOMENT ($\times 10^{18}$)

Pressure	23.10°	25.20°	31.30°	38.50°	48.35°	59.70°
0	1.90	1.91	1.93	1.91	1.92	1.91
50	1.91	1.91	1.92	1.91	1.92	1.91
100	1.90	1.91	1.93	1.92	1.92	1.91
150	1.92	1.91	1.92	1.91	1.92	1.91
200	1.95	1.93	1.94	1.91	1.92	1.91
250	2.01	1.96	1.96	1.91	1.92	1.91
300	2.09	1.98	1.99	1.91	1.92	1.91
350	2.16	2.02	2.02	1.94	1.92	1.91
400	2.24	2.08	2.05	1.97	1.92	1.91
450	2.30	2.12	2.09	2.00	1.92	1.91
500	2.36	2.18	2.11	2.03	1.92	1.91
550	2.45	2.24	2.16	2.06	1.94	1.91
600	2.54	2.31	2.20	2.10	1.96	1.91
650	2.68	2.48	2.22	2.14	1.98	1.91
700	2.87	2.70	2.26	2.18	2.00	1.91
730	3.08	...	...	..	..	1.91
740	...	2.80	...	2.20	2.01	1.91
750	...	...	2.28	..	..	1.91

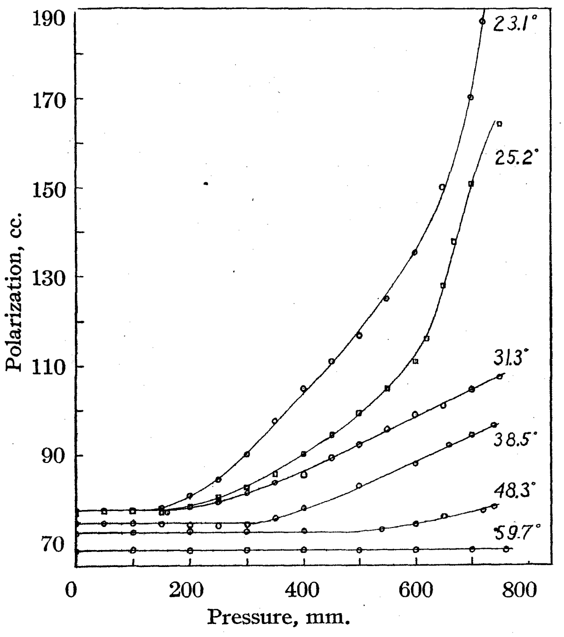


Fig. 2.—Polarization of hydrogen fluoride vapor.

Discussion of Results

Without close analysis, it is evident that the $6HF \rightleftarrows (HF)_6$ (cyclic) equilibrium postulated by some investigators[2,4] cannot be the whole story; such an equilibrium would predict lower polarizations as the ratio of hexamer to monomer increased with increasing pressure, since the dipole moment of a plane ring (Fig. 1A) or of any ring formed by joining the ends of the chain shown in Fig. 1C would be zero. Also, these results invalidate Briegleb's model (Fig. 1B) of a polymeric chain in which the units are consecutively antiparallel, since this structure would have a moment 0 or 1.91 according as the number of HF units was even or odd.

For associated hydrogen fluoride, the polarization is the sum of the contributions from the molecules of each of the several species present, so that the Debye equation becomes

$$P = \frac{4\pi}{3}\sum_{i=1}^{n} N_i\alpha_i = \frac{4\pi}{3}\left(\sum_{i=1}^{n} N_i\alpha_{0i} + \sum_{i=1}^{n} N_i\frac{\mu_i^2}{3kT}\right) \qquad (3)$$

in which α_i, α_{0i} and μ_i are, respectively, the total polarizability, distortion polarizability and dipole moment of the i^{th} species; N_i is the number of molecules of the i^{th} species, and $\sum_{i=1}^{n} N_i = N_A$, the Avogadro number. The index i has integral values from 1 to n corresponding to monomer, dimer, etc., to the n^{th}-mer. The application of equation (2) to the polarization data gives an average dipole moment, which, in terms of the quantities used in equation (3) is

$$\mu = \left(\frac{1}{N_A}\sum_{i=1}^{n} N_i\mu_i^2\right)^{1/2} \tag{4}$$

Similarly, the average distortion polarizability is

$$\alpha_0 = \left(\frac{1}{N_A}\sum_{i=1}^{n} iN_i\right)\alpha_{0_1} \tag{5}$$

Although the distortion polarizabilities of the polymers are larger than that of the monomer, the value 2.0 has been used for MR_D throughout since, in the range of these measurements, the molar refraction should never increase above 2.0 by more than 2, an amount negligible in its effect upon the calculations.

The dipole moments given in Table II are the average values represented by equation (4). In order to obtain values of the degree of association from these average dipole moments, a molecular model is necessary. The most probable structure would seem to be the chain with bond angles of 140° (see Fig. 1C), as indicated by X-ray[9] and electron diffraction[8] studies. As a basis for calculation, it may be assumed, as an approximation, that the moment of each monomeric unit remains unchanged at 1.91 when it forms part of a polymeric chain, and that each such unit is free to rotate with respect to the HF unit to which it is linked by a hydrogen bond, the bond angle being maintained at 140°. Such a polymeric chain would have a dipole moment dependent upon the degree of association, the relationship being obtainable from an equation[18] which, for this particular case, assumes the form

$$\mu = \mu_1(n + 2[(n-1)\cos 40° + (n-2)\cos^2 40° + \ldots + (n-(n-1))\cos^{n-1} 40°])^{1/2} \tag{6}$$

in which n is the degree of association, and μ_1 is the moment of one HF, 1.91. In Fig. 3, a smooth curve is drawn through the values of μ calculated for $n = 1, 2, 3, \ldots, 8$ by means of equation (6). For a mixture of monomer and dimer, dimer and trimer, or any pair of successive polymers, the value of μ calculated from equations (2) and (3) could be used to calculate an average value of n by means of equation (6). This average value of n is a special case of the association factor, z, which may be defined as the ratio of the total number of HF units to the total number of molecules. In view of the small departure of the curve in Fig. 3 from linearity, its abscissas may be treated as giving the approximate values of an association factor, z_m, for the polar molecules of average moment μ.

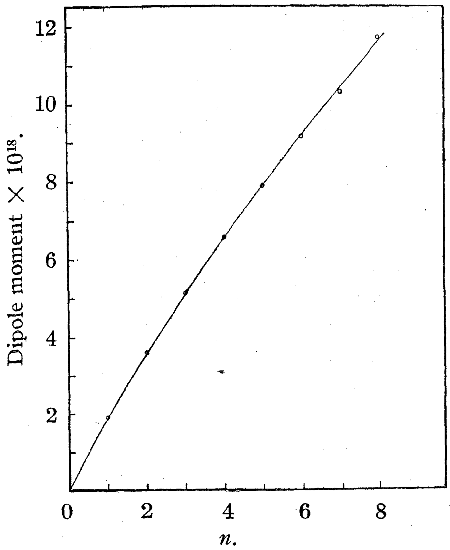


Fig. 3.—Calculated moment of polymeric chain of n units.

Table III gives the values of the association factor z_m estimated by means of the curve in Fig. 3 from the average dipole moment values, and Fig. 4 represents z_m as a function of pressure at the indicated temperatures.

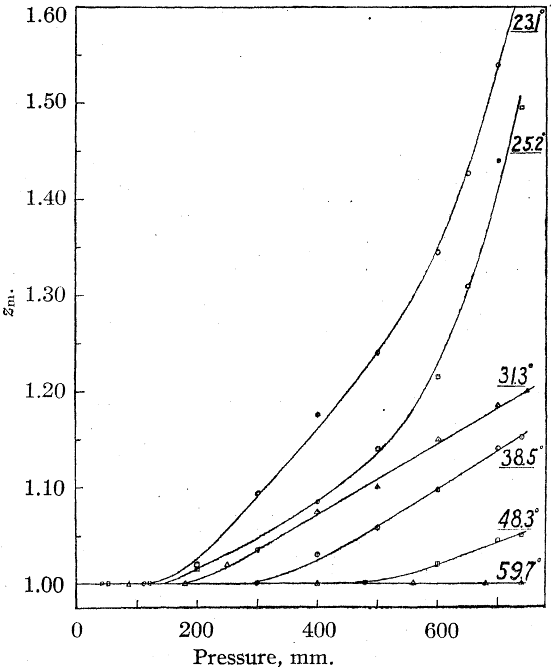


Fig. 4.—Variation of association factor, z_m, with pressure.

It must be kept in mind that since equation (6) postulates random orientation of the units of the chain because of complete freedom of rotation around the bonds, this method of evaluating the degree of association will give low results if any ring formation occurs and slightly high results if the chain is an extended, rigid structure. It will also tend to give high results if the hydrogen bonding raises the hydrogen–fluorine moment above that found for the monomer and assumed to be unchanged in the polymer. On the other hand,

---

[18] Eyring, *Phys. Rev.*, **39**, 746 (1932).

TABLE III

VALUES OF ASSOCIATION FACTOR, z_m

Pressure	23.10°	25.20°	31.30°	38.50°	48.35°	59.70°
0	1.00	1.00	1.00	1.00	1.00	1.00
50	1.00	1.00	1.00	1.00	1.00	1.00
100	1.00	1.00	1.00	1.00	1.00	1.00
150	1.00	1.00	1.00	1.00	1.00	1.00
200	1.02	1.02	1.01	1.00	1.00	1.00
250	1.05	1.03	1.02	1.00	1.00	1.00
300	1.10	1.04	1.04	1.00	1.00	1.00
350	1.13	1.06	1.06	1.01	1.00	1.00
400	1.18	1.09	1.08	1.03	1.00	1.00
450	1.21	1.11	1.09	1.05	1.00	1.00
500	1.24	1.14	1.01	1.06	1.00	1.00
550	1.29	1.18	1.13	1.08	1.01	1.00
600	1.35	1.22	1.15	1.10	1.02	1.00
650	1.43	1.31	1.17	1.12	1.03	1.00
700	1.54	1.44	1.19	1.14	1.04	1.00
730	1.67	..	..	..	..	1.00
740	..	1.50	..	1.15	1.05	1.00
750	..	..	1.20	..	..	1.00

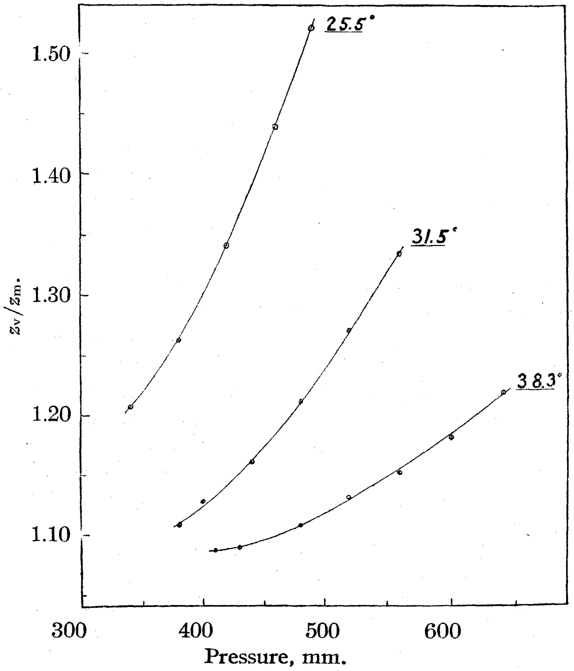


Fig. 5.—Variation of z_v/z_m with pressure.

association factors calculated from vapor density measurements are unaffected by the configuration of the polymers. Consequently, a comparison of the values estimated from the dipole moments with those obtained from vapor density data should make possible a rough estimate of the relative proportion of cyclic structures among the polymers. In Fig. 5 the ratios of the values of the association factor z_v obtained from vapor density measurements[4] to those of z_m are plotted against pressure at different temperatures for the whole range within which the two sets of data overlap. This graph shows that, as association increases, z_v becomes increasingly larger than z_m, by an amount greater than one would expect to be occasioned by any difference in the two methods of averaging. Actual computations for many equilibria assumed between two or more linear molecular species show that the discrepancy between z_v and z_m should be small. That these two association factors are different must then be attributable to the presence of cyclic structures which contribute to z_v but not to z_m. Stabilization of coiled-chain structures in which the dipole moments would largely cancel one another and give small resultant moment to the molecule as a whole would give the same effect as the presence of cyclic structures. Since, however, these coiled-chain structures do not possess the stabilizing factor of the extra bond possessed by the cyclic structures, there appears to be no reason to expect a proportion of coiled-chain structures greater than that corresponding to the random distribution assumed in the calculation of z_m. Contributory evidence along these lines is obtained from the work of Briegleb,[7] who, by assuming that only monomer and dimer were present at low pressures and that successively larger polymers made their appearances at successively higher pressures used vapor density data[5] to calculate the dependence of the concentrations of the individual polymers upon pressure at 28 and at 38°. The average dipole moments calculated by means of equation (6) from these extremely approximate concentrations are considerably higher than those in Table II, just as the values of z_v are higher than those of z_m. The presence of cyclic structures without dipole moment accounts for one discrepancy as well as for the other.

If the angle of 140° in the zig-zag chain indicated by electron diffraction were larger than the actual value, the error introduced in equation (6) would result in too low values for z_m. However, lowering of the angle to 90°, thereby replacing 40° by 90° in equation (6), still leaves the z_m values well below those of z_v.

Conclusions

The dielectric constant measurements and dipole moment calculations established the fact that hydrogen fluoride forms polar and, therefore, more or less linear polymers as indicated by X-ray and electron diffraction measurements. The discrepancy between the association factor calculated from dipole moment and that calculated from vapor density indicates the presence of cyclic polymers, the relative proportion of which increases with increasing association. The adsorption of hydrogen fluoride molecules on the metal surface of the condenser produces no significant error and the dielectric behavior of the adsorbed layer evidences the freedom of molecular orientation found in a liquid. The dipole moment results are consistent with the successive equilibria $HF + (HF)_n \rightleftarrows (HF)_{n+1}$ postulated by Briegleb[6,7] in the interpretation of the vapor densities, but show the incorrectness of the linear model with anti-parallel units which he adopted for the polymer structure. The existence of but one equilibrium, $6HF \rightleftarrows (HF)_6$, with the hexamer a ring, which was found[4] capable of representing the vapor density data, is quite inconsistent with the dipole moment results. The infinitely extended zig-zag chain shown by X-ray analysis[9] to exist in the crystal would, of course, be broken into fragments in the vapor. In the molecular beam indicated by electron diffraction[8] as consisting of these fragments, an appreciable proportion of cyclic structures might have escaped detection and the proportion may actually have been much lower than that existing under the conditions of the dielectric measurements. It is interesting to note that the zigzag structure indicated for the polymeric chain as compared to a rectilinear structure involves an attractive force between the proton of one hydrogen fluoride unit and negative charge localized as by an orbital in the fluorine of the adjacent hydrogen fluoride unit. In other words, the hydrogen bonding, in this case, though electrostatic, is not merely the undirected electrostatic attraction between the charges of a proton and an anion, as often implied in hydrogen bonding. The existence of both linear and cyclic structures in hydrogen fluoride is consistent with the belief of Bernal and Fowler[19] that both should exist in the liquid and with the conclusion of Pauling[10] that the additional bond obtained by ring formation should increase the stabilities of ring structures over open-chain structures when the degree of polymerization is greater than 5.

The work described in this paper was carried out as part of a research project supported by the Office of Naval Research.

Summary

The dielectric polarization of hydrogen fluoride vapor has been measured as a function of pressure at various temperatures above the normal boiling point of 19.4°. The apparatus employed has been described, and the errors due to adsorption of the hydrogen fluoride on the condenser walls have been shown to be unimportant. In the region of temperature and pressure where no molecular association occurs, a dipole moment value identical with that previously found in this laboratory has been obtained. At lower temperatures and higher pressures the experimental results show conclusively that a very considerable fraction of the associated molecules in the vapor state exists in various linear structures of large dipole moment, and that the average degree of association increases rapidly with increasing pressure or decreasing temperature. Further analysis of the data indicates that cyclic structures also exist in equilibrium with the chains, and that the former tend to increase in relative proportion with increase in pressure and decrease in temperature.

PRINCETON, N. J. RECEIVED JULY 2, 1947

---

(19) Bernal and Fowler, *J. Chem. Phys.*, **1**, 515 (1933).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

Perfluorinated Olefins

BY ALBERT L. HENNE AND THOS. H. NEWBY

The synthesis of perfluorinated ethylene and its polymerization to commercial TEFLON, $(CF_2)_n$, have become industrial processes; efforts are now directed at the synthesis of other fully fluorinated olefins in order to study their polymerization characteristics and their ability to copolymerize with $CF_2{=}CF_2$. We report here experiments toward the preparation of $CF_3CF{=}CF_2$, $CF_3CF{=}CFCF_3$, and $CF_3CF_2CF{=}CF_2$.

Synthesis of $CF_3CF{=}CF_2$

Perfluorinated propylene has been prepared by us before, but by a sequence which has too many steps for industrialization.[1] To simplify, we have subjected the easily available[2] $CCl_3CClFCCl_3$ to fluorination with antimony fluoride in the standard way, and have obtained in one step a 70% yield of $CF_2ClCFClCF_2Cl$, from which zinc in alcohol yielded $CF_2ClCF{=}CF_2$ almost quantitatively. From this olefin, it was expected that "allylic" fluorination[3] would easily yield the desired perfluorinated propylene, but this did not appreciably succeed because an allylic rearrangement took place which gave $CF_3CF{=}CClF$ instead of the desired product. The course of the rearrangement was evident from the facts that the rearranged olefin differed from the known[3] $CF_3CCl{=}CF_2$, and that its alkaline oxidation[4] yielded nothing but trifluoroacetic acid.

The desired synthesis was, however, completed as follows. The rearranged compound accepted a mole of chlorine to give the known[1] $CF_3CFClCFCl_2$, which antimony fluoride transformed into the known[1] $CF_3CFClCF_2Cl$. Dechlorination with zinc gave the desired perfluorinated propylene. The sequence is thus a simplified laboratory preparation, but is still too complex for industrial application.

The rearrangement reminded us of a similar case which could not be explained at the time. A

---

[1] Henne and Waalkes, THIS JOURNAL, **68**, 496 (1946).

[2] Henne and Haeckl, *ibid.*, **63**, 2692 (1941).

[3] Henne, Whaley and Stevenson, *ibid.*, **63**, 3478 (1941).

[4] Henne, Alderson and Newman, *ibid.*, **67**, 918 (1945).

sample of $CF_2{=}CFCFCl_2$ had been supplied by Dr. W. T. Miller of Cornell University with a request that it be "allylically" fluorinated to $CF_2{=}CFCF_3$. The operation failed to go further than C_3F_7Cl. The physical properties of this heptafluoride were the same as those of $CFCl{=}CFCF_3$ made by chlorine removal from $CFCl_2CFClCF_3$, as well as those of the rearranged product mentioned above.

Preparation of $CCl_3CFClCCl_3$.—Chlorine was bubbled through 250 ml. of $CH_3CFClCH_2Cl$ in ultraviolet light until the refractive index no longer increased (one week). After washing, neutralizing and drying, vacuum distillation gave 53% of good $CCl_3CFClCCl_3$, b. p. 95° at 9 mm., n_D 1.5194 at 20°, and 47% of incompletely chlorinated material which was successfully rechlorinated.

Preparation of $CF_2ClCFClCF_2Cl$.—In a steel vessel, 216 g. (1.2 mole) of antimony trifluoride was combined under pressure with 44 g. (0.62 mole) of chlorine. This was then heated with 160 g. (0.53 mole) of $CCl_3CClFCCl_3$ at 225° for two hours, then at 150° overnight. The organic material was distilled from the bomb then steamed, to give 110 g. of material n_D 1.358 at 20°. Fractional distillation gave 98 g. (70%) of $C_3F_5Cl_3$, b. p. 72–73°, n_D 1.350 at 22° and a small amount of less fluorinated product.

Anal. Calcd.: Cl, 44.8; mol. wt., 238. Found: Cl, 44.9; mol. wt., 240.

Preparation of $CF_2ClCF{=}CF_2$.—$C_3F_5Cl_3$ (168 g. or 0.706 mole) in 150 ml. of absolute alcohol was refluxed with 65 g. (1 mole) of mossy zinc for two days. The reaction product which distilled through the reflux condenser was liquefied in an ampule cooled with Dry Ice. After washing through water and drying, fractional distillation gave 102 g. (86%) of $CF_2ClCF{=}CF_2$, b. p. 7.6°, and a small amount of unreacted material. Dilution of the reaction mixture with water precipitated an additional 6% of unreacted material. Titration of the chlorine ion in the solution indicated the correct molecular weight for the olefin.

Rearrangement to $CF_3CFC{=}FCl$.—In a steel vessel, 82 g. (0.46 mole) of antimony fluoride was combined with 13 g. (0.18 mole) of chlorine. After cooling, 102 g. (0.16 mole) of $CF_2ClCF{=}CF_2$ was added. The vessel was closed, heated in steam for eighteen hours, then at 125° for nine hours. Distillation gave a small amount of low boiling material, then 84 g. (82%) of a substance, b. p. 7.7 to 7.9° (uncor.), f. p. −156.8 to −159.6°. These properties come close to those reported[1] for the *cis–trans* mixture of $CF_3CF{=}CFCl$, b. p. 7.9°, f. p. −158°.

Synthesis of $CF_3CF{=}CFCF_3$

By means of the lead oxide–hydrogen fluoride procedure,[5] the previously reported[6] $CF_3CCl{=}CClCF_3$ was transformed into $CF_3CFClCFClCF_3$, from which zinc gave an excellent yield of the desired perfluorinated 2-butene. Later, the starting $CF_3CCl{=}CClCF_3$ was prepared in a single, standardized operation[7] from commercial C_4Cl_6, and this improvement made the sequence adaptable to commercial production.

Preparation of $CF_3CClFCClFCF_3$.—In a steel vessel cooled with Dry Ice were placed 239 g. (1 mole) of lead dioxide, 400 g. (20 moles) of liquefied hydrogen fluoride and 240 g. (1.03 mole) of $C_4H_6Cl_2$. After closing, the system was allowed to warm up, while being mechanically rocked. A reaction took place which temporarily raised the pressure to six atmospheres. The reaction mixture was poured onto ice, neutralized while cold, then steamed. The distillate contained 229 g. of a product n_D 1.337 at 25°. This is a mixture of $C_4F_8Cl_2$, b. p. 63°, and $C_4F_6Cl_2$, b. p. 65°, which it is impractical to separate by distillation. In general this mixture accounted for 26% of the desired reaction product and 63% of recovered olefin. To prepare pure $C_4F_8Cl_2$, the mixture was fractionally distilled, and the head fractions treated with permanganate to destroy the olefin. *Anal.* Calcd.: Cl, 26.2. Found: Cl, 24.2.

Preparation of $CF_3CF{=}CFCF_3$.—The mixture of $C_4F_8Cl_2$ and $C_4F_6Cl_2$ was treated with zinc in alcohol. A heating period of sixty hours was needed to complete the reaction. The expected amount of C_4F_8 distilled through the reflux condenser and was received in a Dry Ice cooled ampule. It was purified by fractional distillation; its molecular weight was computed as 270 from the chlorine ion concentration in the reaction mixture (calcd. 271). Its boiling and freezing characteristics indicate a *cis–trans* mixture. From the reaction mixture, C_4F_6Cl was recovered by precipitation with water.

Attempted Synthesis of $C_2F_5CF{=}CF_2$

Several schemes were tried, all of which deviated from the expected paths for the reasons stated.

First Attempt.—$CF_3CCl_2CCl_2CCl_3$ was prepared by extensive chlorination of $CF_3CH{=}CClCCl_3$[6] for reaction with zinc, in the hope that $CF_3CCl_2CCl{=}CCl_2$ would be preferentially obtained. From this derivative, the preparation of $C_2F_5CF{=}CF_2$ would have been the same problem as the synthesis of $CF_3CF{=}CF_2$ from $CCl_3CCl{=}CCl_2$. The zinc reaction could not be mastered, and only small amounts of $CF_3CCl_2CCl{=}CCl_2$ were obtained. This compound was transformed by a conventional fluorination into a pentafluoride presumed to be $C_2F_5CCl{=}CCl_2$ (calcd.: Cl, 42.8; found: 43). Oxidation of the latter gave a fluorinated acid which was not CF_3CO_2H, an indication that the double bond had not shifted to the center of the molecule. This fluorinated acid was not further identified.

Second Attempt.—The starting point was the easily obtained $CCl_3CF_2C_2Cl_5$.[8] Actuated by the observation that perchlorocyclopentene is easily transformed into a hexafluoride rather than a tetrafluoride,[9] we tried to transform the starting material with zinc into $CCl_3CF_2CCl{=}CCl_2$, in order to attempt fluorination of CCl_3 group located just beyond the allylic position. The zinc reaction could not be mastered, but this difficulty was skirted by subjecting the starting material to conventional fluorination, and obtaining thereby a tetra-, a penta- and a hexafluoride formulated as $CCl_3CF_2CCl_2CClF_2$, $CCl_2FCF_2CCl_2CClF_2$ and $CClF_2CF_2CCl_2CClF_2$ on the basis of the known[10] ease of fluorination. Dechlorination of the first two compounds with zinc proceeded quite well and gave the expected olefins $CCl_3CF_2CCl{=}CF_2$ and $CCl_2FCF_2CCl{=}CF_2$, respectively. Both were subjected to fluorination to see whether they would give $CF_3CF_2CCl{=}CF_2$. The reaction proceeded only at high temperature and gave a ma-

---

(5) Henne and Waalkes, This Journal, **67**, 1639 (1945).

(6) Henne, Zimmerschied and Hinkamp, *ibid.*, **68**, 1906 (1945).

(7) Henne and Trott, *ibid.*, **67**, 1820 (1947).

(8) Henne and Hinkamp, *ibid.*, **67**, 1195 (1945).

(9) Henne and Zimmerschied, *ibid.*, **67**, 1235 (1945).

(10) Henne in "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., p. 56.

TABLE I

PHYSICAL CONSTANTS

Compound	B. p., °C. (760 mm.)	F. p., °C.	*t*, °C.	d^t_4	n^t_D	*MR*	*AR*F
$CCl_2FCFClCFCl_2$	154.7	glass	20	1.7624	1.4387	40.4	1.0
$CF_2ClCFClCF_2Cl$	73.7	−72 ± 3	20	1.6631	1.3512	30.8	1.1
$CF_2=CFCF_2Cl$	7.5	glass	1.4	1.5116	1.3050	20.9	1.1
$CFCl=CFCF_3$	8.4	−156	(*cis–trans* mixture)				
$CF_3CCl=CClCF_3$[a]	.....	− 56 to −59	20	1.6203	1.3464	30.7	1.2
$CF_3CFClCFClCF_3$	62.9	− 73 to −75	20	1.6801	1.3100	31.1	1.0
$CF_3CF=CFCF_3$	0.4 to 3.0	−129 to −139	(*cis–trans* mixture)				
$CF_3CCl_2CCl_2CCl_3$		67–69					
$CF_3CF_2CCl=CCl_2$	140.7	.....	20	1.7421	1.4040	35.1	1.2
$CCl_3CF_2CCl_2CClF_2$	209	glass	20	1.8392	1.4551	49.3	1.0
$CCl_2FCF_2CCl_2CClF_2$	171.3	glass	20	1.8047	1.4211	45.0	1.1
$CF_2ClCF_2CCl_2CClF_2$	134.2	glass	20	1.7625	1.3856	40.5	1.2
$CCl_3CF_2CCl=CF_2$	142.4	glass	20	1.7084	1.4254	39.8	1.1
$CCl_2FCF_2CCl=CF_2$	104.1	glass	20	1.6671	1.3840	35.0	1.1
$CF_3CCl_2CClFCF_3$	97.5	glass	20	1.7494	1.3530	35.7	1.1
$CF_3CCl=CFCF_3$ (*cis-trans* mixt.)	32.2	glass	20	1.5482	1.2946	23.7	0.9

[a] Different *cis–trans* isomer ratio than that obtained by Henne, Hinkamp, and Zimmerschied[6] (m. p. −67.3°).

terial which analysis showed to be $C_4F_7Cl_3$ (calcd.: Cl, 37.2; found: Cl, 37.4). The first interpretation was that this was the dichloride of the desired $CF_3CF_2CCl=CF_2$. The two extra chlorine atoms were easily removed with zinc, and the olefin subjected to oxidation to ascertain whether it was the desired one. Instead of giving $C_2F_5CO_2H$, the oxidation yielded nothing but CF_3CO_2H, showing that the double bond had shifted to the center of the molecule. We were therefore forced to admit that an allylic shift had taken place, probably from $CClF_2CF_2CCl=CF_2$ to $CF_2ClCF=CClCF_3$ and that the latter had then been fluorinated to $CF_3CF=CClCF_3$.

Preparation of $CCl_3CF_2CCl=CCl_2$.—In a steel container were placed 211 g. (0.57 mole) of $CCl_3CF_2C_2Cl_5$, 40 g. (0.6 mole) of freshly cut zinc and 665 cc. of absolute alcohol. After closing, heating in a steam-bath was allowed for three days, which brought the pressure to about 4 atm. On pouring out after cooling, 126 g. of organic material and 70 g. of tar were obtained. Distillation at 2 to 3 mm. gave 92 g. of crude $C_4F_2Cl_6$, b. r. 44 to 50°, representing at 31% yield. Redistillation gave a pure material.

Fluorination of $CCl_3CF_2C_2Cl_5$.—The customary procedure was followed. With SbF_3Cl_2 as fluorinating agent, average yields were 6% of $C_4F_6Cl_4$, 23% of $C_4F_5Cl_5$, 40% of $C_4F_4Cl_6$ and 27% of a high polymer.

Dehalogenation of $C_4F_5Cl_5$ and $C_4F_4Cl_6$.—The customary zinc reaction in absolute alcohol proceeded very smoothly and quantitatively.

Fluorination of $C_4F_5Cl_3$ and $C_4F_4Cl_4$.—A mixture of these fluorides, (0.86 mole) was heated with SbF_3Cl_2 (1 mole) in a steel vessel at 200° for sixteen hours. The pressure reached 18 atmospheres. After bleeding off the gases, without obtaining $C_2F_5CCl=CF_2$, an additional heating period of twenty hours was permitted. On working up the reaction products, 143 g. of $C_4F_7Cl_3$ (53% yield) was found boiling at 97°. This material underwent the customary zinc dechlorination to yield C_4F_7Cl easily and quantitatively. The latter on standard oxidation gave exclusively trifluoroacetic acid, the sodium salt of which was analyzed to give 17.6% Na found (16.9 calcd.) and 41.8% F (41.9 calcd.). A search for a chlorofluoro acid gave negative results.

Summary

A synthesis sequence for $CF_3CF=CF_2$ was complicated by a rearrangement. A practical, simple sequence gave $CF_3CF=CFCF_3$. The preparation of $C_2F_5CF=CF_2$ was defeated by rearrangements.

COLUMBUS, OHIO

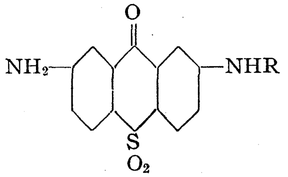
RECEIVED JULY 14, 1947

[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

Studies in the Sulfone Series. IV.[1] Certain Heterocyclic Derivatives of 2,8-Diaminothiaxanthone-5-dioxide

BY E. D. AMSTUTZ, E. A. FEHNEL[2] AND I. M. HUNSBERGER[3]

In a continuation of the work on antitubercular compounds described in the preceding paper of this series,[1] the synthesis of various monosubstituted N-heterocyclic derivatives of 2,8-diaminothiaxanthone-5-dioxide (I–IV) has been attempted to determine if these substances exhibit chemotherapeutically interesting properties in view of their relationships to the simpler materials reported earlier.[4]



I (R = 2-pyridyl)
II (R = 2-pyrimidyl)
III (R = 2-thiazolyl)
IV (R = 2-quinolyl)

The reactions involved in the synthesis of the desired materials are outlined in the accompanying diagram.

For the preparation of the intermediate derivatives, the older route through the 2-thiophenoxybenzoic acids (VI)[5] and the more recently described route through the corresponding aldehydes (VII)[6] both were studied, and the latter method was found to be greatly superior to the former. The condensation of the sodium salts of *p*-iodo- and *p*-bromothiophenol with 2-chloro-5-nitrobenzaldehyde took place readily and in good yields, while with 2-chloro-5-nitrobenzoic acid low yields were obtained even after prolonged refluxing. On oxidation with excess 30% hydrogen peroxide in glacial acetic acid, both the aldehyde (VII) and the acid (VI) gave the identical 5-nitro-2-(*p*-halobenzenesulfonyl)-benzoic acid (VIII).

The ring-closure of the 2-thiophenoxybenzaldehyde (VII) to an equimolecular mixture of the thiaxanthene (IX) and thiaxanthone (X) proceeded readily in cold concentrated sulfuric acid solution. In one experiment the solution was diluted with water as soon as all the aldehyde (VII, Y = I) had dissolved, and the resultant precipitate was separated into its components by repeated fractional crystallization from acetone to yield 83% of the theoretical amount of 2-iodo-8-nitrothiaxanthene (IX, Y = I) and 91% of 2-iodo-8-nitrothiaxanthone (X, Y = I). Similar results were obtained in the bromo series. The same 2-halo-8-nitrothiaxanthones (X) also were obtained by the cyclodehydration of the 5-nitro-2-(*p*-halothiophenoxy)-benzoic acids (VI) in hot concentrated sulfuric acid.

In the present investigation chromium trioxide readily oxidized both IX and X, as well as the equimolecular mixture of these compounds from the aldehyde cyclization, to the desired thiaxanthone-5-dioxide (XIII) in excellent yields.[7]

Reduction of the nitro groups to an amino group was carried out as in the previous paper.[1] Attempts to bring about the simultaneous reduction of the nitro and carbonyl groups of XIII by means of metal–acid combinations were unsuccessful, since reductive dehalogenation led to intractable mixtures which apparently contained large proportions of 2-aminothiaxanthene-5-dioxide.

At 200° 2-iodo-8-aminothiaxanthone-5-dioxide (V, Y = I)[8] reacted smoothly with excess 2-aminopyrimidine in the presence of potassium carbonate and copper powder to give good yields of II, but the reaction with 2-aminopyridine appeared to take a somewhat different course. Since this prod-

---

[1] For the preceding paper in this series see Amstutz and Neumoyer, THIS JOURNAL, **69**, 1925 (1947).

[2] Lehigh Student Chemical Foundation Fellow, 1945–1946. Present address: Department of Chemistry, University of Pennsylvania, Philadelphia 4, Pa.

[3] A. C. S. Predoctoral Fellow, 1946–.

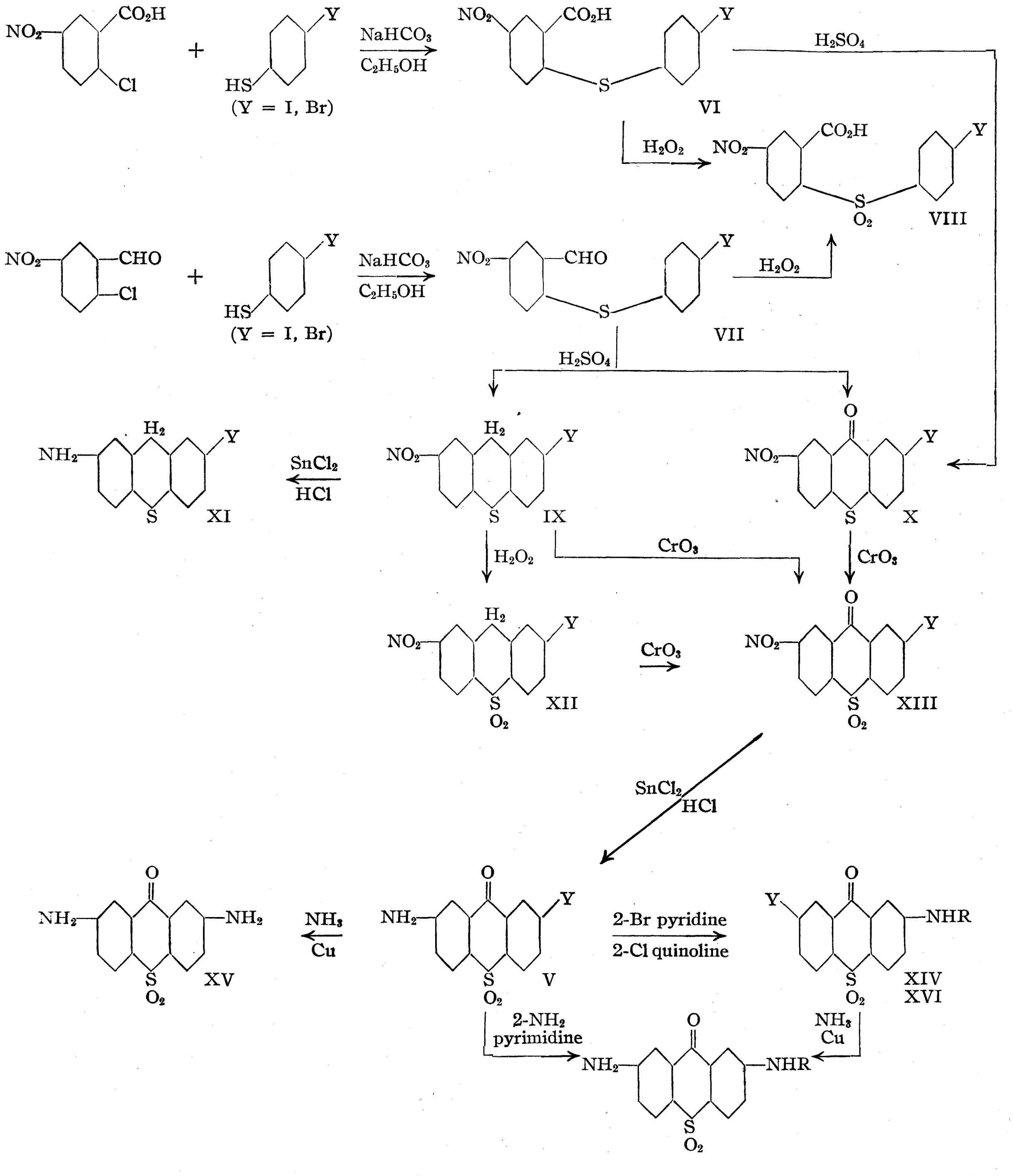
[4] Ref. (1) and Amstutz, Fehnel and Woods, THIS JOURNAL, **69**, 1922 (1947).

[5] Mayer, *Ber.*, **42**, 1132, 3046 (1909); **43**, 584 (1910).

[6] Ref. (1) and Campbell, Dick, Ferguson and Loudon, *J. Chem. Soc.* 747 (1941).

[7] In contrast to the outstanding success reported by Campbell and his associates (6) in oxidizing the thiaxanthene–thiaxanthone mixture to the corresponding thiaxanthone-5-dioxide with 30% hydrogen peroxide, this reagent was found to be completely unsatisfactory for the oxidation of the 2-iodo-8-nitro-(thiaxanthene–thiaxanthone) mixture (IX + X, Y = I), and it gave only moderately good results with the corresponding bromo-(thiaxanthene–thiaxanthone) mixture. It was found that IX (Y = I) and X (Y = I) each rapidly catalyzed the decomposition of hydrogen peroxide and that the methylene group of IX (Y = I) remained unattacked even after repeated treatments with large excesses of fresh hydrogen peroxide in acetic acid. The only product isolated from the hydrogen peroxide oxidation of IX (Y = I) was 2-iodo-8-nitrothiaxanthene-5-dioxide (XII, Y = I), which was obtained in 92% yield. Similar but less clear-cut results were obtained with the corresponding bromo compound (IX, Y = Br), which was not so effective a catalyst for the decomposition of the peroxide. These results may be related to some peculiar observations of Hilditch and Smiles (*J. Chem. Soc.*, **99**, 145 (1911)), who reported that the action of a large excess of 30% hydrogen peroxide on thiaxanthene in boiling acetic acid affords thiaxanthene-5-dioxide in good yield, while the addition of the same reagent to a cold acetic acid solution of thiaxanthene with subsequent refluxing gives thiaxanthone as the sole product.

[8] It was originally hoped that access to the mono-N-heterocyclic compounds of type I–III could be gained by condensation of 2-bromo-8-aminothiaxanthone-5-dioxide (V, Y = Br) with 2-aminoheterocycles, since the yield of the *p*-bromothiophenol intermediate greatly exceeds that of the corresponding iodo compound. Although amination to the diamino compound occurred on heating the bromo compound (V, Y = Br) with ammonia in the presence of copper powder in a sealed tube, various attempts to carry out a similar reaction with several representative amines were uniformly unsuccessful. The recovery of large amounts of unchanged V indicated that the expected activation of the bromine atom by the para sulfonyl group, ((a) Todd and Shriner, THIS JOURNAL, **56**, 1382 (1934); (b) Loudon, *J. Chem. Soc.*, 902 (1939); (c) Loudon and Shulman, *ibid.*, 1618 (1938); (d) Loudon and Robson, *ibid.*, 242 (1937)), was not sufficient to permit its replacement by a substituted amino group.



uct evolved considerable ammonia on treatment with alcoholic potassium hydroxide, it was concluded that the 2-aminopyridine had reacted, at least in part, in the 2-aminopyridone form. This difficulty was circumvented by condensing 2-bromopyridine with the amino group of V (Y = I or Br), thus attaching a N-2-pyridylamino group in the desired position on the thiaxanthone dioxide nucleus.[9] The halogen atom then was replaced with an amino group by treatment of the 2-halo-8-(N-2-pyridyl)-aminothiaxanthone-5-dioxide (XIV) with concentrated aqueous ammonia in the presence of copper powder in a sealed tube at 210–220°. The same product, I, was obtained from both the iodo and bromo intermediates.

---

[9] *Cf.* Gray, *J. Chem. Soc.*, 1202 (1939). The use of 2-chlorothiazole was attempted but with little success, a very complex mixture being obtained in every run. 2-Chloroquinoline behaved more satisfactorily, and eventually the desired product was obtained in small yield.

All of the thiaxanthone dioxide derivatives prepared in this investigation gave characteristic colors, ranging from green to violet, on treatment with zinc dust in warm aqueous-alcoholic alkali.[10] The thiaxanthene dioxides gave similar colors *directly* on treatment with cold dilute aqueous-alcoholic alkali. These colors disappear quickly on exposure to air, especially on shaking, and in the case of the thiaxanthene dioxides can be made to reappear only by the addition of a suitable reducing agent such as zinc dust. These color reactions may involve the formation of semiquinone-type free radicals, but direct evidence on this point is lacking.

Acknowledgment.—The authors wish to express their appreciation to The Wm. S. Merrell Company for defraying a portion of the expenses of this investigation and to Dr. C. R. Neumoyer for his interest and assistance in part of the experimental work.

Experimental

5-Nitro-2-(*p*-iodothiophenoxy)-benzoic Acid (VI, Y = I).—To a warm (50–60°) solution of 85.0 g. (0.42 mole) of 2-chloro-5-nitrobenzoic acid[1] in 800 ml. of 95% ethanol, 400 ml. of water was added slowly followed by 103 g. (0.436 mole) of *p*-iodothiophenol[11] and 73.2 g. (0.87 mole) of sodium bicarbonate. The mixture was refluxed for twenty-two hours, and about two-thirds of the solvent then was removed by distillation. The residue was diluted with a large volume of water to precipitate the product, which was recrystallized from ethanol to yield 37.0 g. of a high-melting acid fraction and 40.0 g. (39%) of a lower-melting neutral fraction, m. p. 120–125°, which appeared to be 4,4′-diiododiphenyl disulfide. The acid fraction was purified by dissolution in hot aqueous sodium carbonate solution and reprecipitation with hydrochloric acid. Repeated crystallization from glacial acetic acid and from ethanol yielded bright yellow crystals, m. p. 244–247°.

Anal. Calcd. for $C_{13}H_8O_4NSI$: S, 7.99; I, 31.6; neut. equiv., 401. Found: S, 8.14; I, 31.6; neut. equiv., 397.

5-Nitro-2-(*p*-bromothiophenoxy)-benzoic Acid (VI, Y = Br).—A mixture of 1.7 g. (0.009 mole) of *p*-bromothiophenol,[12] 1.6 g. (0.008 mole) of 2-chloro-5-nitrobenzoic acid, 1.2 g. (0.021 mole) of potassium hydroxide, and a trace of copper powder in 90 ml. of 95% ethanol was refluxed for twenty-two hours under nitrogen. After about two-thirds of the solvent had been removed by distillation, 100 ml. of water was added to the residue, and the resultant mixture was made acid to congo red by addition of hydrochloric acid. The yellow precipitate was recrystallized from aqueous ethanol to yield 1.0 g. (36%) of yellow microcrystalline powder, m. p. 224–226°. Calcd. for $C_{13}H_8O_4NSBr$: neut. equiv., 354. Found: 357.[13]

5-Nitro-2-(*p*-iodothiophenoxy)-benzaldehyde (VII, Y = I).—A mixture of 98.4 g. (0.416 mole) of *p*-iodothiophenol, 74.2 g. (0.40 mole) of 2-chloro-5-nitrobenzaldehyde,[1] 35.0 g. (0.416 mole) of sodium bicarbonate, 850 ml. of 95% ethanol and 450 ml. of water was refluxed for two hours. The yellow curdy precipitate was washed, dried, and recrystallized from glacial acetic acid to yield 128.6 g. (84%) of yellow needles, m. p. 131–133°.

Anal. Calcd. for $C_{13}H_8O_3NSI$: S, 8.33; I, 33.0. Found: S, 8.21; I, 33.1.

5-Nitro-2-(*p*-bromothiophenoxy)-benzaldehyde (VII, Y = Br).—This compound was prepared by condensing 28.4 g. (0.15 mole) of *p*-bromothiophenol with 26.0 g. (0.14 mole) of 2-chloro-5-nitrobenzaldehyde in the presence of 12.6 g. (0.15 mole) of sodium bicarbonate in 300 ml. of ethanol and 150 ml. of water as in the case of the corresponding iodo compound above; yield, 46.2 g. (98%) of yellow needles, m. p. 123–125°.

Anal. Calcd. for $C_{13}H_8O_3NSBr$: S, 9.49; Br, 23.7. Found: S, 9.50; Br, 23.5.

5-Nitro-2-(*p*-iodobenzenesulfonyl)-benzoic Acid (VIII, Y = I).—A solution of 1.6 g. (0.004 mole) of VI (Y = I) and 2.8 ml. (0.025 mole) of 30% hydrogen peroxide in 35 ml. of glacial acetic acid was refluxed for three hours. Addition of a large volume of water to the cooled mixture precipitated a crude product which was washed with water and recrystallized from ethanol to yield 1.4 g. (81%) of white powder, m. p. 242–246° dec.

Anal. Calcd. for $C_{13}H_8O_6NSI$: S, 7.40; I, 29.3. Found: S, 7.48; I, 29.5.

5-Nitro-2-(*p*-bromobenzenesulfonyl)-benzoic Acid (VIII, Y = Br).—A mixture of 1.0 g. (0.003 mole) of VII (Y = Br), 3.0 ml. (0.027 mole) of 30% hydrogen peroxide, and 20 ml. of glacial acetic acid was refluxed for two hours, cooled and poured into a large volume of water. The precipitate was washed with water and dried; yield, 1.0 g. (90%) of white powder, m. p. 190.5–192°.

Anal. Calcd. for $C_{13}H_8O_6NSBr$: S, 8.31; Br, 20.7; neut. equiv., 386. Found: S, 8.32; Br, 20.5; neut. equiv., 379.

2-Iodo-8-nitrothiaxanthene (IX, Y = I) and 2-Iodo-8-nitrothiaxanthone (X, Y = I).—Ten grams (0.026 mole) of VII (Y = I) was dissolved in 100 ml. of cold concentrated sulfuric acid, and the dark red solution was poured onto 150 g. of cracked ice. The yellow precipitate was washed and dried at 100°. By alternate digestion and recrystallization with hot acetone, this mixture was separated into its components, yielding 4.0 g. (83%) of 2-iodo-8-nitrothiaxanthene as yellow crystals, m. p. 155.5–157.5°, and 4.5 g. (91%) of 2-iodo-8-nitrothiaxanthone as a yellow powder, m. p. 300–303° dec.

Anal. Calcd. for $C_{13}H_8O_2NSI$ (thiaxanth*ene*): S, 8.69. Found: S, 8.54. Calcd. for $C_{13}H_6O_3NSI$ (thiaxanth*one*): S, 8.37. Found: S, 8.22.

2-Iodo-8-nitrothiaxanthone (X, Y = I) also was obtained by the following cyclodehydration of VI (Y = I). Twenty grams (0.050 mole) of VI (Y = I) was dissolved in 180 ml. of concentrated sulfuric acid at 100°. The solution was maintained at this temperature for ninety minutes, allowed to cool to room temperature, and poured onto 600 g. of cracked ice. The resultant precipitate was washed, dried, and recrystallized from acetic anhydride to yield 16.2 g. (84%) of yellow microcrystalline powder, m. p. 295–300° dec. Another recrystallization raised the melting point to 297–301° dec.; a mixed melting point with the corresponding compound obtained from the aldehyde cyclization showed no depression.

2-Bromo-8-nitrothiaxanthene (IX, Y = Br) and 2-Bromo-8-nitrothiaxanthone (X, Y = Br).—The aldehyde (VII, Y = Br) (16.2 g., 0.048 mole) was cyclized in 150 ml. of cold concentrated sulfuric acid as in the case of the corresponding iodo compound above. The yellow thiaxanthene–thiaxanthone mixture was separated into its components by alternate digestion and recrystallization with hot acetic acid, yielding 5.2 g. (67%) of 2-bromo-8-nitrothiaxanthene as yellow crystals, m. p. 162–164.5°, and 7.4 g. (92%) of 2-bromo-8-nitrothiaxanthone as a bright yellow powder, m. p. 282–285° dec.

---

(10) *Cf.* Graebe and Schultess, *Ann.*, **263**, 1 (1891); Ullmann and Lehner, *Ber.*, **38**, 729 (1905); Ullmann and Glenck, *ibid.*, **49**, 2487 (1916).

(11) Prepared in 59% yield by the reduction of *p*-iodobenzenesulfonyl chloride with tin and hydrochloric acid; *cf.* Hubner and Alsberg, *Ann.*, **156**, 325 (1870).

(12) Prepared in 98% yield from *p*-bromobenzenesulfonyl chloride by an adaptation of the method for thiophenol given in "Organic Syntheses," Coll. Vol. I, 2d ed., p. 504 (1941).

(13) This compound was not analyzed, but its formula may be considered established because the product obtained on ring-closure with sulfuric acid was identical with authentic 2-nitro-8-bromothiaxanthone (X, Y = Br) prepared from 5-nitro-2-(*p*-bromothiophenoxy)-benzaldehyde (VII, Y = Br).

Anal. Calcd. for $C_{13}H_8O_2NSBr$ (thiaxanth*ene*): S, 9.95. Found: S, 10.03. Calcd. for $C_{13}H_6O_3NSBr$ (thiaxanth*one*): S, 9.56. Found: S, 9.66.

The cyclodehydration of 1.0 g. (0.003 mole) of VI (Y = Br) in 9 ml. of hot concentrated sulfuric acid by the method used above for the corresponding iodo compound afforded 0.9 g. (95%) of 2-bromo-8-nitrothiaxanthone, m. p. 283–286° dec.; this material did not depress the melting point of the corresponding compound obtained from the aldehyde ring-closure.

2-Bromo-8-aminothiaxanthene (XI, Y = Br).—The solution obtained by passing dry hydrogen chloride into a suspension of 4.1 g. (0.018 mole) of stannous chloride dihydrate in 22 ml. of glacial acetic acid was added to a suspension of 1.6 g. (0.005 mole) of IX (Y = Br) in 6 ml. of glacial acetic acid heated to 80–85°, after which stirring was continued at this temperature for two hours. The white tin complex which precipitated on cooling was removed, treated with cold 10% aqueous sodium hydroxide, thoroughly washed with water, and dried at 100°; yield, 1.4 g. (96%) of yellow powder, m. p. 177–181°. Recrystallization from ethanol then afforded brownish-yellow plates, m. p. 183–184°.

Anal. Calcd. for $C_{13}H_{10}NSBr$: S, 10.99. Found: S, 11.12.

2-Iodo-8-nitrothiaxanthene-5-dioxide (XII, Y = I).—One gram (0.0027 mole) of IX (Y = I) was refluxed for three hours with 3.0 ml. of 30% hydrogen peroxide in 30 ml. of glacial acetic acid, after which the supernatant liquid gave a negative test for hydrogen peroxide (no color with aqueous potassium iodide solution). Another 8.0 ml. of 30% hydrogen peroxide was added in 2-ml. portions at intervals during the next four hours, and the mixture then was allowed to cool to room temperature. The pale yellow precipitate was crystallized from acetic anhydride to yield 1.0 g. (92%) of almost colorless needles, m. p. 229–231°, which gave a deep green color on treatment with aqueous-alcoholic alkali.

Anal. Calcd. for $C_{13}H_8O_4NSI$: S, 7.97. Found: S, 8.11.

2-Bromo-8-nitrothiaxanthene-5-dioxide (XII, Y = Br).—This compound was formed along with the corresponding thiaxanthone dioxide (XIII, Y = Br) when IX (Y = Br) was treated with a slight excess of hydrogen peroxide in boiling acetic acid. When 1.8 g. (0.0056 mole) of the thiaxanthene was refluxed for two hours with 1.5 ml. (0.015 mole) of 30% hydrogen peroxide in 30 ml. of glacial acetic acid, repeated fractional crystallization from acetic acid produced 0.5 g. (28%) of unreacted IX (Y = Br), 0.3 g. (15%) of XIII (Y = Br) melting at 265–268° with previous sintering, and 0.8 g. (41%) of pale yellow crystals of XII (Y = Br), m. p. 205–207°. The last compound gave a deep green color on treatment with aqueous-alcoholic alkali.

Anal. Calcd. for $C_{13}H_8O_4NSBr$: S, 9.07. Found: S, 9.17.

2-Iodo-8-nitrothiaxanthone-5-dioxide (XIII, Y = I).—This compound may be prepared by the chromium trioxide oxidation of the corresponding thiaxanthene (IX) or its dioxide (XII), the thiaxanthone (X), or the thiaxanthene–thiaxanthone mixture (IX + X) from the aldehyde ring-closure.

(a) **From 2-Iodo-8-nitrothiaxanthene-5-dioxide (XII, Y = I).**—A mixture of 0.8 g. of XII (Y = I), 0.5 g. of chromium trioxide, 20 ml. of glacial acetic acid, and a few drops of concentrated sulfuric acid (added as a catalyst) was refluxed for ninety minutes. Filtration of the cooled dark green solution yielded 0.8 g. of tan microcrystalline powder, m. p. 303–305° dec. Recrystallization from acetic anhydride then afforded 0.7 g. of almost colorless crystals, m. p. 303–306° dec.

Anal. Calcd. for $C_{13}H_6O_5NSI$: S, 7.73. Found: S, 7.80.

(b) **From 2-Iodo-8-nitrothiaxanthone (X, Y = I).**—This compound remained unattacked when refluxed for prolonged periods with large excesses of 30% hydrogen peroxide in acetic acid, although the oxidizing agent rapidly disappeared from the reaction mixture (potassium iodide test). Complete oxidation was effected with chromium trioxide as follows: To a suspension of 1.0 g. of X (Y = I) in refluxing glacial acetic acid enough chromium trioxide was added in small portions over a two-hour period to produce a brownish color. Filtration of the cooled mixture afforded 1.1 g. of pale yellow crystals, m. p. 296–298° dec. Recrystallization from a large volume of acetic anhydride yielded 1.0 g. (92%) of almost colorless crystals, m. p. 296–300° dec.

(c) **From the 2-Iodo-8-nitro-(thiaxanthene–thiaxanthone) Mixture (IX + X, Y = I).**—Oxidation of the thiaxanthene–thiaxanthone mixture with excess 30% hydrogen peroxide in boiling acetic acid afforded only low-melting mixtures consisting principally of partially oxidized compounds. Satisfactory results readily were obtained, however, using chromium trioxide as the oxidizing agent. The product from the ring-closure of 114 g. (0.296 mole) of VII (Y = I) with 1140 ml. of sulfuric acid according to the method previously described was sucked as dry as possible on the filter and then transferred directly to a large flask with 1500 ml. of glacial acetic acid. To this mixture was added 125 g. (1.25 moles) of chromium trioxide, and heat was applied cautiously until refluxing began. After the initially exothermic reaction had subsided, refluxing was continued for another two hours by the application of external heat. The white precipitate obtained from the cooled mixture was washed with water and dried. Since no suitable solvent for the recrystallization of this large amount of product could be found, purification was effected by digesting several times with fresh quantities of acetic anhydride. 2-Iodo-8-nitrothiaxanthone-5-dioxide was obtained as a colorless microcrystalline powder, m. p. 300–305° dec.; yield, 116 g. (95%, based on the aldehyde used).

The identity of the products obtained by these different routes was established by the method of mixed melting points. On treatment with zinc dust and warm aqueous-alcoholic alkali all these products gave a green color which was discharged on exposure to air.

2-Bromo-8-nitrothiaxanthone-5-dioxide (XIII, Y = Br).—The thiaxanthene–thiaxanthone mixture obtained from the ring-closure of 43.2 g. (0.128 mole) of VII (Y = Br) with 430 ml. of sulfuric acid was oxidized in 950 ml. of glacial acetic acid by refluxing for four hours with Superoxol (130 ml., 1.28 moles). After cooling to room temperature the mixture was filtered, and the precipitate was washed with sodium bicarbonate solution and water, and dried at 100°. The crude product melted at 244–251° with previous sintering; yield, 41.2 g. (88%). Recrystallization from acetic anhydride then afforded pale yellow crystals, m. p. 270–271° with previous sintering; over-all yield, based on the aldehyde, 79%. This compound did not depress the melting point of the analytically pure material obtained below by chromium trioxide oxidation of the aldehyde-cyclization mixture.

The same compound, m. p. 266–268°, also was obtained by the oxidation of X (Y = Br) with excess 30% hydrogen peroxide in boiling acetic acid.

The analytical sample of XIII (Y = Br) was prepared by the oxidation of a small sample of the aldehyde-cyclization mixture (IX + X, Y = Br) with excess chromium trioxide in acetic acid exactly as in the case of the corresponding iodo compound described above. Recrystallization from acetic anhydride gave almost colorless needles, m. p. 273–275° with previous sintering.

Anal. Calcd. for $C_{13}H_6O_5NSBr$: S, 8.71 Found: S, 8.70.

Like the corresponding iodo compound, XIII (Y = Br) gave a transient green color on treatment with zinc dust and aqueous-alcoholic alkali.

2-Iodo-8-aminothiaxanthone-5-dioxide (V, Y = I).—The reduction of 116 g. (0.28 mole) of XIII (Y = I) with 241 g. (1.07 moles) of stannous chloride dihydrate was effected as described for compound IX. Purification with 15% potassium hydroxide solution yielded 93.9 g

(87%) of bright yellow powder, m. p. 301–304° dec.[14]

Anal. Calcd. for $C_{13}H_8O_3NSI$: S, 8.33. Found: S, 8.26.

This compound (0.5 g.) was aminated by heating with 5 ml. of 12 *N* ammonium hydroxide and a trace of copper powder in a sealed tube for twenty-two hours at 220°. The product was taken up in 6 *N* hydrochloric acid (Darco) and reprecipitated with ammonium hydroxide to yield 0.3 g. of a bright yellow powder, m. p. 286–291° dec.; no depression when mixed with an authentic sample of 2,8-diaminothiaxanthone-5-dioxide (XV)[1] melting at 289–293° dec.

On treatment with zinc dust and aqueous-alcoholic alkali V (Y = I) gave a deep violet color which was discharged on exposure to air.

2-Bromo-8-aminothiaxanthone-5-dioxide (V, Y = Br).—The nitro compound XIII (Y = Br) was reduced as above with stannous chloride (0.076 mole) and hydrogen chloride in acetic acid. A quantitative yield (6.8 g.) of yellow-orange powder, m. p. 310–311°, was obtained. Recrystallization of a small sample from acetone caused no change in the melting point.

Anal. Calcd. for $C_{13}H_8O_3NSBr$: S, 9.49. Found: S, 9.48.

The same peculiar color reaction with zinc dust and alkali was shown by this compound as by its iodo analog.

2-Amino-8-(N-2-pyrimidyl)-aminothiaxanthone-5-dioxide (II).—A mixture of 5.0 g. (0.013 mole) of V (Y = I), 15.0 g. (0.158 mole) of 2-aminopyrimidine,[15] 2.0 g. (0.015 mole) of finely powdered anhydrous potassium carbonate, and a trace of copper powder was heated with stirring at 195–205° for eighty minutes under nitrogen. The dark-colored mixture was cooled slightly and triturated with hot water to remove excess 2-aminopyrimidine and potassium iodide. The finely ground residue was extracted repeatedly with cold 5 *N* nitric acid, treated with decolorizing charcoal, and finally reprecipitated from the combined acid extracts by addition of excess ammonium hydroxide; yield, 4.1 g. (90%) of a bright yellow powder, m. p. 327–335° dec. Digestion of a small sample with hot acetone, in which it is only very slightly soluble, raised the melting point to 335–338° dec.

Anal. Calcd. for $C_{17}H_{12}O_3N_4S$: S, 9.10; N, 15.9. Found: S, 9.04, 9.09; N, 15.7.

The diacetyl derivative of II was prepared by refluxing 1.6 g. (0.0045 mole) with 3.0 g. (0.029 mole) of acetic anhydride in 25 ml. of glacial acetic acid for three hours, cooling to room temperature and diluting with a large volume of water. The gelatinous yellow precipitate was recrystallized from aqueous acetic acid to yield 1.3 g. (66%) of yellow-orange crystals, m. p. 318–321° dec.

Anal. Calcd. for $C_{21}H_{16}O_5N_4S$: S, 7.34; N, 12.84. Found: S, 7.48; N, 12.96.

Condensation of V (Y = I) with 2-Aminopyridine.—In a typical experiment a mixture of 2.0 g. (0.0052 mole) of V (Y = I), 6.0 g. (0.064 mole) of 2-aminopyridine (Reilly Tar and Chemical Co., redistilled), 0.8 g. (0.0058 mole) of finely powdered anhydrous potassium carbonate, and a trace of copper powder was heated and stirred under nitrogen at 190–195° for ninety minutes. The dark-colored melt was cooled and the tarry mass extracted with warm water to remove the excess 2-aminopyridine and inorganic salts. After repeated extractions of the water-insoluble residue with 6 *N* hydrochloric acid, addition of excess ammonium hydroxide to the combined acid extracts precipitated 1.3 g. of yellow-orange powder, m. p *ca.* 150–190° dec. Repeated recrystallization from aqueous ethanol (Norit) afforded 0.4 g. of orange microcrystalline powder, m. p. 233–237° dec. with previous sintering. Digestion with boiling acetone raised the melting point to 235–240° dec. with previous sintering.

Anal. Calcd for $C_{18}H_{13}O_3N_3S$: S, 9.13. Found: S, 8.97.

When this product was refluxed with aqueous-alcoholic alkali for two hours, the evolution of considerable ammonia was observed (olfactory evidence, litmus and hydrogen chloride tests). No ammonia could be detected after three hours of similar treatment of II.

2-Iodo-8-(N-2-pyridyl)-aminothiaxanthone-5-dioxide (XIV, Y = I).—A mixture of 1.0 g. (0.0026 mole) of V (Y = I) and 3.0 g. (0.019 mole) of 2-bromopyridine[16] was stirred and heated on an oil-bath at 155–160° for eight hours. The cooled reaction mixture was diluted with several times its volume of ethanol, and the brownish-yellow precipitate was washed with ethanol, dissolved in a small amount of hot pyridine (Norit), and finally reprecipitated by the addition of four volumes of ethanol; yield, 1.0 g. (83%) of orange microcrystalline powder, m. p. 285–288°. Repeated reprecipitation from pyridine solution then yielded the pure product, m. p. 294–295°.

Anal. Calcd. for $C_{18}H_{11}O_3N_2SI$: S, 6.93. Found: S, 7.06.

2-Bromo-8-(N-2-pyridyl)-aminothiaxanthone-5-dioxide (XIV, Y = Br).—This compound was prepared by the method described above for the corresponding iodo compound, using 3.0 g. (0.0089 mole) of V (Y = Br) and 12.0 g. (0.081 mole) of 2-bromopyridine. After one reprecipitation from pyridine the product melted at 293–297°; yield 3.4 g. (92%). Another reprecipitation afforded the pure compound as an orange microcrystalline powder, m. p. 297–298°.

Anal. Calcd. for $C_{18}H_{11}O_3N_2SBr$: S, 7.72. Found: S, 7.59.

2-Amino-8-(N-2-pyridyl)-aminothiaxanthone-5-dioxide (I).—A mixture of 2.6 g. (0.0063 mole) of XIV (Y = Br), 12 ml. of 12 *N* ammonium hydroxide and a trace of copper powder was heated at 210–220° in a sealed tube for twenty hours. The contents of the tube were diluted with water and filtered, the insoluble residue being taken up in 3 *N* hydrochloric acid, treated with Norit, and reprecipitated with ammonium hydroxide. A second reprecipitation from acid solution yielded 1.5 g. (68%) of yellow-orange powder, m. p. 245–260° dec. Pure 2-amino-8-(N-2-pyridyl)-aminothiaxanthone-5-dioxide was obtained as an orange microcrystalline powder, m. p. 280–282° dec., by recrystallization from aqueous ethanol. The same product (m. p. 279–281° dec., no depression when mixed with the above material) was obtained by the action of ammonium hydroxide on XIV (Y = I) under similar conditions.

Anal. Calcd. for $C_{18}H_{13}O_3N_3S$: S, 9.12; N, 11.97. Found: S, 9.02; N, 11.84.

2-Iodo-8-(N-2-quinolyl)-aminothiaxanthone-5-dioxide (XVI).—A mixture of 1.0 g. (0.0026 mole) of 2-iodo-8-aminothiaxanthone-5-dioxide (V, Y = I) and 2.6 g. (0.016 mole) of 2-chloroquinoline,[17] m. p. 37.5–39° (uncor.), was stirred in a test-tube (reflux condenser) for fifteen and one-half hours at 150–154° (oil-bath temperature), fifty-four hours at 155–165°, and eighteen and one-half hours at 160–170°. The temperature then gradually was raised to 185° during the last hour of heating (total reaction time, eighty-nine hours). After the first twenty-four hours white crystals appeared on the walls of the test-tube, but the main reaction mixture gave a positive test for halogen only after about sixty hours, at which time a catalytic amount of copper powder was added. The cooled mixture was diluted with ether, and from the brown solid obtained on filtration 1.0 g. (79%) of crude 2-iodo-8-(N-2-quinolyl)-aminothiaxanthone-5-dioxide, m. p. 320–321° (uncor., dec.), was obtained by reprecipitation from a pyridine solution with ethanol. This product was used for the amination despite its low sulfur content.

---

[14] Melting point taken in a bath heated to 295° before immersion of sample.

[15] A generous supply of this compound was obtained from the Calco Chemical Division of American Cyanamid Company through the courtesy of Dr. R. O. Roblin, Jr.

[16] Craig, THIS JOURNAL, **56**, 231 (1934).

[17] Prepared from carbostyril (Eastman Kodak Co.) in 63% yield according to the method of Friedlaender and Ostermaier, *Ber.*, **15**, 332 (1882).

Anal. Calcd. for $C_{22}H_{13}O_3N_2SI$: S, 6.26. Found: S, 5.18.

2-Amino-8-(N-2-quinolyl)-aminothiaxanthone-5-dioxide (IV).—A mixture of 0.32 g. (0.00062 mole) of XVI, 10 ml. of concentrated ammonium hydroxide, and a trace of copper powder was heated fifteen hours at 205° in a sealed tube. Water (90 ml.) was added and the insoluble dark-brown solid filtered off. Upon heating this material three times with 10 ml. of approximately 4 *N* hydrochloric acid, removing insoluble material by filtration, and reprecipitating from the cooled filtrate with ammonium hydroxide three impure brown-yellow fractions were obtained from which 8 mg. (3%) of pure 2-amino-8-(N-2-quinolyl)-aminothiaxanthone-5-dioxide was isolated by fractional extractions with boiling dioxane followed by reprecipitation from the cooled solutions with water.

Anal. Calcd. for $C_{22}H_{15}O_3N_3S$: S, 7.99. Found: S, 7.70.[18]

Summary

2-Amino-8-(N-2-pyridyl)-aminothiaxanthone-5-dioxide, 2-amino-8-(N-2-pyrimidyl)-aminothiaxanthone-5-dioxide and 2-amino-8-(N-2-quinolyl)-aminothiaxanthone-5-dioxide have been synthesized for study as possible new antibacterial agents.

[18] Analysis by Dr. Carl Tiedcke.

BETHLEHEM, PENNA. RECEIVED JUNE 21, 1947

[CONTRIBUTION FROM THE OFFICE OF DERMATOLOGY, INDUSTRIAL HYGIENE DIVISION, BUREAU OF STATE SERVICES, U. S. PUBLIC HEALTH SERVICE]

The Allergenic Principles of Poison Ivy. VII. Absorption Spectra of 3-*n*-Pentadecylcatechol and Related Compounds[1]

BY HOWARD S. MASON

In this study the absorption spectra of 3-*n*-pentadecylcatechol and a group of other substituted catechols, catechol derivatives and *o*-quinones have been determined. The feasibility of direct spectrophotometric assay of poison ivy allergens was also investigated.

Experimental

Unless otherwise noted, all substances examined were analytically pure samples previously described[1].

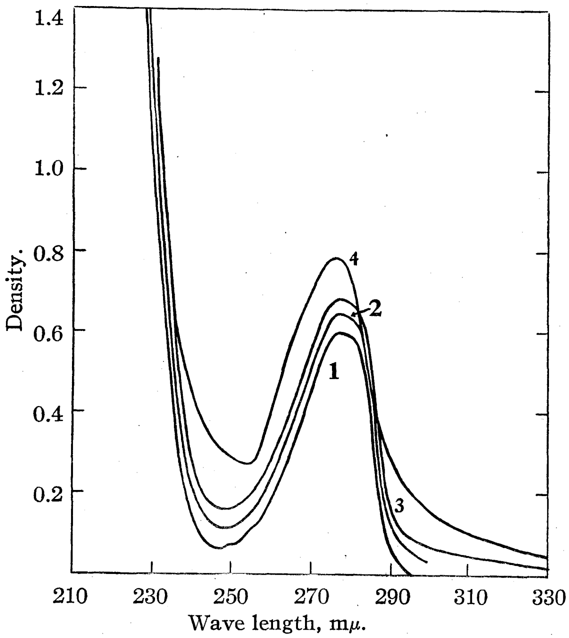


Fig. 1.—Spectrum of 3-*n*-pentadecylcatechol in ethanol. The solution contained 0.102 mg. per ml. The measurements were made at intervals of (1) zero days, (2) fourteen days, (3) thirty days and (4) ninety-one days.

3-*n*-Pentadecyl-*o*-benzoquinone.—This compound was prepared and purified by following the procedure of Willstätter[2] for the preparation of *o*-benzoquinone. It was recrystallized from a mixture of ether and hexane, from which it separated as orange rhomboids sintering and decomposing between 63–67°. The colorless modification could also be obtained by following the procedure of Willstätter and Müller[3] for the preparation of colorless *o*-benzoquinone.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.0; H, 11.0.

***o*-Benzoquinone.**—This compound was readily prepared and recrystallized by the procedures of Willstätter[2] and Goldschmidt.[4] The product consisted of bright red crystals melting and decomposing between 60–70°.

3-*n*-Pentadecylcatechol Diphenylmethylene Ether.—This compound was synthesized by a general method already described[1]. It crystallized as white prisms from methanol and melted at 42°.

Anal. Calcd. for $C_{34}H_{44}O_2$: C, 84.3; H, 9.16. Found: C, 84.0; H, 9.14.

Spectral curves were determined with a Beckman quartz spectrophotometer. The solvent used was ethanol unless otherwise specified. The quartz cells employed were 10 mm. in thickness.

Results

Fresh solutions of 3-*n*-pentadecylcatechol in ethanol displayed maximum absorption at 277 mμ, $\log \epsilon = 3.28$. On standing for several months absorption became more intense, the spectral curve shifting to slightly shorter wave lengths (Fig. 1). The effect of solvent upon the rate of this process was determined by following simultaneously the absorption spectra of identical concentrations of 3-*n*-pentadecylcatechol in ethanol, acetone and hexane. Over a period of forty-five days at 21–24° the spectral changes took place most markedly in acetone and least markedly in hexane (Table I).

Crude extracts of poison ivy also displayed

---

[1] For the previous paper in this series, see Mason, THIS JOURNAL, **69**, 2241 (1947).

[2] Willstätter and Pfannenstiel, *Ber.*, **37**, 4744 (1905).

[3] Willstätter and Müller, *ibid.*, **41**, 2580 (1908).

[4] Goldschmidt and Graef, *ibid.*, **61**, 1858 (1928).

TABLE I

SPECTRAL STABILITY OF SOLUTIONS OF 3-*n*-PENTADECYLCATECHOL

Solvent	Concn. mole/liter	Density at 0 days (mμ)	Density at 45 days (mμ)
Ethanol	0.000156	0.300 (277)	0.384 (277)
Acetone[a]	.000156	.303 (277)	.407 (275)
Hexane[b]	.000156	.326 (273)	.372 (272)

[a] Aliquots of the acetone solution were evaporated in vacuum at room temperature. Spectral curves were determined with ethanolic solutions of the residues. [b] Determination upon hexane solution.

maximum absorption at 277 mμ, and underwent optical transformations upon standing (Fig. 2).

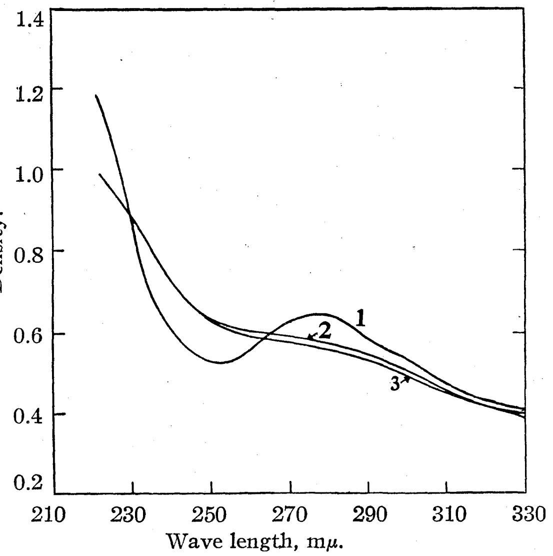


Fig. 2.—Crude poison ivy extract containing 0.0542 mg. of resin per ml. of ethanol at (1) zero days, (2) eighteen days and (3) thirty-two days.

o-Benzoquinone and 3-*n*-pentadecyl-*o*-benzoquinone were unstable in ethanol, chloroform, ether and hexane. The spectral curve of 3-*n*-pentadecyl-*o*-benzoquinone in ethanol (Fig. 3B) developed a maximum at 273 mμ over a period of six days. In hexane solution this substance possessed an initial maximum at 388 mμ, log ε = 3.36 (Fig. 3A). During a period of six days this specific absorption disappeared and only general absorption could be observed. The changing spectral curve of *o*-benzoquinone in ethanol (Fig. 4B) developed a maximum at 282 mμ in twenty-four hours. The chloroform solution displayed an initial maximum at 368 mμ, log ε = 3.23 (Fig. 4A). In three days this shifted to 372 mμ and a new maximum appeared at 273 mμ.

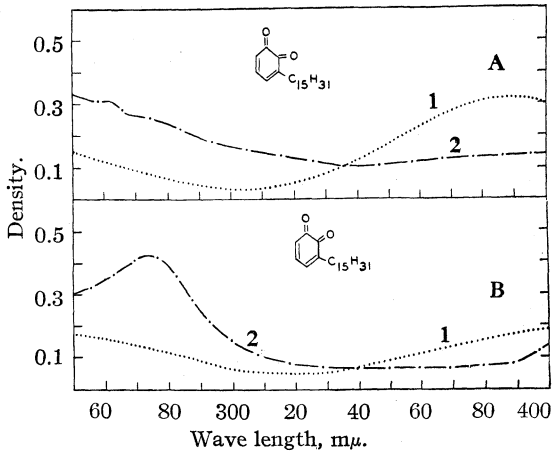


Fig. 3.—A, 3-*n*-pentadecyl-*o*-benzoquinone in hexane, 0.044 mg. per ml. at (1), twenty-five minutes and (2) six days; B, in ethanol, 0.032 mg. per ml. at (1) twenty minutes and (2) six days.

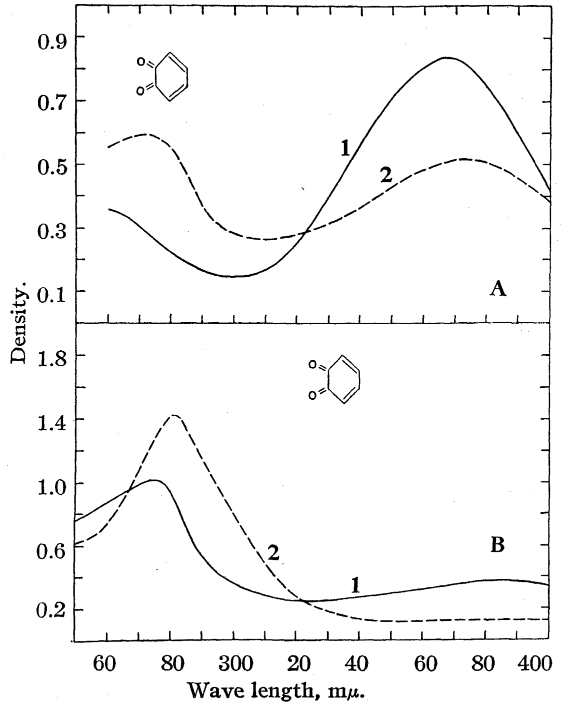


Fig. 4.—A, *o*-benzoquinone in chloroform, 0.053 mg. per ml. at (1) zero days and (2) three days; B, in ethanol, 0.0364 mg. per ml. at (1) twenty minutes and (2) twenty-four hours.

In the following summary of additional spectral curves the principal maxima are given in millimicra and the corresponding log molecular extinction coefficients are enclosed in parentheses.

Catechol	277 (3.36)
3-*n*-Pentadecylcatechol (hexane)	273 (3.32), 280 (3.31)
3-*n*-Propylcatechol	276 (3.35)
4-*t*-Butylcatechol	281 (3.48)
3-Bromocatechol	279.5 (3.41)
Bhilawanol[5]	276.5 (3.32)
Catechol diphenyl	283 (3.68)
methylene ether	279 (3.66), 282 (3.67),
(hexane)	284 (3.70), 290 (3.60)
3-*n*-Pentadecylcatechol diphenylmethylene ether	281 (3.55), 284 (3.55)
3-*n*-Propylcatechol diphenylmethylene ether	281 (3.52)

---

[5] Mason, THIS JOURNAL, **67**, 418 (1945).

3-Bromocatechol diphenylmethylene ether	287 (3.61)
4-*t*-Butylcatechol diphenylmethylene ether	287 (3.73)
Bhilawanol diphenylmethylene ether[5]	280 (3.60)
2,3-Dimethoxy-*n*-pentadecylbenzene	271 (3.18), 277 (3.16)
2,3-Dimethoxy-*n*-pentadecen-1-ylbenzene	271 (3.07), 277 (3.05)

Discussion

Adams and co-workers[6] observed that substitution of alkyl groups in the 4 position of catechol resulted in bathochromic spectral shifts of approximately 5 mμ. This phenomenon has been generalized by Jones[7] as the B-effect, and it has been shown that "the magnitude of the shift depends upon the position of the substituent in the ring system." The absorption spectrum of 4-*t*-butylcatechol, determined in the present study, is consistent with the observation of Adams.[6] However, it has been found that catechol, 3-*n*-propylcatechol, and 3-*n*-pentadecylcatechol display principal absorption (in ethanol) at 277, 276 and 277 mμ, respectively, and that the corresponding diphenylmethylene ethers show principal absorption at 283 281 and 281–284 mμ. The B-effect therefore does not obtain when alkyl groups are attached to the 3 position of catechol.

The increase in intensity of absorption at 277 mμ characteristic of solutions of 3-*n*-pentadecylcatechol and the changes with time in the spectrum of solutions of crude poison ivy extracts limit the applicability of spectrophotometric assay of the poison ivy allergens. However, the results indicate that standard solutions of these allergens are best prepared, from the point of view of chemical stability, in hydrocarbon solvents.

Goldschmidt and Graef[4] have found that, in hexane, *o*-benzoquinone and 4-methyl-*o*-benzoquinone display principal maxima at 363 and 365 mμ, respectively. 3-*n*-Pentadecyl-*o*-benzoquinone shows maximum absorption in the same solvent at 388 mμ. The substitution of an alkyl group in the 3 position of *o*-benzoquinone thus results in a bathochromic shift of unexpected magnitude, suggesting that the α-methylene group may be bonded through hydrogen to the adjacent carbonyl group.[8,9] The major shift of the spectral curves of *o*-benzoquinone and 3-*n*-pentadecyl-*o*-benzoquinone solutions, from initial absorption in the region of 368–388 mμ to final absorption between 273 and 282 mμ indicates that in the solvents investigated benzenoid molecules form from the quinones originally present. In the case of 3-*n*-pentadecyl-*o*-benzoquinone both the position and intensity of the final absorption are consistent with the hypothesis that the changes in the spectrum of aging solutions of 3-*n*-pentadecylcatechol are autoxidative and proceed through the formation of the corresponding *o*-quinone. This in turn is transformed into a benzenoid molecule. In order to characterize this substance attempts at isolation were made using *o*-benzoquinone as a starting material. From ethanolic solutions only catechol and an intractable black polymer were obtained. Upon zinc dust distillation, the polymer yielded biphenyl in small amounts. Some of the absorption in the 273–282 mμ region must therefore be due to the catechols themselves, but no decision with respect to the structures of the remaining solutes can yet be made.

Acknowledgments.—I wish to acknowledge the assistance of Mrs. Dorothy Peterson of the Industrial Hygiene Laboratory, National Institute of Health, in the determination of some of the spectral curves. I am indebted to Mr. Charles A. Kinser for the microchemical analyses.

Summary

1. The spectral curves of 3-*n*-pentadecylcatechol, related substituted catechols, catechol derivatives and *o*-quinones, have been determined.

2. The effects upon absorption spectra of changes in structure and autoxidation of the catechols, and of instability of quinonoid solutes, were observed.

3. The syntheses of 3-*n*-pentadecyl-*o*-benzoquinone and 3-*n*-pentadecylcatechol diphenylmethylene ether are reported.

BETHESDA, MARYLAND RECEIVED JUNE 28, 1947

---

[6] Adams, Cain and Wolff, THIS JOURNAL, **62**, 732 (1940).

[7] Jones, *ibid.*, **67**, 2127 (1945).

[8] Morton and Stubbs, *J. Chem. Soc.*, 1347 (1940).

[9] *Cf.* Marvel, Copley and co-workers, *e. g.*, THIS JOURNAL, **62**, 3109 (1940).

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

Isomerism in the Diels–Alder Reaction

BY H. L. HOLMES, R. M. HUSBAND[1] AND IN PART BY C. C. LEE[1] AND P. KAWULKA[1]

Several cases of isomerism, the nature of which is not yet apparent, have been encountered in the addition of certain dienophiles to conjugated diene systems (diacetylethylene + 1-vinyl-6-methoxy 3,4-dihydronaphthalene,[2] cinnamic acid + dicyclohexenyl,[6] benzalacetophenone + dicyclohexenyl,[6] β-benzoylacrylic acid (and its 2,4-dimethyl derivative) + 2,3-dimethylbutadiene-1,3[3]). The reaction of an ethanol solution of β-benzoylacrylic with 2,3-dimethylbutadiene-1,3[3] gave a good yield of an acid adduct (m. p. 143°) as well as some ester resulting from interaction with the solvent. Saponification of the ester adduct with alcoholic alkali gave not only the above adduct but 1% of a high-melting (189°) isomer. A similar pair of isomers were obtained when the dienophile in the above reaction was β-[2′,4′-dimethylbenzoyl]-acrylic acid.

If the isomerism of the β-benzoylacrylic acid-2,3-dimethylbutadiene adduct is of a steric nature then the normal adduct (m. p. 143°) must have the *cis* configuration, for alcoholic alkali is known to promote the conversion of *cis* esters, bearing an alpha hydrogen, to the *trans* acid.[4] This is not in accord with experimental fact for saponification of the ethyl ester of the normal acid adduct with ethanolic potassium hydroxide regenerated only the normal acid (no trace of an isomeric acid could be detected). Furthermore, the high melting (m. p. 189°) acid adduct has been prepared directly, if in small yield, by heating a toluene solution of β-benzoylacrylic acid with 2,3-dimethylbutadiene (the analogous product was not obtained when β-[2,4-dimethylbenzoyl]-acrylic acid was the dienophile). Finally, *cis*-2-benzoyl-4,5-dimethyl-Δ^4-tetrahydrobenzoic acid, which differed from both of the above isomeric adducts, was prepared by condensing (*cis*) 4,5-dimethyl-Δ^4-tetrahydrophthalic anhydride with benzene. The failure of the *cis* acid to react with an ethereal solution of diazomethane is suggestive of a lactol structure for this adduct, an observation lending further support to the configuration assigned to this adduct. Dimethyl sulfate and alkali were required to effect this esterification. Saponification of the methyl ester of the *cis* acid with ethanolic sodium ethylate gave the normal acid adduct.

From these observations it must be concluded that the normal adduct has the *trans* configuration and that the high melting isomer probably results from the migration of the double bond from the normal position in the adduct to one of conjugation with either the ketone or carboxyl group or with both of these functional groups.

This work combined with the generalization of Bergmann and Eschinazi[5] that in Diels–Alder reactions "the relative position of the substituents in the olefinic component is retained in the adduct" adds further confirmation to Lutz's[6] characterization of the yellow β-benzoylacrylic acid as the *trans* form.

Experimental Part[7]

β-Benzoylacrylic Acid and its 4-Methoxy- and 2,4-Dimethyl Derivatives.—The β-benzoylacrylic acid (m. p. 95–96°) was prepared by the method of Fieser and Fieser[3]; however, a modification[8] of this reaction improved the yield of the 4-methoxy- and 2,4-dimethyl- derivatives to 80 and 75%, respectively. The β-anisoylacrylic acid melted at 133–134°,[9] while the β-[2,4-dimethylbenzoyl]-acrylic acid, previously prepared by Kozniewski and Marchlewski,[10] melted at 112–113°. Ethyl β-anisoylacrylate boiled at 184–187° (3 mm.).

The Diels–Alder Reactions.—The conditions for the addition of β-benzoylacrylic acid, its 4-methoxy- and 2,4-dimethyl derivatives to 2,3-dimethylbutadiene were the same.

A suspension of 12.00 g. of β-benzoylacrylic acid in 10 cc. of sodium-dry toluene was heated in a sealed tube with 6.2 g. of 2,3-dimethylbutadiene-1,3 for one hundred and twenty hours at 125°. A yield of 15.31 g. of the crude adduct (m. p. 120–140°) was recovered. Recrystallization from ether and petroleum ether raised the melting point to 141–142°. No depression of the melting point was observed when mixed with that prepared by Fieser and Fieser. After removal of the last traces of the product, melting at 141–142°, from the mother liquors, a second product (0.12 g.) crystallized which showed a somewhat indefinite melting point. When the sample, alone or mixed with the high melting isomer of Fieser and Fieser, was introduced into the melting point apparatus at 160° and the bath temperature increased at a rapid rate, it melted at 189° with some previous softening. This high melting isomer is unsaturated toward aqueous permanganate solution and bromine in carbon tetrachloride.

In contrast to the results of the previous workers only the product melting at 150–150.5° was recovered (80%) from the addition of β-[2,4-dimethylbenzoyl]-acrylic acid to 2,3-dimethylbutadiene. The addition product (80%), melting at 149–149.5°, was isolated from the analogous reaction with β-anisoylacrylic acid.

These dienophiles were not affected by these conditions, for, when they were heated in toluene under conditions obtaining in the above reactions, they were quantitatively recovered except in the case of β-benzoylacrylic acid. In the latter case 5% of a white crystalline solid melting at 176–177° was formed. The same product resulted from crystallization of β-benzoylacrylic acid from benzene.

Esterification of the Diene Adducts.—The ester adducts were obtained by boiling the acid adducts for four hours

---

[1] Senior students in the College of Engineering. This work is based on theses submitted to the College of Engineering in partial fulfilment of the requirements for the degree of Bachelor of Science in Chemical Engineering.

[2] Goldberg and Müller, *Helv. Chim. Acta*, **23**, 831 (1940).

[3] Fieser and Fieser, THIS JOURNAL, **57**, 1679 (1935).

[4] Bickel, *ibid.*, **60**, 927 (1938).

[5] Bergmann and Eschinazi, *ibid.*, **65**, 1405 (1943).

[6] Lutz, *ibid.*, **52**, 3405, 3423 (1930).

[7] All melting points are corrected. The analyses were done in the analytical laboratory of Dr. Léo Marion, National Research Council, Ottawa, Canada.

[8] Holmes and Trevoy, *Can. J. Research*, **22**, 109 (1944).

[9] Bougault, *Compt. rend.*, **146**, 411 (1908).

[10] Kozniewski and Marchlewski, *Chem. Zentr.*, **77**, 1190 (1906).

TABLE I

THE COMPOSITION AND PHYSICAL CONSTANTS OF THE ETHYL ESTERS

R =	Yield, %	Boiling point, °C.	Mm.	$n^{25}\text{D}$	Formula	Composition, %					
						Theoretical		Found			
						Carbon	Hydrogen	Carbon		Hydrogen	
2-Benzoyl-	73.5[a]	180–181	3	1.5330	$C_{18}H_{22}O_3$	75.49	7.74	75.73	75.48	7.50	7.34
2-[2′,4′-Dimethylbenzoyl]-	85	193–193.5	3	1.5305	$C_{20}H_{26}O_3$	76.40	8.33	76.37	76.23	8.45	8.45
2-[4′-Methoxybenzoyl]-	80	211–212	3	1.5430	$C_{19}H_{24}O_4$	72.12	7.65	72.06	71.99	7.64	7.44

[a] In every case there was a small fraction which boiled slightly higher but on saponification only the starting acid was recovered.

with four times their weight of a solution of absolute ethanol containing sulfuric acid (15% by weight). The reaction mixtures were poured into water, extracted in ether and after washing the ether extracts with water were dried over anhydrous sodium sulfate. After removal of the solvent the esters were distilled under reduced pressure. The analyses and physical constants for these esters are listed in Table I.

Saponification of the ester adducts with ethanolic potassium hydroxide (10% by weight) gave almost quantitative yields of the original acid adducts and no isomeric products could be detected.

***cis*-2-Benzoyl-4,5-dimethyl-Δ⁴-tetrahydrobenzoic Acid.**—A solution of 14.0 g. of 4,5-dimethyl-Δ⁴-tetrahydrophthalic anhydride (m. p. 78–78.5°) in 300 cc. of sodium-dry benzene was added dropwise over a period of 3 hours to a well-stirred and cooled (7–8°) suspension of 23.0 g. of aluminum chloride in 200 cc. of dry benzene. The reaction mixture was allowed to stand seven days at 10–12° and then decomposed in ice and water containing 50 cc. of concentrated hydrochloric acid. The organic layer was separated, the benzene removed by steam distillation and the residual oil dissolved in sodium bicarbonate solution, decolorized (Norit) and acidified. The resulting solid (m. p. 70–80°) was predominantly 4,5-dimethyl-Δ⁴-tetrahydrophthalic anhydride. The major portion of this unchanged starting material was removed in boiling petroleum ether. Several crystallizations of the residual oil from ether and petroleum ether gave 1.0 g. of the acid, melting at 147–148°. When mixed with the low melting adduct (m. p. 141–142°) it melted at 126–127° with previous softening.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.61, 74.42; H, 7.17, 6.99.

The above solid was recovered unchanged from the action of a 100% excess of an ethereal solution of diazomethane. The methyl ester (m. p. 108–110°) was obtained by the portionwise addition of methyl sulfate and sodium hydroxide to this product at 80°.

Conversion of the *cis* Ester to the *trans* Acid (m. p. 141–142°).—The methyl ester (0.5 g.) was refluxed with ethanolic sodium ethylate (0.1 g. of sodium and 2.0 cc. of absolute ethanol) for four hours. The reaction mixture, when cold, was diluted with water and acidified. The resulting solid when crystallized from ether–petroleum ether mixture gave 0.1 g. of cubic crystals, which melted alone or on admixture with *trans*-2-benzoyl-4,5-dimethyl-Δ⁴-tetrahydrobenzoic acid at 139–141°.

Acknowledgments.—We wish to acknowledge our indebtedness to Professor L. F. Fieser for the use of his analytical samples which made a direct comparison with our products possible.

Summary

An examination of the isomeric adducts resulting from the reaction of β-benzoylacrylic acid with 2,3-dimethylbutadiene has revealed that the isomer melting at 141–142° is *trans*-2-benzoyl-4,5-dimethyl-Δ⁴-tetrahydrobenzoic acid. The *cis* isomer (m. p. 147–148°) has been prepared and isomerized, through its methyl ester, to the *trans* form (m. p. 141–142°). The isomer, melting at 189°, probably results from the migration of the double bond from the normal position in the adduct to one of conjugation with some other center of unsaturation.

SASKATOON, SASKATCHEWAN RECEIVED MARCH 21, 1947

2-Hydroxyacetylfuran

BY FRANK KIPNIS, HAROLD SOLOWAY AND JOHN ORNFELT

The preparation of 5-nitro-2-hydroxyacetylfuran has been reported by Stillman and Scott.[1] During work in progress at this Laboratory, we have been interested in the preparation of furan ketols, and, in view of the appearance of the above patent, we wish to announce the synthesis of 2-hydroxyacetylfuran and the furoic acid ester thereof.

Diazoacetylfuran has been prepared[2] by the interaction of furoyl chloride with diazomethane. On treatment of the diazoketone with 2 *N* sulfuric acid, nitrogen was evolved, and, by working up the mixture in the usual manner, hydroxyacetylfuran was obtained in good yield. When the diazoketone was heated with furoic acid in benzene, 2-furoyloxyacetylfuran was produced.

Experimental

2-Hydroxyacetylfuran.—Ten and one-half grams (0.077 mole) of diazoacetylfuran[2] was mixed with 150 ml. of 2 *N* sulfuric acid and 60 ml. of dioxane. A vigorous evolution of nitrogen occurred, and the temperature rose spontaneously to 45°. The mixture was stirred and maintained at that temperature (water-bath) for four hours, at the end of which time the temperature was allowed to drop to 25°. After neutralization with solid potassium carbonate, the solution was filtered and distilled from the steam-bath at reduced pressure, removing all of the dioxane and some of the water. The residue was cooled, salted with sodium chloride and extracted six times with 30 ml. of ether. The solvent layer was dried with calcium sulfate, filtered and stripped, finally under reduced pressure, leaving a crystalline residue. This material was recrystallized three times

---

[1] Stillman and Scott, U. S. Patent 2,416,235 (February 18, 1947).

[2] Burger and Harnest, THIS JOURNAL, **65**, 2382 (1943); Burger, U. S. Patent 2,400,913 (May 28, 1946).

from hexane to give 7.2 g. (74% yield) of material melting at 81–82°.[3] Fehling solution was reduced by the ketol.

Anal.[4] Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.23; H, 4.88.

2-Furoyloxyacetylfuran.—Eleven grams (0.081 mole) of diazoacetylfuran was refluxed for four hours with 11 g. (0.099 mole) of furoic acid in 40 ml. of anhydrous, thiophene-free benzene. The solvent was removed under reduced pressure, and the crystalline residue was triturated with saturated sodium bicarbonate solution, and then with water, and finally recrystallized from aqueous methanol (Darco) and then from much hexane to give 8.1 g. (50% yield) of a product melting at 95°.

Anal. Calcd. for $C_{11}H_8O_5$: C, 59.73; H, 3.85. Found: C, 60.00; H, 3.66.

Summary

2-Hydroxyacetylfuran and 2-furoyloxyacetylfuran have been prepared by the interaction of 2-diazoacetylfuran with dilute sulfuric acid and furoic acid, respectively.

RESEARCH LABORATORIES
AMERICAN HOME FOODS, INC.
MORRIS PLAINS, N. J.

RECEIVED AUGUST 12, 1947

---

(3) Melting points taken with Fisher–Johns apparatus.

(4) Analyses by Oakwold Laboratories, Alexandria, Virginia.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Aliphatic Ketones and Amines Containing the Trifluoromethyl Group

BY REUBEN G. JONES

It is well known that the introduction of fluorine atoms into aliphatic molecules has a profound effect upon the physical and chemical properties. In order to ascertain the effect of fluorine on the pharmacological properties of typical aliphatic compounds, it was of particular interest to prepare some ketones, amines, and alcohols containing the trifluoromethyl group. The compounds reported at this time were derived from trifluoroacetic acid.

Two methods were examined for the preparation of trifluoromethyl benzyl ketone. Trifluoroacetonitrile was allowed to react with benzylmagnesium chloride to produce the desired ketone in 38% yield.

$$CF_3CN + C_6H_5CH_2MgCl \xrightarrow{H_2O} CF_3COCH_2C_6H_5$$

The more convenient reaction of trifluoroacetyl chloride with benzyl zinc chloride gave a 54% yield of the ketone.

$$CF_3COCl + C_6H_5CH_2ZnCl \longrightarrow CF_3COCH_2C_6H_5$$

Both methods would appear to be quite generally applicable to the preparation of trifluoromethyl ketones. Trifluoromethyl phenyl ketone (trifluoroacetophenone[1]) was obtained readily in a yield of 61% by the reaction of trifluoroacetyl chloride with diphenylcadmium.

The pharmacology of these trifluoromethyl compounds will be reported elsewhere. However, it is of interest to note at this time that the acute toxicities were relatively low.

Experimental

Trifluoromethyl Benzyl Ketone.—A. Trifluoroacetonitrile was prepared from 56 g. (0.5 mole) of trifluoroacetamide by the method of Gilman and Jones.[2] The gaseous nitrile was led from the generating flask through glass tubing and introduced below the surface of a stirred solution of benzylmagnesium chloride prepared from 80 g. (0.63 mole) of benzyl chloride and 17 g. of magnesium in a total of 300 ml. of dry ether. When the reaction was complete, the brown ether solution was poured into a mixture of 150 g. of ice and 100 ml. of concentrated hydrochloric acid. The ether layer was separated, washed with water and dilute sodium bicarbonate solution and dried over magnesium sulfate. After evaporation of the ether the residual liquid was distilled through an eighteen-inch packed column under reduced pressure, and 36 g. (38.4% yield) of trifluoromethyl benzyl ketone was obtained as a colorless liquid; b. p. 73–73.5° (20 mm.), 163–163.5° (741 mm.): $n^{25}D$ 1.4625.

Anal. Calcd. for $C_9H_7F_3O$: C, 57.45; H, 3.75. Found: C, 57.05; H, 3.92.

B. Trifluoroacetyl chloride was prepared by the method of Tinker[3] from 57 g. (0.5 mole) of trifluoroacetic acid and 200 ml. of benzoyl chloride. The gaseous trifluoroacetyl chloride was led through a glass tube into a reaction flask containing benzylzinc chloride which was made by adding slowly, with the exclusion of air, 800 ml. of ether solution containing 1.0 mole of benzylmagnesium chloride to 136 g. (1.0 mole) of freshly fused, powdered zinc chloride. The reaction flask was provided with a Dry Ice condenser and the mixture was rapidly stirred. After several hours, the mixture was decomposed with ice and dilute hydrochloric acid. The ether layer was separated, the aqueous layer was washed with three 100-ml. portions of ether, and the combined ether solution was dried over magnesium sulfate. The ether was removed by distillation through a small packed column. From the mid fractions, distilling between 36 and 105°, was obtained 8 g. (14%) of trifluoroacetic acid (isolated as the ammonium salt), and 51 g. (54.3% yield) of trifluoromethyl benzyl ketone was collected at 160–165° (740 mm.); $n^{25}D$ 1.4621.

Trifluoromethylbenzylcarbinol.—A solution of 23.5 g. (0.125 mole) of trifluoromethyl benzyl ketone in 50 ml. of anhydrous ether with 5 g. of 5% palladium–charcoal catalyst was hydrogenated under 60 lb. pressure. The theoretical quantity of hydrogen was taken up in about twenty minutes with evolution of heat. The solution was filtered and distilled to yield 23.0 g. (98%) of trifluoromethylbenzylcarbinol; b. p. 204–204.5° (740 mm.); $n^{25}D$ 1.4678.

Anal. Calcd. for $C_9H_9F_3O$: C, 56.84; H, 4.75. Found: C, 56.74; H, 4.76.

Trifluoromethyl Benzyl Ketoxime.—A solution of 23.5 g. (0.125 mole) of trifluoromethyl benzyl ketone in 100 ml. of methanol was treated with 28 g. (0.4 mole) of powdered hydroxylamine hydrochloride followed by 30

---

(1) Simons and Ramler, THIS JOURNAL, **65**, 389 (1943).

(2) Gilman and Jones, *ibid.*, **65**, 1458 (1943); Swarts, *Bull. sci. acad. roy. Belg.*, **8**, 343 (1922) [*C. A.*, **17**, 769 (1923)].

(3) Tinker, U. S. Patent 2,257,868, Oct. 7, 1941; [*C. A.*, **36**, 495 (1942)].

ml. of 12 *N* sodium hydroxide solution. The mixture was refluxed for sixteen hours and then most of the methanol was removed by distillation. To the residue was added 100 ml. of water, and the mixture was extracted with three 50-ml. portions of ether. The ether solution was dried over magnesium sulfate, the ether was removed, and the oxime was distilled in vacuum to yield 25.0 g. (98%) of product, b. p. 118–119° (20 mm.).

Anal. Calcd. for $C_9H_8F_3NO$: C, 53.20; H, 3.97; N, 6.89. Found: C, 53.87; H, 4.40; N, 6.44.

1,1,1-Trifluoro-2-amino-3-phenylpropane.—A solution of 41 g. (0.20 mole) of trifluoromethyl benzyl ketoxime in 150 ml. of anhydrous ether with 8 g. of 5% palladium-charcoal catalyst was placed in a steel hydrogenation bomb under a pressure of 1450 lb./sq. in. of hydrogen, heated to 150° and agitated. The theoretical quantity of hydrogen was taken up in one hour. The bomb was cooled and opened and the ether solution, after filtration, was extracted with cold dilute hydrochloric acid solution. The aqueous layer was separated, made basic with sodium hydroxide and extracted with ether. After the ether extract had been dried over magnesium sulfate, the ether was evaporated and the amine was distilled at atmospheric pressure; b. p. 189–191° (739 mm.). The yield of clear colorless liquid was 33 g. (87%); n^{25}_D 1.4470.

Anal. Calcd. for $C_9H_{10}F_3N$: N, 7.40. Found: N, 7.56.

The amine hydrochloride, prepared by passing dry hydrogen chloride into a solution of the amine in anhydrous ether, melted at 231–233°.

Anal. Calcd. for $C_9H_{10}F_3N \cdot HCl$: C, 47.95; H, 4.92. Found: C, 47.47; H, 4.89.

Ethyl 3-Hydroxy-4,4,4-trifluorobutyrate.—Ethyl trifluoroacetoacetate was prepared in 83.5% yield from ethyl acetate and ethyl trifluoroacetate according to the directions of Swarts.[4]

To a solution of 27.6 g. (0.15 mole) of ethyl trifluoroacetoacetate in 50 ml. of anhydrous ether was added 0.15 g. of platinum oxide catalyst and the mixture was shaken under an initial hydrogen pressure of 60 lb. Hydrogenation was complete in seven hours. The solution was filtered and distilled, and, after the forerun of ether, the ethyl 3-hydroxy-4,4,4-trifluorobutyrate, 24.8 g. (90% yield), boiled at 177–178° (750 mm.). When 55.2 g. (0.30 mole) of ethyl trifluoroacetoacetate was shaken under 60 lb. hydrogen pressure using 2 g. of 5% palladium-charcoal catalyst, the theoretical quantity of hydrogen was absorbed in three hours. Under high pressure (1200 lb.), 50 g. (0.27 mole) of ethyl trifluoroacetoacetate in 100 cc. of anhydrous ether with 15 g. of 5% palladium-charcoal catalyst absorbed the theoretical quantity of hydrogen in two to three minutes, and no more hydrogen was taken up even when the bomb was heated to 100° and agitated for five hours.

The ester isolated directly from the hydrogenation reaction could not be obtained analytically pure even after several distillations. A pure sample of ethyl 3-hydroxy-4,4,4-trifluorobutyrate was prepared in 90% yield by esterification of 3-hydroxy-4,4,4-trifluorobutyric acid (see below) with ethanol and hydrogen chloride. It has the following properties: b. p. 180–180.2° (748 mm.); m. p. 26.9–27.0°; n^{30}_D 1.3707; d^{30}_{30} 1.275.

Anal. Calcd. for $C_6H_9F_3O_3$: C, 38.71; H, 4.87. Found: C, 38.25; H, 5.09.

3-Hydroxy-4,4,4-trifluorobutyric Acid.—A solution of 35 g. (0.223 mole) of 3-hydroxy-4,4,4-trifluorobutyramide (see below) in 40 ml. of 12 *N* sodium hydroxide solution was heated on the steam-bath for fifteen minutes. The clear solution was cooled in an ice-bath and treated with 60 ml. of 12 *N* hydrochloric acid. The salt was collected on a filter, washed with ether, and the filtrate was extracted with three 100-ml. portions of ether. The combined ether solution was dried over magnesium sulfate and evaporated on the steam-bath. To the residual liquid was added 100 ml. of petroleum ether (b. p. 60–68°) whereupon crystallization quickly took place. The acid was collected and dried in vacuum over calcium chloride. The yield was 34.1 g. (97.2%); m. p. 69.5–70°.

Anal. Calcd. for $C_4H_5F_3O_3$: C, 30.39; H, 3.19. Found: C, 30.43; H, 3.28.

The pure acid was also readily obtained by saponification of the crude ester. It was sparingly soluble in petroleum ether, very soluble in ether, alcohol and water but apparently not hygroscopic.

3-Hydroxy-4,4,4-trifluorobutyramide.—A solution of 4.6 g. (0.025 mole) of crude ethyl 3-hydroxy-4,4,4-trifluorobutyrate in 25 ml. of methanol was saturated with dry ammonia and allowed to stand for three days. The methanol was evaporated, finally under vacuum leaving a mass of colorless prismatic crystals. The product was washed with 10 ml. of dry ether and air dried. It weighed 3.5 g. (90% yield) and melted at 124–125°.

Anal. Calcd. for $C_4H_6F_3NO_2$: N, 8.92. Found: N, 8.73.

The compound was soluble to the extent of about 1 g. per 100 ml. of dry ether, very sparingly soluble in petroleum ether, highly soluble in alcohol or water and not hygroscopic.

N-2′-Hydroxyethyl-3-hydroxy-4,4,4-trifluorobutyramide.—A mixture of 9.3 g. (0.05 mole) of ethyl 3-hydroxy-4,4,4-trifluorobutyrate and 3.5 g. (0.058 mole) of ethanolamine was heated at 140° for four hours. The mixture was distilled in vacuum and, after a small forerun, 9.5 g. (95% yield) of viscous colorless liquid distilled at 186–188° (2 mm.). It crystallized after standing; m. p. 59–61°.

Anal. Calcd. for $C_6H_{10}F_3NO_3$: N, 6.96. Found: N, 7.10.

2-Hydroxy-3,3,3-trifluoropropylamine Hydrochloride.—To a mixture of 150 g. of ice and potassium hypochlorite solution made by dissolving 11.0 g. (0.153 mole) of chlorine in a solution of 33.6 g. of potassium hydroxide in 90 ml. of ice water was added 23.6 (0.15 mole) of 3-hydroxy-4,4,4-trifluorobutyramide. The solution was kept at 0° for twenty minutes, then allowed to warm slowly to room temperature and finally heated on the steam-bath for thirty minutes. The solution was cooled and extracted with ten 100-ml. portions of ether. The ether solution was dried over magnesium sulfate, filtered and saturated with dry hydrogen chloride to yield 13.9 g. (56%) of white crystalline amine hydrochloride; m. p. 147–148°.

Anal. Calcd. for $C_3H_6F_3NO \cdot HCl$: C, 21.76; H, 4.26; N, 8.46. Found: C, 21.93; H, 4.31; N, 8.32.

To 3 ml. of 15% aqueous sodium hydroxide was added 0.5 g. of 2-hydroxy-3,3,3-trifluoropropylamine hydrochloride followed by 0.5 ml. of benzoyl chloride added dropwise with shaking. The resulting white, crystalline dibenzoyl compound, 0.9 g., was collected on a filter and recrystallized from petroleum ether containing a little ethyl acetate; m. p. 126.5–127.5°.

Anal. Calcd. for $C_{17}H_{14}F_3NO_3$: C, 60.53; H, 4.18. Found: C, 60.33; H, 4.11.

Summary

Two general methods for the synthesis of ketones have been applied successfully to the preparation of trifluoromethyl benzyl ketone.

1,1,1-Trifluoro-2-amino-3-phenylpropane has been obtained by hydrogenation of the ketoxime.

Trifluoromethyl benzyl ketone has been hydrogenated to yield trifluoromethylbenzylcarbinol.

3-Hydroxy-4,4,4-trifluorobutyric acid, its ethyl ester, amide, and N-2′-hydroxyethyl amide, and 2-hydroxy-3,3,3-trifluoropropylamine have been made starting from ethyl trifluoroacetoacetate.

INDIANAPOLIS, INDIANA RECEIVED JUNE 27, 1947

---

[4] Swarts, *Bull. sci. acad. roy. Belg.*, [5] **12**, 692 (1926); [*C. A.*, **21**, 2120 (1927)].

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

N-Bromosuccinimide as a Dehydrogenating Agent[1]

BY RODERICK A. BARNES

The structure proof for most hydroaromatic compounds rests upon the fact that treatment with a dehydrogenating agent such as selenium, sulfur, platinum or palladium at temperatures of 250–450°, converts them to known aromatic substances. A large number of cases has accumulated in the literature in which the usual dehydrogenation process has been accompanied by rearrangements, migrations and ring closures. These render the use of such reagents of questionable value in an absolute structure proof.[2]

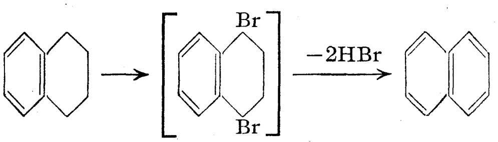
This investigation was undertaken in order to demonstrate the use of a low temperature bromination–dehydrobromination process for achieving dehydrogenation, with N-bromosuccinimide as a selective brominating agent.[3] A procedure has been developed which is satisfactory especially for compounds of the tetralin type which have one hydroaromatic ring attached to a benzenoid ring.

TABLE I

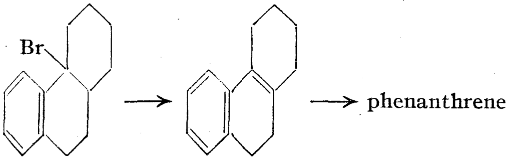
Compound	Product	Yield, %
Tetralin	Naphthalene	74
sym-Octahydroanthracene	Anthracene	69
Tetrahydrophenanthrene	Phenanthrene	79
sym-Octahydrophenanthrene	Phenanthrene	63
as-Octahydrophenanthrene	Phenanthrene	21
	1-Bromophenanthrene[a]	12
Dibenzyl	Stilbene	56
	Stilbene dibromide	10
Acenaphthene	Acenaphthylene	20
	Dihydroxyacenaphthene[b]	8
Decalin	1,5-Dibromonaphthalene	9
	x-Tetrabromo-9,10-octalin	14
Cyclohexene	*m*-Dibromobenzene *p*-Dibromobenzene	58

[a] This product was isolated in only one experiment, phenanthrene being the only pure product in four subsequent experiments. [b] This substance must have resulted by reaction of the dibromide with water and alkali when the mixture was processed as for tetralin.

The preliminary bromination of tetralin can be completed before any appreciable dehydrobromination takes place, which indicates that a fairly stable dibromotetralin must be the intermediate.



In the case of *as*-octahydrophenanthrene, an immediate and exothermic reaction took place with evolution of large amounts of hydrogen bromide. This fact is in agreement with the properties to be expected of the tertiary bromide (I).

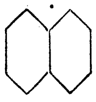


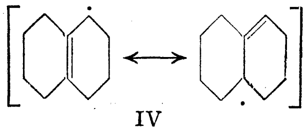
I II

The relatively lower yield of phenanthrene in this case is probably due to the many possibilities for further reaction of the hexahydrophenanthrene (II). The fact that 1-bromophenanthrene was isolated in one experiment is in harmony with the results obtained with decalin. The structure of the brominated phenanthrene was proved by comparison with an authentic sample[4]; both samples were oxidized with chromic anhydride to yield 1-bromo-9,10-phenanthrenequinone[5] (m. p. 238–240°).

Equimolar amounts of decalin and N-bromosuccinimide reacted in the presence of benzoyl peroxide to form a tetrabromoöctalin as the major product. With 3.5–4.0 moles of N-bromosuccinimide a mixture of substances resulted from which there was isolated in addition to the tetrabromide, 1,5-dibromonaphthalene and a small amount of an isomer which melted at 76–78°.[6] The only evidence as to the structure of the tetrabromide was furnished by the observation that 9,10-octalin reacted readily with 4 moles of N-bromosuccinimide to yield the same tetrabromide; no hydrogen bromide was evolved in this reaction.

The formation of the tetrabromide from decalin is consistent with the idea that the N-bromosuccinimide bromination proceeds by way of a free radical intermediate.[7] Thus the intermediate (III) in the initial attack is stable only by virtue of its tertiary character, while the further reaction of 9,10-octalin in which the intermediate (IV) is a resonance-stabilized free radical, proceeds at a very much greater rate with resultant formation


III


IV

---

(1) Presented in part at the Atlantic City meeting of the A. C. S., April, 1947.

(2) Linstead, *Ann. Repts. Chem. Soc.*, **33**, 294 (1936).

(3) Further work is in progress to test this method in cases where the usual dehydrogenations cause rearrangements.

(4) This sample was kindly furnished by Professor W. E. Bachmann; see Bachmann and Boatner, THIS JOURNAL, **58**, 2194 (1936).

(5) This is probably the same substance previously reported by Sandqvist, *Ber.*, **48**, 1149 (1915), m. p. 233–234°, and proved by him to be either 4- or 1-bromophenanthrenequinone. The bromophenanthrenequinone which melts at 126° must therefore be the 4-isomer.

(6) Although analytically pure this substance was never obtained in sufficiently large amounts to permit recrystallization to a pure isomer. 1,4-Dibromonaphthalene melts at 82°.

(7) Hey, *Ann. Repts. Chem. Soc.*, **41**, 191 (1944).

of a tetrabromide even with equimolar quantities of reactants.

Early attempts to aromatize cyclohexene by reaction with 2–3 moles of N-bromosuccinimide failed; however, 6 moles of the reagent produced a mixture of dibromobenzenes in 58% yield. The liquid mixture was found to be largely the meta isomer containing about one third of the solid para isomer. Since benzene does not react with N-bromosuccinimide at an appreciable rate, the dibromobenzenes must have resulted by aromatization of a dibromocyclohexene or dibromocyclohexadiene intermediate.[8]

Experimental[9]

sym-Octahydroanthracene and *sym*-octahydrophenanthrene were prepared by reaction of aluminum chloride with tetralin; they were separated and purified by the method of Schroeter.[10] *as*-Octahydrophenanthrene was prepared by cyclization of 1-β-phenylethyl-1-cyclohexanol with sulfuric acid[11] and 9,10-octalin was prepared according to the direction of Bartlett, Condon and Schneider.[12] The other hydrocarbons used in this work were purified commercial products.

The procedures used in carrying out the dehydrogenations are illustrated by the following examples.

Dehydrogenation of Tetralin.—A mixture of tetralin (250 mg.), N-bromosuccinimide (680 mg.), benzoyl peroxide (10 mg.) and carbon tetrachloride (15 ml.) was refluxed for thirty minutes. No hydrogen bromide was liberated during this time.[13] Potassium acetate (3 g.) and acetic acid (1 ml.) were added and the mixture refluxed for an additional half hour. The reaction mixture was poured onto ice and sodium hydroxide (2 g.). The product was isolated by ether extraction and evaporation of the solvents. The crude crystalline product was sublimed at atmospheric pressure to yield 180 mg. (74%) of pure naphthalene, m. p. and mixed m. p. 79–80°.

Dehydrogenation of *as*-Octahydrophenanthrene.—A solution of the hydrocarbon (0.93 g., $n^{25}\text{D}$ 1.5519) in carbon tetrachloride was refluxed with N-bromosuccinimide (3.56 g.), benzoyl peroxide (200 mg.), potassium acetate (4 g.) and acetic acid (5 ml.) for four hours. The reaction mixture was poured into water and extracted with benzene. The residue after evaporation of the solvents was sublimed at 20 mm. to give 445 mg. of a sticky solid which after two recrystallizations from methanol melted at 96.5–98°; yield 187 mg. (21%). A mixture of this sample and phenanthrene melted at 97–99°; both samples formed picrates which melted at 143–144° separately or when mixed.

The mother liquors from the crystallization contained an oil which gave a positive qualitative test for bromine, however, in all but one experiment no brominated compounds were isolated in pure form. This experiment differed from the others only in that the N-bromosuccinimide used (5.5 moles) was a finely powdered mixture containing 0.1 mole per cent of benzoyl peroxide which had been allowed to stand for several days before use. After sublimation and recrystallization from methanol there was isolated 320 mg. (12% based on 1.48 g. of hydrocarbon) of a substance which melted at 109–110°. A mixed melting point of this sample with an authentic sample of 1-bromophenanthrene[4] showed no depression. Both of the samples were oxidized with chromic anhydride in acetic acid to yield the same 1-bromophenanthrenequinone which melted at 238–240°.

Anal. Calcd. for $C_{14}H_7O_2Br$: C, 58.56; H, 2.46. Found: C, 58.98; H, 2.71. The melting point of a mixture of this substance with 2-bromophenanthrenequinone (m. p. 233–234°) prepared by bromination of phenanthrene[14] was 190–208°.

Reaction of Decalin with N-Bromosuccinimide.—A mixture of decalin (2.76 g.), N-bromosuccinimide (3.56 g.), benzoyl peroxide (200 mg.) and carbon tetrachloride (40 ml.) was refluxed until the solution became colorless (twenty minutes). The reaction mixture was washed with water and the carbon tetrachloride removed. The unchanged decalin was distilled on the water-pump, leaving a residue which crystallized on cooling. Two recrystallizations from ethyl acetate yielded *x*-tetrabromooöctalin which melted at 188–189°.

Anal: Calcd. for $C_{10}H_{12}Br_4$: C, 26.58; H, 2.68; Br, 70.74. Found: C, 25.97; H, 2.81; Br, 71.00.

x-Tetrabromoöctalin (1.35 g.) was the only product isolated from the reaction of 9,10-octalin (1.36 g.) with N-bromosuccinimide (7.12 g.). No hydrogen bromide was evolved in this reaction.

By reaction of decalin (5.0 g.) with 4 moles of N-bromosuccinimide there resulted a semi-solid product which was fractionally crystallized from ethyl acetate and ethanol to yield 2.3 g. (14%) of *x*-tetrabromoöctalin, 1.0 g. (9%) of 1,5-dibromonaphthalene (m. p. 127–129°) and 20 mg. of a substance which melted at 76–78°.

Anal. Calcd. for $C_{10}H_6Br_2$: C, 41.99; H, 2.11. Found: C, 41.54; H, 1.96.

The structure of 1,5-dibromonaphthalene was proved by comparison with an authentic sample prepared from 5-bromo-1-naphthylamine[15] by the method of Hodgson and Whitehurst.[16]

Reaction of Cyclohexene with N-Bromosuccinimide.—Cyclohexene (6.15 g.) was dissolved in carbon tetrachloride (75 ml.) and refluxed for twelve hours with N-bromosuccinimide (80 g.); benzoyl peroxide (3 g.) was added in several portions during this time. The carbon tetrachloride was removed and the residue washed with water, dried and distilled to yield 10 g. (58%) of crude dibromobenzenes which boiled at 215–225°. This material was redistilled at 22 mm. through a 45-cm. Podbielniak column, b. p. 102–103°.

Anal. Calcd. for $C_6H_4Br_2$: C, 30.55; H, 1.70. Found: C, 30.74; H, 1.68.

The redistilled product solidified at −15° and the last trace of solid had melted at 10°. A solution of the mixture (1.0 g.) in petroleum ether (20 ml.) was cooled to −30° and filtered quickly; this procedure was repeated to yield 185 mg. of *p*-dibromobenzene, m. p. and mixed m. p. 86–87°. The petroleum ether was removed from the filtrate and the residue treated with fuming nitric acid (8 ml.) at 0°. The reaction mixture was poured into water and the solid product was filtered and pressed dry on a porous plate, m. p. 55–57°. Crystallization from dilute methanol yielded 640 mg. of 2,4-dibromonitrobenzene which melted at 61.5–62°. This substance and 3,4-dibromonitrobenzene[17] (m. p. 58.5–59°) liquified when mixed at room temperature.

Summary

A procedure has been described for the conversion of hydroaromatic to aromatic compounds at a lower temperature than by the usual methods.

---

[8] Ziegler, *et al.*, *Ann.*, **551**, 80 (1942), have reported that cyclohexadiene reacted only very slowly with N-bromosuccinimide; no monobromodiene was isolated.

[9] All melting points are corrected.

[10] Schroeter, *Ber.*, **57**, 1997 (1924).

[11] Perlman, Davidson and Bogert, *J. Org. Chem.*, **1**, 288 (1936).

[12] Bartlett, Condon and Schneider, THIS JOURNAL, **66**, 1531 (1944).

[13] The liberation of hydrogen bromide during the reaction is characterized by the simultaneous appearance of an orange-red color due to the liberation of free bromine: N-bromosuccinimide + HBr $\rightleftarrows$ Br_2 + succinimide.

[14] Schmidt and Junghans, *Ber.*, **37**, 3558 (1904).

[15] Guareschi, *Ann.*, **222**, 297 (1883).

[16] Hodgson and Whitehurst, *J. Chem. Soc.*, 80 (1947).

[17] Holleman, *Rec. trav. chim.*, **25**, 198 (1906).

The first example of the reaction of N-bromosuccinimide with a saturated hydrocarbon has been reported.

NEW YORK, N. Y. RECEIVED AUGUST 5, 1947

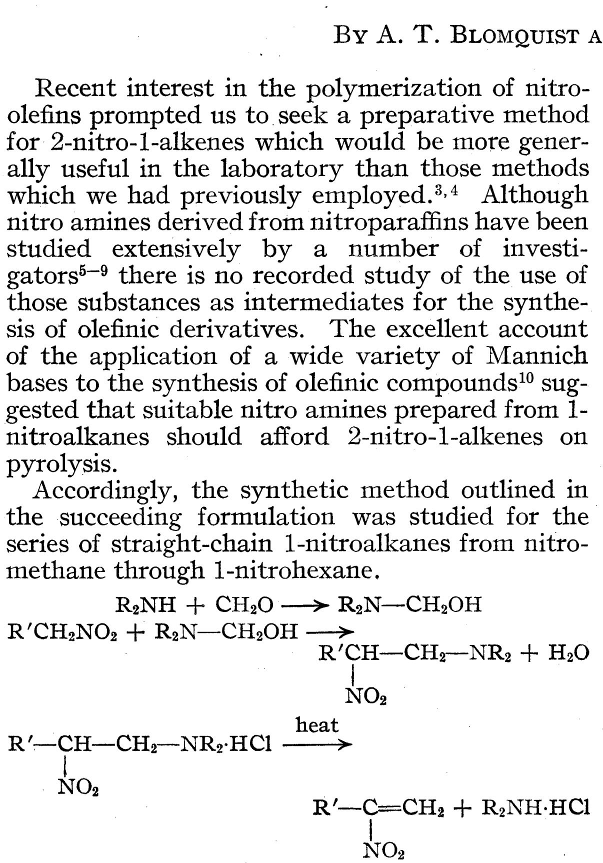
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Preparation of 2-Nitro-1-alkenes from Nitro Amines[1]

BY A. T. BLOMQUIST AND T. H. SHELLEY, JR.[2]

Recent interest in the polymerization of nitroolefins prompted us to seek a preparative method for 2-nitro-1-alkenes which would be more generally useful in the laboratory than those methods which we had previously employed.[3,4] Although nitro amines derived from nitroparaffins have been studied extensively by a number of investigators[5–9] there is no recorded study of the use of those substances as intermediates for the synthesis of olefinic derivatives. The excellent account of the application of a wide variety of Mannich bases to the synthesis of olefinic compounds[10] suggested that suitable nitro amines prepared from 1-nitroalkanes should afford 2-nitro-1-alkenes on pyrolysis.

Accordingly, the synthetic method outlined in the succeeding formulation was studied for the series of straight-chain 1-nitroalkanes from nitromethane through 1-nitrohexane.



$$R_2NH + CH_2O \longrightarrow R_2N{-}CH_2OH$$

$$R'CH_2NO_2 + R_2N{-}CH_2OH \longrightarrow \underset{\displaystyle NO_2}{R'CH}{-}CH_2{-}NR_2 + H_2O$$

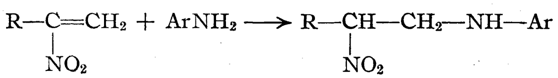
$$\underset{\displaystyle NO_2}{R'{-}CH}{-}CH_2{-}NR_2{\cdot}HCl \xrightarrow{\text{heat}} \underset{\displaystyle NO_2}{R'{-}C}{=}CH_2 + R_2NH{\cdot}HCl$$

Following the procedure of Cerf,[6] Senkus[8] and of Johnson,[9] nitro amines derived from diethylamine, formaldehyde and the 1-nitroalkanes 1-nitropropane through 1-nitrohexane were obtained readily in excellent yield (70–80%) as colorless to pale-yellow liquids which could be distilled without decomposition under reduced pressure. The base derived from nitroethane and diethylamine, however, decomposed violently when its distillation was attempted. By substituting piperidine for diethylamine nitroethane formed a nitroamine which could be purified by distillation without difficulty. Nitromethane, under all conditions studied, afforded only a di-substituted base when treated with N-hydroxymethylpiperidine.

Pyrolysis of the free nitro amines derived from the nitroparaffins was not regarded as a suitable method for obtaining the desired nitroölefins for several reasons. Nitroölefins are known to be reactive toward amines[11,12] and their polymerization is catalyzed by bases.[3] On the other hand, pyrolysis of the nitro amine hydrochlorides would obviate these difficulties. It was observed that thermal decomposition of the several nitro amine hydrochlorides proceeded smoothly and rapidly at moderate temperatures. Initial decomposition started at temperatures in the neighborhood of 100–115° and was complete by gradually raising the pyrolysis temperature to 165–175°. By carrying out the decompositions under reduced pressure (50–100 mm.) the nitroölefins were all removed rapidly from the zone of heating. The several nitroölefins were obtained as blue-green, lachrymatory liquids in excellent yield after purification by redistillation (70–80%).

Since it was not possible to convert nitromethane into a suitable nitro amine, nitroethylene could not be prepared by the procedure described above.

In searching for solid derivatives which might be used to characterize the 2-nitro-1-alkenes attention was given the reaction of aromatic amines with nitroölefins first reported by Wieland and Sakellarios[11] and extended by Worrall.[12] According to these investigators primary aromatic amines should add to the 2-nitro-1-alkenes as follows



$$\underset{\displaystyle NO_2}{R{-}C}{=}CH_2 + ArNH_2 \longrightarrow \underset{\displaystyle NO_2}{R{-}CH}{-}CH_2{-}NH{-}Ar$$

p-Toluidine added rapidly and smoothly to the nitroölefins affording solid crystalline derivatives which were easily purified. Unfortunately, the melting points of all of the *p*-toluidine derivatives prepared were found to lie in a rather narrow temperature range (*ca.* 68–82°).

Some evidence bearing on the structure of these derivatives was obtained through an independent synthesis of one of them, namely, N-(2-nitrobutyl)-*p*-toluidine. It was prepared di-

---

(1) This paper is an abstract of part of the doctoral dissertation presented by T. H. Shelley, Jr., to the Graduate Faculty of Cornell University in June, 1947.

(2) Allied Chemical and Dye Fellow in Chemistry, 1946–1947.

(3) Blomquist, Tapp and Johnson, THIS JOURNAL, **67**, 1519 (1945).

(4) An excellent summary of other methods of preparing nitroolefins is given in the recent article by Gold, *ibid.*, **68**, 2544 (1946).

(5) Henry, *Bull. classe sci., Acad. roy Belg.*, [3] **32**, 36 (1896); [3] **33**, 412 (1897).

(6) Cerf, *Bull. soc. chim. France*, [5] **4**, 1451, 1460 (1937).

(7) Duden, Bock and Reid, *Ber.*, **38**, 2036 (1905).

(8) Senkus, THIS JOURNAL, **68**, 10 (1946).

(9) Johnson, *ibid.*, **68**, 12 (1946); **68**, 14 (1946).

(10) Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303.

(11) Wieland and Sakellarios, *Ber.*, **52**, 903 (1919).

(12) Worrall, THIS JOURNAL, **43**, 919 (1921); *ibid.*, **49**, 1598 (1927).

rectly from 1-nitropropane by condensation with one mole each of *p*-toluidine and formaldehyde according to the method of Johnson.[9] Treatment of 1-nitropropane with two moles of *p*-toluidine and of formaldehyde gave a di-substituted *p*-toluidine derivative, 2-nitro-2-ethyl-1,3-bis-(*p*-toluino)-propane.

Acknowledgment.—The authors wish to express their gratitude to Miss Lois Ann Capella who assisted in much of the preparative and analytical work.

Experimental[13]

Nitroparaffins.—Nitromethane, nitroethane and 1-nitropropane, obtained from the Commercial Solvents Corporation, were freshly distilled before use.

1-Nitrobutane, 1-nitropentane and 1-nitrohexane were prepared by the method of Victor Meyer.[14]

Nitro Amines.—These were prepared by the condensation of the appropriate nitroparaffin with a suitable N-hydroxymethylamine. The preparation of N-(2-nitrobutyl)-diethylamine illustrates the general procedure.

To a solution of 73 g. (1 mole) of redistilled diethylamine in an equal volume of water contained in a 1-liter flask fitted with stirrer, thermometer, dropping funnel and condenser there was added dropwise with rapid stirring 84 cc. (1.0 mole) of formalin (36% solution) over a period of half an hour. The temperature was maintained at 18° during the addition. The reaction mixture was then stirred at room temperature for an additional half hour after the addition of formalin was completed. To this aqueous solution of the N-hydroxymethylamine there was added all at once with rapid stirring 89 g. (1 mole) of 1-nitropropane. This addition was accompanied by an 8–10° rise in temperature. Rapid stirring of the mixture was continued for three to four hours. The two-layer mixture was then extracted with 100 cc. of ether, and the aqueous layer again extracted with 20 cc. of ether following the addition of 10 g. of sodium chloride. The ether solutions were combined, dried with anhydrous magnesium sulfate and distilled under reduced pressure. After removal of the ether the nitro amine was obtained by distillation at 2 mm. pressure under nitrogen. **N-(2-Nitrobutyl)-diethylamine**, 138 g. (79%), was obtained as a pale yellow liquid; b. p. 79° (2 mm.), n^{20}D 1.4405.

Anal. Calcd. for $C_8H_{18}N_2O_2$: mol. wt., 174. Found (by titration): mol. wt., 178, 180.

Some decomposition occurred when the product was distilled at 14 mm. as described by Cerf.[6]

Using the procedure outlined above, the following nitroamines were prepared in 70–75% yield.

N-(2-Nitroamyl)-diethylamine; b. p. 84° (1 mm.), n^{20}D 1.4421. *Anal.* Calcd. for $C_9H_{20}N_2O_2$: mol. wt., 188. Found (by titration): mol. wt., 191, 186.

N-(2-Nitrohexyl)-diethylamine; b. p. 91–93° (1 mm.), n^{20}D 1.4447. *Anal.* Calcd. for $C_{10}H_{22}N_2O_2$: mol. wt., 202. Found (by titration): mol. wt., 204, 202.

N-(2-Nitroheptyl)-diethylamine; b. p. 102–103° (1 mm.), n^{20}D 1.4465. *Anal.* Calcd. for $C_{11}H_{24}N_2O_2$: mol. wt., 216. Found (by titration): mol. wt., 222, 220.

N-(2-Nitropropyl)-diethylamine.—This base derived from nitroethane, when prepared by the general procedure, decomposed violently when attempts were made to distil it at low pressures (1 mm.). However, a product of reasonable purity was obtained by working up the usual reaction mixture from nitroethane and N-hydroxymethyldiethylamine in the following manner. The organic layer was washed three times with cold water, dried over Drierite in the refrigerator for fourteen hours, and finally stripped of low-boiling material by heating to 45° for forty-five minutes under nitrogen at 2 mm. This gave an 83% yield of a golden-yellow liquid; n^{25}D 1.4420, d^{20}_4 0.9751; *MR*D calcd., 44.1; found, 43.1.

N-(2-Nitropropyl)-piperidine.—This base derived from nitroethane and N-hydroxymethylpiperidine was obtained in 41% yield and could be distilled; b. p. 87° (1 mm.), n^{20}D 1.4469.

Anal. Calcd. for $C_8H_{15}N_2O_2$: mol. wt., 171. Found (by titration): mol. wt., 178, 176.

2-Nitro-2-methyl-1,3-bis-(N-piperidyl)-propane.—This substance was formed as an accessory product in the preparation of N-(2-nitropropyl)-piperidine and was isolated as a residue in the distillation of the nitropropylpiperidine. From a 0.5 mole run there was obtained 6 g. of solid material which after crystallization from ethyl alcohol melted at 101.5–102°.[15]

Anal. Calcd for $C_{14}H_{27}N_3O_2$: N, 15.60. Found: N, 15.75.

2-Nitro-1,3-bis-(N-piperidyl)-propane.—All attempts to effect the condensation of nitromethane with N-hydroxymethylamines in a 1:1 mole ratio were unsuccessful. Regardless of the proportion of reactants and the mode of addition nitromethane always condensed with 2 moles of the N-hydroxymethylamine. Thus with N-hydroxymethylpiperidine only 2-nitro-1,3-bis-(N-piperidyl)-propane was formed. Henry[16] claims to have prepared this compound but did not describe its preparation and properties, nor did he report its analysis.

Addition of 0.5 mole of nitromethane to an aqueous solution containing 0.5 mole of N-hydroxymethylpiperidine gave 54 g. (85% based on the amine) of crude product which was obtained as light tan crystals from ethyl alcohol, m. p. 93.5–94°.

Anal. Calcd. for $C_{13}H_{25}N_3O_2$: C, 61.14; H, 9.85; N, 16.46; mol. wt., 255. Found: C, 61.26; H, 9.90; N, 16.57; mol. wt. (cryoscopic in benzene), 253.

This substance was also prepared by adding 2 g. of piperidine to a solution of 1 g. of 2-nitro-1,3-propanediol in 10 cc. of methyl alcohol. After refluxing the mixture for two hours, 1 g. of crystalline material separated on cooling which, after recrystallization from ethyl alcohol, melted at 93.5–94°. A m. p. of a mixture of this preparation and the material obtained from nitromethane showed no depression.

2-Nitro-1-alkenes.—The nitroölefins were obtained by pyrolysis of the respective nitro amine hydrochlorides under reduced pressure. By operating under reduced pressure the nitroölefin was removed rapidly from the zone of heating and losses resulting from thermal polymerization were minimized. As the various nitroölefins were prepared by essentially the same procedure only one of these is described in detail.

2-Nitro-1-pentene.—The hydrochloride of N-(2-nitroamyl)-diethylamine was prepared by passing dry hydrogen chloride for four hours into a cooled stirred solution of 58.2 g. (0.31 mole) of the amine in four times its volume of dry toluene. The initially formed white precipitate later redissolved upon the continued passage of the hydrogen chloride to yield a blue-green solution.[17] This solution was transferred to a 500-cc. Claisen flask and after removal of the toluene and excess hydrogen chloride by heating with a water-bath (final bath temperature 70°) at 50 mm. pressure a white solid remained. Heating was then continued with an oil-bath and at a regulated pressure of 100 mm. The solid began to melt at 90° while at 115–120° it started to decompose smoothly to yield a blue-green liquid distilling at 110–115° (vapor temperature). The pyrolysis was complete within forty-five

---

[13] All melting points and boiling points are uncorrected.

[14] Meyer, *et al.*, *Ann.*, **171**, (1874); **175**, 88 (1875); **180**, 111 (1876).

[15] Henry reported a m. p. of 98–99°; *cf.* ref. 4.

[16] Henry, *Ber.*, **38**, 2027 (1905).

[17] This curious solubility behavior was also observed for the nitro amine hydrochlorides derived from 1-nitropentane and 1-nitrohexane. In preparing the hydrochloride of N-(2-nitrobutyl)-diethylamine in toluene two liquid layers were formed. The hydrochloride of N-(2-nitropropyl)-piperidine separated quantitatively from toluene as a crystalline solid.

minutes with the final temperature within the flask being 165°. The crude distillate, 35.2 g. (99%), was dissolved in ether, the ether solution washed with water and dried over anhydrous magnesium sulfate in the refrigerator. After removal of the ether the crude product was distilled under reduced pressure using a 14 × 0.75 in. column packed with 0.75 in. glass helices. There was obtained 25 g. (75%) of pure product; b. p. 68° (50 mm.), $n^{20}D$ 1.4403.

Anal. Calcd. for $C_5H_9NO_2$: N, 12.17. Found: N, 12.28.

The residue in the pyrolysis was shown to be diethylamine hydrochloride by its m. p. after crystallization from ethyl alcohol (220–224°, lit. 215–223°) and conversion to its benzenesulfonyl derivative, m. p. 59–60°.

2-Nitropropene was obtained similarly by pyrolysis at 105–160° of the hydrochloride of N-(2-nitropropyl)-piperidine under 70 mm. pressure in 50% yield. It was identical with the 2-nitropropene prepared by other methods.[3]

2-Nitro-1-butene was obtained in 73% yield by pyrolysis of the hydrochloride of N-(2-nitrobutyl)-diethylamine at 100–175° under 100 mm. pressure; b. p. 60.5° (50 mm.), $n^{20}D$ 1.4356. It was identical with an authentic sample of 2-nitro-1-butene synthesized by pyrolysis of the benzoate of 2-nitro-1-butanol.[18]

2-Nitro-1-hexene was obtained in 70% yield by pyrolysis of N-(2-nitrohexyl)-diethylamine at 105–165° under 50 mm. pressure; b. p. 81–82° (50 mm.), $n^{20}D$ 1.4462.

Anal. Calcd. for $C_6H_{11}NO_2$: N, 10.86. Found: N, 10.89.

2-Nitro-1-heptene was obtained in 70% yield by pyrolysis of N-(2-nitroheptyl)-diethylamine at 110–150° under 50 mm. pressure; b. p. 93–94° (30 mm.), $n^{20}D$ 1.4482.

Anal. Calcd. for $C_7H_{11}NO_2$: N, 9.76. Found: N, 9.85.

p-Toluidine Derivatives of the 2-Nitro-1-alkenes.—Solid derivatives of the nitroölefins were readily obtained through reaction with *p*-toluidine. The general procedure used in their preparation is described. To 5 g. of the pure 2-nitro-1-alkene, cooled to 0–5°, there was added an equivalent amount of *p*-toluidine. The solution became warm and deep red in color. After maintaining the reaction mixture at 60° for five minutes it was cooled to room temperature and the crude product crystallized. Pure derivatives, as bright yellow solids, were obtained in 80–95% yield after one recrystallization from ethyl alcohol. These compounds are listed in Table I.

TABLE I

N-(2-NITROALKYL)-*p*-TOLUIDINES

Compound, *p*-toluidine	M. p., °C.	N analyses, % Calcd.	N analyses, % Found
N-(2-Nitropropyl)-	81.5–82.5	14.42	14.38
N-(2-Nitrobutyl)-	67.5–68.5	13.45	13.37
N-(2-Nitroamyl)-	72 –72.5	12.60	12.86
N-(2-Nitrohexyl)-	68.5–69	11.86	12.18
N-(2-Nitroheptyl)-	72.5–73.5	11.19	11.51

The *p*-toluidine derivatives of samples of 2-nitropropene and 2-nitro-1-butene prepared by other methods[3] were identical with those described in Table I.

N-(2-Nitrobutyl)-*p*-toluidine (Table I) was also prepared by an independent method. Using the procedure of Johnson,[9] 1-nitropropane, formaldehyde and *p*-toluidine reacted to give a 26% yield of the crude *p*-toluidine derivative, m. p. 60–66°. After recrystallization from methanol its m. p., 67.5–68.5°, was not depressed when mixed with the toluidine derivative prepared from 2-nitro-1-butene.

2-Nitro-2-ethyl-1,3-bis-(*p*-toluino)-propane, a di-substituted *p*-toluidine derivative, was prepared as a check on the mono-substituted derivative described above. To a refluxing mixture of 107 g. (1 mole) of *p*-toluidine, 44.5 g. (0.5 mole) of 1-nitropropane, 1 g. of potassium hydroxide and 300 cc. of ethyl alcohol, 82 g. (1 mole) of 37% formalin solution was added over a period of six hours. After refluxing an additional two hours and standing at room temperature for two days the mixture was cooled in ice and filtered. There was obtained 35 g. (25%) of light tan crystals melting at 101–102° which were recrystallized from ethyl alcohol, m. p. 103–104°.

Anal. Calcd. for $C_{19}H_{25}N_3O_2$: N, 12.84. Found: N, 12.73.

Summary

A series of 2-nitro-1-alkenes has been readily obtained by thermal decomposition of appropriate nitro amine hydrochlorides derived from 1-nitroalkanes.

The 2-nitro-1-alkenes may be characterized by crystalline solid derivatives formed by their reaction with *p*-toluidine.

ITHACA, N. Y.

RECEIVED JULY 28, 1947

---

[18] Tapp, Thesis, Cornell University, 1943.

[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY OF WESTERN RESERVE UNIVERSITY]

Reactions with Tetraphenylcyclopentadienone. II. Condensation with 1-Phenyl-1,3-butadiene[1]

BY OLIVER GRUMMITT AND ERNEST I. BECKER[2]

2,3,4,5-Tetraphenylcyclopentadienone (tetracyclone) is of interest in diene chemistry through its addition reactions with α,β-unsaturated carbonyl compounds[3] and with conjugated dienes.[4,5] In the case of butadiene the adduct contains two tetracyclone groups as the result of 1,2 and 3,4 addition at the 2,5 positions of the tetracyclone ring.[4] With cyclopentadiene only one tetracyclone reacts, the addition occurring at the 2,3 double bond and at the 2,5 positions of tetracyclone.[5]

These addition reactions are usually considered

---

(1) Presented before the Division of Organic Chemistry at the Atlantic City meeting of the American Chemical Society, April 15, 1947.

(2) Sherwin-Williams Research Fellow in Organic Chemistry, 1946. Present address: Polytechnic Institute of Brooklyn, Brooklyn, New York.

(3) For example, with maleic anhydride: *cf.* Dilthey, Schommer, and Trosken, *Ber.*, **66B**, 1627 (1933), and Allen and Sheps, *Can. J. Research*, **11**, 171 (1934).

(4) Dilthey, Schommer, Hoschen and Dierichs, *Ber.*, **68B**, 1159 (1935).

(5) Grummitt, Klopper and Blenkhorn, THIS JOURNAL, **64**, 604 (1942).

to be Diels–Alder reactions.[6] Although tetracyclone has an α,β-unsaturated carbonyl group, and therefore might behave as a dienophile, it characteristically reacts as a conjugated diene. In the presence of tetracyclone a conjugated diene behaves as a dienophile. In terms of the structures associated with typical Diels–Alder reactions, tetracyclone and the diene show reversed functions.

A survey of the addition reactions of 1-phenyl-1,3-butadiene has shown that most reagents preferentially add 3,4 instead of 1,2 or 1,4.[7] Furthermore, unsymmetrical reagents which add 3,4 usually obey Markownikoff's rule. Since styrene also shows normal addition in most cases, this behavior of phenylbutadiene is in accord with the principle of vinylogy.[8] As a continuation of the study of the mode of addition of both tetracyclone and phenylbutadiene, an investigation of the reaction of these compounds is reported here.

Although 1-phenyl-1,3-butadiene has been made by several different reactions,[7] the synthesis of this hydrocarbon in good yields proved to be quite difficult. The reaction of cinnamaldehyde and methylmagnesium bromide to give methylstyrylcarbinol followed by dehydration of this carbinol was tried first.[9] Although the carbinol can be made in 80–90% yields, dehydration of it gave poor yields because of rapid polymerization of the hydrocarbon during dehydration. The relatively high boiling point of phenylbutadiene aggravates this problem, because it cannot be quickly removed from the reaction mixture, as is possible for lower boiling hydrocarbons.

von der Heide[10] modified this synthesis by hydrolyzing the intermediate Grignard addition compound in acid solution so that phenylbutadiene was formed without isolation of the methylstyrylcarbinol. This reaction also gave low yields until the conditions of hydrolysis were thoroughly explored. By hydrolysis in 30% sulfuric acid solution under carefully controlled conditions of time and temperature, it is now possible to prepare 1-phenyl-1,3-butadiene consistently in 70–80% yields.

In the absence of an inhibitor phenylbutadiene polymerizes more rapidly than 1,3-butadiene.[11] To facilitate work with this compound several inhibitors were tested at a concentration of 1% and at a temperature of 100°. The experiments summarized in Table I were run by noting the time required for samples to flow vertically in 7-mm. reaction tubes. The interval of time elapsed for the flow time to exceed one second was arbitrarily taken as the inhibition period.

TABLE I

POLYMERIZATION INHIBITORS FOR 1-PHENYL-1,3-BUTADIENE[12]

Inhibitor	Inhibition period, hr.
Blank	<9.5
Picric acid	21
m-Dinitrobenzene	21
Phenyl-β-naphthylamine	21
Diphenylamine	21
Triphenylamine	<9.5
p-Phenylenediamine	<9.5
Hydroquinone	<9.5
t-Butylcatechol	5
Benzoquinone	9.5
Chloranil	5

The aromatic nitro compounds and certain of the amines are considerably more effective than the phenols and quinones. Phenyl-β-naphthylamine was selected as the most suitable inhibitor. It is interesting to note that this compound is relatively less effective for styrene and 3,4-dichlorostyrene.[13]

Tetracyclone and 1-phenyl-1,3-butadiene were found to react almost quantitatively at 80° in a 1/1 mole ratio, thus resembling the addition to cyclopentadiene.[5] Two structurally isomeric products are possible (chart 1): (A) is the result of 1,2 addition and (B) of 3,4 addition. Since the reaction product was a single compound, it presumably had either the (A) or (B) structure. To establish this structure it was desirable to convert the six-membered ring to a benzenoid ring. As the first step in this process, an effort was made to eliminate the endocarbonyl group by thermal decomposition. However, this characteristic reaction of endocarbonyl compounds[6b] could not be carried out because of a competitive dissociation of the adduct to tetracyclone and phenylbutadiene.[14]

In order to stabilize the adduct it was hydrogenated with the consumption of one equivalent of hydrogen. If the structure of the adduct is assumed to be (B), hydrogenation probably occurred in the styryl side chain (C), since Dilthey[15] has shown the ring double bond to be stable under the conditions employed here. The hydrogenated adduct proved to be sufficiently resistant to decomposition that heating at 180° or above eliminated the endocarbonyl group to give the cyclohexadiene derivative (D). Aromatization of (D) was effected by chloranil at 140° or by palladium on charcoal at 240°. Decarbonylation and aromatization occurred consecutively when (C) was refluxed in *p*-cymene with the palladium catalyst.

---

(6) For a review of the chemistry of tetracyclone and related compounds see (a) Norton, *Chem. Rev.*, **31**, 398 (1942), and (b) Allen, *ibid.*, **37**, 209 (1945).

(7) Becker, Ph.D. thesis, Western Reserve University, 1946.

(8) Fuson, *Chem. Rev.*, **16**, 1 (1935).

(9) Klages, *Ber.*, **35**, 2649 (1902); Strauss, *ibid.*, **42**, 2882 (1909).

(10) von der Heide, *ibid.*, **37**, 2101 (1904).

(11) Whitby and Gallay, *Can. J. Research*, **6**, 220 (1932).

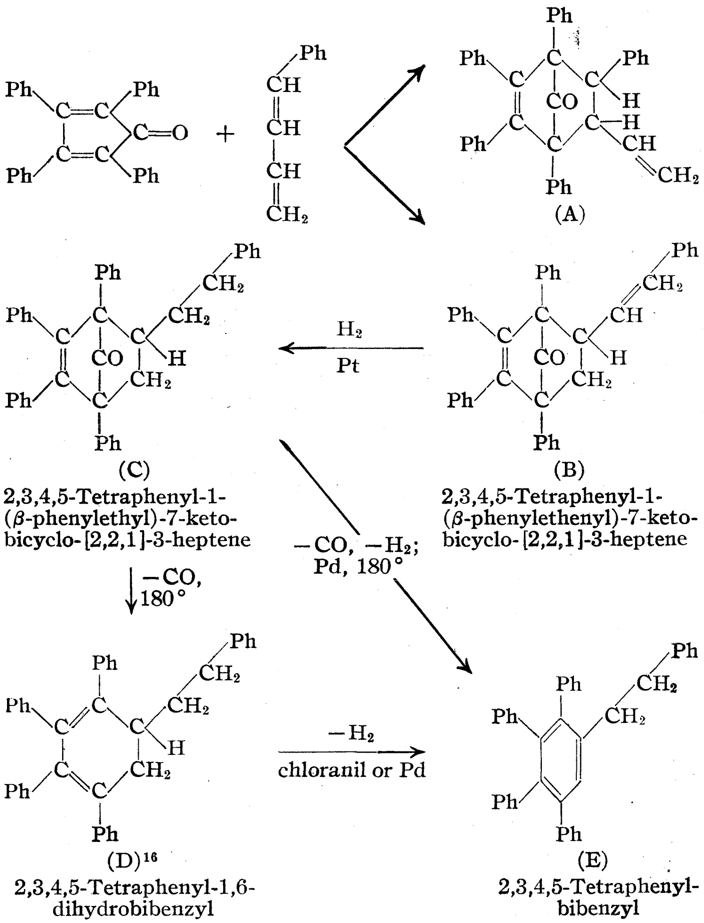
(12) We are indebted to Robert M. Vance of this Laboratory for these experiments.

(13) Frank and Adams, THIS JOURNAL, **68**, 908 (1946).

(14) A similar reverse reaction was noted in the case of cyclopentadiene.[5] This is also typical of many Diels-Alder adducts: *cf.* the work of Bachmann and Kloetzel, THIS JOURNAL, **60**, 481 (1938), on the reactions of maleic anhydride with polycyclic aromatic hydrocarbons.

(15) Dilthey and Quint, *J. prakt. Chem.*, [2] **128**, 143 (1930).

CHART 1



(A)

(B)
2,3,4,5-Tetraphenyl-1-(β-phenylethenyl)-7-keto-bicyclo-[2,2,1]-3-heptene

(C)
2,3,4,5-Tetraphenyl-1-(β-phenylethyl)-7-keto-bicyclo-[2,2,1]-3-heptene

(D)[16]
2,3,4,5-Tetraphenyl-1,6-dihydrobibenzyl

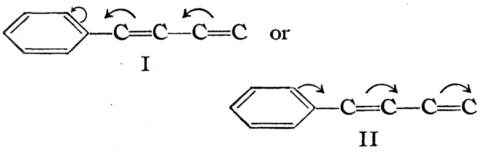
(E)
2,3,4,5-Tetraphenylbibenzyl

The final product (E) is 2,3,4,5-tetraphenylbibenzyl, or, if adduct (A) had formed, the corresponding product is pentaphenylethylbenzene.

Attempts to establish the structure of the benzene derivative by oxidation to tetraphenyl- or pentaphenylbenzoic acid were unsuccessful. However, the non-crystallizable oxidation products responded to qualitative tests for a benzoin, thus pointing to structure (E). Conclusive evidence for (E) was obtained by an independent synthesis from tetracyclone with 4-phenyl-1-butyne[17] or with 4-phenyl-2-bromo-1-butene.

The authentic 2,3,4,5-tetraphenylbibenzyl from these reactions proved to be identical with the product (E) from the tetracyclone–phenylbutadiene sequence of reactions. Therefore, tetracyclone added 3,4 to 1-phenyl-1,3-butadiene in preference to 1,2 addition. This result is in accord with most addition reactions of this diene.[7]

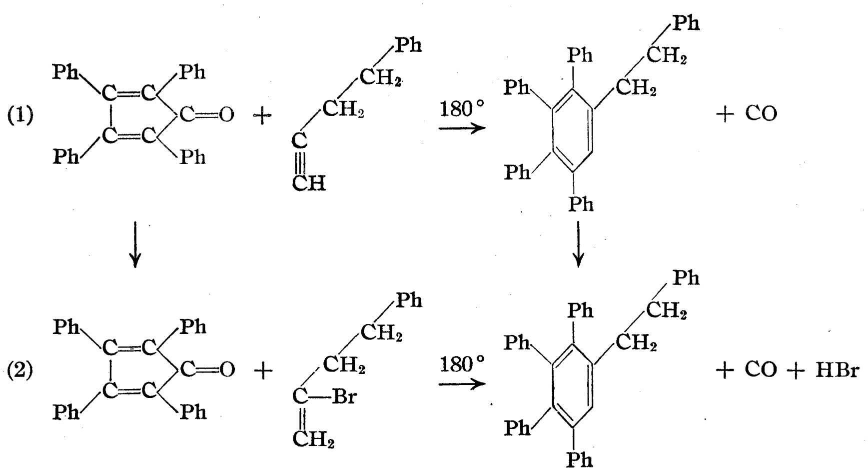
The explanation for the preferential 3,4 addition is two-fold: first, the steric hindrance from the phenyl group at the 1,2 double bond would favor 3,4 addition, especially in the case of large molecules such as tetracyclone.[18] Possibly of greater importance is the nature of the activated phenylbutadiene molecule. According to the usual electronic interpretations,[19] the butadienyl side chain could be activated in the course of addition of polar reactants by electron displacements toward or away from the ring



I

II

Because of the *conjugated* bonds in the side chain this polarization affects *both* double bonds, thus making addition to either double bond theoretically possible, but also creating the greatest relative charge on the terminal carbon atom. There-



---

[16] The position of the double bonds in this compound was not established.

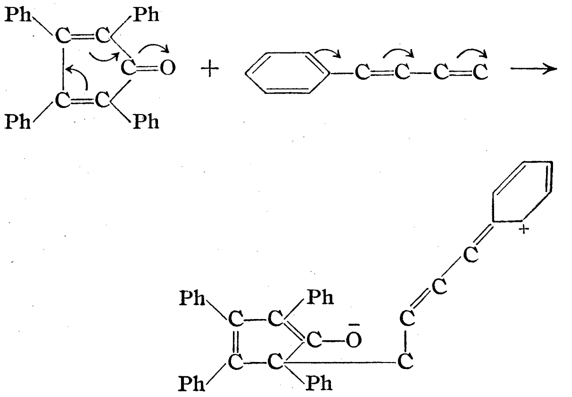
[17] Tetracyclone reacts with acetylene, phenylacetylene and other acetylenic compounds by addition to the triple bond. The resulting endocarbonyl derivatives very readily lose carbon monoxide. See Dilthey, *et al.*, *Ber.*, **66B**, 1627 (1933).

[18] In the addition of maleic anhydride (Robey, Morrell and Weise, THIS JOURNAL, **63**, 627 (1941)) and of sulfur dioxide (Craig, *ibid.*, **65**, 1006 (1943)) to piperylene, it has been shown that the steric hindrance from the methyl group in the *cis* piperylene will retard addition, but the *trans* isomer shows normal reactivity. The phenylbutadiene used in this experiment is very likely a mixture of geometric isomers (Wright, *J. Org. Chem.*, **1**, 457 (1936)). Presumably, the steric factor would be significant only in the case of the *cis* isomer.

[19] Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 245.

fore addition is usually initiated at this point with the result that 3,4 addition occurs more frequently. The direction of the polarization is postulated as in II, *i. e.*, the ring acts as an electron donor, in order to account for the normal addition of unsymmetrical reagents.[20]

The reactivity of tetracyclone in this reaction would result from a polarization in its conjugated system to make carbon atom 5 electrophilic. Thus the first step in the addition



This activated intermediate complex can have various structures. The form in which ring closure occurs to give the adduct (B) would have a nucleophilic number 2 carbon atom in tetracyclone and an electrophilic number 3 carbon atom in phenylbutadiene. This mechanism, which is comparable to that frequently proposed for orthodox Diels–Alder additions,[21] accounts for the behavior of tetracyclone as a conjugated diene rather than as an α,β-unsaturated carbonyl derivative.[22]

Experimental

Preparation of Reactants.—Tetraphenylcyclopentadienone was made by the condensation of benzil and dibenzyl ketone in alcoholic base.[15,23]

Since adequate directions for preparing 1-phenyl-1,3-butadiene are not in the literature, considerable time and effort were expended in finding the optimum conditions described here. In a 1-liter three-necked flask fitted with a mercury seal stirrer, reflux condenser protected with a calcium chloride tube, a 125-ml. dropping funnel, and a nitrogen inlet tube are placed 0.515 mole of methylmagnesium bromide in 250–350 ml. (1.5–2.0 *N*) of ether. The Grignard reagent is cooled to 0–10° with stirring and under a current of nitrogen, and a solution of 66.1 g. (0.5 mole) of cinnamaldehyde in 60 ml. of absolute ether is added so that the temperature does not exceed 10°. This addition requires about one hour. The cinnamaldehyde should be freshly purified by washing with sodium carbonate solution, then with water, dried over Drierite, and distilled under nitrogen; b. p. 101–102° (2–3 mm.), $n^{20}\text{D}$ 1.6195.

The contents of the reaction flask are transferred to a 500-ml. dropping funnel. The apparatus is reassembled, omitting the nitrogen inlet tube and drying tube, and 175 ml. of 30% (by weight) sulfuric acid placed in the flask. With vigorous stirring and without cooling, the Grignard addition compound is rapidly added to the acid solution. With an efficient reflux condenser this time of addition is five to seven minutes. The mixture is then heated at gentle reflux on the steam-bath until the *total* time of hydrolysis is twenty minutes. The conditions of this hydrolysis are very important in determining the yield of phenylbutadiene. Vigorous stirring was attained by a Hershberg[24] nichrome-wire stirrer run at 1500–1700 r. p. m. The time of addition and of reflux are critical in avoiding polymerization of the product and contamination by methylstyrylcarbinol.

The contents of the flask are *immediately* transferred to a 1-liter separatory funnel, the lower aqueous layer is discarded, and the ether solution is washed successively with (1) 50 ml. of water, (2) a mixture of 50 ml. of 5% sodium hydroxide solution and 50 ml. of saturated ammonium chloride solution, and (3) 50 ml. of water. Before each washing the air in the funnel is displaced by nitrogen. When the second wash solution is added, 0.3 g. of phenyl-β-naphthylamine is dissolved in the ether solution. The washed solution is dried with 20 g. of anhydrous sodium sulfate for one-half hour and then overnight with 15 g. of anhydrous potassium carbonate.

The ether solution is distilled to a volume of 80–100 ml. on the steam-bath, cooled, and dried further by shaking with 15 g. of potassium carbonate for five to ten minutes. The solution is filtered into a 125 ml. modified Claisen flask[25] and distilled under nitrogen at reduced pressure into a receiver containing 0.3 g. of phenyl-β-naphthylamine. The crude phenylbutadiene is collected at 81–85° (10–11 mm.); the yield is 52–54 g., 80–83% of the theoretical. To remove traces of water and methylstyrylcarbinol, this distillate is dried with 5 g. of potassium carbonate, filtered and redistilled. The distillate consists of 47–49 g. (72–75%), b. p. 78–81° (8 mm.), $n^{20}\text{D}$ 1.6070. The reactions with tetracyclone were run with this product.

A highly purified sample of 1-phenyl-1,3-butadiene was made by distilling the above product through a 12-plate, glass helix packed column of the total reflux variable take-off type and collecting a middle fraction representing about 50% of the sample taken. The following physical constants were noted: b. p. 86° (11 mm.), $n^{25}\text{D}$ 1.6088 ± 0.0002, d^{25}_4 0.9237 ± 0.0002. A qualitative test for nitrogen by sodium fusion and formation of Prussian blue was negative, showing that phenyl-β-naphthylamine had not distilled.

Anal. Calcd. for $C_{10}H_{10}$: C, 92.25; H, 7.75. Found: C, 92.25; H, 7.81.

Tetracyclone–Phenylbutadiene Adduct (B).—In a typical experiment 2.50 g. (0.019 mole) of 1-phenyl-1,3-butadiene, 7.00 g. (0.018 mole) of tetracyclone (m. p. 219–220°), and 0.01 g. of phenyl-β-naphthylamine in 50 ml. of reagent-grade benzene were refluxed on the steam-bath for four hours. No carbon monoxide, as indicated by tests with palladium chloride solution, was evolved. Benzene and unreacted phenylbutadiene were removed by steam distillation and the residual pink solid dried at 50° to give 9.40 g. (100%), m. p. 170–175° (dec.). Crystallization from 90 ml. of a 1:1 mixture of benzene and petroleum ether (b. p. 60–70°) gave 6.0 g. of almost colorless fine needles, m. p. 178–180° (dec.). A second crop weighed 2.05 g. and melted 177–180° (dec.). The behavior on melting is noteworthy: at 140–145° the colorless crystals began to turn pink. The color deepened with increasing temperature and at 178–181° the solid melts to a deep red liquid.

Anal. Calcd. for $C_{39}H_{30}O$: C, 91.02; H, 5.88; mol.

---

[20] Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 247.

[21] Price, "Reactions at Carbon–Carbon Double Bonds," Interscience Publishers, Inc., New York, N. Y., 1946, p. 49.

[22] It is not suggested that all reactions of tetracyclone proceed by this mechanism. The addition of maleic anhydride and similar molecules probably differ in mechanism because of the electron deficient character of the carbon–carbon double bond in maleic anhydride.

[23] Johnson and Grummitt, "Organic Syntheses," **23**, 92 (1943).

[24] Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 313 (1936).

[25] "Organic Syntheses," Coll. Vol. I, 130 (1941); Fig. 9(b).

wt., 515. Found: C, 91.11; H, 5.93; mol. wt., 517 (cryoscopic in benzene).[26]

This product is unsaturated with respect to bromine in bromobenzene and potassium permanganate in acetone. It does not give a positive ketone test with 2,4-dinitrophenylhydrazine reagent.[27] It is very soluble in benzene and acetone, moderately soluble in ethyl acetate, slightly soluble in ethyl alcohol and insoluble in petroleum ether. When a benzene or ethyl acetate solution is boiled, decomposition occurs, as shown by the formation of a pink color.

Attempted Decarbonylation of (B).—Experiments were run in refluxing toluene (b. p. 110°), chlorobenzene (b. p. 132°), bromobenzene (b. p. 155°), and *p*-cymene (b. p. 175°). For example, a solution of 1.0 g. of the addition compound (B) in 15 ml. of chlorobenzene was refluxed in a 25-ml. flask fitted with a nitrogen inlet tube. The top of the condenser was attached to a trap and to a gas bubbler containing 2–3 ml. of 0.025% palladium chloride. After two hours of refluxing no more carbon dioxide was evolved. The product, 0.8 g. of dark red solid melting 80–84°, was recovered by steam distillation, filtration, and drying at 50°. Repeated crystallization from benzene–petroleum ether (60–70°) gave only impure products of wide melting range. Examination of the solids under the microscope showed that fine, black crystals, closely resembling tetracyclone, were present. Varying the reaction temperatures by the use of other solvents gave no better results. Apparently the product of decarbonylation and the tetracyclone from dissociation could not be separated.

Hydrogenation of (B).—The hydrogenated addition compound (C) was made by low pressure hydrogenation of (B) in ethyl acetate solution with 5% palladium on charcoal as the catalyst. Ten and three-tenths grams (0.020 mole) of (B) in 200 ml. of absolute ethyl acetate plus 0.5 g. of catalyst was hydrogenated at about 30 lb. pressure in a Burgess–Parr apparatus. In three minutes the pressure drop indicated the consumption of 0.023 mole of hydrogen. After filtration of the catalyst, concentration of the filtrate to 120 ml., and cooling to 0°, 6.2 g. of colorless, thick flat crystals, m. p. 207–208.5° (dec.), was obtained. Two successive crops from the mother liquor made the total yield 7.64 g., 74% of the theoretical. Crystallization from 1:1 benzene–petroleum ether (60–70°) did not alter the melting point behavior.

Anal. Calcd. for $C_{39}H_{32}O$: C, 90.65; H, 6.25; mol. wt., 517. Found: C, 90.53; H, 6.34; mol. wt., 514 (cryoscopic in benzene).

This product is saturated with respect to bromine in bromobenzene but unsaturated to potassium permanganate in acetone. Unlike compound (B), a boiling benzene or ethyl acetate solution does not decompose it.

Decarbonylation of (C).—A solution of 8.0 g. (0.015 mole) of compound (C) in 200 ml. of purified *p*-cymene was refluxed under a current of nitrogen until a positive test for carbon monoxide with palladium chloride solution was no longer obtained. This required about twelve hours. After steam distillation of the product and crystallization from benzene–petroleum ether (60–70°), 6.1 g., 81%, of light orange crystals melting 142–144° were obtained. The decarbonylation can also be run in the absence of a solvent by heating (C) in an oil-bath at 220–225° for one hour under nitrogen, but the yield of product melting 142–144° was only 63%. Repeated crystallizations from benzene–petroleum ether (30–35°) and acetone–ethyl alcohol gave almost colorless crystals melting 145–146°.

Anal. Calcd. for $C_{38}H_{32}$: C, 93.39; H, 6.61; mol. wt., 489. Found: C, 93.65; H, 6.70; mol. wt., 488 (cryoscopic in benzene).

Compound (D) was unsaturated to both bromine and potassium permanganate solutions. The position of the double bonds was not established, but the structure shown in Chart 1 is very probable because the double bonds are conjugated with respect to each other and to the aromatic double bonds of the phenyl substituents.

Dehydrogenation of (D) with Chloranil.—A solution of 500 mg. (1.02 millimoles) of (D) and 264 mg. (1.07 millimoles) of chloranil (m. p. 298–300°) in 5 ml. of xylene was refluxed for twenty-four hours. After cooling and filtering to remove tetrachlorohydroquinone, the filtrate was washed twice with 10-ml. portions of 4% potassium hydroxide solution, once with water, and steam distilled to remove xylene. The residue was crystallized three times from benzene–petroleum ether (60–70°) to give 247 mg., 49% of the theoretical yield, of solid melting 129–131°.

Dehydrogenation of (D) with Palladium.—In the catalytic dehydrogenation apparatus described by Fieser[28] 0.98 g. (2.0 millimoles) of (D) and 0.2 g. of 5% palladium on charcoal were refluxed in 5 ml. of 1-methylnaphthalene (b. p. 238–240°)[29] for six hours. During this time 88% of the calculated amount of hydrogen was evolved. After steam distilling to remove the solvent and crystallization of the residue from benzene–petroleum ether (60–70°), there was obtained 0.81 g., 83% of the theoretical yield, melting 134–138°. A mixed melting point with the impure product from the chloranil dehydrogenation gave 133–137° and with compound (D), 125–142°. Compound (E) is saturated to both bromine and potassium permanganate. For analysis a sample melting 135–137° was made by recrystallization.

Anal. Calcd. for $C_{38}H_{30}$: C, 93.79; H, 6.21; mol. wt., 487. Found: C, 93.65; H, 6.27; mol. wt. (Rast camphor), 491.

Combined Dehydrogenation and Decarbonylation of (D).—A mixture of 4.0 g. (7.7 millimoles) of (C) and 0.5 g. of 5% palladium on charcoal in 100 ml. of *p*-cymene was refluxed for eight and one-half hours. Carbon monoxide was evolved until the last fifteen minutes of heating. After steam distilling and crystallizing from benzene–petroleum ether, the product consisted of 3.0 g. (80%) melting 136–140°. A mixed melting point with (D) of melting point 135–137° gave 136–140°. Further crystallizations of the 136–140° product did not purify it. It was concluded that the palladium catalyzed dehydrogenation of (D) was the best method of preparation.

Chromic Acid Oxidation of (E).—Several attempts were made to oxidize (E) to 2,3,4,5-tetraphenylbenzoic acid, but only oils or impure solids could be obtained. For example, a solution of 2.5 g. of chromium trioxide in 4 ml. of water and 4 ml. of acetic acid was added dropwise to a solution of 1.55 g. (3.2 millimoles) of (E) in 5 ml. of acetic acid. After the exothermic reaction subsided, the product was isolated by pouring the mixture onto ice, filtering, and washing the solid with water. The solid was dissolved in 50 ml. of 1:1 benzene–ether and this solution was extracted with 10 ml. of 5% sodium carbonate solution. Acidification of the alkaline extract gave only 10 mg. of brown solid melting 40–50°, which was not investigated further. The benzene–ether solution yielded an oil which could not be crystallized. When this oil was dissolved in alcoholic potassium hydroxide and heated, a deep red-purple color formed, reminiscent of the behavior of benzoin-benzil mixtures.[30] Attempts to oxidize the oil further with sodium peroxide were unsuccessful. The original aqueous filtrate was extracted with ether in a continuous extractor and the ether extract yielded about 0.1 g. of solid melting 116–120°, which was shown to be benzoic acid by a mixed melting point.

---

[26] The molecular depression constant used was 5.49 deg./mole. This value was found experimentally by carefully determining the freezing point depression of several solutions of pure naphthalene in benzene. The constant frequently given in the literature of 5.12 was determined under *equilibrium* conditions (Bury and Jenkins, *J. Chem. Soc.*, 688 (1934). Such conditions do not exist in the usual cryoscopic molecular weight determination.

[27] Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 65.

[28] Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Company, New York, N. Y., 1941, p. 462.

[29] Grummitt and Buck, This Journal, **65**, 295 (1943).

[30] Michaelis and Fetcher, *ibid.*, **59**, 1246 (1937).

4-Phenyl-2-bromo-1-butene.—Although the synthesis of this compound has been reported,[31] the difference in boiling points observed makes it desirable to give the details of this synthesis. Benzylmagnesium chloride, made from 25.3 g. (0.20 mole) of distilled benzyl chloride (b. p. 72–73° (24 mm.)) and 4.9 g. (0.20 atom) of magnesium in 100 ml. of absolute ether, was added to 40 g. (0.20 mole) of 2,3-dibromo-1-propene[32] (b. p. 73–76° (75 mm.)) in 100 ml. of absolute ether so as to maintain a slow reflux. The mixture was then refluxed for two hours, followed by hydrolysis in 80 ml. of saturated ammonium chloride solution and 120 g. of ice. The ether layer was washed, dried, etc., and vacuum distilled; the forerun consisted of 12 g. of 2,3-dibromo-1-propene and the 4-phenyl-2-bromo-1-butene distilled at 85–87° (4–5 mm.). A residue of 11.1 g. was crystallized from methyl alcohol and shown to be bibenzyl by a mixed melting point. After twice redistilling the product, a fraction boiling 90–91° (4–5 mm.) showed d^{25}_{4} 1.2860 and n^{25}_{D} 1.5467. Previously reported[31]: b. p. 77–78° (5 mm.), d^{20}_{4} 1.2901, n^{20}_{D} 1.5450.

Anal. Calcd. for $C_{10}H_{11}Br$: C, 56.89; H, 5.25; Br, 37.86. Found: C, 56.48; H, 5.16; Br, 38.02 (Carius).

4-Phenyl-1-butyne.—Sodamide was prepared from 3.1 g. (0.133 atom) of sodium by the method of Murray and Cloke,[33] and the reaction with 10 g. (0.0474 mole) of 4-phenyl-2-bromo-1-butene was carried out according to Johnson and McEwen.[31] The product distilled at 72–78° (11 mm.) and weighed 3.9 g. (64%); n^{25}_{D} 1.5192. The mercury derivative, bis-(4-phenyl-1-butynyl)-mercury, melted 83.5–84.5°; reported, 83.5–84.5°.[31]

2,3,4,5-Tetraphenylbibenzyl from Tetracyclone and 4-Phenyl-1-butyne.—A solution of 1.0 g. (7.68 millimoles) of the acetylenic compound and 2.88 g. (7.50 millimoles) of tetracyclone in 15 ml. of *p*-cymene was refluxed under a slow current of nitrogen until carbon monoxide was no longer evolved (about five and one-half hours). The product was isolated by steam distillation and crystallization from a solution of 10 ml. of benzene and 50 ml. of petroleum ether (60–70°) to give 2.44 g. (67%) of fine, colorless crystals melting 135–137°. A mixed melting point with compound (E) gave 135–137°.

Anal. Calcd. for $C_{38}H_{30}$: C, 93.79; H, 6.21; mol. wt., 487. Found: C, 93.57; H, 6.42; mol. wt. (Rast camphor), 476.

With dioxane substituted for *p*-cymene as the solvent, the condensation required 204 hours and the yield of product melting 135–137° was 57%.

2,3,4,5-Tetraphenylbibenzyl from Tetracyclone and 4-Phenyl-2-bromo-1-butene.—A solution of 0.78 g. (3.70 millimoles) of the butene derivative and 1.36 g. (3.54 millimoles) of tetracyclone in 15 ml. of cymene was refluxed under a slow current of nitrogen for twenty-nine and one-half hours. During this time carbon monoxide and hydrogen bromide were evolved. The product was isolated as before. The yield was 1.04 g. (60%) melting 135–137°. A mixed melting point with a 2,3,4,5-tetraphenylbibenzyl prepared above showed no depression.

To show that the hydrogen bromide was eliminated from the adduct and not from the 4-phenyl-2-bromo-1-butene, a model experiment was run in which a solution of 0.78 g. of the butene derivative in 15 ml. of *p*-cymene was refluxed for sixteen hours. No hydrogen bromide was evolved during this time. The easy elimination of hydrogen bromide from the addition compound is due to the reactivity of the tertiary bromine atom and is comparable to the behavior of Diels–Alder addition compounds of chloromaleic anhydride.[34]

Summary

1-Phenyl-1,3-butadiene can be synthesized from cinnamaldehyde and methylmagnesium bromide in 70–80% yields. Phenyl-β-naphthylamine is an effective polymerization inhibitor for this hydrocarbon. 1-Phenyl-1,3-butadiene and 2,3,4,5-tetraphenylcyclopentadienone react in a 1/1 mole ratio to give 2,3,4,5-tetraphenyl-1-(β-phenylethenyl)-7-keto-bicyclo[2,2,1]3-heptene. The structure of the adduct was proven by degradation to 2,3,4,5-tetraphenylbibenzyl. The latter compound was synthesized independently from tetracyclone and 4-phenyl-1-butyne or 4-phenyl-2-bromo-1-butene. This reaction demonstrates further that the preferred mode of addition to 1-phenyl-1,3-butadiene is 3,4. This process is the result of steric hindrance by the phenyl group and of polarization throughout the butadienyl side chain by electron displacements away from the ring.

CLEVELAND, OHIO RECEIVED JULY 24, 1947

---

[31] Johnson and McEwen, THIS JOURNAL, **48**, 469 (1926).

[32] Lespieau and Bourguel, "Organic Syntheses," Coll. Vol. I, 209 (1941).

[33] Murray and Cloke, THIS JOURNAL, **58**, 2014 (1936).

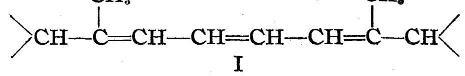
[34] Synerholm, THIS JOURNAL, **67**, 1229 (1945).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WISCONSIN]

Acetylenic Glycols Related to Natural Polyenes[1]

BY LENA F. DEEMER, LEO LUTWAK AND F. M. STRONG

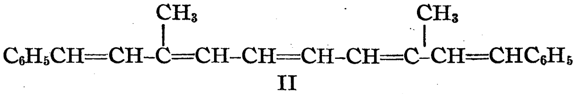
In connection with the general problem of the synthesis of carotenoid pigments and related compounds, it seemed of interest to attempt to prepare substances corresponding in structure to the central ten carbon atoms common to nearly all the natural carotenoids (formula I). Substances of this type



$$>CH-\overset{CH_3}{\overset{|}{C}}=CH-CH=CH-CH=\overset{CH_3}{\overset{|}{C}}-CH<$$

I

bearing terminal substituents which would facilitate further lengthening of the carotenoid chain were desired. As far as the authors are aware the only previously synthesized compound having the carbon skeleton in question is 3,8-dimethyl-1,10-diphenyldeca-1,3,5,7,9-pentaene (II), which was prepared by Kuhn and Wallenfels in 1938.[2]



$$C_6H_5CH=CH-\overset{CH_3}{\overset{|}{C}}=CH-CH=CH-CH=\overset{CH_3}{\overset{|}{C}}-CH=CHC_6H_5$$

II

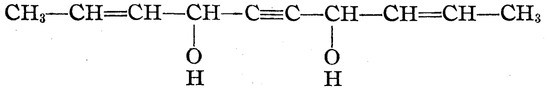
The recent work of Heilbron and collaborators

---

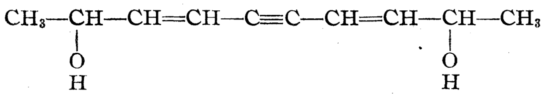
[1] Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported in part by a grant from the Winthrop Chemical Company.

[2] Kuhn and Wallenfels, *Ber.*, **71**, 1891 (1938).

on the anionotropic rearrangement of certain acetylenic glycols[3] as typified, for example, by the ready conversion of III to IV appeared to offer a possible route to substances of the desired structure.

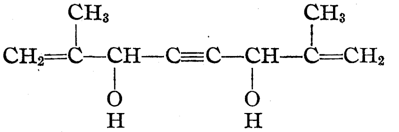

$CH_3-CH=CH-\underset{OH}{CH}-C\equiv C-\underset{OH}{CH}-CH=CH-CH_3$

III


$CH_3-\underset{OH}{CH}-CH=CH-C\equiv C-CH=CH-\underset{OH}{CH}-CH_3$

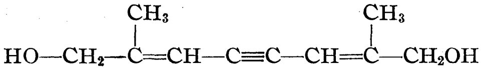
IV

Accordingly, 2,7-dimethyl-octa-1,7-diene-4-yn-3,6-diol, V, was prepared by condensation of 2-methylacrolein with acetylene, and was subjected to rearrangement by acidic reagents. Jones and


$CH_2=\overset{CH_3}{C}-\underset{OH}{CH}-C\equiv C-\underset{OH}{CH}-\overset{CH_3}{C}=CH_2$

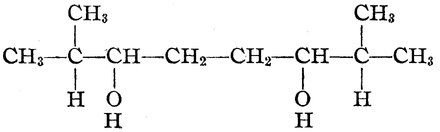
V

McCombie observed that the allylic shift occurred less readily with substances having terminal vinyl groups,[4] and similar behavior was encountered in the present instance. Nevertheless, the isomeric glycol, 2,7-dimethyl-octa-2,6-diene-4-yn-1,8-diol, VI, was obtained, albeit in poor yield.


$HO-CH_2-\overset{CH_3}{C}=CH-C\equiv C-CH=\overset{CH_3}{C}-CH_2OH$

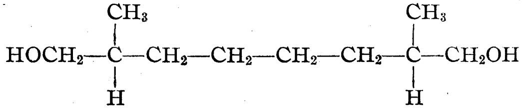
VI

The structure of V was confirmed by an independent synthesis of the saturated glycol, VII,


$CH_3-\underset{H}{\overset{CH_3}{C}}-\underset{OH}{CH}-CH_2-CH_2-\underset{OH}{CH}-\underset{H}{\overset{CH_3}{C}}-CH_3$

VII

and the corresponding diketone, which were identical with the reduction product of V and the corresponding diketone, respectively. A similar check on the structure of VI failed, since no solid reduction product or derivative thereof was obtained to compare with the saturated glycol, VIII, which was prepared by another method. How-


$HOCH_2-\underset{H}{\overset{CH_3}{C}}-CH_2-CH_2-CH_2-CH_2-\underset{H}{\overset{CH_3}{C}}-CH_2OH$

VIII

ever, the ultraviolet absorption spectrum of VI (Fig. 1) is convincing evidence that the three unsaturated linkages in V have actually been brought into conjugation. As expected, V showed no selective absorption in the ultraviolet.

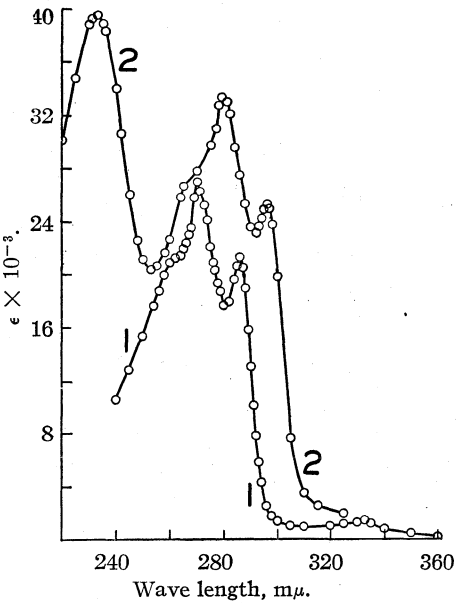


Fig. 1.—Curve 1, absorption spectrum of VI in alcohol solution; curve 2, dibenzoate of VI in alcohol solution.

Preliminary attempts selectively to hydrogenate VI to the corresponding triene and to oxidize it to the dialdehyde by Oppenheimer's method have been unsuccessful.

Experimental

α-Methylacrolein.—The commercial product[5] was distilled shortly before use, and yielded about 50% of a water-white product, b.p. 61–68° (741 mm.) plus higher boiling material. Operations involving this substance or its unsaturated condensation products were carried out under nitrogen and in peroxide-free solvents previously saturated with nitrogen. Usually a trace of hydroquinone was also added.

2,7-Dimethyl-octa-1,7-diene-4-yn-3,6-diol, V.—A solution of ethylmagnesium bromide in ether was prepared from 24 g. (1.0 gram atom) of magnesium turnings in a 1-liter, three-necked, round-bottom flask fitted with a stirrer, reflux condenser, dropping funnel and gas inlet tube. Tank acetylene purified by successive passage through water, concentrated sulfuric acid, calcium chloride and magnesium perchlorate was bubbled through the solution with continuous stirring for twenty-four hours at room temperature. Ether was added as necessary to maintain the volume at approximately 200 cc. At the end of this period analysis of the reaction mixture, by decomposing a small aliquot in water and measuring the proportion of the resulting gas absorbed by ammoniacal cuprous chloride solution, indicated that approximately 80% of the theoretical amount of acetylene di-magnesium bromide had been formed.

A solution of 70 g. (1.0 mole) of α-methylacrolein in 50 cc. of ether was then introduced over a period of one hour, and stirring was continued for two hours longer. Careful addition of 250 cc. of 10% sulfuric acid, followed by filtration, shaking out with ether, drying over "Drierite," and removing the solvent gave 69 g. of a red-brown, viscous liquid. This was distilled from a Claisen flask and yielded 7.2 g. of a pale yellow, mobile liquid, b.p. 30–110° (0.6 mm.) and 42.9 g. (52%) of a yellow, viscous oil, b. p. 135–140° (0.4 mm.). Earlier attempts to distil the crude product through a Vigreux column led to de-

---

(3) Heilbron, Jones and Raphal, *J. Chem. Soc.*, 268 (1943).

(4) Jones and McCombie, *ibid.*, 262 (1943).

(5) Obtained from Eastman Kodak Company, *cf.* Hearne, Tamele and Converse, *Ind. Eng. Chem.*, **33**, 805 (1941).

composition with formation of water and much lower yields.

Redistillation of the lower-boiling material gave a colorless oil, b. p. 165–170° (741 mm.), which formed a semicarbazone, m. p. 169–170°. The same substance was obtained from the higher boiling fraction of the commercial α-methylacrolein. It does not appear to be identical with the hydrate or dimer studied by Gilbert and Donleavy.[6]

The higher boiling fraction crystallized almost completely on standing at 0°. The solid was washed free from oil with benzene, and on recrystallization from benzene formed colorless rectangular crystals, m. p. 70.5–71.5°.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.9; H, 8.49.

On quantitative microhydrogenation 10.45 and 8.30 mg. absorbed 5.90 and 4.60 cc. of hydrogen (S. T. P.), respectively. *Anal.* Calcd. for $C_{10}H_{14}O_2$: 4 moles of hydrogen per mole. Found: 4.19, 4.12.

The glycol showed no appreciable light absorption in the range 2200–4000 Å. Although attempts to prepare the diacetate, dibenzoate and diphenylurethan were made, no derivative was obtained, and no esterification appeared to occur.

In one preparation the product was found to melt at 88–91°. *Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C. 71.8; H, 8.01. The lower melting isomer was also obtained in this case by redistillation of the mother liquors.

In other runs the product did not always crystallize. Redistillation of one such product gave a colorless, viscous oil, b. p. 126–130° (0.04 mm.). *Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.26; H, 8.47.

2,7-Dimethyl-octa-4-yn-3,6-diol.—A solution of 36 g. of isobutyraldehyde in 20 cc. of ether was added dropwise with stirring during one hour to an ether solution of acetylene dimagnesium bromide prepared from 12 g. (0.5 gram-atom) of magnesium. After two hours of additional stirring the reaction mixture was worked up as described for compound V. Removal of the solvent left 30 g. of a reddish-yellow, viscous oil which largely solidified at 0°. The solid, recrystallized from benzene, formed colorless diamond-shaped crystals, m. p. 104–105°. A second product, flat plates, m. p. 61–63°, was obtained from the mother liquors. Two isomers, m. p. 69–70° and 105–106°, have been reported.[7] The total yield of the purified products was 27% of the theoretical. The higher melting product was analyzed. *Anal.* Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 69.97; H, 10.61.

2,7-Dimethyloctane-3,6-diol, VII.—A solution of 2.12 g. of V, m. p. 70.5–71.5°, in 10 cc. of ethanol was shaken with 100 mg. of platinum oxide catalyst in an atmosphere of hydrogen until no further absorption of hydrogen occurred. Removal of the catalyst and solvent left 1.8 g. of a light amber viscous oil which possessed a distinct lemon odor. The oil partly solidified at 0° forming two types of crystals which were separated mechanically after triturating the pasty mass with a little cold benzene. Needles, m. p. 79–80°, and flat hexagons, m. p. 124–125°, were obtained.

2,7-Dimethylocta-4-yn-3,6-diol was similarly reduced, and formed an oil also possessing a lemon odor which on standing deposited needle crystals, m. p. 68–70°. Recrystallization from benzene raised the m. p. to 79–81.5°, and a mixture with the lower melting isomer above showed no depression. None of the higher melting isomer was obtained.

Anal. Calcd. for $C_{10}H_{22}O_2$: C, 68.9; H, 12.7. Found: C, 69.12; H, 12.74.

2,7-Dimethyloctane-3,6-dione.—To a solution of 2.0 g. of VII (mixed isomers) obtained from the reduction of V, in 20 cc. of benzene was added with continuous stirring over a period of one hour a mixture of 12.8 g. of sodium dichromate, 9 cc. of concentrated sulfuric acid, 30 cc. of water and 5 cc. of glacial acetic acid. The temperature was maintained at 5° during this time. The mixture was stirred for six hours longer at room temperature, the organic product collected in benzene, the extract washed with 5% sodium bicarbonate solution, then with water, dried over "Drierite" and the solvent removed. Since the oily product, 1.18 g., showed no tendency to crystallize, the dioxime was prepared. It separated from dioxane in irregular flat plates, m. p. 174–175°.

Anal. Calcd. for $C_{10}H_{20}O_2N_2$: C, 59.97; H, 10.07. Found: C, 60.5; H, 10.03.

The oily mixture of isomers resulting from the hydrogenation of 2,7-dimethylocta-4-yn-3,6-diol was similarly oxidized, and converted to the dioxime, which melted at 173.5–175° and gave no depression when mixed with the dioxime from V and VII. The literature reports the m. p. of this dioxime as 173–174°.[8]

2,7-Dimethylocta-2,6-diene-4-yn-1,8-diol, VI.—A mixture of 3 g. of V, m. p. 70.5–71.5°, 40 cc. of 95% ethanol and 160 cc. of 5% sulfuric acid was stirred under reflux for seven hours at 55° (±2°). The mixture was cooled, extracted with ether, washed with 5% sodium bicarbonate solution, then with water and dried over "Drierite." Removal of the solvent left 2.8 g. of a red-brown viscous oil. Molecular distillation at 1×10^{-4} mm. from a pot-type still gave 2.65 g. of a pale yellow, oily product which partially crystallized on standing. The solid after repeated crystallizations from benzene, weighed 0.29 g. and melted at 109–110°.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.8; H, 8.24.

The absorption spectrum in absolute ethanol was measured with a Beckman Universal spectrophotometer. Maxima were observed at 2700, 2860 and 3330 Å. with molecular extinction coefficients, at these wave lengths of 27,020, 21,140 and 1,430, respectively (Fig. 1, curve 1).

The dibenzoate was obtained readily and was crystallized from alcohol as needles, m. p. 108.5–109°.

Anal. Calcd. for $C_{24}H_{22}O_4$: C, 77.0; H, 5.92; saponification equivalent, 187.2. Found: C, 77.6; H, 5.72; saponification equivalent, 187.4.

The absorption curve of the dibenzoate is given in Fig. 1, curve 2.

It was found that the yield of VI, as measured by spectrophotometric analysis of the reaction mixtures, could be considerably improved by rearranging V with dry hydrogen chloride in absolute ethanol.[9] When held for one to two hours at 50–55° in a solution containing 1 g. of V and 100–200 milliequivalents of hydrogen chloride in 125 cc., the yield of VI was increased to approximately 45%. However, the product from such runs could not be induced to crystallize.

α,α-Dimethylsuberic Acid.—This substance was prepared by the method of Steele[10] from diethyl methylmalonate and 1,4-dichlorobutane. The crude dibasic acid, b. p. 150–160° (5 mm.) was crystallized from chloroform, m. p. 133.5–134°.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.4; H, 8.91; neutral equivalent, 101.1. Found: C, 59.2; H, 9.43; neutral equivalent, 100.8.

A second isomer was obtained from the mother liquors by crystallization from Skellysolve "B," m. p. 88.5–90°. *Anal.* Calcd. for $C_{10}H_{18}O_4$: C, 59.4; H, 8.91; neut. equiv., 101.1. Found: C, 58.9; H, 9.08; neut. equiv., 101.0.

Steele[10] likewise obtained two isomers melting at 132–133° and 91–92°, respectively.

The higher melting isomer formed a diamide, m. p. 214–215°. (*Anal.* Calcd. for $C_{10}H_{20}O_2N_2$: C, 59.96; H,

---

(6) Gilbert and Donleavy, THIS JOURNAL, **60**, 1737 (1938).

(7) Krestinskii and Mariin, *Ber.*, **60**, 1866 (1927).

(8) Spasov, *Bull. soc. chim.*, [5] **4**, 1658 (1937).

(9) Heilbron, Jones, McCombie, Lacey and Raphel, *J. Chem. Soc.*, **77** (1945).

(10) Steele, THIS JOURNAL, **53**, 4939 (1933).

10.07. Found: C, 60.3; H, 9.99), and a bis-*p*-bromophenacyl ester, m. p. 125–126° (*Anal.* Calcd. for $C_{26}H_{28}O_6Br_2$: C, 52.38; H, 4.73. Found: C, 52.38; H, 4.71).

2,7-Dimethyloctane-1,8-diol, VIII.—Thirteen grams of α,α-dimethylsuberic acid, m. p. 133.5–134°, was esterified with methanol and concentrated sulfuric acid in the usual manner and yielded 12.5 g. of the dimethyl ester, b. p. 128° (3–5 mm.). *Anal.* Calcd. for $C_{12}H_{22}O_4$: sapon. equiv., 115.2. Found: sapon. equiv., 117.3. This ester was dissolved in alcohol and hydrogenated in a high pressure bomb over 2.5 g. of copper chromite catalyst at 200–250°.[11] Removal of the catalyst and solvent left 7.98 g. of a colorless, viscous oil, which could not be crystallized. It was characterized by preparation of the bis-3,5-dinitrobenzoate, which was recrystallized from benzene, m. p. 175–176°. *Anal.* Calcd. for $C_{24}H_{26}O_{12}N_4$: C, 51.24; H, 4.66. Found: C, 52.19; H, 4.62.

A sample of VI, 0.0528 g., m. p. 108.5–109.5°, was hydrogenated in alcohol solution with platinum oxide catalyst. The theoretical amount of hydrogen was absorbed. Removal of the catalyst and solvent left 0.0506 g. of a colorless, viscous oil. Several such preparations were converted to the bis-3,5-dinitrobenzoate. The products were oily and resisted all attempts at crystallization.

Summary

Acetylene and α-methylacrolein have been condensed to yield 2,7-dimethylocta-1,7-diene-4-yn-3,6-diol, which was rearranged to 2,7-dimethyl-octa-2,6-diene-4-yn-1,8-diol.

MADISON, WIS. RECEIVED JULY 25, 1947

---

(11) The assistance of Prof. Homer Adkins in carrying out this hydrogenation is gratefully acknowledged.

[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

The Iodination of Certain Phenylsulfonamido- and Amino-heterocycles[1]

BY ROBERT G. SHEPHERD AND CATHERINE E. FELLOWS

Introduction

In a study of variously substituted sulfanilamido- and metanilamido-pyrimidines, the unique antimalarial effect of halogen substitution in the 5-position of the pyrimidine ring was discovered.[2] The preparation of iodinated pyrimidines was investigated in this connection and also because of their particular suitability for the preparation of cyano analogs.[2b] A satisfactory preparative method has now been found in the use of iodine and mercuric acetate. Using pyrimidines and other aromatic nuclei, this method was compared with the usual procedures involving iodine chloride and iodine in alkaline solution with the results set forth in the experimental section and Table II. Certain relationships of reactivity to structure were also investigated.

Experimental

The properties and analyses of the new compounds prepared in the subsequent procedures are listed in Table I by the Roman numerals accompanying them in the text.

Iodination of Aminoheterocycles. 2-Aminopyrimidine.—A solution of 23 g. (0.24 mole) of this amine in 200 cc. of water was treated with 32 g. (0.1 mole) of mercuric acetate and the mixture stirred for two minutes on the steam-bath. The initial yellow precipitate quickly turned to a thin white slurry which was treated at 70° with a solution of 50.8 g. (0.2 mole) of iodine in 200 cc. of hot dioxane. All of the iodine reacted during a half hour of stirring during which time considerable evaporation occurred. The thick slurry was poured into several volumes of 15% potassium iodide solution and washed on the filter with fresh iodide solution until white. Recrystallization from absolute alcohol (25 cc./g.) gave mercury-free **2-amino-5-iodopyrimidine** (I). Methanol and acetic acid are equally satisfactory purification solvents.

Iodination in hot acetic acid, as used for the sulfonamides, gave an orange-colored product in only 30% yield along with a large amount of mercury-containing tar.

The structure of the product was determined by conversion into 2-phenylsulfonamido-5-iodopyrimidine, the constitution of which had been previously demonstrated.[2b]

2-Aminopyridine.—The first method applied to this amine gave a 60% yield of product which was separated from the tarry by-product by ethylene dichloride extraction after the potassium iodide treatment. 5-Iodination was established by comparison (mixed m. p.) with **2-amino-5-iodopyridine** prepared according to the literature.[3]

Using two moles of iodine and one of mercuric acetate, **2-amino-3,5-diiodopyridine** (VIII) was obtained by hot ethylene dichloride extraction. After recrystallization from 95% alcohol (10 cc./g.) and ethylene dichloride (*ca.* 3 cc./g.), the melting point was 12° higher than that reported by Caldwell, *et al.*[4] Its identity was confirmed by nitrogen and iodine analyses and by conversion[4] to 2-hydroxy-3,5-diiodopyridine identical (mixed m. p.) with that prepared[4] by iodination of 2-hydroxypyridine. This amine differs from the mono-iodo derivative in being relatively insoluble in dilute acid and less soluble in ether.

Sulfonamides from Aminoheterocycles (Compounds VI, IX, X and XIII).—In this and other reactions of various benzenesulfonyl chlorides with amines in pyridine, the purification of the products has been aided materially by the addition of hot glacial acetic acid to the reaction mixture and isolation by cooling. The colored and alkali-insoluble materials which are thrown down by the usual addition of water remain in solution in this procedure which seems to have general application. The procedure for XIII given below illustrates the method.

A boiling solution of 3.5 g. (0.02 mole) of benzenesulfonyl chloride and 4.4 g. (0.02 mole) of 2-amino-5-iodopyrimidine in 3.2 cc. (0.04 mole) of dry pyridine was heated for fifteen minutes, allowing evaporation of the pyridine, to a final reaction temperature of about 150°. The temperature was then reduced to 105° for forty-five minutes and the crystalline mass was treated with 10 cc. of boiling glacial acetic acid and filtered at 30°: The 2-

---

(1) Presented before the Division of Organic Chemistry at the Chicago meeting of the American Chemical Society, September 12, 1946.

(2) (a) English, Clark, Clapp, Seeger and Ebel, THIS JOURNAL, **68**, 453 (1946); (b) English, Clark, Shepherd, Marson, Krapcho and Roblin, *ibid.*, **68**, 1039 (1946).

(3) v. Schickh, German Patent 473,213 (1929).

(4) Caldwell, Tyson and Lauer, THIS JOURNAL, **66**, 1479 (1944).

TABLE I

IODO DERIVATIVES AND RELATED INTERMEDIATES

	Name	M. p.,[a] °C.	Empirical formula	Analyses,[b] % Calcd. N	Found N
I	2-Amino-5-iodo-Pm[c]	224–225	$C_4H_4IN_3$	19.0	19.0[d]
II	2-(4-Nitrophenylsulfonamido)-5-iodo-Pm	290	$C_{10}H_7IN_4O_4S$	13.8	13.8
III	2-Sulfanilamido-5-iodo-Pm	269	$C_{10}H_9IN_4O_2S$	14.9	14.9
IV	2-(N^4-Acetylsulfanilamido)-5-iodo-Pm	284–285	$C_{12}H_{11}IN_4O_3S$	13.4	13.2
V	2-(N^3-Acetylmetanilamido)-5-iodo-Pm	270–271	$C_{12}H_{11}IN_4O_3S$		[e]
VI	2-(4-Nitrophenylsulfonamido)-Pm	273	$C_{10}H_8N_4O_4S$		[f]
VII	N^1-Methyl 2-(N^3-acetylmetanilamido)-Pm	189–190	$C_{13}H_{14}N_4O_3S$	18.3	18.1
VIII	2-Amino-3,5-diiodo-Py[g]	147–148[h]	$C_5H_4I_2N_2$	8.1	7.8[i]
IX	2-(4-Nitrophenylsulfonamido)-5-iodo-Py	220	$C_{11}H_8IN_3O_4S$	10.4	10.2
X	2-(N^4-Acetylsulfanilamido)-5-iodo-Py[k]	247	$C_{13}H_{12}IN_3O_3S$	10.1	10.2
XI	4′-Iodobenzenesulfonanilide	159–160	$C_{12}H_{10}INO_2S$	3.9	3.9
XII	Mercury bis-(2-phenylsulfonamido-Pm)	260	$C_{20}H_{16}HgN_6O_4S_2$		[m]
XIII	2-Phenylsulfonamido-5-iodo-Pm	255–256	$C_{10}H_8IN_3O_2S$		[n]
XIV	2-(3-Nitrophenylsulfonamido)-5-iodo-Pm	256–257	$C_{10}H_7IN_4O_4S$		[n]

[a] Corrected values obtained by rapid heating. The m. p.'s above 200° were accompanied by decomposition with the exception of the first compound. [b] The values given are the average of two results differing by less than 0.3. Performed in this Laboratory under the direction of Dr. J. A. Kuck. [c] Pm = pyrimidine. [d] Calcd.: C, 21.7; H, 1.8. Found: C, 21.6 by Van Slyke wet combustion; H, 2.1. [e] Calcd.: C, 34.5; H, 2.7. Found: C, 34.7; H, 3.0. [f] Calcd.: C, 42.9; H, 2.9. Found: C, 42.8; H, 2.7. [g] Py = pyridine. [h] Caldwell, *et al.* (ref. 4), reported a m. p. of 135–137°. [i] Calcd.: I, 73.4. Found: I, 73.2. [k] This compound has been reported in French Patent 846,191 (1939) (through *C. A.*, **35**, 1185 (1941)) to melt at 234°. [m] Calcd.: Hg, 30.0. Found: Hg, 30.1. [n] Ref. 2b.

phenylsulfonamido-5-iodopyrimidine (XIII) was washed with acetic acid, 5 *N* hydrochloric acid (to remove the unreacted amine) and water. Yield was 78%; m. p. 255–256° unchanged by mixture with material prepared by iodination of 2-phenylsulfonamidopyrimidine.[5]

By this method, compounds IX and X were obtained in 80% yield from 2-amino-5-iodopyridine[3] which reacted rapidly at 70–80°. The products were identical with those prepared from the corresponding sulfonamides by the iodination method described below.

Iodination of Phenylsulfonamidoheterocycles (Compounds II, IV, V, IX, X, XIII and XIV).—With the sulfonamides, it was necessary for rapid reaction to use two equivalents (1 mole) of mercuric acetate. The reaction proceeded to completion rapidly at 120° but only slowly at 60°. It was generally preferable to add this salt to the refluxing iodine–acetic acid solution of sulfonamide. The effect of the mercuric acetate could not be duplicated by the use of sodium acetate or pyridine in the acetic acid medium or by the use of a pyridine or aqueous alkaline medium.

A. **Method.**—One mole of the phenylsulfonamidoheterocycle was almost completely dissolved in boiling glacial acetic acid (0.6–4 liters) and treated with 1.15 moles of iodine. The heating was stopped and one mole of powdered mercuric acetate was added with vigorous shaking. In some cases, an immediate precipitation of the mercury salt of the product occurred and in all cases, silky yellow leaves of mercuric iodide formed after a few minutes. The reaction mixture was kept almost at the boiling point by intermittent heating during twenty to thirty minutes. The excess iodine was removed only by long heating and neither this nor use of more iodine with brief heating produced any significant increase in yield. The product was precipitated by addition to 1–2 volumes of 15% potassium iodide solution. The solid was filtered and thoroughly washed on the filter with fresh potassium iodide solution and water. The material at this point contained too little mercury to be detected with ammonium sulfide solution. However, precipitation from alkaline solution and hydrogen sulfide treatment changed the white suspension to gray. This test was negative after recrystallization from glacial acetic acid (10–80 cc./g.) or purification through the sodium salt. The latter was carried out by solution in ammonia followed by addition of excess sodium hydroxide or by treatment of a slurry in several volumes of water with 1.5 moles of 5 *N* alkali.

B. **Proof of Structure.**—To show that the position of iodination was the same in nitro- and acetaminophenylsulfonamido heterocycles, compounds IV, V and X were also prepared by acetylation (as for the preparation of compound VII) of the corresponding amines obtained from the reductions described below. In each case, the product was identical by mixed melting point with the material obtained by iodination of the acetaminophenylsulfonamide. Also, the amine III obtained from this reduction was shown to be identical with the amine prepared by acid hydrolysis of 2-(N^4-acetaminophenylsulfonamido)-pyrimidine after iodination.

Compounds IV and V were shown to be 5-iodopyrimidines by hydrolysis to 2-amino-5-iodopyrimidine (I) in 80% yield by the action of 65% sulfuric acid for one-half hour at the boiling point.

The proof of structure of the mono-iodo phenylsulfonamidopyridines (IX and X) is described in the preceding section. Attempted reaction of these products with more iodine failed to produce any di-iodination even under more drastic conditions.

Qualitative Test for Iodine.—Earlier work[6] on certain iodoacetyl compounds had disclosed a useful qualitative test for iodine. The test employs concentrated sulfuric acid and is based primarily on the observation of the characteristic purple vapor of iodine which is evolved from the brown iodine solution. The brown color of the solution is often masked or duplicated by organic decomposition products but the color of the vapor and the subsequent formation of a characteristic crystalline sublimate make the test specific for iodine. The sensitivity is limited only by the minute amount of iodine required to produce a visible color. Since most substances dissolve in concentrated sulfuric acid at room temperature, it is possible to take advantage of the fact that iodine is formed from a sample test at a temperature characteristic of its chemical combination. Thus, iodine, inorganic iodides and various addition complexes[7] give the test at 20–30° while iodoacetyl compounds

---

(5) English, Chappell, Bell and Roblin, THIS JOURNAL, **64**, 2516 (1942).

(6) Shepherd, Ph.D. Dissertation, The Johns Hopkins University, 1940.

(7) *E. g.*, the addition compound formed from 2-aminopyridine and iodine chloride: German Patent 503,920 (1930) and English Patents 264,508 and 283,576 (1927).

require moderate heating. Only at or near the boiling point is the iodine liberated from *unactivated* aromatic combination. These facts make it possible in many cases to distinguish between reagent, by-product (such as mercuric iodide) and desired product.

Reduction of Nitro Compounds II, IX and XIV.—When the nitrosulfonamide was boiled with one mole of commercial ammonium sulfide solution for two minutes, a heavy precipitate formed. A second precipitation occurred after addition of another mole of sulfide solution and six minutes of boiling. The red-brown mixture was added to excess 60% acetic acid and the solid purified by solution in dilute (1:3) ammonia (10 cc./g.) with charcoal treatment. The colorless filtrate was mixed with one volume of 5 *N* sodium hydroxide and after cooling, the sodium salt was separated and washed with alkali. After solution in warm 20% alcohol (10 cc./g.), the product was precipitated by addition to excess 60% acetic acid. Yields were 75–85% of amine III, 2-sulfanilamido-5-iodopyridine and 2-metanilamido-5-iodopyrimidine.

Comparatively brief heating with ammonium sulfide was used to avoid possible removal of the iodine.

N^1-Methyl-2-(N^3-acetylmetanilamido)-pyrimidine (VII).—The corresponding metanilamide[2b] (1 g.) was boiled with 2 cc. of glacial acetic acid and treated with 2 cc. (5 equivalents) of acetic anhydride. The product obtained on cooling was purified by recrystallization from 10 cc. of absolute alcohol.

2-Sulfanilamido-5-iodopyrimidine (III).—The insolubility of the alkali salts of IV and III and of the acid salts of III made the usual hydrolytic methods unsatisfactory for the preparation of this sulfanilamide. This difficulty was overcome by utilizing the high solvent power of 60% sulfuric acid (8.5 cc./g.) and a reaction time of three minutes at the boiling point. A 25% yield of 2-amino-5-iodopyrimidine was obtained in addition to 65% of the desired product.

In general, the iodine substitution produces a marked change in solubility of the salts of the phenyl, pyridine and pyrimidine sulfonamides. The parent compounds form very water-soluble sodium salts and less soluble ammonium salts while the corresponding iodo derivatives form very insoluble sodium salts which are precipitated from the solution of the highly soluble ammonium salts. These characteristics formed the basis for very sharp separation methods in several instances. Introduction of the iodine also causes the hydrochlorides of the metanilamido- and sulfanilamido-pyrimidines to lose their water solubility.

4-Iodoacetanilide.—Reaction of acetanilide with one mole of iodine and mercuric acetate occurred rapidly in glacial acetic acid at 90° and the iodo derivative was precipitated by addition of potassium iodide solution. This product, melting at 184°, was identical with that obtained by iodination with iodine chloride[8] or by acetylation of 4-iodoaniline.

In connection with the benzene *versus* heterocyclic specificity of the reagents, an equimolar mixture of acetanilide and 2-phenylsulfonamidopyrimidine was iodinated in two ways. Iodination with iodine and mercuric acetate in boiling acetic acid gave roughly equal yields of the iodo derivatives of each. However, iodine chloride reacted only with the acetanilide present in the mixture.

4′-Iodobenzenesulfonanilide (XI).—Benzenesulfonanilide slowly reacted with iodine chloride in acetic acid with the result shown in Table II. The reaction was rapid when iodination was carried out with six equivalents of iodine in 8 *N* potassium hydroxide solution. Neither of these products was further iodinated by treatment with an excess of either reagent. The iodinated sulfonamide was isolated only in low yield from the mercuric acetate iodination in acetic acid owing to the formation of mercury-containing tar and the consumption of several moles of iodine.

The products precipitated from the reaction mixtures above were purified by solution in 1.5 *N* sodium hydroxide (7 cc./g.) to obtain the crystalline sodium salts. The iodo derivatives obtained by acidification of the aqueous salts all gave no depression of the melting point of the sulfonamide prepared in 69% yield from 4-iodo-aniline and benzenesulfonyl chloride by the glacial acetic acid method.[9]

Comparative Iodinations of Various Aromatic Nuclei.—The iodination results with different nuclei are summarized in Table II for purposes of comparison. The alkaline iodine procedure of v. Schickh[3] was used except for aniline in which case sodium bicarbonate is more suitable. Iodine chloride experiments were carried out in boiling glacial acetic acid for three hours employing a 10–20% excess of reagent. The mercuric acetate iodinations were conducted in boiling glacial acetic acid for the sulfonamides and in aqueous dioxane at 70° for the amines. The reactivity of acetanilide toward all three reagents was destroyed by the para-sulfonamido substitution in N^4-acetylsulfanilamide.

TABLE II

IODINATION OF VARIOUS NUCLEI BY IODINATING AGENTS

Compound	Per cent. yield and product from I_2–KOH	ICl	I_2–$Hg(OAc)_2$
Aniline	80, 4-I[a]	[b]	Tar
Acetanilide	0, SM[c]	80, 4-I	92, 4-I
Benzenesulfonanilide	60, 4′-I	70, 4′-I	[d], 4′-I
2-Aminopyridine	90, 5-I	0, [e]	20, 3,5-I_2[f]
2-(N^4-Acetylsulfanilamido)-Py[g]	0, SM	0, SM	77, 5-I
2-Aminopyrimidine	Trace[h]	15, 5-I	70, 5-I
2-Phenylsulfonamido-Pm[k]	0, SM	0[m]	69, 5-I
N^1-Methyl-2-(N^3-acetylsulfanilamido)-Pm	0, SM	0, SM	0, SM
2-Aminothiazole	[n]		Tar
2-(N^4-Acetylsulfanilamido)-pyrazine			0, dec.[o]

[a] "Organic Syntheses," Coll. Vol. II, 347 (1943). [b] Some control of substitution up to tri-iodoaniline can be obtained by using one, two or three moles; *cf.* ref. 8. [c] SM = starting material recovered after attempted reaction. [d] Very low due to side-reactions. [e] An addition complex is formed which iodinates only on heating with alkali; *cf.* ref. 7. [f] With one mole of iodine, a 60% yield of mono-substituted product was obtained. [g] Py = Pyridine. [h] About 0.3% of 2-amino-5-iodopyrimidine was isolated and identified. [k] Pm = Pyrimidine. [m] The lack of reaction here contrasts with the ready halogenation by chlorine and bromine; see ref. 2b. [n] Some non-ionic iodination product was formed but has not yet been characterized. [o] No evidence of iodination even when heating was carried to the decomposition point with partial recovery of starting material.

The results with 2-(4-nitrophenylsulfonamido)-pyridine were similar to those tabulated for the acetamino analog, the third reagent giving an 88% yield of mono-iodo derivative. The phenyl-substituted derivatives of 2-phenylsulfonamidopyrimidine were unreactive except to iodine–mercuric acetate which gave the following yields of 5-iodopyrimidines: 3-nitro, 67%; 4-nitro, 74%; 3-acetamino, 63%, and 4-acetamino, 80%. The ring N-methylated pyridine, 1-methyl-2-(N^4-acetylsulfanilimido)-1,2-dihydropyridine,[9a] reacted with iodine–mercuric acetate at 60–70° but the reaction appeared to take another course since very water-soluble products were formed. With 2-(N^4-acetylsulfanilamido)-thiazole, alkaline iodine gave a non-ionic iodination product and iodine–mercuric acetate caused a rapid reaction at 90° yielding water-soluble products.

Mercury bis-(Phenylsulfonamidopyrimidine) (XII).—A solution of 6.4 g. (0.02 mole) of mercuric acetate in 50 cc. of boiling glacial acetic acid was added to 4.7 g. (0.02 mole) of 2-phenylsulfonamidopyrimidine in 75 cc. of boil-

---

[8] Michael and Norton, *Ber.*, **11**, 107 (1878).

[9] Shepherd, *J. Org. Chem.*, **12**, 275 (1947).

[9a] Shepherd, *et al.*, THIS JOURNAL, **64**, 2532 (1942).

ing acetic acid and the clear mixture evaporated to about 50 cc. Slight cooling gave a heavy white precipitate which was washed with acetic acid and recrystallized from 90 cc. of acetic acid; yield was 85%.

Material, identical by mixed melting point, resulted from treatment of a cold solution of 2-phenylsulfonamidopyrimidine in 2.5% ammonia (8 cc./g.) with excess 16% mercuric acetate solution in water.

Both materials gave an immediate test for mercury on treatment with ammonium sulfide solution. The same result was obtained with the mercury derivative (m. p. 300°) of 2-phenylsulfonamido-5-chloropyrimidine[2b] which was prepared in hot acetic acid.

Discussion

The absence of iodination in those cases (SM) of Table II where the starting material was recovered was confirmed by the delicate qualitative test for iodine described above. This table illustrates the greater reactivity of iodine–mercuric acetate compared to the other reagents. The direct di-iodination of 2-aminopyridine is to be preferred from the standpoint of yield and time required to the four-step synthesis previously employed.[4] Preparation of iodo derivatives from the phenylsulfonamidopyrimidines themselves by the method described is more satisfactory than from sulfonylation of the iodoamine.[10] It is of interest to point out the retention of the high reactivity of the heterocyclic nucleus toward iodine–mercuric acetate after substitution with the deactivating sulfonamido group (Table II) and the heterocyclic specificity of this reagent in the presence of a benzene-activating acetamino group (IV, V and X). The undiminished reactivity of the nitrophenylsulfonamides (intermediate to II, IX and XIV) is in contrast to the results of chlorination of analogous sulfonamides where nitro substitution has been reported to reduce either the rate[11] or extent[12] of halogenation of the N-substituent. A further contrast with chlorination results is found in the case of benzenesulfonanilide (Table II) which has been observed to undergo *ortho* chlorination in an alkaline medium[13] and *para* chlorination under acidic conditions.[14] The most striking effect of simple structural variation on reactivity toward mercury-induced iodination is the lack of reaction caused by N^1-methylation of 2-(N^3-acetylmetanilamido)-pyrimidine (Table II).

Since the effect of mercuric acetate on pyrimidine iodinations could not be duplicated by other substances, the possibility of intermediate mercuration was investigated. This was shown to be unlikely and, instead, the intermediate appears to be the mercury salt of the sulfonamide. This salt might facilitate iodination by making possible the formation of N-iodine intermediates but the importance of the rearrangement of such compounds in halogenations is made questionable by the work of Orton, *et al.*[15] The high reactivity of the phenylsulfonamido- heterocycles to iodine–mercuric acetate in contrast to their lack of reactivity with other iodinating agents suggests the possibility that a covalent structure peculiar to the mercury salt is responsible for the high reactivity observed.

Acknowledgment.—We are indebted to Dr. Jackson P. English for his interest and counsel during the course of this investigation.

Summary

Iodine and mercuric acetate has been found particularly suitable for iodination of certain heterocyclic nuclei.

2-Aminopyrimidine, 2-aminopyridine and various phenylsulfonamido derivatives of both amines could be iodinated in the 5-position of the heterocyclic ring exclusively.

The hitherto unreported di-iodination of 2-aminopyridine has been accomplished by this method.

4′-Iodobenzenesulfonanilide was prepared by three iodination procedures as well as by coupling 4-iodoaniline in glacial acetic acid.

A mercury bis-sulfonamide salt was prepared and is discussed in relation to the iodination of the phenylsulfonamido-heterocycles.

STAMFORD, CONNECTICUT RECEIVED NOVEMBER 14, 1946

---

[10] 2-Amino-5-iodopyrimidine is less reactive toward sulfonyl chlorides than the parent amine, a property shared by the corresponding chloro and bromo compounds (ref. 2).

[11] Jones, *J. Chem. Soc.*, 1231 (1936).

[12] Schuloff, Pollak and Riesz, *Ber.*, **62B**, 1846 (1929).

[13] Raper, Cohen and Thompson, *J. Chem. Soc.*, **85**, 372 (1904).

[14] Wallach and Huth, *Ber.*, **9**, 426 (1876).

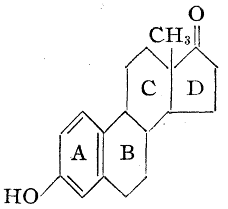
[15] Orton, *et al.*, *J. Chem. Soc.*, **95**, 1456 (1909); *ibid.*, 998 (1928).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

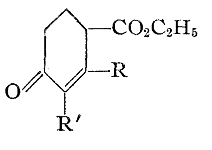
Synthetic Sterols. I. Model Experiments Employing Hagemann's Ester

BY JOHN A. HOGG

The procedure herein reported has been designed and carried out with the view of obtaining a new and somewhat general method of constructing the molecular framework of estrone (I). A special advantage of the method is that the four asymmetric centers present in octahydrophenanthrene compounds of the estrone type may be introduced in pairs in such a way that the isomer problem is simplified.



(I)



(II)

Hagemann's ester[1] (3-methyl-4-carboethoxycyclohexene-2-one-1 or II, $R = CH_3$ and $R' = H$) has been prepared by Bergmann and Weizmann,[2] and by Smith and Rouault,[3] by the condensation of formaldehyde with ethyl acetoacetate in the presence of piperidine with subsequent selective decarboethoxylation by heating with sodium ethoxide. Conclusive experiments[4] have shown that the alkylation of Hagemann's ester with alkyl halides and sodium ethoxide involves the 2-position.

When this fundamental reaction was applied in this work using *m*-methoxyphenethyl bromide[5] as the alkylating agent with sodium ethoxide in anhydrous ethanol, the yields were unsatisfactory due to extensive alcoholysis. 3-Methyl-2-(*m*-methoxyphenethyl)-4-carboethoxycyclohexene-2-one-1 (III) was, however, prepared in 58% yield by the use of sodamide as the basic catalyst in liquid ammonia. When hydrogenated at two atmospheres using a Pd–Norite catalyst, III absorbed an equivalent amount of hydrogen to give IV which was cyclized with concentrated sulfuric acid without further purification. A 65% over-all yield of crude V was obtained after hydrolysis, with alcoholic potassium hydroxide.

The structure of V was confirmed by selenium dehydrogenation to 1-methyl-7-methoxyphenanthrene (XIII). The picrate of the latter was prepared. The acid (V) was converted into its methyl ester (VI) with diazomethane.

Since Hudson and Hauser[6] were successful in the use of triphenylmethylsodium and alkyl halides for the alkylation of simple ethyl dialkylacetates, VI was subjected to a similar treatment. The characteristic wine-red color of triphenylmethyl sodium was found to disappear in an hour's time, whereupon treatment with methyl iodide produced a vigorous reaction. The hydrolysis of the resulting mixture of geometrical isomers in alcoholic potassium hydroxide required prolonged refluxing. The two forms of 1,2-dimethyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid (VII α, β) were easily separated since their sparingly soluble potassium salts differed in water solubility. One of them, which is regarded as the β (or *cis*) form, was present in small amounts and appeared after acidification of the aqueous alkaline filtrate. The α-form was obtained in 80% yield while only 2% of the β-form was obtained.

The α-form of VII was heated at 350° with selenium powder to yield 1,2-dimethyl-7-methoxyphenanthrene (VIII). This was confirmed by comparison with an authentic sample prepared from 1-keto-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (IX).[5,7] The latter was hydrolyzed to X[7] and treated with an equivalent of methylmagnesium iodide. The resulting crude product (XI) was dehydrogenated with selenium to give VIII.

The cyclization of III was also effected directly with concentrated sulfuric acid to give, after hydrolysis, a yellow acid, 1-methyl-7-methoxy-3,4,-9,10-tetrahydrophenanthrene-2-carboxylic acid (XII, R = H), which readily decomposed at its melting point and was best purified through its methyl ester (XII, $R = CH_3$). This yellow acid is probably of the structure indicated because its color and instability are best accounted for by conjugation. Selenium dehydrogenation of XII ($R = CH_3$). Selenium dehydrogenation of XII (R = H) resulted in 1-methyl-7-methoxyphenanthrene. The picrate of this phenanthrene derivative showed no depression in melting point when mixed with the picrate of that obtained from V by an identical procedure.

The original investigation of the condensation of ethyl acetoacetate with aldehydes under the influence of basic catalysts was first carried out by Knoevenagel and Klages.[8] Horning, Denekas and Field[9] have extended the work of the latter investigators so that the preparation of 5-substituted

---

[1] Hagemann, *Ber.*, **26**, 876 (1893).

[2] Bergmann and Weizmann, *J. Org. Chem.*, **4**, 267 (1939).

[3] Smith and Rouault, THIS JOURNAL, **65**, 631 (1943).

[4] (a) Kötz, Blendermann, Mahnert and Rosenbusch, *Ann.*, **400**, 77 (1913); (b) Kötz and Auger, *Ber.*, **44**, 466 (1911); (c) Rabe and Pollack, *ibid.*, **45**, 2926 (1912).

[5] Hunter and Hogg, THIS JOURNAL, **68**, 1676 (1946).

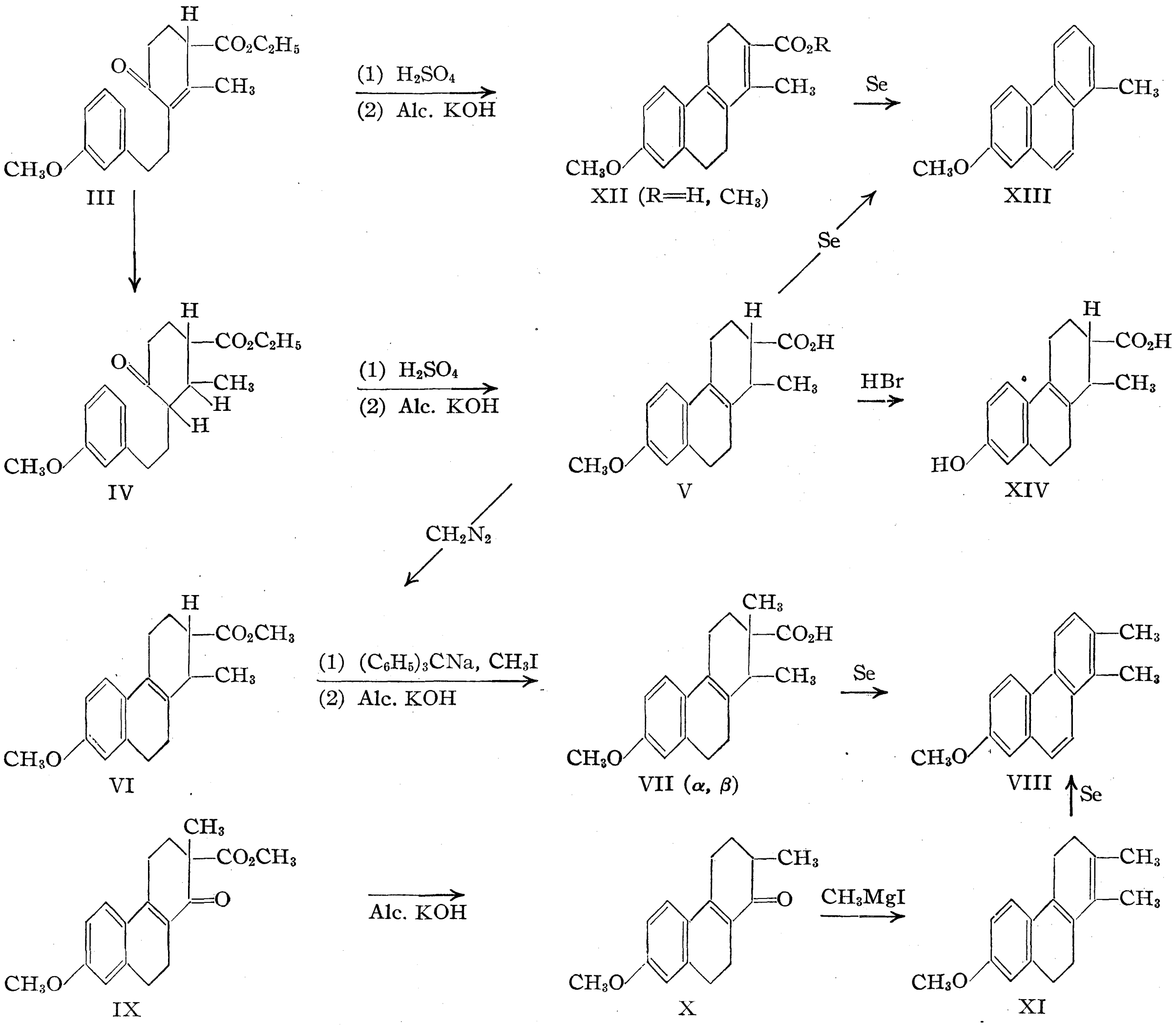
[6] Hudson and Hauser, *ibid.*, **62**, 2457–2459 (1940).

[7] Bachmann, Kushner and Stevenson, *ibid.*, **64**, 974 (1942).

[8] Knoevenagel and Klages, *Ann.*, **281**, 94 (1894).

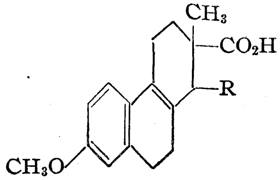
[9] Horning, Denekas and Field, *J. Org. Chem.*, **9**, 547 (1944).

CHART I



"Hagemann esters" is easily carried out. Mannich and Fourneau[10] have prepared Hagemann's ester by the condensation of 1-diethylaminobutanone-3 with ethyl acetoacetate in the presence of sodium ethoxide. Other β-keto esters would be expected to yield compounds of type II (R′ = H and R variable) under similar circumstances. The variable nature of the products which may be synthesized by the method outlined in Chart I becomes apparent.

The two asymmetric centers present in the geometric isomers VII α and VII β correspond to those between the C and D rings of estrone (I). The resolution of VII α and VII β into their respective optical antipodes would result in a total of four stereoisomers (*d*-VII α, *l*-VII α, *d*-VII β and *l*-VII β). By the hydrogenation of the double bond, one would theoretically expect to obtain from each of these four isomers four additional diastereoisomeric compounds, or a total of sixteen forms which correspond to the sixteen theoretical isomers of the estrone molecule. In a procedure of this sort, the number of chemical species present for separation in any single operation is reduced to a minimum. The method may be regarded as applicable to a systematic approach to the difficult stereoisomeric problem associated with the synthesis of estrone (I). The synthesis of a compound of type XV for this purpose would follow the preparation of a material of type II, where R is of a nature chosen to facilitate the construction of the D ring of estrone. Work along these lines is now in progress.



XV

---

[10] Mannich and Fourneau, *Ber.*, **71**, 2090 (1938).

The following table (I) records the dosage required to bring about an estrous response in the rat when bioassayed subcutaneously by the Kahnt–Doisy method.

TABLE I

Compound	M. p., °C.	Activity (γ)
V	192–193	22.5
VIIα	206–207	0.24
VIIβ	172–173	5.1
XII (R = H)	192–195 (dec.)	56
XIV	.....	20
Estrone		1.0

Experimental

3-Methyl-2-(*m*-methoxyphenethyl)-4-carboethoxycyclohexene-2-one-1 (III).—To 250 cc. of liquid ammonia containing 0.2 g. of hydrated ferric nitrate was added 13 g. (0.563 mole) of sodium in a piecewise manner with cooling only when necessary to facilitate the speed of addition. The mixture was stirred until the blue color was replaced by gray. The resulting suspension was cooled in an alcohol–Dry Ice-bath, and 102.5 g. (0.563 mole) of Hagemann's ester was added as rapidly as possible with the continued application of the cooling bath. The deep-red reaction mixture was stirred without cooling for twenty minutes and was then cooled again while 300 cc. of dry toluene and 50 cc. of sodium-dried ether were added. The cooling bath was removed and the mixture was stirred two hours at room temperature until nearly all of the ammonia had escaped. Then the reaction vessel was heated to boiling, whence the sodio derivative appeared as a yellow precipitate (some reddish gummy material collected on the sides).

One hundred and twenty grams (0.563 mole) of *m*-methoxyphenethyl bromide was added and the suspension was refluxed under a nitrogen atmosphere for eighteen hours. The resulting mixture was washed with dilute hydrochloric acid and then with water. The toluene layer was dried over magnesium sulfate, and the toluene was removed under reduced pressure. After a small forerun, distillation of the residue yielded 102 g. (58%) of III boiling at 180–184° (0.3 mm.).

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.2; H, 7.58. Found: C, 71.6; H, 7.41.

1-Methyl-2-carboxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (V) from Reduction and Cyclization of III.—Thirty-three grams (0.104 mole) of III in 100 cc. of 95% ethanol was hydrogenated at 35 lb. pressure using 4 g. of palladium–Norite catalyst.[11] The theoretical amount of hydrogen was absorbed in forty-five minutes. After filtration and removal of the solvent there remained a water-white oil of fruity odor. This oil was cooled to −20° in an alcohol–Dry Ice-bath, and to this was added 80 cc. of concentrated sulfuric acid which had been similarly cooled. The viscous content of the flask was stirred with a thermometer as the temperature was allowed to rise slowly. It was necessary to apply cooling from time to time. At no time was the temperature allowed to rise above 10°. After twenty minutes of shaking and stirring, the temperature was allowed to rise to 20°, and the mixture was then poured on a large excess of cracked ice (total reaction time was thirty minutes). A light-colored gum formed which was extracted with ether. The ether was removed, and the residue was hydrolyzed by refluxing for one hour in 200 cc. of a 6% solution of potassium hydroxide in 95% ethanol and 20 cc. of water. The alcohol was then removed under vacuum and diluted with water. The water solution was washed with ether and then acidified with concentrated hydrochloric acid. The acid came out as an oil and quickly solidified. There was obtained 18.5 g. (65%) of crude acid which melted at 174–178°. Two recrystallizations from 95% ethanol raised the melting point to 192–193°. The over-all yield of pure V was 14.2 g. or 50% of the theoretical.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 75.00; H, 7.35. Found: C, 74.95; H, 7.25.

One attempt to demethylate V with 48% hydrobromic acid yielded an oil, presumably (XIV).

Methyl 1-Methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylate.—A solution of 7.5 g. of V in ether was treated with an excess of ethereal diazomethane. The solvent was removed, and the residue was recrystallized from 95% ethanol to yield 7.3 g. (93%) of VI as plates melting at 107–108°.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.60; H, 7.68. Found: C, 75.61; H, 7.71.

1-Methyl-7-methoxyphenanthrene (XIII) from the Selenium Dehydrogenation of V.—One gram of V was heated for three hours with 6 g. of selenium powder at 350°. The reaction was carried out in a 50-cc. round-bottom flask turned at a 45° angle, with an outlet tube containing a restriction placed inside the flask and sealed with a movable glass bead. The outlet tube and flask were equipped with standard taper joints. The bead permitted the escape of hydrogen selenide and carbon dioxide without distillation of the product through the outlet. When the product collected on the upper sides of the reaction vessel the contact with selenium metal was renewed by rotating the flask.

The product was extracted with chloroform, filtered and the solvent was removed. The solid residue (0.7 g.) was distilled in vacuum over sodium to yield 0.5 g. of a white solid melting at 120–124°. Several recrystallizations of part of this from 95% ethanol raised the melting point to 132–133°. The reported melting point of 1-methyl-7-methoxyphenanthrene (XIII)[12] is 133–134°.

Purification was more easily effected through its picrate. The remainder of the crude product and mother liquors was treated with 25 cc. of a saturated alcoholic solution of picric acid. On cooling, orange needles developed which melted at 138–139° after one recrystallization from 95% ethanol.

Anal. Calcd. for $C_{22}H_{17}O_8N_3$: C, 58.70; H, 3.75; N, 9.32. Found: C, 58.70; H, 3.88; N, 9.39.

1-Methyl-2-carboxy-7-methoxy-3,4,9,10-tetrahydrophenanthrene (XII, R = H) from the Cyclization of III.—To 10 g. of III cooled in an Erlenmeyer flask to −20° was added 30 cc. of concentrated sulfuric acid also cooled to near its freezing point. The temperature was maintained at or below 10° until the main reaction had ceased, and the temperature was then allowed to rise to 20° as in the cyclization of IV. The contents of the flask were poured into a beaker of cracked ice, and the resulting gum was extracted with ether. After the removal of the ether the residue was hydrolyzed in 100 cc. of 10% alcoholic potassium hydroxide. The solvent was removed in vacuum, and the residue was diluted with water. After one extraction with ether the aqueous solution was acidified with dilute hydrochloric acid. There was formed 5.0 g. (58.5%) of a yellow product which melted at 175–188° with evolution of carbon dioxide. The material was further purified by recrystallization from acetic acid with considerable loss due to decomposition. The acid is soluble in 95% ethanol only with difficulty. The pure product melts at 192–195° (dec.).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.60; H, 6.67. Found: C, 75.62; H, 6.65.

The methyl ester (XII, R = CH_3) was obtained by treating the acid with ethereal diazomethane. The ester melts at 112–113°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.10; H, 7.05. Found: C, 75.32; H, 7.09.

1-Methyl-7-methoxyphenanthrene (XIII) from the Selenium Dehydrogenation of XII (R = H).—One-half gram of XII (R = H) was heated at 300° for six hours in an open tube with 2 g. of selenium powder. The product

---

[11] Hartung, THIS JOURNAL, **50**, 3370 (1928).

[12] Short and Stromberg, *J. Chem. Soc.*, 516–520 (1937).

was extracted with chloroform. The solvent was removed and the residue was distilled under vacuum from sodium. After solution in ethanol and the addition of a saturated ethanolic picric acid solution, an orange picrate was deposited which melted at 138–139°. A mixed melting point with the picrate obtained from the product obtained in the selenium dehydrogenation of V was not depressed.

The Angular Methylation of 1-Methyl-2-carbomethoxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (VI).—A solution of triphenylmethyl sodium was prepared in ether and titrated according to the directions of Renfrow and Hauser.[13] An equivalent amount (0.0255 mole) of triphenylmethyl sodium was added to an ether solution of 7.3 g. (0.0255 mole) of VI in 300 cc. of sodium-dried ether in a 500-cc. glass-stoppered Erlenmeyer flask. All operations were carried out under an atmosphere of dry nitrogen.

The deep, wine-colored solution was allowed to stand at room temperature with occasional shaking for one hour, at which time the red color had faded to a light orange.

The addition of 25 cc. of methyl iodide caused the ether to reflux, and a copious precipitate of sodium iodide soon developed. After standing overnight the ether was removed, and the residue was refluxed eight hours with 10 g. of potassium hydroxide, 10 cc. of water and 200 cc. of 95% ethanol. The alcohol was removed under vacuum on the steam-bath, and the residue was diluted with water. The potassium salt was insoluble in water at ordinary temperature. Filtration gave a mixture of triphenylmethane and the salt. The filtrate was saved. Several washings with ether removed the triphenylmethane, leaving the white crystalline salt, which weighed 7 g., and represents a yield of 85% in the form of the salt. The latter was dissolved in 250 cc. of boiling water containing enough alcohol to effect solution. Acidification while hot with hydrochloric acid yielded nearly the theoretical amount of acid melting at 197–201° (softens at 190°). Recrystallization from 95% ethanol yielded 5.8 g. (80%) of needles in bundles melting at 206–207°. This compound is 1,2-dimethyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.60; H, 7.68. Found: C, 75.88; H, 7.79.

The aqueous alkaline filtrate was acidified with hydrochloric acid to give 1.0 g. of a tacky solid which was dissolved in 25 cc. of 95% ethanol. After standing for two days, 150 mg. of beautiful prisms formed which melted at 171–173° with previous softening at 167°. One further crystallization from the same solvent raised the melting point to 172–173°. This product is regarded as the β (or *cis*) form of VII. *Anal.* Calcd. for $C_{18}H_{22}O_3$: C, 75.60; H, 7.68. Found: C, 75.61; H, 7.98.

1,2-Dimethyl-7-methoxyphenanthrene (VIII) from 1,2-Dimethyl-2-carboxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (VII α).—One gram of VII α was treated with 7 g. of selenium metal in the same manner as V. After distillation from sodium under vacuum there was obtained 0.5 g. of a solid material melting at 120–125°. Several recrystallizations from methanol yielded prisms of 1,2-dimethyl-7-methoxyphenanthrene (VIII) melting at 154–155°. 1,2-Dimethyl-7-methoxyphenanthrene[14] is reported to melt at 154–155°.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.70; H, 6.73. Found: C, 86.61; H, 6.94.

The melting point of this material when mixed with an authentic sample of 1,2-dimethyl-7-methoxyphenanthrene, as prepared in the following experiment, was 154–155°.

Synthesis of 1,2-Dimethyl-7-methoxyphenanthrene (VIII).—1-Keto-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene[7] (X, m. p. 66–67°) was prepared by the alcoholic alkaline hydrolysis of 1-keto-2-methyl-2-carboethoxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene[6,7] (IX) in 63% yield.

To a solution of X (1 g.) in sodium-dried ether was added an excess of methylmagnesium iodide. The Grignard addition product was hydrolyzed with dilute sulfuric acid. The ether layer was separated, washed with water, and dried over magnesium sulfate. The solvent was removed, and the crude residue, which solidified readily, was heated four hours at 350° with 2 g. of selenium powder. After extraction with chloroform and distillation from sodium there was obtained 0.5 g. of a solid material which melted at 130–140°. After several recrystallizations from methanol there were obtained prisms of 1,2-dimethyl-7-methoxyphenanthrene melting at 154–155°.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.70; H, 6.73. Found: C, 86.80; H, 6.89.

This product was shown to be identical with that obtained in the previous experiment by the method of mixed melting points.

Acknowledgment.—The author wishes to extend his feeling of appreciation to Drs. James H. Hunter and Harold G. Kolloff for their helpful support and advice in behalf of this work. Miss Margery LePage has been of invaluable technical aid and Messrs. Harold Emerson and William Struck and Misses Celia Triemstra and Barbara Fausnaugh have carried out the analytical work involved.

Thanks are due to Dr. Marvin H. Kuizenga and Messrs. John Nelson and Stanley Lyster of the Department of Pharmacology and Endocrinology, The Upjohn Company, for the estrogenic assays involved.

Summary

Model experiments have been successfully completed which offer several advances in the problems associated with the synthesis of estrone and estrogenic substances:

1. A new method for the synthesis of the hydrophenanthrene portion of the estrone molecule has been developed. The method lends itself well to further development of the D-ring.
2. The procedure includes a method of introducing the angular methyl group ultimately required in sterol synthetic work.
3. An essentially important feature embodied in the method is a systematic approach to the stereoisomeric problem which complicates sterol synthesis.
4. Several potent estrogenic materials have been prepared. The α- and β-forms of 1,2-dimethyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid display estrogenic activity when tested by the Kahnt–Doisy method in the order of *0.240* γ and *5.1* γ, respectively.

KALAMAZOO, MICHIGAN RECEIVED JUNE 27, 1947

---

[13] Renfrow and Hauser, "Organic Synthesis," Vol. XIX, John Wiley and Sons, Inc., New York, N. Y., 1939, p. 83.

[14] Haworth and Sheldrick, *J. Chem. Soc.*, 864 (1934).

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

The Chloro- and Bromoisobutyronitriles

BY CALVIN L. STEVENS[1]

As early as 1898, Henry[2] reported the isolation of a mixture of α-chloroisobutyronitrile (V) and methacrylonitrile from the reaction of acetone cyanohydrin with phosphorus pentachloride. Later the preparation of α-chloroisobutyronitrile[3,4] and α-bromoisobutyronitrile[5] from the reaction of acetone cyanohydrin with phosphorus pentachloride and phosphorus tribromide, respectively, was described.

Since sizeable amounts of α-chloroisobutyronitrile was needed in this Laboratory, the development of a method that would give this compound in good yields was undertaken. During this investigation, the halonitriles obtained by the procedures of the earlier workers from acetone cyanohydrin were found to have the halogen in the β- rather than in the α-position. The purpose of this paper is to describe the preparation of the α- and β-chloro- and bromoisobutyronitriles by reactions that produce known structures, and to report a new method for the preparation of α-chloro and α-bromoisobutyronitrile in high yields.

Authentic samples of α-chloro and α-bromoisobutyronitriles were prepared by dehydration of the corresponding α-haloisobutyramides. α-Chloroisobutyramide was prepared from isobutyric acid (I) by the sequence of reactions I to IV.

$$\underset{\text{I}}{(CH_3)_2CHCOOH} \xrightarrow{SO_2Cl_2}$$

$$(CH_3)_2CClCOOH + ClCH_2CH(CH_3)COOH \xrightarrow{SOCl_2}$$

$$(CH_3)_2CClCOCl + ClCH_2CH(CH_3)COCl$$

$$\big\downarrow \text{II} \qquad\qquad \text{III}$$

$$\underset{\text{IV}}{(CH_3)_2CClCONH_2} \xrightarrow{P_2O_5} \underset{\text{V}}{(CH_3)_2CClCN}$$

The chlorination of I by the method of Kharasch and Brown,[6] followed by the fractionation of the mixture of the chloroacid chlorides II and III, gave a 16% yield of α-chloroisobutyryl chloride (II) and a 36% yield of β-chloroisobutyryl chloride (III). Kharasch and Brown[6] showed the lower boiling chloroacid chloride to be α-chloroisobutyryl chloride by hydrolysis to the known α-chloroisobutyric acid[7]; the higher boiling, isomeric chloroacid chloride is, therefore, β-chloroisobutyryl chloride (III). The α-chloroisobutyryl chloride (II) was converted to α-chloroisobutyronitrile (V) in 59% yield. The dehydration of α-bromoisobutyramide[8] gave α-bromoisobutyronitrile in 86% yield. These α-halonitriles are different from the halonitriles prepared from acetone cyanohydrin.[3,4,5]

β-Chloro and β-bromoisobutyronitrile may be prepared by the addition of the appropriate hydrogen halide to methacrylonitrile. In this manner, β-chloroisobutyronitrile[9] was prepared in 79% yield and β-bromoisobutyronitrile in 72% yield. These β-haloisobutyronitriles correspond in physical properties to the halonitriles obtained from the reaction of acetone cyanohydrin with phosphorus pentachloride and phosphorus tribromide, to which the α-halo structures had been assigned.[3,4,5] Further evidence that the halogen is in the β-position is the fact that methyl β-chloroisobutyrate (VIII) prepared from III is identical with the ester obtained from VI by the following sequence of reactions

$$CH_2{=}C(CH_3)CN \xrightarrow{HCl} \underset{\text{VI}}{ClCH_2CH(CH_3)CN} \xrightarrow[HOCH_3]{HCl}$$

$$\underset{\text{VII}}{ClCH_2CH(CH_3)C(OCH_3){=}NH{\cdot}HCl} \left[\begin{array}{l} \xrightarrow{H_2O} \underset{\text{VIII}}{ClCH_2CH(CH_3)COOCH_3} \\ \xrightarrow{\Delta} \underset{\text{IX}}{ClCH_2CH(CH_3)CONH_2} \end{array} \right.$$

β-Chloroisobutyramide (IX) could not be prepared in the pure state by the action of ammonia on the acid chloride (III). However, methyl β-chloroiminoisobutyrate hydrochloride (VII), derived from the nitrile (VI), was quantitatively pyrolyzed to β-chloroisobutyramide. A sample of β-bromoisobutyramide was prepared by hydration of the β-bromonitrile with sulfuric acid.[10]

The formation of the β-chloronitrile (VI) from the reaction of acetone cyanohydrin with phosphorus pentachloride undoubtedly results from the initial formation of methacrylonitrile and the subsequent addition of hydrogen chloride, which is present in the reaction mixture, to this nitrile.

---

(1) Wisconsin Alumni Research Foundation Research Assistant to Professor S. M. McElvain, 1944–1947.

(2) Henry, *Chem. Zentr.*, **69**, II, 661 (1898).

(3) Sobierański and Chrzaszczewski, *Roczniki Chem.*, **7**, 470 (1927); *C. A.*, **22**, 2146 (1928).

(4) McElvain and Fajardo-Pinzon, THIS JOURNAL, **67**, 690 (1945).

(5) Chrzaszczewski and Popiel, *Roczniki Chem.*, **7**, 74 (1927); *C. A.*, **22**, 1343 (1928).

(6) Kharasch and Brown, THIS JOURNAL, **62**, 925 (1940).

(7) Balbiano (*Ber.*, **11**, 1693 (1878)) and Ostropjatow (*J. Russ. Phys.-Chem. Soc.*, **28**, 50 (1896)) established the structure of α-chloroisobutyric acid by its conversion to α-hydroxyisobutyric acid.

(8) The structure of the amide was established by Bischoff (*Ber.*, **24**, 1044 (1891)), who prepared it from both the ester and the acid bromide of α-bromoisobutyric acid. This acid has been converted into α-hydroxyisobutyric acid by Fittig and Thomson (*Ann.*, **200**, 86 (1880)) and by Hell and Waldbauer (*Ber.*, **10**, 449 (1877)).

(9) Berthet, *Bull. classe sci. Acad. roy. Belg.*, **27**, 212 (1941); *C. A.*, **37**, 3400 (1943).

(10) McElvain, "The Characterization of Organic Compounds," Macmillan Co., New York, N. Y., 1946, p. 146.

The validity of this conclusion is shown by the fact that with milder conditions than those previously employed,[3,4] methacrylonitrile was isolated in 35% yield from the reaction of phosphorus pentachloride on acetone cyanohydrin.

During this investigation a new method of preparation of α-chloro- and α-bromoisobutyronitriles was developed. When equimolar amounts of isobutyronitrile and phosphorus pentachloride were heated under reflux, hydrogen chloride was evolved smoothly; distillation of the reaction mixture yielded α-chloroisobutyronitrile (78%) and phosphorus trichloride (80%). This reaction is represented as

$$(CH_3)_2CHCN + PCl_5 \longrightarrow (CH_3)_2CClCN + PCl_3 + HCl$$

The chloronitrile obtained from this reaction is identical with the one (V) prepared by the dehydration of α-chloroisobutyramide (IV). Also, the chloroamide corresponding to the chloronitrile prepared from isobutyronitrile is identical with IV.

α-Bromoisobutyronitrile was prepared in a similar manner from an equimolar mixture of bromine, isobutyronitrile and phosphorus tribromide. The α-bromoisobutyronitrile was isolated in 76% yield and is identical with the bromonitrile obtained by the dehydration of α-bromoisobutyramide.[8]

The assistance of Professor S. M. McElvain is gratefully acknowledged.

Experimental

α-Chloroisobutyramide.—To a solution of 150 ml. of concentrated ammonium hydroxide, which was cooled in an ice-bath and stirred vigorously, 17 g. of α-chloroisobutyryl chloride[6] was added at such a rate that the temperature did not rise above 10°. After the addition was finished, the reaction mixture was stirred for fifteen minutes and then the precipitated amide was filtered from the cold solution and dried. An additional 1 g. of amide was obtained when the filtrate was concentrated to 25 ml. and cooled. The dried solid was recrystallized from ethyl acetate; 10.1 g. (70%) of α-chloroisobutyramide, m. p. 115–118°, was obtained from the ethyl acetate solution and by concentration of the mother liquors. A sample, recrystallized from water, melted at 117–119°.

Anal. Calcd. for C_4H_8ClNO: Cl, 29.2; N, 11.5. Found: Cl, 29.2; N, 11.6.

α-Chloroisobutyronitrile. (a) From α-Chloroisobutyramide.—α-Chloroisobutyramide (21 g., 0.17 mole) and phosphorus pentoxide (30 g., 0.21 mole) were thoroughly mixed and placed in a flask equipped with a short still-head, which was attached to a Dry Ice trap. The mixture was heated to 150°; after about ten minutes at this temperature, α-chloroisobutyronitrile began to distil from the reaction flask. After 12.5 g. of nitrile had been collected and the rate of distillation began to diminish, the pressure within the system was reduced to 100 mm. In this way an additional 2.6 g. of nitrile was collected in the cold trap. The total yield of α-chloroisobutyronitrile was 15.1 g. (84%); b. p. 114–116°, $n^{25}D$ 1.4045; d^{25}_4 0.9808.

(b) From Isobutyronitrile.—A mixture of 25 g. (0.36 mole) of isobutyronitrile and 75 g. (0.36 mole) of phosphorus pentachloride was heated to the refluxing temperature. Hydrogen chloride was evolved smoothly and within an hour the solid phosphorus pentachloride had disappeared. After refluxing the clear solution until the hydrogen chloride ceased to be evolved (three hours), the reaction mixture was fractionated through a column of 8 theoretical plates. The first fraction consisted of 39.4 g. (80%) of phosphorus trichloride, b. p. 74–76°. After an intermediate fraction of 2.5 g., b. p. 76–114°, the α-chloroisobutyronitrile (29 g., 78%) was collected at 114–116°; $n^{25}D$ 1.4049.

Anal. Calcd. for C_4H_6ClN: Cl, 34.3; N, 13.5. Found: Cl, 33.8; N, 13.3.

One gram of this nitrile was heated with 2 g. of sulfuric acid and poured onto cracked ice. The precipitated amide, 0.9 g., was filtered, dried, and recrystallized from petroleum ether; m. p. 118–120°. The mixed melting point of this amide with the α-chloroisobutyramide made from the known α-chloroisobutyryl chloride showed no depression, m. p. 118–120°.

β-Chloroisobutyronitrile.—Dry hydrogen chloride was passed into 10 ml. of ether until 4.6 g. (0.12 mole) was absorbed, and then 8.4 g. (0.12 mole) of methacrylonitrile was added. After the ether solution had stood for twelve hours at room temperature, it was distilled; 10.2 g. (79%) of β-chloroisobutyronitrile,[9] b. p. 50–52° (6 mm.); $n^{25}D$ 1.4323; d^{25}_4 1.061, was obtained. This nitrile contained 13.2% nitrogen (calcd. 13.5%).

The chloronitrile obtained from the reaction of phosphorus pentachloride with acetone cyanohydrin by the procedure of Sobieranski and Chrzaszczewski[3] had the same physical properties as that prepared above from methacrylonitrile.

Methyl β-Chloroiminoisobutyrate Hydrochloride.—A solution of 15.8 g. (0.15 mole) of β-chloroisobutyronitrile in 5.1 g. (0.16 mole) of absolute methyl alcohol was cooled in an ice-bath and treated with hydrogen chloride until 5.9 g. (0.16 mole) was absorbed. The resulting homogeneous liquid was placed in a refrigerator for twenty-four hours, during which time it solidified. An equal volume of ether was added and the salt filtered off, dried in a desiccator, and triturated with ether. After drying again, the methyl β-chloroiminoisobutyrate hydrochloride weighed 25.7 g. (99%).

Anal. Calcd. for $C_5H_{11}Cl_2NO$: ionic Cl, 20.6. Found: ionic Cl, 20.6.

β-Chloroisobutyramide.—Five grams of the methyl β-chloroiminoisobutyrate hydrochloride was heated to 115° until methyl chloride ceased to be evolved. The resulting amide, which crystallized on cooling, melted at 100–103°; the yield was quantitative. One recrystallization from a mixture of petroleum ether and ethyl acetate gave 3.2 g. (92%) of β-chloroisobutyramide, m. p. 104–105°.

Anal. Calcd. for C_4H_8ClNO: N, 11.5. Found: N, 11.4.

One gram of the β-chloroisobutyronitrile, prepared from methacrylonitrile, was heated with 1.5 g. of sulfuric acid and then poured onto 5 g. of cracked ice. The precipitate was filtered off and recrystallized from a mixture of benzene and petroleum ether. The yield of β-chloroisobutyramide, m. p. 102–104°, was 0.25 g. This amide is identical with the one prepared from the β-chloronitrile obtained from acetone cyanohydrin.

Attempts to recover the remainder of the amide from the water solution by evaporation led only to an impure product, m. p. 70–85°. All attempts to prepare β-chloroisobutyramide from β-chloroisobutyryl chloride gave a product that melted over a wide range (m. p. 60–80°) even after numerous recrystallizations. This material undoubtedly contained a considerable amount of the dehydrochlorination product from the β-chloroisobutyric acid derivative.

Methyl β-Chloroisobutyrate.—Eight grams of methyl β-chloroiminoisobutyrate hydrochloride was shaken with 15 ml. of water until the salt completely dissolved. Within twenty minutes at room temperature the solution became turbid and the methyl β-chloroisobutyrate began to form a separate layer. After three hours the ester was separated and the aqueous layer extracted with ether. The ether extracts and product were combined, dried, and concentrated. Distillation under reduced pressure gave

5.4 g. (85%) of methyl β-chloroisobutyrate,[11] b. p. 93–95° (106 mm.); $n^{25}D$ 1.4242; d^{25}_4 1.1031. This ester contained 25.6% chlorine (calcd. 26.0%).

Methyl β-chloroisobutyrate also was prepared from the β-chloroisobutyryl chloride obtained from the chlorination of isobutyric acid with sulfuryl chloride.[6] The ester so obtained had physical properties identical with those of the methyl β-chloroisobutyrate prepared from β-chloroisobutyronitrile.

The Isolation of Methacrylonitrile from the Reaction of Acetone Cyanohydrin with Phosphorus Pentachloride.—This reaction was carried out in ether solution instead of benzene[3] to facilitate the isolation of methacrylonitrile. To a solution of 25 g. (0.3 mole) of acetone cyanohydrin in 25 ml. of absolute ether, 31 g. (0.15 mole) of phosphorus pentachloride was added slowly with cooling and stirring. As the ether was heated to the refluxing temperature, the phosphorus pentachloride dissolved and hydrogen chloride was evolved. After two hours of refluxing, 50 ml. of ether was added and the reaction mixture poured onto cracked ice. The layers were separated, the aqueous layer was extracted with ether, and then the combined ether solutions were dried and the ether evaporated. The only products that could be isolated from the residue were 3.5 g. (35% based on the phosphorus pentachloride) of methacrylonitrile, b. p. 86–90°, and 7 g. of unchanged acetone cyanohydrin; 5 g. of undistillable material remained in the flask. Hydrogen chloride was passed into the methacrylonitrile fraction at 50° until 1.5 g. was absorbed. Distillation of this reaction product gave 3 g. (57%) of β-chloroisobutyronitrile, b. p. 52–56° (9 mm.); $n^{25}D$ 1.4330.

α-**Bromoisobutyronitrile.** (a) **From** α-**Bromoisobutyramide.**—The α-bromoisobutyramide[8] used in this preparation was made by allowing α-bromoisobutyryl bromide, b. p. 162–163°, to react with concentrated ammonium hydroxide in the cold; after recrystallization from petroleum ether, it melted at 147–148°. The amide (18.6 g., 0.11 mole) and phosphorus pentoxide (21.3 g., 0.15 mole) were intimately mixed and heated under reflux at 140° for four hours. The α-bromonitrile was distilled from the reaction mixture at atmospheric pressure until the rate of distillation diminished, then the last of the nitrile was collected by evacuation of the system to 100 mm. and condensation of the volatile material in a cold trap. Redistillation gave 14 g. (86%) of α-bromoisobutyronitrile, b. p. 137–139°; $n^{25}D$ 1.4460; d^{25}_4 1.376.

(b) **From Isobutyronitrile.**—A mixture of 25 g. (0.36 mole) of isobutyronitrile and 98 g. (0.36 mole) of phosphorus tribromide was cooled in an ice-bath and 58 g. (0.36 mole) of bromine added with shaking. The reaction mixture was heated gently until hydrogen bromide ceased to be evolved (three hours), after which time the mixture was fractionated. The first fraction, after a small forerun, was α-bromoisobutyronitrile, b. p. 137–140°. The product was slightly colored due to an excess of bromine; however, the color was removed by washing an ether solution of the nitrile with a sodium bisulfite solution. Redistillation gave 40.4 g. (76%) of the water-white α-bromoisobutyronitrile, b. p. 138–140°; $n^{25}D$ 1.4447.

Anal. Calcd. for C_4H_6BrN: Br, 54.0; N, 9.45. Found: Br, 53.7; N, 9.2.

β-**Bromoisobutyronitrile.**—This nitrile was prepared in the same manner as the β-chloronitrile. From 9.5 g. (0.12 mole) of hydrogen bromide and 7.9 g. (0.12 mole) of methacrylonitrile, 12.6 g. (72%) of β-bromoisobutyronitrile, b. p. 60–62° (5 mm.), $n^{25}D$ 1.4680, d^{25}_4 1.465, was isolated.

Anal. Calcd. for C_4H_6BrN: Br, 54.0; N, 9.45. Found: Br, 53.7; N, 9.1.

β-**Bromoisobutyramide** was prepared by gently heating 0.5 g. of the β-bromonitrile and 0.75 g. of sulfuric acid on a hot plate until a reaction occurred and then pouring the mixture onto a small amount of cracked ice. The precipitated amide, 0.2 g., was filtered and recrystallized from petroleum ether, m. p. 103–105°.

Anal. Calcd. for C_4H_8BrNO: N, 8.4. Found: N, 8.1.

Summary

α-Chloroisobutyronitrile and α-bromoisobutyronitrile have been prepared by the dehydration of the corresponding amides; α-chloroisobutyramide is described for the first time.

β-Bromoisobutyronitrile was prepared by the addition of hydrogen bromide to methacrylonitrile. This nitrile has the same properties as the compound isolated from the reaction of phosphorus tribromide with acetone cyanohydrin, to which the α-bromoisobutyronitrile structure had been assigned by earlier workers. Similarly, the β-chloroisobutyronitrile corresponds to the nitrile isolated from the reaction of phosphorus pentachloride on acetone cyanohydrin.

A new and simpler method is described for the preparation of α-chloro and α-bromoisobutyronitriles in high yields by the halogenation of isobutyronitrile with the appropriate phosphorus pentahalide.

MADISON, WISCONSIN RECEIVED JUNE 28, 1947

---

[11] Zalkind and Markov, *J. Applied Chem.* (*U. S. S. R.*), **10**, 1042 (1937); *C. A.*, **32**, 1652 (1938).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

The Mercuration of 5-Nitroguaiacol[1,2]

BY NATHAN L. DRAKE, HILLMAN C. HARRIS[3] AND CHARLES B. JAEGER, JR.[4]

The present work was undertaken to determine the structure of the compounds obtained by direct mercuration of 5-nitroguaiacol. In addition to the present work, other chemical, pharmacological and clinical studies are in progress and will be reported elsewhere.

For our purpose, it was of fundamental importance that the 5-nitroguaiacol used be authentic and pure. Undoubtedly all of the possible mononitroguaiacols have been prepared,[5] but no fully satisfactory characterization of them has appeared in the literature. One of us has developed a complete characterization of the mononitroguaiacols,[6] as well as a synthesis of pure 5-nitroguaiacol. Details of the synthesis appear in the Experimental Section of this paper.

2-Amino-5-nitroanisole is a well-known dye intermediate. It is converted readily in high yield to 4-nitroguaiacol by treatment under reflux with aqueous alkali. 4-Nitroguaiacol whose melting point is 102–103°, melts at 96–97° when mixed with 5-nitroguaiacol, whose melting point is 104–104.5°. Both of these nitroguaiacols are converted by dimethyl sulfate and alkali to the same nitroveratrole. Furthermore, they yield different amines, and these amines are converted through their diazonium salts to different hydroxyguaiacols.

Inasmuch as the structure of 4-nitroguaiacol, prepared as above, seems hardly debatable, it is reasonable to conclude that the nitroguaiacol whose melting point is 104–104.5° is 5-nitroguaiacol.

The product from the mercuration of 5-nitroguaiacol with mercuric acetate in aqueous acetic acid in the presence of sodium acetate is an orange colored, amorphous solid having no clearly defined melting point. It is soluble in none of the usual organic solvents except glacial acetic acid. The position of the mercury in the isomers which comprise this product has been demonstrated by the method of Dimroth.[7]

Analyses for mercury show that the product contains 49–54% mercury (depending upon the exact mercuration conditions), which indicates a mixture of mono- and dimercurated derivatives, containing up to 60% dimercurated compound.

Replacement of mercury by bromine[7] yields a mixture of bromonitroguaiacols from which two compounds were isolated by a prolonged and tedious fractional crystallization. The first, I, was a monobromonitroguaiacol, whose melting point was 151–152°; the second, II, was a dibromonitroguaiacol which melted at 119–120°.

Only two monobromoguaiacols are mentioned in the literature.[8,9] Raiford and Silker have very kindly furnished us with a sample of their compound, which they characterized as 4-bromo-5-nitroguaiacol (m. p. 118–119°). Mixed melting point tests showed this to be different from our monobromonitroguaiacol. We have been unable to repeat the synthesis of the compound reported by Robertson following his directions for the bromination of 5-nitroguaiacol. He cites no evidence of the source of his 5-nitroguaiacol; we have not been able to brominate 5-nitroguaiacol by any of the usual methods.

The identity of compound I was established by eliminating the nitro group by reduction, diazotization of the resulting amine, and reaction of the diazonium salt with hypophosphorous acid.[10] This series of reactions yielded a product which melted at 62–63° and which was found to be 6-bromoguaiacol; an authentic sample was obtained from 6-nitroguaiacol[8] by replacement of the nitro group with bromine by way of the amine according to the Sandmeyer method. Compound I is, therefore, 6-bromo-5-nitroguaiacol.

A similar series of reactions starting with II gave a dibromoguaiacol which melted at 64–65°. An identical product was synthesized from 4-nitroguaiacol by bromination followed by replacement of the nitro group with bromine in the same way as before. Compound II is, therefore, 4,6-dibromo-5-nitroguaiacol. This was confirmed by the replacement of the nitro group of II by bromine; the substance thus obtained was the same tribromoguaiacol formed by direct bromination of guaiacol,[11] namely, 4,5,6-tribromoguaiacol.

Experimental

Guaicol Acetate.—Redistilled guaiacol (b. p. 204–205°) was acetylated by mixing it (124 g., 1 mole) with acetic anhydride (204 g., 2 moles) and 1 ml. of concentrated sul-

---

[1] From a thesis submitted to the Graduate School of the University of Maryland by Hillman C. Harris in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1946.

[2] This work was supported during 1941–1944 by a grant from Lynch and Company of St. Louis, Mo.

[3] Present address: E. I. du Pont de Nemours and Co., Inc., Wilmington, Delaware.

[4] Associated with Lynch and Co., 2939 Frederick Avenue, Baltimore, Maryland.

[5] Cardwell and Robinson, *J. Chem. Soc.*, **107**, 250 (1915); Cousin, *Chem. Zentr.*, **70**, I, 877 (1899); Kauffmann and Franck, *Ber.*, **39**, 2725 (1906); Klemenc, *Monatsh.*, **33**, 704 (1912); Paul, *Ber.*, **39**, 2777 (1906); Pollecoff and Robinson, *J. Chem. Soc.*, **113**, 647 (1918); Reidel, *Chem. Zentr.*, **84**, II, 1181 (1913) (abstract of German Patent 264,012); Reverdin and Crepieux, *Ber.*, **36**, 2258 (1903); Reverdin and Crepieux, *ibid.*, **39**, 2725 (1906); Rupe, *ibid.*, **30**, 3446 (1897); Wegscheider and Klemenc, *Monatsh.*, **31**, 734 (1910).

[6] Jaeger, unpublished results.

[7] Dimroth, *Ber.*, **35**, 2032 (1902).

[8] Robertson, *J. Chem. Soc.*, **93**, 788 (1911).

[9] Raiford and Silker, *J. Org. Chem.*, **2**, 346 (1937).

[10] Kornblum, "Organic Reactions, Roger Adams, Editor-in-Chief, Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 262.

[11] Zagilorami, *Gazz. chim. ital.*, **62**, 570 (1932); *C. A.*, **27**, 72 (1933).

furic acid as catalyst and distilling the mixture until the acetic acid formed in the reaction was removed, as indicated by a still-head temperature equivalent to the boiling point of acetic anhydride. The reaction mixture was then cooled, washed with cold water, dried over calcium chloride, and fractionated under reduced pressure. The yield was 124 g. of guaiacol acetate which boiled at 123–124° (13 mm.).

5-Nitroguaiacol.—A solution of guaiacol acetate (135 g., 0.813 mole) in 120 ml. of glacial acetic acid was added all at once to a solution of 115 ml. of fuming nitric acid (sp. gr. 1.5) in 180 ml. of glacial acetic acid in a beaker of at least 3-liters capacity. The temperature rose slowly at first and then more rapidly, and an extremely vigorous nitration took place with much fuming and boiling and copious evolution of red-brown fumes. For safety this reaction was carried out under a closed hood. About ten minutes after the boiling had subsided, the mixture was poured over several liters of crushed ice and water. The oily precipitate first formed crystallized at once when it was stirred. The crystalline product was washed by decantation several times with cold water, separated by filtration, further washed with cold water until free from acid, and dried in a vacuum desiccator over concentrated sulfuric acid.

The crude 5-nitroguaiacol acetate so obtained was hydrolyzed by suspending it in 650 ml. of hot 10% sodium hydroxide and heating the mechanically stirred mixture to a temperature just below the boiling point until solution was complete. After addition of 65 g. of solid sodium chloride, the well-stirred mixture was cooled to 5°, and the thick precipitate of the sodium salt of 5-nitroguaiacol filtered off, pressed as dry as possible on the filter, and washed with a little cold, saturated sodium chloride solution. The product was dissolved in 1.5–2 liters of water and filtered. The solution was acidified with concentrated hydrochloric acid and the product separated by filtration, washed with water and dried in a vacuum desiccator over concentrated sulfuric acid. The material was purified by vacuum distillation (b. p. 110–112° (1 mm.)) and by recrystallization from benzene. The yield of material which melted at 104–104.5° was 57.7 g. (42%, based on guaiacol acetate). It is possible that the vacuum distillation may be unnecessary since the product from hydrolysis is fairly pure.

Nitration by the usual methods yields products containing appreciable amounts of 3-nitroguaiacol which is separated from 5-nitroguaiacol only with great difficulty. *Anal.* Calcd. for $C_7H_7NO_4$: C, 49.71; H, 4.15. Found: C, 49.91; H, 4.22.

Mercuration of 5-Nitroguaiacol.—5-Nitroguaiacol (100 g.) and 400 g. of mercuric acetate were dissolved in 3.5 liters of a 35% aqueous solution of acetic acid, containing 1% of sodium acetate. The solution was stirred mechanically and heated on a steam-bath for six hours, during which time an orange precipitate formed and gradually became thicker and deeper in color. After six hours, the mixture was cooled, the product separated by filtration, washed well with water, and dissolved in hot, dilute alkali; the solution was filtered through kieselguhr and the product precipitated with the desired acid. The yield was 290–325 g. (acetoxymercuri compound). *Anal.* Calcd. for $C_9H_9O_6NHg$: Hg, 46.90. Calcd. for $C_{11}H_{11}O_8NHg_2$: Hg, 58.45. Found: Hg, 48.90.[12]

Other runs were made in which the mercurated product contained up to 54% mercury. It appears that slight variations in procedure greatly affect the relative amounts of mono and di-mercurated products obtained.

Bromomercuri Derivative.—Fifty grams of acetoxymercuri compound was dissolved in hot 1 *N* potassium hydroxide and the solution filtered through kieselguhr. Hydrobromic acid (48%) was added dropwise, with stirring, to the cooled solution, until the yellow bromomercuri derivative had precipitated completely.

The product was separated by filtration, washed thoroughly with water, and pressed as dry as possible on the filter. It was dried in a vaccum desiccator over concentrated sulfuric acid. Yield was 51 g. *Anal.* Calcd. for $C_7H_6O_4NBrHg$: Hg. 44.71. Calcd. for $C_7H_5O_4NBrHg_2$: Hg, 56.18. Found: Hg, 46.50.

Dimroth Reaction (Mercurated 5-Nitroguaiacol and Bromine.—Fifty grams of bromomercuri derivative was dissolved in 500 ml. of glacial acetic acid on a steam-bath. Bromine was added slowly to the mechanically stirred solution while frequent tests for free bromine (starch–iodide paper) were made. When a positive test for free bromine persisted for thirty minutes, addition of bromine was halted and the solution was stirred for thirty minutes longer; about 18 g. of bromine was required. Excess bromine was destroyed by a little sodium bisulfite and the acetic acid was removed by distillation under reduced pressure. The residue was taken up in hot 1 *N* potassium hydroxide and the solution filtered through kieselguhr (or centrifuged) to remove inorganic mercury salts. Acidification by means of hydrochloric acid precipitated a yellow crystalline product which was contaminated with a small amount of gummy material. After it has been dried in an oven at 100°, the product was taken up in anhydrous ether, treated with 1–2 drops of bromine, and filtered. The ether solution was extracted with 1 *N* potassium hydroxide, and the bright red aqueous layer freed from ether by boiling and then acidified with hydrochloric acid. The crystalline product was separated by filtration, washed with water and dried *in vacuo* in an Abderhalden pistol over phosphorus pentoxide at the boiling point of ethyl alcohol. The yield was 23 g.; the product melted at 109–122°. *Anal.* Calcd. for $C_7H_6BrNO_4$: Br, 32.22. Calcd. for $C_7H_5Br_2NO_4$: Br, 48.89. Found: Br, 37.10.

Unsuccessful attempts were made to separate this mixture into pure components by fractional distillation and by fractional crystallization from a variety of solvent combinations. Separation was finally achieved by a prolonged and tedious fractional crystallization from aqueous acetic acid (50% by volume). The general procedure indicated by Morton[13] was used, and fractions of similar melting point were combined. For final purification, the end-products were washed thoroughly with cold water and recrystallized from methanol–water. From 20 g. of mixture were obtained 10.7 g. of a yellow crystalline compound, I, m. p. 151–152° and 2.2 g. of a second compound, II, m. p. 119–120° and 5.1 g. of intermediate fractions. *Anal.* I: Calcd. for $C_7H_6BrNO_4$: C, 33.87; H, 2.44; Br, 32.22. Found: C, 33.96; H, 2.53; Br, 32.33. II: Calcd. for $C_7H_5Br_2NO_4$: C, 25.71; H, 1.54; Br, 48.89. Found: C, 25.59; H, 170; Br, 48.51.

6-Bromo-5-nitroguaiacol Acetate.—One gram of product, I, above was acetylated with 0.5 ml. of acetic anhydride with a trace of concentrated sulfuric acid as catalyst. The solid product was recrystallized from a methanol–water mixture (*ca.* 4–1). The yield was 1 g. (85%); the substance melts at 126–127°. *Anal.* Calcd. for $C_9H_8BrNO_5$: C, 37.27; H, 2.78. Found: C, 37.40; H, 2.90.

4,6-Dibromo-5-nitroguaiacol Acetate.—Using the same procedure as in the previous experiment, 0.5 g. of product, II, was acetylated with 0.3 ml. of acetic anhydride. The yield was 0.52 g. (92%); the substance melts at 135–136°. *Anal.* Calcd. for $C_9H_7Br_2NO_5$: C, 29.30; H, 1.91. Found: C, 29.50; H, 2.13.

6-Bromoguaiacol from I.—Two grams of I was reduced with tin and hydrochloric acid. The solution was diluted with water, filtered, and freed from tin by treatment with hydrogen sulfide. After excess hydrogen sulfide had been removed by boiling, the residual solution was concentrated under reduced pressure to a volume of about 15 ml. Two ml. of concentrated hydrochloric acid was added and the solution was cooled to 5° and the amine diazotized by the slow addition of a cold solution of 0.6 g. of sodium nitrite in 5 ml. of water, using starch–iodide indicator. To the cold diazonium salt solution was added 16 g. of cold 50%

---

[12] Analyses for mercury by gravimetric and/or volumetric methods of Jamieson, *Ind. Eng. Chem.*, **4**, 206 (1919). Decompositions were effected by fuming nitric acid, *cf.* Hart and Herschfelder, THIS JOURNAL, **42**, 2680 (1920).

[13] Morton, "Laboratory Technique in Organic Chemistry," The McGraw-Hill Book Co., Inc., New York, N. Y., 1935.

hypophosphorous acid. The temperature was maintained at 0–5° for one hour and then the solution was stored in a refrigerator at 5–10° for twenty hours. Steam distillation of this solution yielded a crystalline product which was recrystallized from an ethanol–water mixture (*ca.* 5:1). The yield was 0.46 g. (28%); the product melted at 62–63° and showed no depression of melting point when mixed with varied quantities of 6-bromoguaiacol. *Anal.* Calcd. for $C_7H_7BrO_2$: Br, 39.38. Found: Br, 39.76.

4-Nitroguaiacol.—2-Amino-5-nitroanisole (50 g.) (Eastman Kodak Co. product No. P 2329 recrystallized from ethanol, m. p. 140–141°) was hydrolyzed with a solution of 50 g. of sodium hydroxide in 450 ml. of water by heating at the boiling point for thirty hours under reflux. When the reaction mixture was cooled, the sodium salt of 4-nitroguaiacol crystallized in bright red needles. The cold solution was filtered and the red crystals dissolved in 1.5 liters of hot water; the solution was filtered, cooled, and acidified with hydrochloric acid. The 4-nitroguaiacol was separated by filtration and dissolved in benzene; the solution was dried by removing the benzene–water azeotrope by distillation. The product was then crystallized from the dry benzene. The yield was 43.2 g. (86%); the 4-nitroguaiacol melted at 102–103°. *Anal.* Calcd. for $C_7H_2NO_4$: C, 49.71; H, 4.17. Found: C, 49.61, 49.86; H, 4.15, 4.21.

6-Bromo-4-nitroguaiacol from 2-Amino-3-bromo-5-nitroanisole.—The anisole derivative (20 g.) was heated in a bomb at 130° under pressure for four and one-half hours with 4 g. of sodium hydroxide in 100 ml. of water. Six grams of starting material was recovered unchanged. The filtered alkaline solution was boiled to expel ammonia and acidified. The yellow product was recrystallized from an ethanol–water mixture (5:1). The yield was 13 g. (93%); this specimen of 6-bromo-4-nitroguaiacol melted at 150° (dec.), and was found to be identical with the substance described directly below.

6-Bromo-4-nitroguaiacol from Bromination of 4-Nitroguaiacol.—A solution of 11.7 g. of 4-nitroguaiacol in 100 ml. of glacial acetic acid was brominated by the slow addition of 12.5 g. of bromine in 40 ml. of glacial acetic acid. After 1–2 ml. of the bromine solution had been added, the mixture was warmed with a flame until the evolution of hydrobromic acid was evident, whereupon addition of the solution of bromine was continued during one hour; stirring was continued one hour longer and the reaction mixture was then poured into 300 ml. of cold water. The yellow precipitate was separated by filtration and recrystallized from an ethanol–water mixture (5:1). The yield was 12.1 g. (70.3%); the product melted at 150° (dec.)

6-Bromo-nitroguaiacol Acetate.—6-Bromo-4-nitroguaiacol (1 g.) was acetylated in the presence of a trace of sulfuric acid by means of 0.5 ml. of acetic anhydride. The product was recrystallized from a methanol–water mixture (3.5:1). The yield was 1.1 g. (91%) of a substance which melted at 102–103°. *Anal.* Calcd. for $C_9H_8BrNO_5$: C, 37.27; H, 2.78. Found: C, 37.13; H, 2.90.

4,6-Dibromoguaiacol from 6-Bromo-4-nitroguaiacol.—6-Bromo-4-nitroguaiacol (4 g.) was reduced with tin and hydrochloric acid. The solution was diluted, filtered and freed from tin by treatment with hydrogen sulfide. After the solution had been boiled to rid it of excess hydrogen sulfide, it was concentrated under diminished pressure to a volume of *ca.* 30 ml. Three ml. of concentrated hydrochloric acid was added, the solution was cooled to 0° by immersion in an ice and salt mixture, and the dissolved amine salt was diazotized by the addition of a cold solution of 1.2 g. of sodium nitrite in 20 ml. of water. Starch–iodide paper was used as indicator. A solution of cuprous bromide was prepared as follows: 5 g. of crystallized copper sulfate was dissolved in 16 ml. of boiling water and 2.4 g. of potassium bromide was dissolved in the hot solution. To this hot solution was added slowly a solution of 1.1 g. of sodium pyrosulfite ($Na_2S_2O_5$), and 0.75 g. of sodium hydroxide in 8 ml. of water. The precipitated cuprous bromide was then washed twice with water by decantation and dissolved in 15 ml. of 40% hydrobromic acid. This solution was heated in an apparatus arranged for steam distillation and the cold diazonium solution above was added dropwise while the mixture steam-distilled simultaneously. The white solid which crystallized in the distillate was separated by filtration and recrystallized from aqueous ethanol. The yield was 1.2 g. (25.5%); the product melted at 64–65°. *Anal.* Calcd. for $C_7H_6Br_2O_2$: C, 28.02; H, 2.14; Br, 56.70. Found: C, 28.13; H, 2.23; Br, 56.59.

4,6-Dibromoguaiacol from II.—One and one-half grams of II was reduced with tin and hydrochloric acid. As before, the solution was diluted with water, filtered, freed of tin by treatment with hydrogen sulfide, and concentrated under reduced pressure to 15 ml. whereupon 3 ml. of concentrated hydrochloric acid was added. The solution was then cooled to 0° and the dissolved amine salt diazotized by addition of a cold solution of 0.36 g. of sodium nitrite dissolved in 15 ml. of water again using starch–iodide paper as an indicator. To the cold diazonium salt solution was added 10 g. of a cold 50% solution of hypophosphorous acid. The solution was maintained at 0–5° for one hour and then kept in a refrigerator at 5–10° for twenty-four hours. When the resultant solution was steam distilled, a white solid crystallized in the distillate and was separated by filtration and recrystallized from an ethanol–water mixture. The yield was 0.4 g. (31%); the product melted at 63–64°.

This product proved to be identical with that previously obtained from 6-bromo-4-nitroguaiacol. Mixed melting point tests resulted in no depression in melting point.

4,5,6-Tribromoguaiacol from II.—One and one-half grams of II was reduced with tin and hydrochloric acid, freed from tin, concentrated and diazotized as in the previous experiments. A solution of cuprous bromide in hydrobromic acid was prepared and the cold diazonium solution added dropwise to it while steam was blown through the mixture. A white crystalline product was filtered from the distillate and recrystallized from an ethanol-water mixture. The yield was 0.31 g. (18.7%), m. p. 114–116°. This product shows no depression in melting point when mixed with varied quantities of authentic 4,5,6-tribromoguaiacol.

4-Hydroxyguaiacol from 4-Aminoguaiacol.—A solution of 4.2 g. of the amine obtained by reduction of 4-nitroguaiacol was dissolved in 33 ml. of water and 33 ml. of concentrated sulfuric acid. This solution was diluted with 300 ml. of water and treated at −8°, with a solution of 2.1 g. of sodium nitrite dissolved in a small amount of water. After the diazotization was complete, the solution was warmed quickly and heated on a water-bath for thirty minutes. Extraction with ether followed by evaporation of the ether yielded 1.3 g. of product which melted at 80–82°. Two recrystallizations from benzene raised the melting point to 90–91°. *Anal.* Calcd. for $C_7H_8O_3$: C, 59.99; H, 5.76. Found: C, 60.09; H, 5.80.

5-Aminoguaiacol from 5-Nitroguaiacol.—5-Nitroguaiacol was reduced in ether at 70–100° in the presence of Raney nickel at a pressure of 1600 p. s. i. of hydrogen. The yield of a product which melted at 131–133° was 79%. Substantially the same yield was obtained using Adams catalyst and alcohol as solvent. Recrystallization from benzene yielded a product which melted at 130–131°. *Anal.* Calcd. for $C_7H_9O_2N$: C, 60.43; H, 6.45. Found: C, 60.44, 60.55; H, 6.44, 6.44.

5-Hydroxyguaiacol from 5-Aminoguaiacol.—The method used was like that described above for the preparation of 4-hydroxyguaiacol; 2.8 g. of amine yielded 1.5 g. of product. The 5-hydroxyguaiacol melted at 71–72° after two recrystallizations from benzene and ligroin. *Anal.* Calcd. for $C_7H_8O_3$: C, 59.99; H, 5.76. Found: C, 59.95; H, 5.74.

4-Nitroveratrole from 4- and 5-Nitroguaiacol.—Methylation of 4-nitroguaiacol by means of dimethyl sulfate and alkali yielded a product which, after recrystallization from ligroin and then from alcohol, melted at 97–98°. *Anal.* Calcd. for $C_8H_9NO_4$: C, 52.46; H, 4.95. Found: C, 52.47; H, 5.03.

Methylation of 5-nitroguaiacol yielded a product which, after recrystallization from ligroin, melted at 96–97°. A mixture of this substance and the one obtained from 4-nitroguaiacol melted at 96–97°.

Summary

It has been shown that the mercuration of 5-nitroguaiacol results principally in the formation of 6-acetoxymercuri-5-nitroguaiacol and 4,6-diacetoxymercuri-5-nitroguaiacol.

In the course of the work three new compounds, 6-bromo-5-nitroguaiacol, 4,6-dibromo-5-nitroguaiacol and 4,6-dibromoguaiacol, have been prepared and characterized.

Evidence has been offered that the substance mercurated was in fact 5-nitroguaiacol and not an isomer.

COLLEGE PARK, MD. RECEIVED MAY 1, 1947

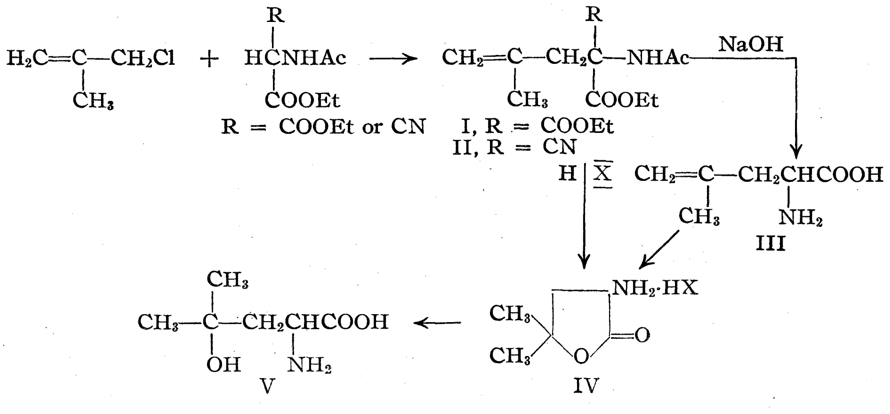
[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

Amino Acid Intermediates: α-Amino-γ-lactones

BY JEANNE FILLMAN AND NOEL ALBERTSON

α-Amino-γ-lactones have been used not only for the synthesis of γ-hydroxyamino acids, but also for the preparation of such amino acids as methionine[1] and canaline.[2] In general, the lactones have been prepared by the reaction of the appropriate oxide with a malonic or acetoacetic ester. For example, γ-hydroxyproline has been synthesized from epichlorohydrin and malonic ester[3] and γ-hydroxyleucine (V) recently was synthesized from isobutylene oxide and actamidomalonic ester.[4] In the latter instance the condensation product was an oil so that hydrolysis gave glycine as an impurity difficult to remove.

Since lactones may also be prepared from β,γ- and γ,δ-unsaturated acids,[5] a possible route to γ-hydroxyamino acids would involve condensation of an allyl halide with an acylaminomalonic or acylaminocyanoacetic ester and conversion to the amino acid *via* the lactone.



Methylallyl chloride has been reported to condense with acetamidomalonic ester in 79% yield[6] and with acetamidocyanoacetic ester in 82% yield[7] of recrystallized product (I and II, respectively). Hydrolysis of I with hydrochloric acid for four hours gave an 85% yield of γ-hydroxyleucine lactone hydrochloride (IV). The same lactone was obtained on acid hydrolysis of the cyano intermediate (II) or methylallylglycine (III), the latter amino acid being obtained from I or II by basic hydrolysis.[7] Conversion of the lactone to γ-hydroxyleucine was accomplished by means of the flavianate according to the procedure of Dakin.[4]

This method of synthesizing γ-hydroxyleucine is simpler experimentally and gives better yields and a purer[8] product than the method using isobutylene oxide.

One would normally expect a γ-hydroxy acid to form a lactone, but Dakin points out that γ-hydroxyleucine does not readily give a lactone on boiling with hydrochloric acid. This is in marked contrast to the phenyl isocyanate derivative which has been obtained only in the form of the lactone. However, it has been found that under proper conditions (refluxing for five and one-half hours with concentrated hydrochloric acid) γ-hydroxyleucine is converted to the lactone hydrochloride as shown by mixed melting point and chlorine analysis. At the end of three and one-half hours the conversion was not yet complete, so that lactonization of this hydroxy acid requires relatively strenuous treatment. This is especially surprising in view of the structure of γ-hydroxyleucine. Since "substituent alkyl groups decidedly

---

(1) (a) Hill and Robson, *Biochem. J.*, **30**, 246 (1936); (b) Livak, Britton, Van der Weele and Murray, THIS JOURNAL, **67**, 2218 (1945).

(2) Kitagawa, *J. Agr. Chem. Soc. Japan*, **12**, 871 (1936); *C. A.*, **31**, 1362 (1937).

(3) Leuchs, *Ber.*, **38**, 1937 (1905).

(4) Dakin, *J. Biol. Chem.*, **154**, 549 (1944).

(5) Fittig, *Ann.*, **208**, 94 (1881); **283**, 47, 269 (1894); *Ber.*, **27**, 2658 (1894).

(6) Albertson and Archer, THIS JOURNAL, **67**, 308 (1945).

(7) Albertson, *ibid.*, **68**, 450 (1946).

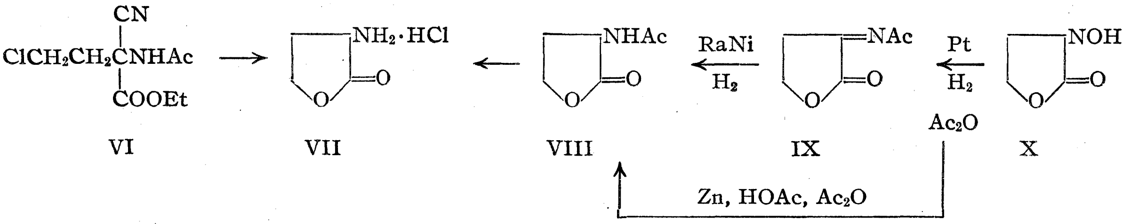
(8) Apparently the product prepared by Dakin (ref. 4) still contained a trace of glycine since it gave a phenyl isocyanate derivative melting at 188–189° with slight previous softening. We found that this derivative melted at 200–201°. The lactone (IV) gave a phosphotungstate, a copper salt, a Reinecke salt and a flavianate in agreement with the derivatives reported by Dakin.

favor the formation of lactones[9]" one might have anticipated an almost spontaneous lactonization. In contrast to the hydroxyamino acid (V) the unsaturated acid (III) is readily converted to the lactone by hydrochloric acid.

Inasmuch as Sorensen has prepared allylglycine in high yields by hydrolyzing allyl *o*-carboxybenzamidomalonic acid with concentrated hydrochloric acid,[10] it is apparent that allylglycine is not converted to the lactone under these conditions. It has been found, however, that either hydrobromic or hydriodic acid will convert allylacetamidocyanoacetic ester to the lactone, whereas the use of hydrochloric acid results in the formation of allylglycine. The lactone was converted to the benzoyl derivative and one *dl*-form was isolated.

In an attempt to extend this method of synthesis to γ-hydroxyproline the commercially available 1,3-dichloropropene was condensed with acetamidocyanoacetic ester and the product hydrolyzed with hydrochloric acid to give ω-chloro allylglycine. "Lactonization" of this amino acid should give the known α-amino-δ-chloro-γ-valerolactone from which γ-hydroxyproline has previously been prepared.[11] However, no lactone could be obtained by treatment of ω-chloroallylglycine with hydrobromic, hydriodic, sulfuric, perchloric or periodic acids or with hydrogen chloride in acetic acid, probably because of steric effects.

Inasmuch as γ-halogen substituted acids are also useful in the preparation of lactones an alternative synthesis of α-amino-γ-lactones would involve the preparation and hydrolysis of a γ-halogen substituted acetamidocyanoacetic ester. It was found that hydrochloric acid readily converted β-chloroethylacetamidocyanoacetic ester, VI, to the known α-amino-γ-butyrolactone hydrochloride, VII, an intermediate in the synthesis of methionine[1] and canaline.[2]



The β-chloroethylacetamidocyanoacetic ester was synthesized from ethylene chlorobromide and sodioacetamidocyanoacetic ester in toluene. Previous attempts to condense ethylene chloride or ethylene bromide with acylaminomalonic esters have been unsuccessful.[12] However, these attempted syntheses were carried out in alcohol in which case the sodium ethylate was undoubtedly basic enough to remove HX from the ethylene halide to form a vinyl halide which would escape from the condenser.

It is interesting to note that Painter[13] attempted to prepare β- and γ-halogen amino acids by hydrolysis of appropriately halogen substituted benzamidomalonic esters but was unable to isolate the desired amino acids after hydrolysis. It is very likely that, at least in the case of the γ-halogen acids, lactones were formed on hydrolysis.

An attempt to react VI with potassium benzohydroxamate with a view to synthesizing canaline was unsuccessful. Replacement of the chlorine by iodine still gave negative results.

An alternative synthesis of α-amino-γ-butyrolactone hydrochloride involved reductive acetylation of the readily available α-oximino-γ-butyrolactone followed by hydrolysis of the intermediate α-acetamido-γ-butyrolactone, VIII.[14] Although zinc dust reduced the oxime to the acetamido compound, catalytic reduction with a platinum catalyst in acetic anhydride solution resulted in the uptake of only one mole of hydrogen to give α-acetimido-γ-butyrolactone, IX. With a Raney nickel catalyst, IX was rapidly and quantitatively reduced to the acetamido compound VIII. Upon hydrolysis this gave α-amino-γ-butyrolactone hydrochloride identical with that previously prepared. Hydrolysis of the intermediate α-acetimido-γ-butyrolactone gave ammonium chloride as the only crystalline product.

Experimental

γ-Hydroxyleucine Lactone Hydrochloride (IV).—Seventy-one and six-tenths grams of diethyl methylallylacetamidomalonate[6] was refluxed for four hours with 250 ml. of concentrated hydrochloric acid. The resulting solution was concentrated *in vacuo* and the residue taken up in hot ethanol. Upon cooling and filtering there was obtained 28.8 g. of product. By concentrating the filtrate and cooling an additional 8.3 g. was obtained, m. p. 207–209°. The yield was 85%. An analytical sample, recrystallized from ethanol, melted at 208–209°.

Anal. Calcd. for $C_6H_{11}NO_2 \cdot HCl$: C, 43.51; H, 7.31; N, 8.46; Cl, 21.41. Found: C, 43.50; H, 7.20; N, 8.26; Cl, 21.49.

When methylallylacetamidocyanoacetic ester (II)[7] or methylallylglycine (III)[7] was used in the above experiment the same lactone was obtained.

The benzoyl derivative, recrystallized from aqueous methanol, melted at 176°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: N, 6.01. Found: N, 6.01.

The carbobenzoxy derivative, recrystallized from aqueous ethanol, melted at 91–93°.

---

[9] Schmidt, "A Textbook of Organic Chemistry," 2nd English ed., D. Van Nostrand Co., Inc., New York, N. Y., 1932, p. 230.

[10] Sorensen, *Ber.*, **41**, 3388 (1908).

[11] McIlwain and Richardson, *Biochem. J.*, **33**, 45 (1939).

[12] Dunn and Smart, *J. Biol. Chem.*, **89**, 41 (1930).

[13] Painter, THIS JOURNAL, **62**, 232 (1940).

[14] This compound has been prepared by reductive acetylation of α-keto-γ-butyrolactone phenylhydrazone using Raney nickel catalyst: Snyder, Andreen, Cannon and Peters, *ibid.*, **64**, 2082 (1942).

Anal. Calcd. for $C_{14}H_{17}NO_4$: N, 5.32. Found: N, 5.32.

The phenyl isocyanate derivative, recrystallized from aqueous methanol, melted at 200–201°.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.86; H, 6.41; N, 11.30.

The lactone gave a flavianate which decomposed at 273–276°.

γ-Hydroxyleucine (V).—Twenty-eight grams of γ-hydroxyleucine lactone hydrochloride (IV) was converted to γ-hydroxyleucine by use of flavianic acid according to the procedure of Dakin.[4] There was obtained 20.6 g. of amino acid melting at 220–222° when dried at 65°.

Anal. Calcd. for $C_6H_{13}NO_3\cdot H_2O$: N, 8.50. Found: N, 8.52.

When dried at 100° *in vacuo*, the amino acid lost water and melted at 230–232°.

Anal. Calcd. for $C_6H_{13}NO_3$: N, 9.52. Found: N, 9.38.

The amino acid gave a flavianate, reineckate and phosphotungstate agreeing in properties with those reported by Dakin.[4]

Lactone from α-Hydroxyleucine.—Five grams of γ-hydroxyleucine was refluxed for five and one-half hours with 1:1 hydrochloric acid. The solution was concentrated *in vacuo* and the residue recrystallized from ethanol, m. p. 208–209°. It did not depress the melting point of γ-hydroxyleucine lactone hydrochloride.

Anal. Calcd. for $C_6H_3NO_3\cdot HCl$: Cl, 193.1. Calcd. for $C_6H_{11}NO_2\cdot HCl$: Cl, 21.49. Found: Cl, 21.30.

When γ-hydroxyleucine was refluxed with hydrochloric acid for only three and one-half hours the reaction mixture was a mixture of hydroxy amino acid and lactone.

Allylglycine.—Allylacetamidocyanoacetic ester was refluxed with hydrochloric acid (6 ml. of 1:1 aqueous acid per gram of ester) for five hours. The solution was charcoaled, filtered and concentrated *in vacuo*. The residue was taken up in water and made basic with sodium hydroxide to expel ammonia. The mixture was then made just acid with hydrochloric acid, cooled and filtered to give platelets melting at 170–190°. Three recrystallizations from water gave crystals, m. p. 212–215°.

Anal. Calcd. for $C_5H_9NO_2$: N, 12.17. Found: N, 12.08.

Benzoyl-*dl*-allylglycine.—Three grams of the above lactone was benzoylated in the usual manner. The product, twice recrystallized from water, melted at 105–106°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: N, 6.39. Found: N, 6.33. Bromine titration indicated 1.00 double bonds.

Benzamido-γ-hydroxynorvaline Lactone.—Hydrolysis of allylacetamidocyanoacetic ester was carried out as above with either hydrobromic or hydriodic acid. However, as soon as the ammonia had been expelled from the basic solution benzoyl chloride was added. The benzoyl derivative was isolated in the usual manner, freed of benzoic acid with Skellysolve B and recrystallized from small volumes of ethanol. The product was triturated with ether and finally recrystallized from water, m. p. 140–141°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: N, 6.39. Found: N, 6.41. It absorbed no bromine.

ω-Chloroallylglycine.—1,3-Dichloropropene[15] was condensed with acetamido-cyanoacetic ester and the resulting product hydrolyzed with hydrochloric acid according to methods previously described.[7] The yield of ω-chloroallylglycine, recrystallized from aqueous ethanol, was 38% m. p. 236°.

Anal. Calcd. for $C_5H_8ClNO_2$: N, 9.30. Found: N, 9.38.

The benzoyl derivative, recrystallized from aqueous ethanol, melted at 150–151°.

Anal. Calcd. for $C_{12}H_{12}ClNO_3$: Cl, 13.97. Found: Cl, 13.68.

When chloroallylglycine was refluxed for four hours with hydrobromic, hydriodic, sulfuric, perchloric or periodic acid and the mixture then benzoylated only benzoyl-ω-chloroallylglycine was obtained. Hydrogen chloride in acetic acid gave only the amino acid hydrochloride.

β-Chloroethylacetamidocyanoacetic Ester (VI).—To a solution of 11.5 g. of sodium in 150 ml. of dry alcohol there was added 85 g. of ethyl acetamidomalonate. The alcohol was distilled off and toluene was dripped in simultaneously until no more alcohol remained. Then 338 g. of ethylene chlorobromide was added and the mixture refluxed twenty-nine hours. The precipitated sodium bromide (47 g.) was removed by filtration and the filtrate concentrated *in vacuo*. The residual oil (93.6 g.) was dissolved in alcohol and diluted with ice water. There was thus obtained 65 g. of crystalline product.

The product gave a precipitate when boiled with alcoholic silver nitrate and ammonia when boiled with sodium hydroxide. Probably a small amount of bromoethylacetamidocyanoacetic ester was also obtained in this reaction.

An analytical sample, recrystallized several times from ethyl acetate–Skellysolve B, melted at 109.5–111.5°.

Anal. Calcd. for $C_9H_{13}ClN_2O_3$: N, 12.04. Found: N, 11.46.

α-Amino-γ-butyrolactone Hydrochloride from VI.—When chloroethylacetamido-cyanoacetic ester was refluxed with concentrated hydrochloric acid for five hours, the solution concentrated to dryness, and the residue recrystallized several times from 95% alcohol the product was α-amino-γ-butyrolactone hydrochloride. The melting point was not depressed when mixed with a sample (m. p. 198–199.5°) obtained by the hydrolysis of 3,6-bis-(β-hydroxyethyl)-2,5-diketopiperazine.

α-Acetimido-γ-butyrolactone (IX).—Reduction of 11.5 g. of α-oximino-γ-butyrolactone[14] was effected in the presence of 0.3 g. of Adams platinum oxide catalyst, 28 ml. of acetic anhydride and 72 ml. of acetic acid at 50° and 50 lb. pressure. The residue, after removal of the solvent and catalyst, was washed well with water and recrystallized from methanol. The product, 7.0 g. of long needles, melted at 156°.

Anal. Calcd. for $C_6H_7NO_3$: N, 9.93. Found: N, 10.04.

Hydrolysis of this compound with hydrochloric acid gave ammonium chloride.

α-Acetamido-γ-butyrolactone (VIII) from IX.—A solution of 1.41 g. of α-acetimido-γ-butyrolactone was reduced in two minutes with a Raney nickel catalyst in ethanol. The product, after recrystallization from ethyl acetate, melted at 79–81°.[14] It did not depress the melting point of a sample prepared by reductive acetylation of (X) as described below. Hydrolysis of the product with hydrochloric acid gave α-amino-γ-butylactone hydrochloride.

α-Acetamido-γ-butyrolactone (VIII) from X.—A solution of 4.6 g. of oxime (X) in 100 ml. of acetic acid and 30 ml. of acetic anhydride was stirred during the addition of 12 g. of zinc dust portionwise. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was recrystallized from benzene–Skellysolve B and then ethyl acetate. Yield was 3.6 g. melting at 72–76°. Another recrystallization from ethyl acetate raised the melting point to 81–83°.

Summary

A synthetic approach to the synthesis of γ-hydroxyamino acids involving condensation of an allyl halide with an acylaminomalonic or acylaminocyanoacetic ester, hydrolysis to the lactone and conversion to the amino acid has been illustrated by the preparation of γ-hydroxyleucine.

The lactone of γ-hydroxynorvaline has also been synthesized by the same procedure, but the method failed to give the requisite α-amino-δ-chlo-

---

[15] A commercial sample obtained from Columbia Organic Chemicals Co., Inc., was used. Nearly all boiled at 104–106° at 761 mm., $n^{25}D$ 1.4651. It was therefore mainly the α form. *Cf.* Hatch and Moore, *ibid.*, **66**, 285 (1944).

ro-γ-valerolactone required for the synthesis of γ-hydroxyproline.

The preparation of α-amino-γ-butyrolactone by hydrolysis of β-chloroethylacetamidocyanoacetic ester is described.

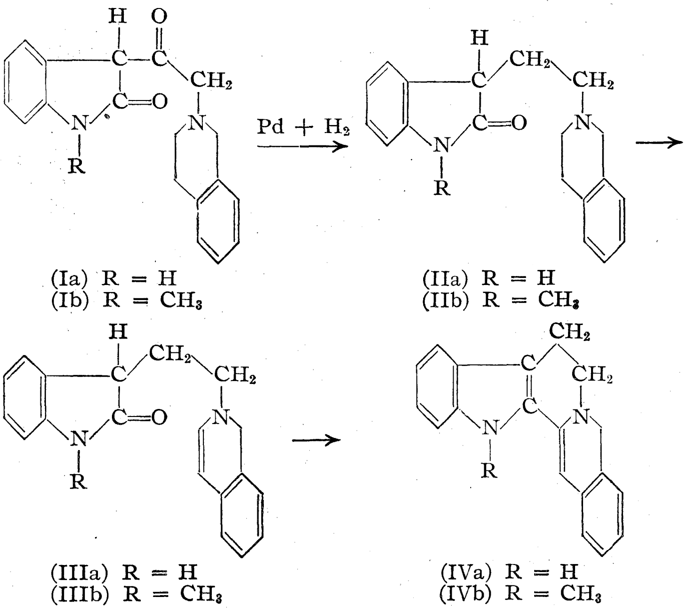
RENSSELAER, N. Y. RECEIVED JUNE 21, 1947

[CONTRIBUTION FROM DE PAUW UNIVERSITY AND FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Studies in the Indole Series. VIII. Yohimbine (Part 1). The Mechanism of Dehydrogenation of Yohimbine and Related Compounds[1]

BY PERCY L. JULIAN, ARTHUR MAGNANI, JOSEF PIKL[2] AND WILLIAM J. KARPEL

The work reported in this communication had its origin in attempts to synthesize the basic ring structure of yohimbine by a procedure presented schematically with formulas I → IV.



(Ia) R = H
(Ib) R = CH_3

(IIa) R = H
(IIb) R = CH_3

(IIIa) R = H
(IIIb) R = CH_3

(IVa) R = H
(IVb) R = CH_3

At the time this investigation began, which was more than a decade ago, the successful preparation of the desired 3-(N-tetrahydroisoquinolylacetyl)-oxindole (Ia) from oxindole and ethyl N-tetrahydroisoquinolyl acetate,[3] as well as the reduction of Ia to 3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIa) could be predicted[4] and indeed was ultimately realized in practice. Sufficient information was also available then and later to indicate that, once compound IIIa were available, enolization of the hydrogen atom at position 3 of the oxindole nucleus could be used for ring closure. The crux of the whole synthesis, however, rested upon the ability to dehydrogenate IIa to IIIa, and this in turn directed closer attention to the end-products from the dehydrogenation of yohimbine and indeed to the mechanism of this dehydrogenation.

When the synthesis of the yohimbine ring structure outlined above was projected the accepted formula for yobyrine, one of the principal dehydrogenation products of yohimbine, was IVa.[5] This structure, like IIIa, is that of a 1,2-dihydroisoquinoline and repeated efforts to prepare 1,2-dihydroisoquinolines hitherto have resulted in failure.[6] Only one case of such a preparation is reported in the literature, namely, that of Cooke and Gulland[7] who claim dehydrogenation of 2-methyltetrahydroisoquinoline to 2-methyl-1,2-dihydroisoquinoline with palladous chloride. Their evidence, however, is poor and subject to question. Our early failures to dehydrogenate IIb to 1-methyl-3-(2-N-dihydroisoquinolylethyl)-oxindole (IIIb) threw grave doubt upon the validity of IVa as representing the structure of yobyrine, despite the fact that the continuous conjugation in IVa might presumably favor the formation of a 1,2-dihydroisoquinoline in the case of the dehydrogenation of yohimbine to yobyrine. Moreover, Pruckner and Witkop[8] in the meantime proposed a new structure for yobyrine, involving a mechanism for the dehydrogenation of yohimbine more consistent with our experiences and those of others. Their results we have substantiated by a complete synthesis of yobrine.[9]

Both 1-methyl-3-(N-tetrahydroisoquinolylacetyl)-oxindole (Ib) and its unmethylated analog, (Ia), on catalytic reduction gave material whose empirical analyses correspond to substances IIb and IIa, respectively. There seems to be no fundamental difference in this case between reduction of the unmethylated and methylated acyl oxindoles such as Horner has indicated.[10]

---

[1] Presented in part as Indole Paper VIII before the Spring Meeting of the American Chemical Society at Boston, in April, 1939. For Paper IX in this series, see THIS JOURNAL, **67**, 1203 (1945).

[2] Present address: Jackson Laboratory, du Pont Company, Wilmington, Delaware.

[3] Wedekind and Oechslen, *Ber.*, **36**, 1161 (1903).

[4] Julian, Pikl and Wantz, THIS JOURNAL, **57**, 2026 (1935).

[5] Barger and Scholz, *Helv. Chim. Acta*, **16**, 1343 (1933).

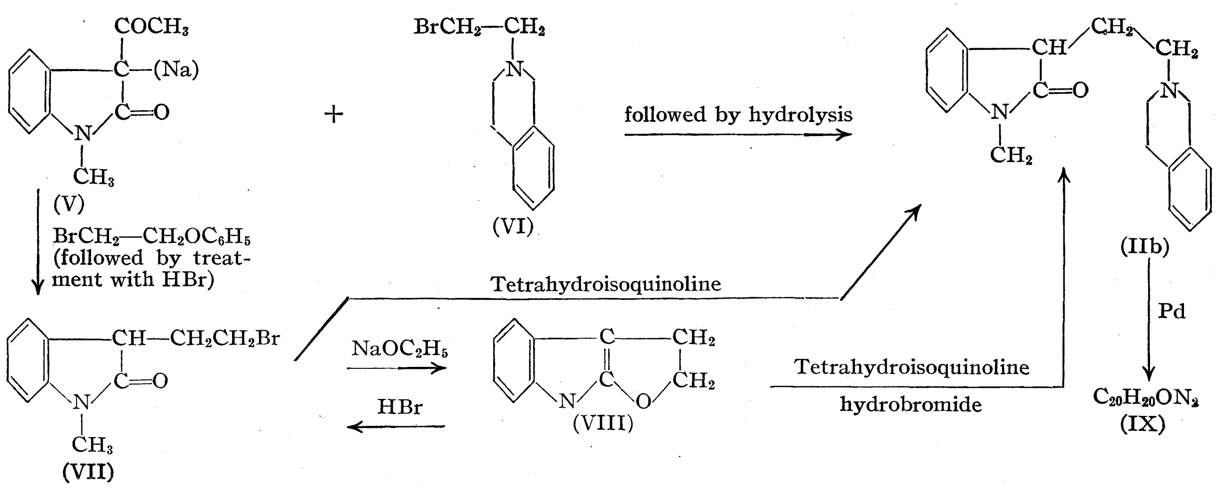
[6] Young and Robinson, *J. Chem. Soc.*, **275** (1933); Perkin, *ibid.*, 815 (1916); Reichert and Hoffmann, *Arch. Pharm.*, **274**, 281 (1936).

[7] Cooke and Gulland, *J. Chem. Soc.*, 872 (1939).

[8] Pruckner and Witkop, *Ann.*, **554**, 127 (1943).

[9] See communication following this one, THIS JOURNAL, **70**, 180 (1948).

[10] Horner, *Ann.*, **548**, 119–120 (1941).



Because, up to quite recently 1-methyloxindole was more readily available to us than oxindole itself, and because the reduction of Ib led to two substances much more readily separable than the mixture obtained from reducing the unmethylated analog, we have employed Ib as a model in this study.

The reduction product of Ib is a fairly constant boiling oil in high vacuum and yields a hydrochloride that for a long time was thought to be a single entity. The recovered base from it, however, has been separated into two substances. The one of these is 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIb), melting at 167°. The other is 1-methyl-2,3-dihydro-3-N-tetrahydroisoquinolylacetylindole (X), which we have been unable to induce to crystallize but which gave a pure crystalline hydrochloride. The formation of these two substances could be predicted by assuming, as a first reaction, 1,4-addition of hydrogen to each of the two possible enolic modifications of Ib.

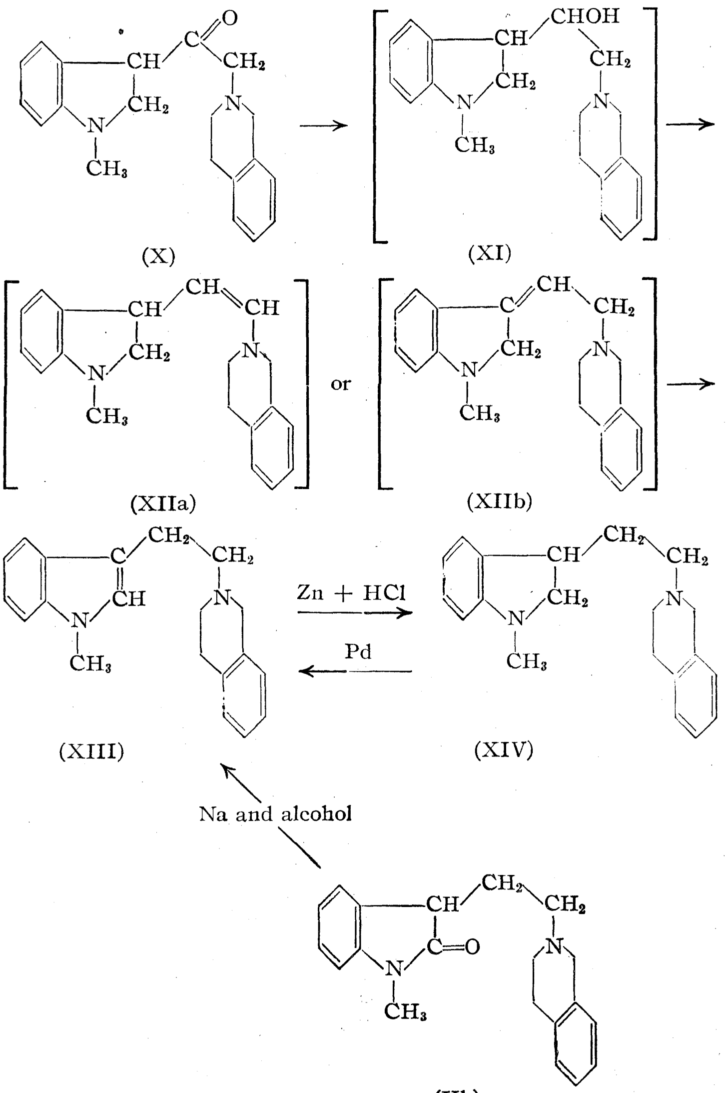
The constitution of our 167° melting compound (IIb) has been proved by two other unequivocal syntheses, schematically illustrated by formulas V → IIb and VII → VIII → IIb. Neither synthesis however proved to be an improvement over the reduction of Ib as far as yield is concerned. The reaction of the sodium salt of 1-methyl-3-acetyloxindole (V) with 1-bromo-2-N-tetrahydroisoquinolylethane (VI) resulted in poor yields of IIb, primarily because of the tendency of VI to condense with itself at elevated temperatures. The reaction of 1-methyl-3-(2-bromoethyl)-oxindole (VII) with tetrahydroisoquinoline in the cold led to 2,3-dihydro-8-methylfuro[2,3-b]indole (VIII) in quantitative yield. Heating the latter, however, with tetrahydroisoquinoline hydrobromide or heating the original mixture of VII and tetrahydroisoquinoline, resulted in a difficultly separable mixture of IIb and another substance whose constitution is not certain but the empirical analyses of which show the formula $C_{20}H_{20}ON_2$ (IX).

The constitution of the second product secured on the reduction of Ib, namely, X, has been demonstrated as diagrammatically outlined by reactions X → XIV, XIV → XIII, and IIb → XIII When the product (X) was reduced with sodium and alcohol it yielded a solid, m. p. 82°, containing no oxygen (XIII). This solid was identical with the compound secured on reducing IIb with sodium and alcohol. Considerable experience in this Laboratory (unpublished work) has convinced us that the transformation IIb → XIII is typical of oxindoles of this general character and compound XIII is therefore 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-indole and the mechanism of its formation from X is suggested in formulas XI and XIIb (or XIIa) of the diagram referred to above.

What is very significant for indole chemistry is the discovery here of a most interesting reduction of a 2,3-dihydro-3-acyl-indole (X) into a 3-alkyl indole (XIII) with sodium and alcohol. We hope to report later on the general application of this spontaneous rearrangement of XIIb or XIIa into XIII.

The dehydrogenation of IIb yielded considerable isoquinoline and about a 30% yield of a crystalline substance, m. p. 182°, of the formula $C_{20}H_{20}ON_2$ having the correct analysis for IIIb. All attempts to effect ring closure on this compound failed and we are loathe to assign to it the structure of a 1,2-dihydroisoquinoline (IIIb). Moreover, this dehydrogenation product is identical with the product (IX) which arises on treating IIb with tetrahydroisoquinoline hydrobromide. It is indeed difficult to explain how a 1,2-dihydroisoquinoline of structure IIIb would arise in such a reaction. The absorption spectrum of compound IX indicates that it is still an oxindole and does not give any additional peak which might be expected for the increased conjugation of a 1,2-dihydroisoquinoline. We have, therefore, concluded that dehydrogenation of yohimbine or compounds related to it like IIb does not lead to 1,2-dihydroisoquinolines and the projected synthesis of the yohimbine ring structure via IIIb is not possible.

Having failed to effect ring closure *via* IIIb →



(X) (XI) (XIIa) or (XIIb) (XIII) (XIV) (IIb)

IVb, we next attempted this through dehydrogenation of 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-indole (XIII). If the initial dehydrogenation attack were at the 3,4-position of the tetrahydroisoquinoline nucleus, such a ring closure should be possible. On carrying out the reaction, however, quantitative cleavage of XIII took place, giving isoquinoline and 1-methyl-2-ethylindole. Likewise a selenium dehydrogenation of IIb gave quantitatively isoquinoline. These findings are of great significance as they indicate that cleavage at the nitrogen atom is the preferred reaction on dehydrogenation of these compounds related to yohimbine. It has been demonstrated clearly by Scholz[11] that the so-called "tetrahydroyobyrine," one of the two principal degradation products of yohimbine with selenium, is the product of just such a cleavage. Pruckner and Witkop[8] have suggested that similarly, in the case of formation of the other dehydrogenation product of yohimbine, namely, yobyrine, the focal point of dehydrogenation is at the other vulnerable linkage to the nitrogen atom, instead of at the 3,4-position of the tetrahydroisoquinoline nucleus, as suggested by Barger and Scholz.[5] Thus, instead of structure IVa, they suggest that yobyrine is 3-*o*-xylyl-4-carboline. Our findings certainly support such a view for the mechanism of dehydrogenation.

Experimental

Tetrahydroisoquinoline.—The tetrahydroisoquinoline was prepared from distilled Eastman Kodak Co. "Practical" isoquinoline by catalytic hydrogenation[12] using copper chromite as described by Cromwell.[13] It distilled at 114–115° at 14 mm. pressure.

Ethyl N-Tetrahydroisoquinolylacetate.[3]—A mixture of 64.6 g. of tetrahydroisoquinoline, 50 g. of ethyl chloroacetate, 40 g. of finely powdered sodium carbonate and 200 cc. of benzene was refluxed vigorously for one hour on the steam-bath. Water was added, the benzene solution separated and distilled. The main fraction consisted of 72 g. boiling at 178–183°, 15 mm. Upon redistilling all fractions 74 g. of the ester was obtained, 180–182° (15 mm.).

1-Methyl-3-(N-tetrahydroisoquinolylacetyl)-oxindole (Ib).—To a solution of sodium ethylate from 5.5 g. of sodium in 60 cc. of absolute alcohol, a mixture of 37.5 g. of ethyl N-tetrahydroisoquinolylacetate and 24 g. of 1-methyloxindole[14] was added. After heating for one hour on the steam-bath, the mass was cooled and 55 g. of sodium salt was obtained after filtering and washing with absolute alcohol. The salt was suspended in 250 cc. of cold ethanol (ice-bath) dissolved by the addition of 5 *N* hydrochloric acid and then diluted with 600 cc. of ice water. Then the solution was made alkaline by the slow addition of sodium carbonate solution, and crystallization was induced by vigorous scratching. Yield was 42 g., m. p. 194–196°; on recrystallization from 95% ethanol, m. p. 199–200°.

Anal. Calcd. for $C_{20}H_{20}O_2N_2$: C, 74.98; H, 6.31. Found: C, 75.32; H, 6.77.

Like other oxindole ketones of this type which we have prepared, the compound was cleaved readily by strong acids and bases.

3-(N-Tetrahydroisoquinolylacetyl)-oxindole (Ia).—This acyloxindole was prepared in the same manner as described above for the N-methyl analog. From 22 g. of oxindole and 38 g. of ethyl N-tetrahydroisoquinolylacetate there was obtained 30 g. of the acyloxindole after crystallization from ethanol, m. p. 268–270°.

Anal. Calcd. for $C_{19}H_{18}O_2N_2$: C, 74.49; H, 5.92. Found: C, 74.63; H, 5.99.

Catalytic Reduction of 1-Methyl-3-(N-tetrahydroisoquinolylacetyl)-oxindole (Ib).—To 8.0 g. (0.025 mole) of the oxindole ketone dissolved in 80 cc. of glacial acetic acid was added 1.33 cc. of sulfuric acid followed by 0.8 g.

---

(11) Scholz, *Helv. Chim. Acta*, **18**, 923 (1935).

(12) We are indebted to Dr. Robert Baker and Mr. Ralph Olberg of Northwestern University for their coöperation in preparing a quantity of tetrahydroisoquinoline.

(13) Cromwell and Cram, THIS JOURNAL, **65**, 304 (1943).

(14) R. Stolle, *J. prakt. Chem.*, [2] **128**, 1–20 (1930).

of palladium oxide.[15] The solution was heated to 80° and hydrogenated at this temperature at 40–45 lb. pressure until two moles had been absorbed (four to six hours). While shaking, a precipitate usually separated which slowly went into solution as hydrogenation proceeded. The acetic acid was distilled under vacuum to a small volume, water was added, and if necessary hydrochloric acid added to give complete solution. The solution was extracted with ether to remove non-basic material, made basic with excess alkali, extracted with ether and the residue after evaporation of the ether subjected to distillation. Low boiling material proved to be tetrahydroisoquinoline (picrate, m. p. 199°) formed by cleavage. The main product distilled at 195–205° (bath temperature), 0.01 mm. pressure; yield 6.5 g., pale yellow oil. For analysis the oil was redistilled; b. p. 200–202° bath temperature (0.01 mm.).

Anal. Calcd. for $C_{20}H_{22}ON_2$: C, 78.43; H, 7.19. Found: C, 78.09; H, 7.35.

Treating the oil in alcohol solution with concentrated hydrochloric acid and then adding ether to make an ether–alcohol solution consisting of 30% alcohol gave 4.8 g. of crystalline hydrochloride, m. p. 183–186°. Recrystallization from ether–alcohol gave 4.0 g. of the hydrochloride melting at 186–188°.

Anal. Calcd. for $C_{20}H_{23}ON_2Cl$: C, 70.07; H, 6.72. Found: C, 70.08, 69.89; H, 7.31, 6.80.

The oil obtained from the hydrogenation was believed to be a single compound until it was found that a concentrated ethereal solution of the oil on long standing deposited sandy crystals, m. p. 163–165°, which proved to be 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIb).

To separate the solid from the mixture, the hydrochloride of the mixture was repeatedly crystallized from ether–alcohol solution as described above. The hydrochloride of the solid, being more soluble, became concentrated in the mother liquors. The solid obtained from the mother liquors on rendering alkaline amounted to 5–7% of the weight of the original oil mixture, and crystallized readily from methanol, white prisms, m. p. 167°.

Anal. Calcd. for $C_{20}H_{22}ON_2$: C, 78.43; H, 7.19. Found: C, 78.24; H, 7.25.

It readily formed a hydrochloride crystallizing from ether–alcohol as white needles, m. p. 238–239°.

Anal. Calcd. for $C_{20}H_{23}ON_2Cl$: C, 70.07; H, 6.72. Found: C, 70.39; H, 6.51.

The picrate of the solid was prepared by adding an equimolecular quantity of picric acid in benzene to a hot solution of the solid in benzene. It was sparingly soluble in alcohol and in benzene, crystallizing as yellow needles, m. p. 208–209° dec.

Anal. Calcd. for $C_{26}H_{25}O_8N_5$: C, 58.32; H, 4.67. Found: C, 58.71; H, 4.54.

The other product of the hydrogenation, obtained as a colorless oil from its purified hydrochloride, is 1-methyl-2,3-dihydro-3-(N-tetrahydroisoquinolylacetyl)-indole (X). It distilled cleanly, b. p. 215–217°, (1 mm.).

Anal. Calcd. for $C_{20}H_{22}ON_2$: C, 78.43; H, 7.19. Found: C, 78.38; H, 7.48.

Its hydrochloride crystallized as fine white needles from ether–alcohol solution, m. p. 190–191°.

Anal. Calcd. for $C_{20}H_{23}ON_2Cl$: C, 70.07; H, 6.72. Found: C, 70.40; H, 6.99.

Catalytic Reduction of 3-(N-Tetrahydroisoquinolylacetyl)-oxindole (Ia).—The oxindole ketone (4.6 g.) was dissolved in 50 cc. of glacial acetic acid and there was added 1.5 g. of sulfuric acid and 0.5 g. of palladium oxide. The hydrogenation was carried out at 40–45 lb. pressure and at 75–80°. The time required for absorption of two moles of hydrogen was five hours. No precipitate formed in the solution. The reaction products were worked up as described above in the reduction of Ib. The acid soluble fraction distilled cleanly in high vacuum as a viscous pale yellow oil which slowly set to a glassy solid, b. p. 205–208° bath temperature (0.001 mm.).

Anal. Calcd. for $C_{19}H_{20}ON_2$: C, 78.05; H, 6.89. Found: C, 77.50; H, 6.72.

All attempts to crystallize the product from ether, alcohol, petroleum ether and combinations of these solvents failed. Likewise, although a hydrochloride and a picrate formed neither of these could be induced to crystallize. Further work on this compound was reserved for a later date and the work described in this paper was performed on the N-methyl analog which seemed to offer less complications in subsequent reactions.

Synthesis of 1-Methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIb).—(a) From Sodium Salt of 1-Methyl-3-acetyloxindole (V) and 1-Bromo-2-N-tetrahydroisoquinolylethane (VI).—The sodium salt of the 1-methyl-3-acetyloxindole was prepared by adding a solution of sodium in absolute alcohol to a hot alcoholic solution of the acetyloxindole, care being taken to avoid an excess of sodium.

For the preparation of 1-bromo-2-N-tetrahydroisoquinolylethane, bromohydrin was treated with two moles of tetrahydroisoquinoline to yield 2-N-tetrahydroisoquinolylethanol,[16] b. p. 120–123° (2 mm.). This was converted into the bromo-compound by refluxing with 48% hydrobromic acid.[17] The bromo compound was isolated as the hydrobromide, insoluble white salt in acetone, and crystallized as white needles from acetone–alcohol mixture, m. p. 238–239°. It was analyzed by determining the amount of bromide ion in aqueous solution.

Anal. Calcd. for $C_{11}H_{15}NBr_2$: Br, 24.9. Found: Br, 25.4.

For use in the following condensation, the hydrobromide was suspended in ether and shaken with dilute alkali. The ethereal solution was washed with water, dried and the ether removed *in vacuo*.

A mixture of 6.0 g. of sodium salt of 1-methyl-3-acetyloxindole, 6.0 g. of 1-bromo-2-N-tetrahydroisoquinolylethane, 0.5 g. of sodium iodide, and 60 cc. of dry acetone was heated in a sealed tube at 100° for twenty-four hours. The resulting reddish solution was filtered to remove insoluble salts and the acetone removed. The residue was taken up in ether and washed with alkali to remove unchanged acetyloxindole. For deacylation, the remaining product was refluxed for twenty minutes in 20 cc. of absolute alcohol containing 1.0 g. of sodium, and poured into water. Washing the ether extract with water removed the greater portion of the reddish color. After removal of the ether and distilling there was obtained 2.1 g. of yellow oil distilling at 200–215° bath temperature (2 mm.). From the ethereal solution cooled overnight 0.25 g. of solid, m. p. 167°, was obtained. It was identical to the 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIb) obtained by hydrogenation of the oxindole ketone (Ib). It also gave an identical picrate. On long standing the ethereal mother liquor deposited a further crop (0.2 g.) of the solid. A similar run heated at 140–150° gave the same results.

Upon heating the 1-bromo-2-N-tetrahydroisoquinolylethane alone on the water-bath, it quickly darkened and turned into a semisolid. A sample of the solid isolated from it melted over 300° and had no definite melting point. At lower temperatures the bromo compound did not react with the sodium salt of the 3-acetyloxindole. It was possible to run the reaction in dioxane heated at 80–90° for twenty-four hours. However, no increase in the yield of desired solid, m. p. 167°, was obtained.

(b) **From 1-Methyl-3-(2-bromoethyl)-oxindole (VII).**—1-Methyl-3-(2-phenoxyethyl)-oxindole was prepared by heating a mixture of 21.0 g. of sodium salt of 1-methyl-3-acetyloxindole, 100 g. of phenoxyethyl bromide, 15 cc.

---

(15) Obtained from American Platinum Works, Newark, New Jersey. Platinum oxide was not found suitable for these reductions.

(16) Skita, *Ber.*, **57**, 1981 (1924).

(17) *Cf.* "Organic Syntheses," Coll. Vol. II, 91 (1943).

of dry acetone and 5.0 g. of sodium iodide under reflux in a metal-bath for fifteen hours at 150–160°. The reddish solution was diluted with ether and washed with alkali to remove unchanged acetyloxindole. Upon distillation at diminished pressure 84 g. of phenoxyethyl bromide was removed. The residue was boiled for thirty minutes in 100 cc. of absolute alcohol containing 5.0 g. of sodium to remove the acyl group and poured into water. The product was taken up in ether, washed with water to remove colored materials, and distilled after removal of the solvent. There was obtained 15.0 g. of pale yellow oil which on standing slowly crystallized. A sample crystallized from petroleum ether as silky needles, m. p. 57°.

Anal. Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41. Found: C, 76.23; H, 6.36.

1-Methyl-3-(2-bromoethyl)-oxindole (VII) was obtained from the 1-methyl-3-(2-phenoxyethyl)-oxindole by treating with hydrobromic acid.[18] There was obtained 11.5 g. of colorless oil, b. p. 165–168° (2 mm.), which crystallized on standing as white needles from petroleum ether, m. p. 63°.

Anal. Calcd. for $C_{11}H_{12}ONBr$: C, 51.98; H, 4.75. Found: C, 52.23; H, 4.78.

2,3-Dihydro-8-methylfuro[2,3-b]indole (VIII) was obtained quantitatively from the bromoethyloxindole (VII); (a) by heating in benzene solution with tetrahydroisoquinoline, (b) by reaction with tetrahydroisoquinoline alone in the cold, and (c) by treating in alcoholic solution with sodium ethoxide. The reaction in each case was rapid and required only ten to fifteen minutes for completion. With tetrahydroisoquinoline, the hydrobromide of the base separated from the mixture. The dihydrofuroindole was dissolved in ether and the basic materials removed by washing with dilute acid. The residue after removal of the ether was either crystallized directly or distilled, b. p. 152–155° (12 mm.). It crystallized from petroleum ether as white prisms, m. p. 84°.

Anal. Calcd. for $C_{11}H_{11}ON$: C, 76.30; H, 6.36. Found: C, 76.42; H, 6.38.

Upon refluxing with ten times its weight of 48% hydrobromic acid for six hours the bromoethyloxindole (VII) was formed, m. p. 52–53°.

To obtain 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIb) 50.8 g. of the bromoethyloxindole (VII) (0.1 mole) and 26.6 g. of tetrahydroisoquinoline (0.2 mole) were mixed and heated gently on the steam-bath. The mixture solidified and was essentially a mixture of the dihydrofuroindole (VIII) and tetrahydroisoquinoline hydrobromide. This mixture was heated under nitrogen in a metal bath to 190° for three hours. The mixture was made alkaline and taken up in ether. A separation of basic from non-basic materials was made by washing with dilute acid. The basic fraction contained in the aqueous acidic washes was isolated in the usual manner and distilled. The low boiling fraction (5.0 g.) consisted of tetrahydroisoquinoline which was removed on the water pump. The main fraction was distilled in high vacuum. There was obtained 33.0 g. of yellow oil, b. p. 170–175° (0.005 mm.). It was dissolved in ether, concentrated, and allowed to crystallize. Two crops were obtained from ether; the ether was replaced with methanol and two further crops obtained. A total of 6.3 g. of solid was obtained, m. p. 146–150°, which proved to be a 50–50 mixture of the tetrahydroisoquinolylethyloxindole (IIb) and of a compound (IX), m. p. 182°.

The mixture was separated by fractional crystallization from ether and from methanol, and also mechanically. The compound (IX) is less soluble in methanol, but more soluble in ether than the tetrahydroisoquinolylethyloxindole (IIb) and crystallized in smaller prisms which when impure had a rose color. The tetrahydroisoquinolylethyloxindole (IIb) after crystallization from methanol melted at 166–167° and gave a picrate melting at 208° dec. The crude compound (IX) from the mixture melted at 172–178°. Treatment with norite in methanol removed all color and the compound crystallized as small colorless prisms, m. p. 182°.

Anal. Calcd. for $C_{20}H_{20}ON_2$: C, 78.92; H, 6.62; N, 9.19. Found: C, 78.71, 78.76; H, 6.76, 6.49; N, 9.19.

A picrate readily formed by admixing hot alcoholic solutions containing equimolecular quantities of the compound and picric acid; yellow prisms, m. p. 198° dec.

Anal. Calcd. for $C_{26}H_{23}O_8N_5$: C, 58.53; H, 4.34. Found: C, 58.42; H, 4.36.

Attempt to Dehydrogenate 1-Methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIb).—One gram of the tetrahydroisoquinolylethyloxindole (IIb), m. p. 167°, was intimately mixed with 0.3 g. of palladium black[19] and the mixture heated at 60–80 mm. pressure for one hour at 190–200°. No further liberation of gas took place after forty minutes. The products of the reaction were then directly distilled. The low boiling fraction consisted of isoquinoline (picrate, m. p. 220°) indicating that some cleavage had occurred. The main fraction, 0.6 g. reddish oil distilled at 180–185° bath temperature (0.02 mm.). From a concentrated ethereal solution of the oil, there was obtained 0.25 g. of a solid compound, m. p. 172–175°. Recrystallized from methanol, it melted at 182° and gave no depression when mix-melted with compound (IX) obtained above.

Anal. Calcd. for $C_{20}H_{20}ON_2$: C, 78.92; H, 6.62; N, 9.19. Found: C, 78.78; H, 6.68; N, 9.07.

Its picrate, prepared as described above, melted at 198° dec.

All attempts to dehydrogenate at temperatures below 175° gave the tetrahydroisoquinolylethyloxindole back unchanged. Upon heating the tetrahydroisoquinolylethyloxindole alone at 200° for one hour 70% of it was recovered. The remainder was an uncrystallizable oil, but none of the 182° compound was isolated. However, when 0.3 g. was heated under identical conditions for the dehydrogenation with tetrahydroisoquinoline hydrobromide, a reddish oil was obtained from which 0.08 g. of the 182° compound was isolated with no recovery of the original.

Attempts to Ring Close Compound (IX).—Compound IX was at first thought to be 1-methyl-3-(2-N-dihydroisoquinolylethyl)-oxindole (IIIb) and several attempts at ring closure were made. Heating the compound in phosphorous oxychloride did not effect ring closure. Trials in which phosphorus pentoxide was added to a refluxing solution of the compound in xylene gave the compound back unchanged. In other attempts the compound was treated first with phosphorus pentachloride and then with aluminum chloride in nitrobenzene solution.[20] When the reactions were carried out at room temperature the solid was recovered unchanged. Similarly, at the temperature of the steam-bath, the solid was again recovered. Under more drastic conditions (175°) some of the solid was recovered and the remainder was converted into tar and halogenated products. Since all attempted ring closures failed, we felt that the compound was not a 1,2-dihydroisoquinoline.

Reduction of 1-Methyl-2,3-dihydro-3-N-tetrahydroisoquinolylacetylindole (X).—To a hot solution of 6.0 g. of the dihydro-tetrahydroisoquinolylacetyl-oxindole in 260 cc. of absolute ethanol was added 25.0 g. of sodium in portions over a period of two hours. The alcoholic solution, after removing the greater portion of the alcohol *in vacuo*, was diluted with water and the products were extracted with ether. The ethereal solution was washed with 10% hydrochloric acid to remove the basic materials. The basic fraction proved to be XIII which was crystallized directly from petroleum ether, yielding 3.1 g. of white prisms, m. p. 80–81°. A sample upon distillation gave a colorless oil, b. p. 190–192°, bath temperature (0.001 mm.), which solidified on cooling. Recrystallized from petroleum ether it melted at 82°.

---

[18] *Cf.* Boyd-Barrett and Robinson, *J. Chem. Soc.*, 320 (1932).

[19] Willstätter and Waldschmidt, *Ber.*, **54**, 123 (1921); *cf.* Späth and Lederer, *ibid.*, **63**, 120, 2102 (1930).

[20] *Cf.* Von Braun, *ibid.*, **57**, 908 (1924).

Anal. Calcd. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.63. Found: C, 83.02; H, 7.88.

The picrate prepared by admixing equimolecular portions of the compound and picric acid in benzene solution, first precipitated as an oil but crystallized when moistened with methanol. Recrystallization from benzene gave fine yellow needles, m. p. 161°.

Anal. Calcd. for $C_{26}H_{25}O_7N_5$: C, 60.11; H, 4.85. Found: C, 60.47; H, 4.85.

Reduction of XIII with Zinc and Hydrochloric Acid.—A Clemmensen reduction was attempted on the ketone X without success. The Clemmensen procedure was employed on XIII on the assumption at that time that we were dealing with the hydroxy compound (XI). To a solution of 1.5 g. of XIII in 40 cc. of 50% acetic acid, 10 cc. of concentrated hydrochloric acid and 10 g. of freshly amalgamated 20-mesh zinc were added. The mixture was heated on the steam-bath for five hours with a further addition of 5 cc. of hydrochloric acid every hour. The acetic acid was removed *in vacuo* and the material taken up in ether after the addition of enough strong alkali to solubilize the zinc hydroxide. The ethereal solution was washed with water, then with 10% hydrochloric acid and the basic material obtained from the acidic washings. On distilling, 1.4 g. of 1-methyl-2,3-dihydro-3-(2-N-tetrahydroisoquinolylethyl)-indole (XIV) was obtained as a colorless oil, b. p. 190–195°, bath temperature (0.1 mm.).

Anal. Calcd. for $C_{20}H_{24}N_2$: C, 82.14; H, 8.27. Found: C, 82.17; H, 8.25.

When the dihydroindole was treated with one mole of picric acid in methanol, a dark red colored monopicrate was obtained, m. p. 155°.

Anal. Calcd. for $C_{26}H_{27}O_7N_5$: C, 59.88; H, 5.22. Found: C, 59.92; H, 5.20.

Upon treating the monopicrate in methanol with an additional mole of picric acid, a yellow dipicrate was obtained, m. p. 176°.

Anal. Calcd. for $C_{32}H_{30}O_{14}N_8$: C, 51.20; H, 4.03. Found: C, 51.30; H, 4.48.

This characteristic of such dihydroindoles to give red monopicrates and yellow dipicrates has been previously observed by Julian and Pikl.[21]

1-Methyl-3-(2-N-tetrahydroisoquinolylethyl)-indole (XIII). (a) Reduction of the Ethyloxindole (IIb).—The ethyloxindole (IIb) (2.0 g.) was dissolved in 50 cc. of absolute ethanol and over a period of two hours there was added 12.0 g. of sodium and 100 cc. of absolute ethanol in portions. The alcohol solution, after removal of part of the alcohol *in vacuo*, was diluted with water and the products extracted with ether. The ethereal solution was washed with dilute acid to remove the basic fraction which was isolated in the usual manner and was distilled. There was obtained 1.4 g. of pale yellow oil, b. p. 180–185° bath temperature which on exposure to air turned reddish, especially when warmed. A sample was redistilled for analysis, b. p. 180–182° (0.008 mm.).

Anal. Calcd. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.63. Found: C, 82.54; H, 8.10.

The picrate formed by heating equimolecular portions of the oil and picric acid in methanol was a red oil which on standing solidified, m. p. 155–157° dec. Recrystallization from methanol gave yellow needles, m. p. 161° dec.

Anal. Calcd. for $C_{26}H_{22}O_7N_5$: C, 60.11; H, 4.85. Found: C, 60.30; H, 4.64.

Struck by the similarity between this picrate and that of the sodium reduction product of X, we examined the two picrates and found them identical. On seeding the distillate, from which the picrate was formed, it crystallized and melted at 82°.

(b) Dehydrogenation of the Dihydroindole (XIV).—A mixture of 0.69 g. of the dihydroindole and 0.22 g. of palladium black was heated to 195–200° for forty minutes. The evolution of gas was quite vigorous during the first fifteen minutes. The mixture after heating was deeply colored. On distillation there was obtained 0.54 g. of yellow oil which becomes colored on standing, b. p. 175–180° bath temperature (0.006 mm.). A sample was redistilled for analysis, b. p. 175–177° at the same pressure.

Anal. Calcd. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.63. Found: C, 82.46; H, 7.28.

This oil likewise crystallized on seeding with the 82° melting solid (XIII) and the two proved to be identical.

The picrate formed by adding an equimolecular quantity of picric acid to a solution of the base in benzene was an oil which crystallized from benzene–methanol, m. p. 153–156° dec. When recrystallized from methanol it gave yellow needles, m. p. 161°. A mixed melting point with the picrate obtained above from the reduction of the ethyloxindole (IIb) gave no depression.

Anal. Calcd. for $C_{26}H_{25}O_7N_5$: C, 60.11; H, 4.85. Found: C, 59.91; H, 4.74.

Attempted Ring Closure of XIII by Dehydrogenation with Selenium.—1.0 g. of the solid, m. p. 82°, was intimately mixed with 0.7 g. of selenium and heated in a distillation tube. At 290–300° reaction ensued. Heating was continued for ten minutes. Working up and distillation in the usual manner gave 0.45 g. (the theoretical quantity) of isoquinoline, identified by its picrate, m. p. 222°.

Attempted Ring Closure of IIb by Dehydrogenation with Selenium.—In exactly the same manner as above 1.0 g. of IIb gave almost quantitatively isoquinoline.

Summary

1. For attempted synthesis of the basic ring structure of yohimbine, 1-methyl-3-(2-N-tetrahydroisoquinolylacetyl)-oxindole and its unmethylated analog have been prepared.

2. On catalytic reduction 1-methyl-3-(2-N-tetrahydroisoquinolylacetyl)-oxindole yields two products, 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole and 1-methyl-2,3-dihydro-3-(2-N-tetrahydroisoquinolylacetyl)-indole. The constitution of each product has been proved.

3. The conversion of a 1,2-dihydro-3-acyl-indole into the corresponding 3-alkyl indole by reduction with sodium and alcohol (followed by loss of water and rearrangement) is recorded.

4. Attempts to prepare the basic ring structure of yohimbine by ring closure on the dehydrogenation product of 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole failed. The dehydrogenation product is therefore probably not the desired 1,2-dihydroisoquinoline.

5. The dehydrogenation of yohimbine and related compounds seems to result primarily in cleavage at the nitrogen atom of the tetrahydroisoquinoline nucleus.

CHICAGO, ILLINOIS RECEIVED[22] JULY 21, 1947

---

(21) Julian and Pikl, THIS JOURNAL, **57**, 539, 563 (1935).

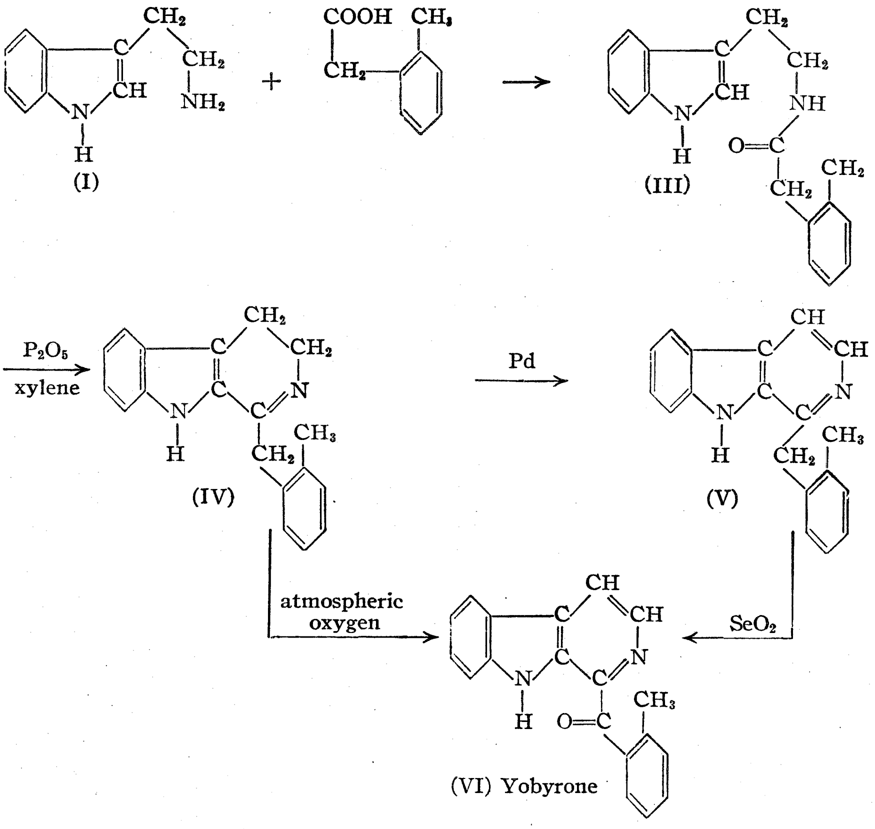
(22) Original manuscript received September 9, 1946.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Studies in the Indole Series. X. Yohimbine (Part 2). The Synthesis of Yobyrine, Yobyrone and "Tetrahydroyobyrine"

BY PERCY L. JULIAN, WILLIAM J. KARPEL, ARTHUR MAGNANI AND EDWIN W. MEYER

In a previous communication[1] we have adduced new evidence and discussed investigations of others to show that on dehydrogenation of the alkaloid yohimbine with selenium, cleavage of the molecule takes place at the nitrogen atom of the tetrahydroisoquinoline nucleus. The reaction was first discovered by Mendlik and Wibaut[2] who gave the names yobyrine and tetrahydroyobyrine to the two principal products arising from this degradation, in the mistaken notion that both of them possessed the same fundamental ring skeleton. Recently Witkop[3] has given convincing evidence to indicate that yobyrine is 3-*o*-xylyl-4-carboline (V). Several years ago Scholz,[4] in a beautiful piece of work, proposed for "tetrahydroyobyrine" the structure XIII. Thus the name is a misnomer and "tetrahydroyobyrine" is actually 2-[3-(5,6,7,8-tetrahydroisoquinolyl)]-3-ethylindole.



In the present communication we are reporting the successful synthesis of both yobyrine and "tetrahydroyobyrine."[5] Our synthesis of yobyrine is, generally speaking, an application of the procedure worked out by Späth and Lederer[6] for the Harmala alkaloids. *o*-Tolylacetic acid (II) was prepared in 65% yield from *o*-xylene *via o*-xylyl bromide secured by the method of Atkinson and Thorpe.[7] This acid was condensed with tryptamine (I)[8] and the amide thus formed subjected to ring closure with phosphorus pentoxide in boiling xylene to produce dihydroyobyrine (IV). Dehydrogenation of IV with palladium black gave yobyrine (V).[9]

A novel synthesis of yobyrone (VI) was discovered in the atmospheric oxidation of dihydroyobyrine (IV). This compound had previously been prepared by the oxidation of yobyrine with chromic acid[4] and with selenium dioxide.[3,9] Comparison of our synthetic yobyrine and yobyrone with the products of natural origin showed their identity in all respects.

For final proof of structure and synthesis of "tetrahydroyobyrine" (XIII), the other principal degradation product of yohimbine with selenium, we needed 3-*n*-butyrylisoquinolines. 3-Acylisoquinolines have hitherto been unknown and a procedure had to be devised for their preparation.

---

[1] Julian, Magnani, Pikl and Karpel, THIS JOURNAL, **70**, 174 (1948).

[2] (a) Mendlik and Wibaut, *Rec. trav. chim.*, **48**, 191 (1929); (b) **50**, 91 (1931); (c) Wibaut and Van Gastel, *ibid.*, **54**, 85 (1935).

[3] Witkop, *Ann.*, **554**, 83 (1943).

[4] Scholz, *Helv. Chim. Acta*, **18**, 923 (1935).

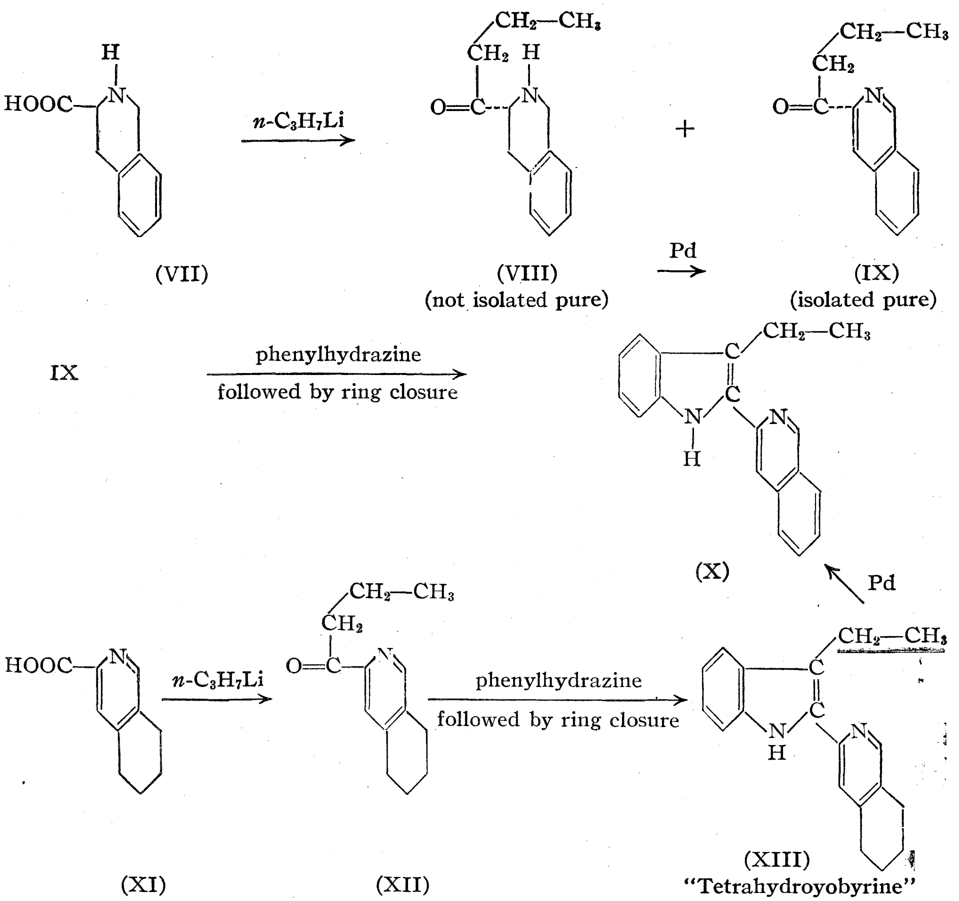
[5] We have employed the name tetrahydroyobyrine in quotation marks throughout the manuscript rather than the proper chemical name. This is done purely for clarity because the name "tetrahydroyobyrine" is so strongly embedded in the literature that confusion might result if we discarded it, even though it is a misnomer.

[6] Späth and Lederer, *Ber.*, **63**, 120, 2102 (1930).

[7] Atkinson and Thorpe, *J. Chem. Soc.*, 1695 (1907).

[8] Hoshino and Majima, *Ber.*, **58**, 2042 (1925).

[9] After the submission of our original manuscript, the English Journal in which there appeared an almost identical synthesis of yobyrine by Clemo and Swan, *J. Chem. Soc.*, 617 (1946), was received by our library. This part of our original manuscript has, therefore, been abbreviated to include only a skeleton description of the synthesis of yobyrine and such new data in connection therewith as Clemo and Swan did not report.



A modification of the procedure of Pictet and Spengler[10] for the preparation of 3-carboxy-1,2,3,-4-tetrahydroisoquinoline (VII) from β-phenylalanine, gave the acid in 61% yield. On treating this acid with n-propyllithium,[11] a mixture of 3-butyryl-1,2,3,4-tetrahydroisoquinoline (VIII) and its dehydrogenation product, 3-butyrylisoquinoline (IX), was obtained. The ketone (VIII) resisted isolation in pure form but IX could be obtained in pure crystalline form and characterized. The mixture on dehydrogenation with palladium black gave pure IX. When the Fischer indole synthesis with phenylhydrazine was applied to either IX or the mixture of VIII and IX, 2-(3-isoquinolyl)-3-ethylindole (X) was obtained, identical with the product secured from "tetrahydroyobyrine" by dehydrogenation with palladium black.[3] Thus the constitution of "tetrahydroyobyrine" is firmly established by this complete synthesis of its dehydrogenation product.

To complete the synthesis of "tetrahydroyobyrine" itself, 3-carboxy-5,6,7,8-tetrahydroisoquinoline (XI) was prepared by the method of Scholz.[4] Treatment with propyllithium gave the desired ketone, namely, 3-butyryl-5,6,7,8-tetrahydroisoquinoline (XII), an oil which was readily purified and characterized by means of its crystalline picrate. This ketone underwent the Fischer indole reaction, giving "tetrahydroyobyrine" (XIII) identical in all respects with the product of natural origin. Taken together these syntheses of 2-(3-isoquinolyl)-3-ethylindole (X) and 2-[3-(5,6,7,8-tetrahydroisoquinolyl)]-3-ethylindole ("tetrahydroyobyrine") (XIII) represent virtually a complete synthesis of "tetrahydroyobyrine" and demonstrate conclusively the constitution of this product.

Experimental

Tryptamine (VI).—The method of Hoshino and Majima[8] was found to be the simplest route to this substance. For good yields of the amine, it was found desirable to employ ethyl iodide instead of the bromide for the Grignard complex.

***o*-Tolylacetic Acid (VII).**—*o*-Xylene was brominated by the method of Atkinson and Thorpe[7] to obtain *o*-xylyl bromide. The bromide was converted into the nitrile by treating it with potassium cyanide in the manner described in "Organic Synthesis" for the preparation of benzyl cyanide.[12] The nitrile was hydrolyzed to the acid by refluxing for five hours with 55% sulfuric acid. Upon cooling, the crystalline acid was filtered, washed with cold water and dried. It was recrystallized from aqueous methanol, m. p. 87–88°. The yield based on *o*-xylene was 65% and this procedure, therefore, constituted a very convenient route to the acid.

***o*-Tolylacetyltryptamine (VIII).**—At room temperature, mixing tryptamine with *o*-tolylacetic acid produces the

---

[10] Pictet and Spengler, *Ber.*, **44**, 2034 (1911).

[11] Gilman and Van Ess, THIS JOURNAL, **55**, 1258 (1933); Gilman, Langham and Moore, *ibid.*, **62**, 2327 (1940).

[12] "Organic Syntheses," Coll. Vol. I, 107 (1941).

acetate salt of the amine, m. p. 170°. To prepare the amide 4.5 g. of tryptamine and 5.0 g. of the acid were heated at 195–200° for forty minutes. During the first twenty minutes there was vigorous liberation of water from the melt. After cooling, the brown residue was dissolved in ether and washed with 2% bicarbonate solution and 2% hydrochloric acid to remove unchanged acid and amine. The amide was obtained from the concentrated ethereal solution by the addition of petroleum ether (b. p. 35–60°). There was obtained 6.75 g., m. p. 96–97°. Recrystallized from ether–petroleum ether it melted at 97°.

Anal. Calcd. for $C_{19}H_{20}ON_2$: C, 78.05; H, 6.90. Found: C, 78.12; H, 7.04.

Ring Closure of *o*-Tolylacetyltryptamine (VIII) to Dihydroyobyrine (IX).—To a refluxing solution of dry xylene containing 0.58 g. of the amide there was added portionwise under an atmosphere of nitrogen 5.0 g. of phosphorus pentoxide over a forty-minute period. Heating was continued for an additional fifteen minutes. The mixture was cooled in an ice-bath and 30 ml. of 5% hydrochloric acid was added slowly with agitation. Enough methanol was added to dissolve the red gummy product upon vigorous agitation. The neutral products were removed from the acidic solution by ether extraction. The dihydroyobyrine (IX) was obtained from the acidic solution by basifying and extracting with ether. Crystallization from ether–petroleum ether (b. p. 35–60°) gave 0.35 g., m. p. 175–177°. Upon recrystallization from ether–petroleum ether it was obtained as clusters of fine white needles, m. p. 178–179°.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61. Found: C, 83.27; H, 6.65.

The mother liquor of crystallization on standing turned red and upon slow evaporation of the solvent, yellow crystals separated from the solution. They were digested with cold methanol and filtered, m. p. 172–175°. A mixed melting point with the dihydroyobyrine (IX) gave a depression. The compound distilled at 195–200° bath temperature (0.009 mm.) as a yellow oil which solidified on cooling. Crystallization from methanol gave yellow plates, m. p. 185°, which when admixed with known yobyrone gave no depression in melting point. It was found advisable, therefore, when recrystallizing the dihydroyobyrine to filter the product promptly to avoid contamination with yobyrone.

Yobyrine (IV) by Dehydrogenation of Dihydroyobyrine (IX).—An intimate mixture of 0.5 g. of dihydroyobyrine and 0.5 g. of palladium black was heated to 185–190° in a metal-bath at 20–25 mm. pressure for a half hour. Upon direct distillation, the product had a tendency to sublime. There was obtained 0.4 g. of colorless oil distilling at 200–205° bath temperature (0.001 mm.) which quickly crystallized on cooling, m. p. 209–211°. Crystallization from benzene gave 0.35 g. of needles, m. p. 211–212°. A sample crystallized from aqueous methanol also gave needles, m. p. 213°.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92. Found: C, 83.90; H, 5.90.

It was identical in every respect with the yobyrine obtained from the dehydrogenation of yohimbine with selenium by the method of Mendlik and Wibaut.[2] The yobyrine from natural sources melted at 213° and a mixed melting point with the synthetic yobyrine showed no depression.

Samples of the synthetic and natural yobyrine were each oxidized with selenium dioxide in boiling xylene[2] to yield yobyrone. In each instance, the yobyrone distilled at 190–195° bath temperature (0.008 mm.) and gave yellow plates on crystallizing from methanol, m. p. 185°. A mixed melting point of the two samples gave no depression.

The absorption spectrum of the synthetic material showed maxima at 237, 289, 327, 337 and 348mμ and minima at 269 and 299mμ, the same values as displayed by material of natural origin.[9]

3-Carboxy-5,6,7,8-tetrahydroisoquinoline.—This acid was prepared by the ozonization of tetrahydroyobyrine[2] essentially according to the method of Scholz.[4] However, it has been found that unless precautions are taken to ensure the decomposition of the ozonide, considerable difficulty is experienced in working up the reaction mixture. This is best accomplished by allowing the ozonized reaction mixture, after the addition of water, to stand for three–four hours at room temperature before proceeding. In this fashion 2.55 g. (72%) of the intermediate amide, m. p. 150–151°, was obtained from 3.2 g. of tetrahydroyobyrine. The amide was then hydrolyzed as described by Scholz[4] but for a period of eight hours. The product, 3-carboxy-5,6,7,8-tetrahydroisoquinoline, m. p. 203–206° dec., was obtained in a 95% yield.

3-*n*-Butyryl-5,6,7,8-tetrahydroisoquinoline.—A solution of *n*-propyllithium in 90 ml. of anhydrous ether was prepared under nitrogen from 1.0 g. of lithium metal and 10.5 g. of *n*-propyl bromide. Titration of an aliquot of the ethereal solution indicated the presence of 2.6 g. of *n*-propyllithium. After dilution to 125 ml. with anhydrous ether, 1.5 g. of 3-carboxy-5,6,7,8-tetrahydroisoquinoline was added to the ether solution. The mixture was stirred for eighteen hours, then decomposed with ice and extracted with ether. The ether extract was washed with water and the basic material separated with 3% hydrochloric acid. The acidic solution was made alkaline with 5% sodium hydroxide solution and extracted with ether. After washing the ethereal solution with water and drying, the solution was concentrated. There remained 1.5 g. of a light brown oil. Upon distillation at 6×10^{-3} mm., there was obtained 0.85 g. of a pale yellow oil which came over at 130–135° bath temperature. This material was not analytically pure but was employed for further experimentation. For purification for analysis the ketone was converted into the picrate which was recrystallized twice from methanol. The picrate was then decomposed and the base distilled.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.73; H, 8.54; N, 6.71.

The picrate of this ketone, lemon yellow crystals, melted at 128° after recrystallization from methanol.

Anal. Calcd. for $C_{19}H_{20}N_4O_8$: C, 52.78; H, 4.66 Found: C, 52.90; H, 4.96.

"*Tetrahydroyobyrine.*"—A mixture of 691 mg. of crude 3-*n*-butyryl-5,6,7,8-tetrahydroisoquinoline and 414 mg. of phenylhydrazine was heated *in vacuo* on the steam-bath for one-half hour (water loss, 59 mg.). The mass was taken up in 25 ml. of anhydrous ethanol and while chilled in an ice-bath, saturated with dry hydrogen chloride. After standing at room temperature for one hour, the mixture was refluxed for one and one-half hours. The solution was then chilled in an ice-bath and the solid hydrochloride separated by filtration. This material, 0.2 g., is being further investigated. The filtrate was concentrated under partial vacuum with gentle warming to remove the ethanol. The residue was covered with ether and shaken with 5% sodium hydroxide solution. The ether extract was washed with water, dried and concentrated. There remained 0.9 g. of a brown gum which was crystallized from 3 ml. of methanol. This gave 180 mg. of pale yellow crystals which melted at 158–162°. A second crop of 100 mg., m. p. 154–157°, was isolated from the mother liquor. The total yield amounted to 30%. The "tetrahydroyobyrine" after purification by sublimation at 4×10^{-2} mm. and crystallization from methanol melted at 164.5°. It showed no depression in melting point when mixed with an authentic sample of "tetrahydroyobyrine."

3-Carboxy-1,2,3,4-tetrahydroisoquinoline.—This acid was previously prepared by Pictet and Spengler.[10] However, the following procedure is much simpler and has given consistently better results. A mixture of 75 g. of β-phenylalanine, 170 ml. of formalin (36%, neutral) and 575 ml. of concentrated hydrochloric acid was heated on a steam-bath for one-half hour with occasional swirling. After the addition of another 75 ml. of formalin and 150 ml. of concentrated hydrochloric acid, the mixture was heated for three hours. It was chilled and the solid separated by filtration. The filter cake was dissolved in 1000 ml. of hot water and 2000 ml. of hot ethanol was added. While still hot, the solution was neutralized to congo red with 10% ammonium hydroxide solution. After cooling, the crystalline mass was filtered, washed with ethanol and dried. The acid, 49.5 g. (61%), melted at 326°, dec. One recrystallization from aqueous ethanol gave glistening plates which melted at 335°, dec.[13]

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26. Found: C, 67.51; H, 6.15.

3-*n*-Butyrylisoquinoline.—A solution of *n*-propyllithium in 190 ml. of anhydrous ether was prepared from 3.3 g. of lithium and 30.0 g. of *n*-propyl bromide. An aliquot of the ethereal solution when titrated with standard acid indicated that the total solution contained 8.0 g. of *n*-propyllithium. Six grams of 3-carboxy-1,2,3,4-tetrahydroisoquinoline was added to the alkyllithium solution. This mixture was stirred for fifteen hours, decomposed with ice and extracted with ether. The water-washed, dried ethereal solution was concentrated to 5.5 g. of a red-brown, viscous oil. This oil was distilled at 7×10^{-3} mm. and the fraction, 2.9 g., distilling at 126° was collected. Higher boiling materials were present. The 2.9 g. of pale yellow sirup was redistilled at 5×10^{-3} mm. The fraction distilling at 115° amounted to 2.6 g. Efforts to obtain a pure compound from this material either through fractional distillation or fractional crystallization of the picrate were unsuccessful. From analytical data this material appeared to be, essentially, a mixture of 3-*n*-butyryl-1,2,3,4-tetrahydroisoquinoline and 3-*n*-butyrylisoquinoline. This was further substantiated by dehydrogenation. A 100-mg. sample of the mixture was heated with 100 mg. of palladium black at 160–170° (20 mm.) for fifteen minutes. The product was then distilled from the reaction mixture at 140° (0.5 mm.); yield practically quantitative of crystalline material, m. p. 62–65°. One recrystallization from petroleum ether (b. p. 35–60°) gave cream-colored needles of 3-*n*-butyrylisoquinoline melting at 72–73°.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.02. Found: C, 78.21; H, 6.66; N, 6.81.

The picrate of this ketone, fine yellow prisms, melted at 161–163° (sintering at 151°) after several recrystallizations from methanol.

Anal. Calcd. for $C_{19}H_{16}N_4O_8$: C, 53.28; H, 3.77. Found: C, 53.43; H, 4.02.

2-(3-Isoquinolyl)-3-ethylindole.—A 2.7-g. sample of the mixture of 3-*n*-butyrylisoquinoline and 3-*n*-butyryl-1,2,3,4-tetrahydroisoquinoline was treated with 1.56 g. of phenylhydrazine at steam-bath temperature for thirty minutes. The liberated water was then removed *in vacuo* (water loss, 180 mg.). The residual material was taken up in 85 ml. of anhydrous ethanol and while chilled in an ice-bath saturated with dry hydrogen chloride. The mixture was allowed to stand at room temperature for thirty minutes and then refluxed for one and one-half hours. The crystalline material which formed on chilling was separated and the filtrate was concentrated *in vacuo* to the point of crystallization. After cautious dilution with ether, the hydrochloride was filtered and washed with ether–ethanol. This material weighed 0.7 g. and melted at 220–225°. Recrystallization of a small sample from ethanol raised the melting point to 233–235°. The bulk of the material was hydrolyzed with 5% sodium hydroxide solution and extracted with ether. The ether solution was washed with water, dried and concentrated. The residue was crystallized from ethanol. A total of 0.3 g. of tan crystals, m. p. 126–129°, was obtained in two crops. Purification by sublimation (8×10^{-3} mm.) and recrystallization from aqueous methanol gave fine needles melting at 132°. This gave no depression with an authentic sample of 2-(3-isoquinolyl)-3-ethylindole prepared from tetrahydroyobyrine by palladium dehydrogenation.[3] Furthermore, the absorption spectrum is practically identical with that described by Witkop and Pruckner[14] for the isoquinolyl-indole.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.93. Found: C, 83.44; H, 5.41.

The picrate of 2-(3-isoquinolyl)-3-ethylindole melted at 208° dec., after crystallization from methanol.

Anal. Calcd. for $C_{25}H_{19}N_5O_7$: C, 59.88; H, 3.82. Found: C, 59.71; H, 3.82.

Some effort was made to isolate from the residual material the indole corresponding to the 3-(1,2,3,4-tetrahydroisoquinolyl) ketone. However, to date, resolution of this material has been unsuccessful. This phase is under further investigation.

Summary

1. Yobyrine, a degradation product of the alkaloid yohimbine, has been synthesized by condensation of tryptamine with *o*-tolylacetic acid, followed by ring closure and dehydrogenation. Its structure is therefore completely elucidated and yobyrine is shown to be 3-*o*-xylyl-4-carboline.

2. The preparation of yobyrone by air oxidation of dihydroyobyrine is reported.

3. The first synthesis of so-called "tetrahydroyobyrine" is herewith recorded and confirms its structure as 2-[3-(5,6,7,8-tetrahydroisoquinolyl)]-3-ethylindole.

CHICAGO, ILLINOIS

RECEIVED[15] JULY 21, 1947

---

[13] Pictet and Spengler[5] reported a melting point of 311° for this acid.

[14] Witkop and Pruckner, *Ann.*, **554**, 127 (1943).

[15] Original manuscript received September 9, 1946.

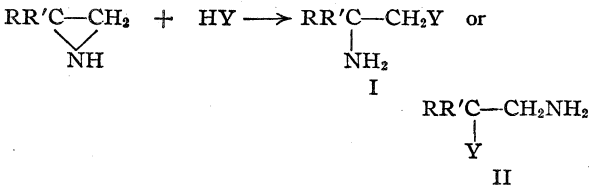
[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORY, BROWN UNIVERSITY]

Reactions of Ethylenimines: With Ammonia and Amines

BY LEALLYN B. CLAPP

Ammonia and amines[1] in aqueous solution react with imines to give α,β-diamines and polymeric substances. The reaction between ethylenimine and various amines to give N-substituted ethylenediamines has also been carried out under anhydrous conditions in the presence of aluminum chloride[2] as a catalyst. Coleman and Callen used aqueous reactions in working up the reaction mixtures, however, which introduces some obvious disadvantages. The present paper deals with the reactions of homologs of ethylenimine with amines and liquid ammonia in the presence of ammonium chloride as a catalyst at elevated temperature and pressure. The α,β-diamines, ethylenediamine, isobutylenediamine and 1,2-butylenediamine, which are very difficult to isolate completely free from water when prepared by wet methods, can be obtained in anhydrous condition by the present method. The yields are 55–68%.

When the three-membered ring in an unsymmetrically substituted ethylenimine breaks in the presence of a substance, HY, containing an active hydrogen, products of type I and II are possible.



$$RR'C(-CH_2)NH + HY \longrightarrow RR'C(NH_2)-CH_2Y \text{ (I) or } RR'C(Y)-CH_2NH_2 \text{ (II)}$$

A few such reactions are recorded in the literature. Hydrolysis of unsymmetrical C-substituted imines in acid solution gives products indicating a break in the ring at the tertiary carbon[3] rather than at the primary (or secondary[4]) carbon. In reactions other than hydrolysis (catalytic hydrogenation[5] and addition of hydrogen bromide[6]), the cyclic imine ring breaks at the primary carbon. It was found that when HY is a primary or secondary amine, the rupture is predominantly at the primary carbon, yielding product I, although some of type II was obtained in three cases (Table II).

Competition in the addition of HY to the imine is furnished by molecules of the imine itself, the result of which is a polymer. Polymerization becomes important when the reaction between an imine and liquid ammonia is allowed to proceed at room temperature (Table I). It was reduced to a minimum by more rapid reactions at elevated temperature and pressure.

Polymerization may terminate at the dimeric stage to form a piperazine. The work of Jones[7] on the mechanism of polymerization suggests a symmetrical piperazine.

Proof that the principal product in the reactions of imines and amines is of type I where Y is –NHR or –NRR′ was obtained in the following way. When morpholine was treated with 2-ethylethylenimine, the only product isolated was shown to be N-β-aminobutylmorpholine by synthesizing it by a series of known reactions. Formaldehyde and morpholine were condensed to methylolmorpholine, which then condensed with 1-nitropropane by the method of Cerf de Mauny[8] to give N-β-nitrobutylmorpholine. This substance was reduced to the corresponding diamine. The N-β-aminobutylmorpholine prepared by the two methods gave the same phenylthiourea.

When 2,2-dimethylethylenimine was treated with 2-amino-2-methyl-1-propanol, the product was N-2-(β-aminoisobutylamino)-2-methyl-1-propanol. This was synthesized by the method of Senkus[9] and the phenylthiourea derivative in each case was the same compound.

In the reaction between aniline and 2,2-dimethylethylenimine, two products resulted, b. p. 110–111° (3 mm.) and 145–146° (3 mm.), respectively. The lower boiling compound is 2-amino-2-methyl-1-phenylaminopropane and the second compound is assumed to be 1-amino-2-methyl-2-phenylaminopropane. Johnson[10] has reported the first compound, b. p. 110° (3 mm.), 99° (1 mm.). Two products were also obtained in the reaction with 2-ethylethylenimine and aniline (also cyclohexylamine) and are assumed to bear a like relation to each other.

These last three cases indicate that the product of type (I) is only the predominant one and not the exclusive product in the reaction of an amine and an imine.

Only traces of products were found in the reactions between 2,2-dimethylethylenimine and diethylamine, di-*n*-butylamine and *n*-dodecylamine. Probably there is not enough room for the secondary amino nitrogen of diethylamine and di-*n*-butylamine to approach the primary carbon of the imine (where the bond is to be ruptured) and hence no reaction takes place at all. Added import is given to this view from the fact that the expected products are readily synthesized from a condensation of the secondary amine, formaldehyde, and

---

[1] Wilson, U. S. Patent 2,318,729 (1943), U. S. Patent 2,318,730 (1943).

[2] Coleman and Callen, This Journal, **68**, 2006 (1946).

[3] Cairns, *ibid.*, 63,871 (1941).

[4] Campbell, Campbell, McKenna and Chaput, *J. Org. Chem.*, **8**, 103 (1943).

[5] Karabinos and Serijan, This Journal, **67**, 1856 (1945); Campbell, Sommers and Campbell, *ibid.*, **68**, 140 (1946).

[6] Gabriel and Ohle, *Ber.*, **50**, 804 (1917).

[7] Jones, *J. Org. Chem.*, **9**, 484 (1944).

[8] Cerf de Mauny, *Bull. soc. chim.*, [5] **4**, 1460 (1937).

[9] Senkus, This Journal, **68**, 10 (1946).

[10] Johnson, *ibid.*, **68**, 14 (1946).

2-nitropropane to a nitroamine, followed by a catalytic reduction.[11] Johnson[10] suggests that the nitroamine is formed, first, by a condensation of the amine and formaldehyde to a methylolamine succeeded by a second condensation to form the nitroamine. These reactions are not subject to the steric effects pictured for the rupture of the imine ring.

When the imines were heated with amines without ammonium chloride present, essentially all the original imine was recovered. The imines alone in the presence of ammonium chloride at 100° for one week gave polymers having properties described by Jones.[7]

Experimental

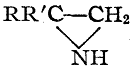
1,2-Butylenediamine.—Thirty-five grams of 2-ethylethylenimine[12] with 5.3 g. of ammonium chloride and 500 cc. of liquid ammonia were heated in an iron bomb (capacity, 3 liters) by an air-bath to 100 ± 2° for fifty-one hours (maximum gage pressure, 800 lb., in about five hours). After the excess ammonia was allowed to boil away (carrying about 5 g. unreacted imine along), the reaction mixture was distilled rapidly from the dissolved ammonium chloride. The distillate was then fractionally distilled through an insulated bubble-cap column (4 bubble caps). One gram of unreacted imine, 19 g. of pure 1,2-butylenediamine, b. p. 140° (55% yield), 1 g. of an oil, b. p. 160–240°, and 2 g. of residue, were obtained.

It is concluded from results of other reactions carried out in similar manner (Table I) that the best yields of α,β-diamines obtain under the following conditions: temperature 100°, a forty-fold excess of liquid ammonia, about 0.2 mole of catalyst per mole of imine, and more than twelve hours heating time.

The head of the iron reactor was sealed with a lead washer and was also equipped with a thin iron blow-out patch obtained from the American Instrument Company. The system was similar in construction to the type which may be purchased from that company.

TABLE I

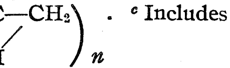
REACTIONS OF RR'C—CH₂ WITH LIQUID AMMONIA[a]



$RR'C\text{—}CH_2$ with NH bridging (ethylenimine ring)

R	R'	Wt. of imine, g.	NH₄Cl, g.	Time, hrs.	Temp., °C.	Max. pressure, lb.	Recovered imine, %	Diamine, %	Polym.,[b] %
H	H	35	8	40	100	740		55	24[c]
H	H	40	2	100	25	150		15	38[d]
Et	H	37	0.2	54	70	380	65	11	9
Et	H	28	5.3	50	70	430	40	14	45
Et	H	35	1	46	100	760	74	11	12
Et	H	35	5.3	51	100	800	4	55	10
Et	H	35	5.3	12	100	780	3	48	10
Et	H	36	8	72	25	150	8		87
Me	Me	35	1	100	25	135	3	7	74
Me	Me	35	8	46	100	800		68	16
Me	Me	40	8	46	100	640		58	27

[a] Five hundred cc of liquid ammonia was used in all reactions except the last where 250 cc. was used. [b] Percentage based on formula



$\left(RR'C\text{—}CH_2 \atop NH\right)_n$. [c] Includes 19% diethylenetriamine. [d] Includes 20% piperazine.

The higher polymeric products obtained as designated in Table I from the reaction of ammonia with 2-ethylethylenimine were subjected to fractional distillation. Sixty-two grams of material, b. p. 150–255°, from the rapid distillation of the reaction mixture of ammonia and 2-ethylethylenimine was redistilled and various fractions collected. By a Kjeldahl nitrogen analysis, an estimate of the amount of nitrogen liberated with nitrous acid treatment, and/or the appearance of an insoluble nitroso compound, the probable content of these polymeric products was deduced: fraction b. p. 150–195°, mostly 1,2-butylenediamine; b. p. 195–235°, polymer and 2,5-diethylpiperazine; above 235°, polymer and a diethylenetriamine derivative.

A Diethylpiperazine.—From the fraction b. p. 195–235° just mentioned, 2 g. of a solid separated on standing at zero for several days. Three recrystallizations from acetone gave 0.5 g. of white crystalline plates, m. p. 87–89°, resembling piperazine in odor and crystalline character. It formed a white hydrochloride and an insoluble oily nitroso compound. This compound is probably 2,5-diethylpiperazine.

Anal. Calcd. for $C_8H_{18}N_2$: N, 19.70. Found: N, 19.56, 19.59.

Two-tenths gram of the piperazine was converted to the dibenzamide derivative, m. p. 167–168°.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: N, 7.99. Found: N, 8.13.

β-Nitrobutylmorpholine.—Using the method of Cerf de Mauny,[8] a condensation of methylolmorpholine and 1-nitropropane gave a 75% yield of β-nitrobutylmorpholine, b. p. 130–135° (10 mm.).

β-Aminobutylmorpholine. Method A.—The β-nitrobutylmorpholine was reduced to the corresponding diamine (following Cerf de Mauny[8] again) in alcohol using zinc amalgam[12a] and hydrogen chloride gas with a yield of 58%; b. p. 218–223°.

Method B.—Eight grams (0.11 mole) of 2-ethylethylenimine was sealed with 11 g. (0.15 mole) of morpholine and 0.1 g. of ammonium chloride in a glass tube and heated to 80° for twenty-four hours. The reaction mixture was distilled once rapidly from the solid ammonium chloride and then fractionally distilled through an insulated bubble-cap column (4 bubble-caps). The β-aminobutylmorpholine was collected, b. p. 220–222°; yield 8 g., 50%. With the same quantity of imine, a three-fold and a ten-fold excess of morpholine gave yields of 85 and 95%, respectively.

Phenylthiourea derivatives were made from portions of the products obtained by Methods A and B, which gave m. p.'s 138–139 and 140–141°, respectively. The mixed melting point gave no depression.

N-2-(β-Aminoisobutylamino)-2-methyl-1-propanol. Method A.—In the manner just described (Method B above) 9 g. of pure N-2-(β-aminoisobutylamino)-2-methyl-1-propanol was obtained, b. p. 233° (yield 20%)[13] from 25 g. (0.28 mole) of 2,2-dimethylethylenimine and 79 g. (0.9 mole) of 2-amino-2-methyl-1-propanol. After standing, the oil changed to a solid, m. p. 51–53°.

Method B.—N-2-(β-nitroisobutylamino)-2-methyl-1-propanol was prepared by the method described by Senkus.[9] Reduction of this compound at three atmospheres pressure of hydrogen with platinum oxide (Adams catalyst) gave 61% yield of N-2-(β-aminoisobutylamino)-2-methyl-1-propanol, b. p. 231–233°.

Phenylthiourea derivatives of the products from methods A and B gave m. p. 133–134° and 132–134°, respectively, and a mixed melting point gave no depression.

The results of other reactions between 25 g. of each of the two imines and a three-fold excess of various amines are shown in Table II, along with a number of derivatives and the analyses. The derivatives were all prepared by standard methods; the nitrogen analyses were run by the semi-

---

[11] Johnson, *ibid.*, **68**, 12 (1946).

[12] Imines were prepared by the method of Wenker, *ibid.*, **57**, 2328 (1935); see also refs. 3 and 7.

[12a] Adams, "Organic Reactions," Vol. I, p. 163.

[13] Mr. C. E. Schilling in this Laboratory increased the yield to 40% by carrying out the reaction at 108° for fifty hours.

TABLE II

α,β-DIAMINES ($RR'CNH_2$—$CH_2NR''R'''$) AND THEIR DERIVATIVES

R''	R'''	Temp., °C.	Time, hrs.	Yield, %	B. p., °C.	$n^{20}D$	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Phenylthiourea M. p., °C.	Phenylthiourea Nitrogen, % Calcd.	Phenylthiourea Nitrogen, % Found	Benzamide M. p., °C.	Benzamide Nitrogen, % Calcd.	Benzamide Nitrogen, % Found
$R = CH_3$ $R' = CH_3$															
H	C_2H_5	80	41	42	140–141	1.4300	$C_6N_{16}N_2$	24.12	23.85				106–108[c]	8.35	8.15
H	n-C_4H_9	100	49	84	183–185	1.4345	$C_8H_{20}N_2$	19.43	19.19	104–105	15.04	15.01	105–106[b]	7.95	8.03
H	C_6H_{11}	100	50	82	230–230.5	1.4672	$C_{10}H_{22}N_2$	16.46	16.32	116–117	13.76	13.74	176–177[b]	7.40	7.42
C_4H_8O	(morpholine)	80	25	85	208–210	1.4677	$C_8H_{18}N_2O$	17.71	17.60	153–153.5	14.32	14.24	119–121	10.68	10.53
H	$C(CH_3)_2CH_2OH$	80	25	20	233.5[d]		$C_8H_{20}N_2O$	17.49	17.34	133–134[e]	14.23	14.21			
H[f]	C_6H_5	100	50	40	110–111[g]	1.5450	$C_{10}H_{16}N_2$	17.06	16.85	132.5–133	14.03	13.81	145.5–147[b]	7.52	7.30
[h]	[i]			23	145–146[g]	1.5270	$C_{10}H_{16}N_2$	17.06	17.16				193–194	10.44	10.35
$R = H$ $R' = C_2H_5$															
H	H	100	51	55	140	1.4490	$C_4H_{12}N_2$	31.80	31.72	174[a]	15.63	15.50	186–187[b]	9.45	9.38
H	C_2H_5	80	25	20	156–157	1.4431	$C_6H_{16}N_2$	24.12	23.92	110–111	16.72	16.65	115–116[b]	8.64	8.71
H	n-C_4H_9	100	48	68	199–200	1.4422	$C_8H_{20}N_2$	19.43	19.17	105–106.5	15.04	14.80			
n-C_4H_9	n-C_4H_9	100	48	20	238–239	1.4463	$C_{12}H_{28}N_2$	13.99	13.82	54–55	12.53	12.42			
C_2H_5	C_2H_5	100	100	54	173	1.4347	$C_8H_{20}N_2$	19.43	19.20	73–74	15.04	15.02			
H	C_6H_{11}	100	50	55	242–244	1.4711	$C_{10}H_{22}N_2$	16.46	16.45	108–109.5	13.76	13.74	82–83[c]	7.20	7.41
	[j]			12	265–270	1.4832	$C_{10}H_{22}N_2$	16.46	16.45	148–148.5[a]	12.72	12.80			
C_4H_8O	(morpholine)	80	25	85	222	1.4660	$C_8H_{18}N_2O$	17.71	17.48	140–141	14.32	14.24			
H	$CH(C_2H_5)CH_2OH$	100	50	51	258–260	1.4706	$C_8H_{20}N_2O$	17.49	17.42	159.5–160[k]	11.19	11.01	185–186	7.60	7.50
H	$C_{12}H_{25}$	100	48	60	162–163[g]	1.4550	$C_{16}H_{36}N_2$	10.93	10.93				102–102.5	6.03	5.95
H	C_6H_5	100	100	19	125–126[g]	1.5491	$C_{10}H_{16}N_2$	17.06	16.92	118–119[a]	12.88	12.73	117–118[b]	7.52	7.47
	[i]			9	164–165[g]	1.5275	$C_{10}H_{16}N_2$	17.06	17.13	156–157	14.03	13.78			
CH_3	C_6H_5	120	100	14	124–125[l]	1.5354	$C_{11}H_{18}N_2$	15.72	15.97	112–113	13.41	13.23	115–115.5	9.92	9.93

[a] Diphenylthiourea. [b] Dibenzamide. [c] *p*-Bromobenzenesulfonamide. [d] M. p., 51–53°. [e] The phenylthiourea derivative of a sample of this compound obtained from Commercial Solvents Corporation through the courtesy of Dr. Murray Senkus gave a m. p. 133°. [f] Forms an oxalate, m. p. 190.5–191°. *Anal.* Calcd. for $C_{12}H_{18}N_2O_4$: N, 11.02. Found: N, 11.07 [g] Boiling point at 3 mm. [h] Forms an oxalate, m. p. 225–226°. *Anal.* Calcd. for $C_{12}H_{18}N_2O_4$: N, 11.02. Found: N, 10.89. [i] Assumed to have the structure $RR'C(NHC_6H_5)CH_2NH_2$. [j] Assumed to have the structure $CH_3CH_2CH(NHC_6H_{11})CH_2NH_2$. [k] Oxalate. [l] Boiling point at 5 mm.

micro Kjeldahl method; and all melting points were taken in a copper block with an ASTM thermometer calibrated for 40-mm. immersion.

Summary

1. An improved method of preparing anhydrous α,β-diamines (both amine groups primary) has been found.

2. A number of α,β-diamines (one amine group primary and the other secondary or tertiary) and their derivatives have been prepared.

3. It has been shown that cyclic ethylenimine rings rupture preferentially but not exclusively at the primary carbon atom in the presence of amines and ammonium chloride, an acid catalyst.

PROVIDENCE, R. I. RECEIVED MAY 2, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORY, VICTOR CHEMICAL WORKS]

Allyl Esters of Phosphonic Acids. I. Preparation and Polymerization of Allyl and Methallyl Esters of Some Arylphosphonic Acids

BY A. D. F. TOY

The use of organic esters of phosphoric acid as plasticizers for various resins is well known. These phosphorus containing esters have been of special importance because they not only are good plasticizers, but also impart a certain degree of flame resistance to the resins with which they are used. All these esters are incorporated with the resin as physical mixtures, but their usefulness is probably due to the fact that they serve as excellent hydrogen bonding agents.[1] It was thought to be of interest to study some phosphorus compounds which are not only plasticizers, but which (a) by themselves are capable of undergoing the process of polymerization into a resin or (b) upon mixing with other polymerizable monomers are capable of actually copolymerizing with and modifying the latter. Certain allyl esters of phosphoric acid, and substituted phosphoric acids, have been found to be modifiers for compounds such as styrene through copolymerization.[2] These compounds have been suggested for use in the preparation of polymeric materials.[3]

In our study of the chemistry of the esters of the organic phosphonic acids it has been noted that these substances are significantly different in many respects from the corresponding trisubstituted alkyl and aryl phosphates. For example, dioctyl benzenephosphonate possesses a somewhat higher thermostability than trioctyl phosphate. Likewise

---

(1) Audrieth and Toy, THIS JOURNAL, **64**, 1553 (1942).

(2) Britton and Marshall, U. S. Patent 2,186,360 (1940).

(3) Whitehill and Barker, U. S. Patent 2,394,829 (1946).

we have found that the allyl phosphonates also have somewhat different properties from those characterizing the related esters of phosphoric acid.

The present paper is the first of a series dealing with the allyl esters of phosphonic acids. The preparation and polymerization of allyl and methallyl esters of benzene-, *p*-toluene- and *p*-chlorobenzenephosphonic acids are described. These substances are capable of being polymerized into hard, transparent, infusible and insoluble resins when heated in the presence of a peroxide catalyst.

In the synthesis of these substances, a new convenient process was developed for the preparation of dichloroarylphosphine oxide based upon the action of chlorine on a slurry of phosphoric anhydride in a dichloroarylphosphine (equation 1).

$$3ArPCl_2 + P_2O_5 + 3Cl_2 \longrightarrow 3ArPOCl_2 + 2POCl_3 \quad (1)$$

The allyl esters were then obtained by reaction between the dichloroarylphosphine oxide and allyl alcohol in the presence of pyridine (equation 2).

$$ArPOCl_2 + 2ROH + 2C_5H_5N \longrightarrow ArPO(OR)_2 + 2C_5H_5N.HCl \quad (2)$$

Experimental

Dichloroarylphosphine Oxides

Dichlorophenylphosphine Oxide.—Dichlorophenylphosphine (1611 g., 9 moles) was placed in a 3-liter 3-necked flask equipped with a reflux condenser, stirrer, thermometer and a chlorine inlet; 511 g., 3.6 moles of finely divided phosphoric anhydride was added and slurried with the dichlorophenylphosphine. Chlorine gas was then passed into the slurry. The heat of reaction caused the temperature to rise to around 150°. However, as more phosphorus oxychloride was formed, it refluxed and lowered the liquid temperature to around 130°. The rate of the introduction of chlorine was such as to maintain steady reflux of the phosphorus oxychloride. The reaction was complete in about four hours as indicated by the fact that the temperature began to drop. The addition of chlorine was then discontinued and the mixture fractionated. After the removal of most of the phosphorus oxychloride at atmospheric pressure, the dichlorophenylphosphine oxide was obtained by distillation under reduced pressure, b. p. 137–138° at 15 mm. or 104° at 4 mm. The yield was 1550 g. (88.4%), $n^{25}D$ 1.5581, sp. gr. 1.197 at 25°. The identity of the product was verified (a) by hydrolysis to benzenephosphonic acid, melts at 161–162° (uncor.), and (b) by the fact that no depression was observed in a mixed melting point determination with the compound obtained by the oxidation of benzenephosphinic acid.

Dichloro-*p*-tolylphosphine Oxide.—In an initial experiment a slurry of 200 g. (1.035 mole) of dichloro-*p*-tolylphosphine and 54 g. (0.38 mole) of phosphoric anhydride was chlorinated at 35–40° to avoid possible ring or side chain chlorination. Upon completion of the reaction, the mixture was fractionated. The dichloro-*p*-tolylphosphine oxide obtained boiled at 140–142° at 11 mm. The yield was found to be 190 g. (87.5%), $n^{25}D$ 1.5542, sp. gr. 1.154 at 25°.

That chlorination of the tolyl radical does not occur is indicated by the fact that even better yields are obtained at higher temperatures. In another experiment the chlorination reaction was carried out rapidly at 145° using 150 g. of dichloro-*p*-tolylphosphine and 40 g. of phosphoric anhydride. A yield of 140 g. (91.7%) was obtained under these conditions.

Anal. Calcd. for $CH_3C_6H_4POCl_2$: P, 14.8; Cl, 34.0. Found: P, 15.0; Cl, 34.1.

The compound is therefore identical with that previously described by Michaelis and Paneck.[4]

Dichloro-*p*-chlorophenylphosphine Oxide.—A slurry of 200 g. (0.936 mole) of dichloro-*p*-chlorophenylphosphine and 50 g. (0.352 mole) of phosphoric anhydride was chlorinated at 35–40°. Upon completion of the chlorination, the mixture was fractionated. The product so obtained boils at 121–123° at 3 mm. and is a water-white liquid. The yield was found to be 192 g. (88%), $n^{25}D$ 1.5743, sp. gr. 1.302 at 25°. This compound had previously been prepared by Michaelis[5] by the reaction of *p*-chlorophenylphosphorus tetrachloride with sulfur dioxide.

Anal. Calcd. for $ClC_6H_4POCl_2$: P, 13.5; Cl, 46.5. Found: P, 13.4; Cl, 47.0.

Allyl Esters of Arylphosphonic Acids

Diallyl Benzenephosphonate. (a) By the Action of Dichlorophenylphosphine Oxide on Allyl Alcohol in the Presence of Pyridine.—In a 3-liter 3-necked flask, equipped with a stirrer, a thermometer and a dropping funnel were placed 464 g. (8 moles) of allyl alcohol and 632 g. (8 moles) of pyridine. To this mixture was added with stirring 780 g. (4 moles) of dichlorophenylphosphine oxide. The temperature of the addition was maintained at 2 to 5° by means of an ice-salt-bath. Six hours were required for the addition. Upon completion of the addition the mixture was allowed to come to room temperature. Four hundred cc. of water was then added, the oily layer separated was distilled immediately under reduced pressure. Prolonged standing of the crude wet ester causes some hydrolysis. In effecting the distillation, it was necessary to raise the temperature slowly and during this process, to maintain the pressure at about 20 mm. up to 50°, at less than 10 mm. from 50 to 100°, and at less than 5 mm. up to 120°. In heating the crude ester to the distillation point, gaseous products were evolved which made it difficult to maintain the necessary low pressure unless a high free air capacity pump was used or the heating carried out slowly. Heating of the material too rapidly at too high a pressure caused some decomposition and resulted in low yields of the product. In any event, it was essential to avoid heating the residue to a temperature much above 170°, to prevent rapid decomposition. The distillation of the product was best carried out at 1 to 2 mm. in the presence of a little copper resinate inhibitor. The yield of the distilled product was 777 g. (81.6%), b. p. 128° at 1 mm., $n^{25}D$ 1.5128, sp. gr. 1.1097 at 25°.

Anal. Calcd. for $C_6H_5PO(OCH_2CH{=}CH_2)_2$: P, 13.0. Found: P, 12.96.

In another experiment, the original reaction was carried out at 25–30° instead of 2–5°. The yield of the distilled product was found to be 71%.

Substitution of dimethylaniline for pyridine was found to give lower yields and a product of lesser purity.

The reactions between dichlorophenylphosphine oxide and allyl alcohol in the presence of pyridine were also carried out using hexane and benzene as reaction media. While pyridine hydrochloride precipitates under these conditions, yields were consistently lower and more difficulty was experienced in working up the reaction mixture for isolation of the diallyl ester. Employment of a 20% excess of allyl alcohol using hexane as solvent did not appreciably increase the yield.

(b) By the Action of Dichlorophenylphosphine Oxide on Sodium Allylate in Toluene Solution.—To 46 g. (2 moles) of sodium dispersed in 2500 cc. of toluene there was added a 100% excess, 232 g. (4 moles) of allyl alcohol at 80–90°. The mixture was heated at 100° until all sodium had disappeared. To this slurry there was then added 195 g. (1 mole) of dichlorophenylphosphine oxide at 0 to 5°. The mixture was allowed to come to room temperature and then heated to 40°. Upon cooling, 900 cc. of water was added and the toluene layer separated and subjected to fractional distillation, yielding 100 g. (42%)

---

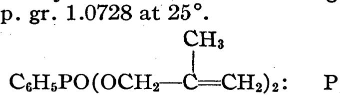
[4] Michaelis and Paneck, *Ann.*, **212**, 203–239 (1882).

[5] Michaelis, *ibid.*, **293**, 193–325 (1896).

of a product, b. p. 148–158° at 6 mm. This yellowish compound was not very pure since it polymerized to give a yellowish gel under conditions where pure diallyl benzenephosphonate would have polymerized into a very hard and strong solid.

The pure diallyl benzenephosphonate is soluble in water to the extent of 2 g. per liter. It is soluble in most of the common organic solvents. It absorbs carbon dioxide readily. It is stable at room temperature with very little change over a period of more than a year. However, when it was stored in the presence of 4.5% benzoyl peroxide, it became a gel after forty days at room temperature.

Dimethallyl Benzenephosphonate.—Three hundred and ninety grams (2 moles) dichlorophenylphosphine oxide was allowed to react with 316 g. (4 moles) of pyridine and 288 g. (4 moles) of methallyl alcohol at 2–5°. The reaction mixture was processed as described for diallyl benzenephosphonate. The water-white product boils at 140–143° at 2–3 mm. The yield was found to be 285 g. (53.5%), $n^{25}D$ 1.5057, sp. gr. 1.0728 at 25°.

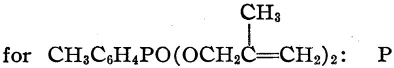


Anal. Calcd. for $C_6H_5PO(OCH_2\text{—}\overset{CH_3}{\overset{|}{C}}{=}CH_2)_2$: P, 11.66. Found: P, 11.84.

Diallyl *p*-Toluenephosphonate.—Seventy grams (0.335 mole) of dichloro-*p*-tolylphosphine oxide was allowed to react with 39 g. (0.67 mole) of allyl alcohol and 53 g. (0.67 mole) of pyridine at 2–5°. The crude diallyl *p*-toluenephosphonate was dried over anhydrous magnesium sulfate and then distilled. It boils at 134–136° at 1 mm. The yield was 47 g. (55.6%), $n^{25}D$ 1.5120, sp. gr. 1.089 at 25°.

Anal. Calcd. for $CH_3C_6H_4PO(OCH_2CH{=}CH_2)_2$: P, 12.3. Found: P, 12.4.

Dimethallyl *p*-Toluenephosphonate.—Seventy grams (0.335 mole) of dichloro-*p*-tolylphosphine oxide and 48.5 g. (0.67 mole) of methallyl alcohol and 53 g. (0.67 mole) of pyridine were allowed to react under conditions outlined above. The product boils at 146–149° at 1 mm. The yield was found to be 63 g. (67.2%), $n^{25}D$ 1.5070, sp. gr. 1.057 at 25°.

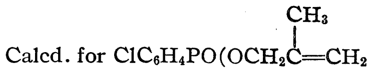


Anal. Calcd. for $CH_3C_6H_4PO(OCH_2\overset{CH_3}{\overset{|}{C}}{=}CH_2)_2$: P, 11.1. Found: P, 11.1.

Diallyl *p*-Chlorobenzenephosphonate.—Seventy-five grams (0.327 mole) of dichloro-*p*-chlorophenylphosphine oxide was allowed to react with 38 g. (0.655 mole) of allyl alcohol and 52 g. (0.658 mole) of pyridine. The diallyl *p*-chlorobenzenephosphonate was found to boil at 136–139° at 2 mm. The yield was 35 g. (40%), $n^{25}D$ 1.5208.

Anal. Calcd. for $ClC_6H_4PO(OCH_2CH{=}CH_2)_2$: P, 11.4; Cl, 13.0. Found: P, 11.6; Cl, 13.05.

Dimethallyl *p*-Chlorobenzenephosphonate.—Seventy grams (0.305 mole) of dichloro-*p*-chlorophenylphosphine oxide was allowed to react with 47.5 g. (0.66 mole) of methallyl alcohol and 52 g. (0.66 mole) of pyridine. The dimethallyl *p*-chlorobenzenephosphonate boiled at 137–140° at 1 mm. The yield was found to be 50 g. (53.8%). $n^{25}D$ 1.5162, sp. gr. 1.145 at 25°.



Anal. Calcd. for $ClC_6H_4PO(OCH_2\overset{CH_3}{\overset{|}{C}}{=}CH_2)_2$: P, 10.3; Cl, 11.8. Found: P, 10.5; Cl, 11.9.

Polymerization

In a preliminary study of the polymerization of the allyl esters of the arylphosphonic acids, it was found that all are capable of polymerizing into hard, clear, infusible and insoluble resins. The first experiments were carried out using 10-cc. samples of the monomer catalyzed with 2% benzoyl peroxide. The solution was put under nitrogen atmosphere and heated in an oil-bath at 85–90°, for eighteen to twenty hours. The monomer first became a viscous liquid, then a gel and finally a hard solid. The color of these resins varied from water-white to light yellow. The hardness of the resins when polymerized under identical conditions was found to depend on the chemical constitution of the monomer. The polymerization characteristics of these esters are very similar to those of the allyl esters of the organic dibasic acids.[6] The allyl arylphosphonate resins were found to possess the interesting property of flame resistance, being self-extinguishing when removed from the flame. The monomeric esters were also found to be capable of copolymerization with such unsaturated organic compounds as vinyl acetate, methyl methacrylate, diallyl esters of organic dibasic acids and unsaturated polyesters.

Acknowledgments.—The author expresses thanks to Dr. Howard Adler for his helpful advice and encouragement and to Mr. A. R. Wreath for the chemical analyses.

Summary

1. The preparation of dichlorophenyl-, dichloro-*p*-tolyl- and dichloro-*p*-chlorophenylphosphine oxides may be affected readily by chlorination of a slurry of phosphoric anhydride and the corresponding dichloroarylphosphine.

2. The dichloroarylphosphine oxides have been converted into the diallyl and dimethallyl esters of the arylphosphonic acids by action of the respective alcohols in the presence of pyridine.

3. The diallyl and dimethallyl esters of benzene-, *p*-toluene- and *p*-chlorobenzenephosphonic acids undergo peroxide catalyzed polymerization to form clear, infusible, insoluble resins and also are capable of copolymerization with various unsaturated organic compounds.

Chicago Heights, Illinois Received July 9, 1947

---

[6] Simpson, *J. Soc. Chem. Ind.*, **65**, 107 (1946).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF POLAROID CORPORATION]

Absorption Spectra. V. The Ultraviolet and Visible Spectra of Certain Polyene Aldehydes and Polyene Azines[1]

BY ELKAN R. BLOUT AND MELVIN FIELDS

In this paper we should like to report the results of some studies on the ultraviolet and visible absorption spectra of certain compounds containing conjugated double bonds. The substances studied were aldehydes of the generic formula, I

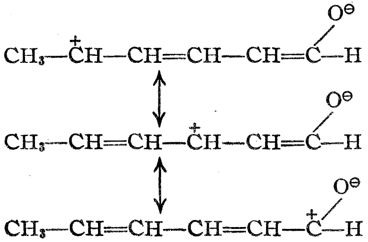
$$R-(CH{=}CH)_n-CHO \qquad \text{I}$$

where R is methyl or α-furyl and n ranges up to 7, and azines of the generic formula, II

$$R-(CH{=}CH)_n-CH{=}N-N{=}CH-(CH{=}CH)_n-R \qquad \text{II}$$

where R is methyl or α-furyl. Previous workers, notably Kuhn and his school, have prepared many compounds of the polyene type and have reported their absorption spectra. Their results on aldehydes of the Type I,[2,3] which did not extend beyond $n = 3$, are in essential agreement with our measurements.

The absorption spectra of the homologous series of aliphatic polyene aldehydes containing as many as seven conjugated carbon–carbon double bonds are shown in Figs. 1 and 2. The spectra of these compounds are characterized by a single intense absorption band which, in the higher members of the series, is accompanied by a weaker band at shorter wave lengths. As the length of the conjugated system is increased, both bands move toward longer wave lengths, but show no evidence of fine structure typical of the polyene hydrocarbons.[4] The intense band may probably be correlated with electronic transitions to relatively highly ionic states in which forms such as III (shown for 2,4-hexadienal) are prominent contributors. It is noteworthy that in the polyene aldehyde series the principal band lies at considerably longer wave lengths than the principal band of the aliphatic polyene hydrocarbon with the same number of carbon atoms. The carbonyl group produces a bathochromic effect by lengthening the conjugated system, increasing the number of resonance forms and thereby reducing the energy necessary to effect transitions from the ground state to the first excited state.[5]



$$\begin{gathered}CH_3-\overset{+}{C}H-CH{=}CH-CH{=}\overset{O^{\ominus}}{C}-H\\ \updownarrow\\ CH_3-CH{=}CH-\overset{+}{C}H-CH{=}\overset{O^{\ominus}}{C}-H\\ \updownarrow\\ CH_3-CH{=}CH-CH{=}CH-\overset{+\,O^{\ominus}}{C}-H\end{gathered}$$

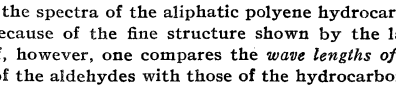
III

TABLE I

Compound	Total no. of double bonds	λ max. in mμ	Spectral solvent
2,4-Hexadiene	2	227[a]	Hexane
Crotonaldehyde	2	212[b]	Hexane
2,4,6-Octatriene	3	263[c]	Hexane
		263[c]	Ethanol
2,4-Hexadienal	3	263[b]	Hexane
		271[c]	Ethanol
2,4,6,8-Decatetraene	4	295[c,d]	Hexane
2,4,6-Octatrienal	4	306[b]	Hexane
2,4,6,8,10,12-Tetradecahexaene	6	358[c,e]	Chloroform
2,4,6,8,10-Dodecapentaenal	6	380[c]	Chloroform

[a] Booker, Evans and Gillam, *J. Chem. Soc.*, 1453 (1940). [b] See ref. 2. [c] Present work. [d] Kuhn and Grundmann, *Ber.*, **71**, 442 (1938), report maxima at 272, 284, 296 and 320 mμ. We find maxima at 272, 283, 295 and 310 mμ with the 295 maximum the most intense. [e] See also Kuhn, *Angew. Chem.*, **50**, 703 (1937).

The spectra of the α-furyl polyene aldehydes (shown in Figs. 3 and 4) exhibit the same general characteristics as those of the aliphatic polyene aldehydes. In the furyl series the second less intense absorption band first appears in the trienal. In line with an earlier observation on the lower members of the series[3] we find that the higher furyl polyene aldehydes absorb at approximately the same wave lengths as the aliphatic polyene aldehydes containing the same total number of double bonds (Table II). Although the linear extension of the conjugated system in the furyl aldehydes is decreased by the presence of two of the double bonds in a ring, the increased contribution of dipolar forms such as IV (shown for 5-α-furyl-



IV

---

[1] For the last paper in this series see Blout, Eager and Gofstein, THIS JOURNAL, **68**, 1983 (1946).

[2] Hausser, Kuhn, Smakula and Hoffer, *Z. physik. Chem.*, **29B**, 371 (1935).

[3] Hausser, Kuhn, Smakula and Deutsch, *ibid.*, **29B**, 378 (1935).

[4] Kuhn and Grundmann, *Ber.*, **71B**, 442 (1938).

(5) It is also possible that a group such as the carbonyl has an additional effect on the absorption due to its polar character. Since less energy is necessary to effect charge separation in a system containing a polar group, it is reasonable to assume that such a system will absorb light of longer wave lengths than a system containing an equal number of conjugated double bonds and no polar group. Comparison of the spectra of the aliphatic polyene aldehydes with the spectra of the aliphatic polyene hydrocarbons offers difficulty because of the fine structure shown by the latter compounds. If, however, one compares the *wave lengths of maximum absorption* of the aldehydes with those of the hydrocarbons this difficulty is obviated. These data are summarized in Table I. Except for the lowest members of the series, the data are in line with these considerations.

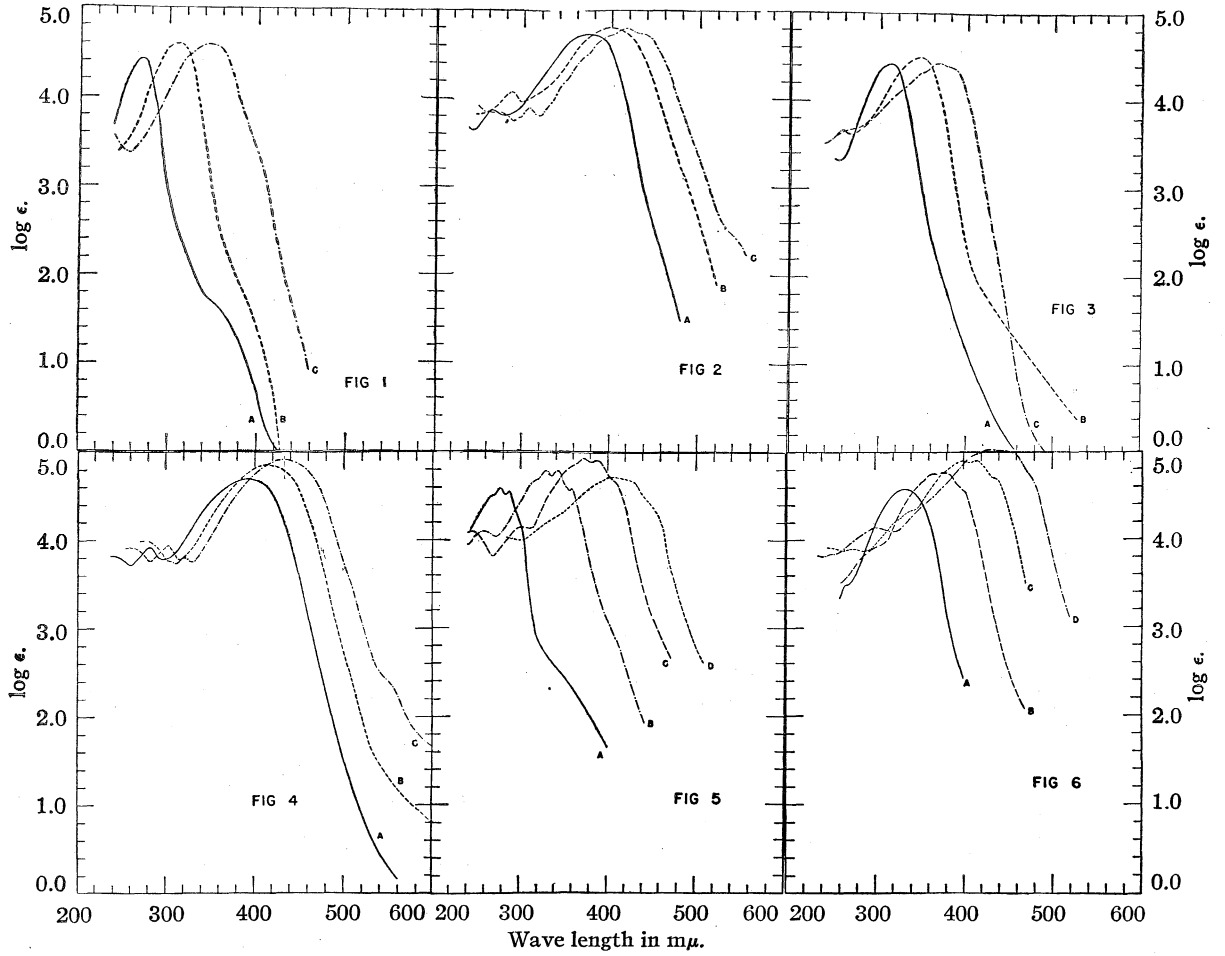


Fig. 1.—A, —— 2,4-hexadienal; B, - - - - - - - - - 2,4,6-octatrienal; C, —·—·— 2,4,6,8-decatetraenal (all in dioxane solution).

Fig. 2.—A, —— 2,4,6,8,10-dodecapentaenal; B, - - - - - - - - - 2,4,6,8,10,12-tetradecahexaenal; C, —·—·—· 2,4,6,8,-10,12,14-hexadecaheptaenal (all in dioxane solution).

Fig. 3.—A, —— 3-α-furylacrolein; B, - - - - - - - - - 5-α-furyl-2,4-pentadienal; C, —·—·—· 7-α-furyl-2,4,6-heptatrienal (all in dioxane solution).

Fig. 4.—A, —— 9-α-furyl-2,4,6,8-nonatetraenal; B, - - - - - - 11-α-furyl-2,4,6,8,10-undecapentaenal; C, —·—·—· 13-α-furyl-2,4,6,8,10-tridecahexaenal (all in dioxane solution).

Fig. 5.—A, —— crotonaldehyde azine (dioxane solution); B, —·—·—·— 2,4-hexadienal azine (dioxane solution); C, — — — 2,4,6-octatrienal azine (dioxane solution); D, - - - - - - - - - 2,4,6,8-decatetraenal azine (tetrachloroethylene solution).

Fig. 6.—A, —— furfural azine; B, — — — — 3-α-furylacrolein azine; C, - - - - - - - - - - 5-α-furyl-2,4-pentadienal azine; D, —·—·—· 7-α-furyl-2,4,6-heptatrienal azine (all in dioxane solution).

2,4-pentadienal) probably is sufficient to allow absorption at approximately the same wave length as the corresponding non-cyclic compound with the same number of double bonds. The increased contribution of forms such as IV may in turn be correlated with the ready acceptance of a positive charge by the ring oxygen atom.

In Fig. 7 we have plotted the wave lengths of the absorption maxima of the aliphatic and α-furyl polyene aldehydes as a function of the number of carbon–carbon double bonds. The plot for the main absorption bands, although definitely not a straight-line function with the lower members of the series, shows some evidence of linearity for several of the higher homologs. The position of the shorter wave length maximum appears to be a linear function of the number of double bonds for those members of the series examined. We have calculated the ratio of the wave length of maximum absorption of the longer wave length band to that of the shorter wave length band,[6] and find that in both series it decreases with increasing *n*. In this respect the absorption bands of the polyene aldehyde series differ from those of the

---

[6] *Cf.* the second order bands described by Lewis and Calvin, *Chem. Rev.*, **25**, 273 (1939).

TABLE II

Compound	Color	Observed m. p., °C. (cor.)	Crystn. solvent	λ max. in mμ	log ε	λ max. in mμ	log ε	λ max. in mμ	log ε
Crotonaldehyde	Colorless	(B. p. 102.4)[a]		220[l]	4.17	322[l]	1.45		
2,4-Hexadienal	Colorless	(B. p. 63–63.5(15))[b]		271[l]	4.39	270[m]	4.43		
2,4,6-Octatrienal	Faint yellow	55.5–57.0[b]	Hexane	315[l]	4.57	312[m]	4.60		
2,4,6,8-Decatetraenal	Yellow	105.5–107[c]	Hexane	240[l]	3.52	351[l]	4.34	343[m]	4.60
				353[l]	4.61				
2,4,6,8,10-Dodecapentaenal	Golden yellow	166–167[d]	Ethanol	263[l]	3.97	377[l]	4.71		
				264[m]	3.76	370[m]	4.76	380[n]	4.76
				268[o]	3.93	380[o]	4.86		
2,4,6,8,10,12-Tetradecahexaenal	Red-orange	195–196[e]	Chloroform	285[m]	4.05	393[m]	4.81	399[n]	4.71
2,4,6,8,10,12,14-Hexadecaheptaenal	Deep red	219–220[e] (dec.)	Chloroform	305[m]	3.89	415[m]	4.80		
				310[n]	4.03	424[n]	4.85		
Crotonaldehyde azine	Light yellow	96–97[f]	Hexane	275[l]	4.59	283[l]	4.56		
				267[m]	4.51	275[m]	4.60	285[m]	4.55
2,4-Hexadienal azine	Yellow	175–176[g]	Methanol	~259[m,q]	4.10	327[m]	4.80	342[m]	4.80
				358[m]	4.57				
2,4,6-Octatrienal azine	Yellow-orange	232–233[g]	Dioxane	245[m]	4.10	304[m]	4.14	372[m]	4.94
				~389[m,q]	4.92				
2,4,6,8-Decatetraenal azine	Red-orange	dec. >250		343[p]	3.63	410[p]	4.20	438[p]	4.17
				~450[p,q]	3.93				
Furfural	Colorless	60.8(20)[h]		270[m]	4.17	313[m]	1.78		
3-α-Furylacrolein	Colorless	50.5–51.0[i]		312[m]	4.42				
5-α-Furyl-2,4-pentadienal	Light yellow	65–67[i]		346[m]	4.47				
7-α-Furyl-2,4,6-heptatrienal	Yellow	111–112[j]	Ether–ligroin	260[m]	3.72	366[m]	4.43	(382)[m]	(4.39)
9-α-Furyl-2,4,6,8-nonatetraenal	Orange	151–152[j]	Ethanol	282[m]	3.91	389[m]	4.69		
11-α-Furyl-2,4,6,8,10-undecapentaenal	Red	195–196[j]	Chloroform	260[m]	3.90	300[m]	3.91	412[m]	4.86
13-α-Furyl-2,4,6,8,10,12-tridecahexaenal	Deep red	219–219.5[j]	Chloroform	280[m]	3.98	320[m]	3.80	429[m]	4.92
Furfural azine	Light yellow	110–111.5[k]	Ethanol	334[m]	4.58				
3-α-Furylacrolein azine	Yellow	164–165[i]	Ethanol	364[m]	4.76	378[m]	4.78		
5-α-Furyl-2,4-pentadienal azine	Golden yellow	204–205[i]	Ethanol	398[m]	4.90	413[m]	4.90		
7-α-Furyl-2,4,6-heptatrienal azine	Reddish-bronze	241.5–242.5 (dec.)	Dioxane	300[m]	4.15	430[m]	5.04	444[m]	5.04

[a] Young, THIS JOURNAL, **54**, 2498 (1932). [b] Ref. 11. [c] Ref. 9. [d] Ref. 12. [e] Ref. 10. [f] Ref. 15. [g] Kuhn and Hoffer, *Ber.*, **68**, 2164 (1930). [h] Mains, *Chem. Met. Eng.*, **26**, 779 (1919). [i] Ref. 15. [j] Ref. 14. [k] Minunni, *Gazz. chim. ital.*, **29**, II, 467 (1899). Absorption spectra solvents: [l] ethanol, [m] dioxane, [n] anisole, [o] chloroform, [p] tetrachloroethylene. [q] ~denotes an inflection point.

carotenoid and diphenyl polyene series where the ratio of the wave length of maximum absorption of the longest wave length band to that of a shorter wave length band increases with the length of the chain and approaches 2.

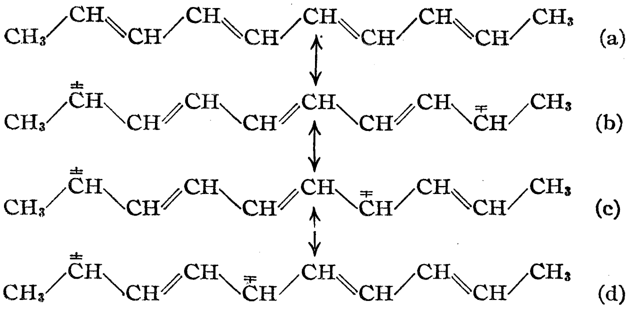
As suggested by Lewis and Calvin[6] for the diphenyl polyenes, we have also plotted the square of wave length of maximum absorption *versus* the number of double bonds for both of the polyene aldehyde series. Other investigators[7] have noted that in these cases the lowest members of the series show a linear relation between λ^2 and n. Calculated from our data, the points for the four higher homologs of each type also fall on straight lines, albeit different ones from those of the lower members.

The spectra of the aliphatic polyene azines, II, where n = 1, 2, 3 and 4 are shown in Fig. 5. Besides the expected bathochromic shift with increasing chain length, one observes some evidence of band splitting of the type seen in the aliphatic polyene hydrocarbons. Experimental difficulties, due to the insolubility of these compounds, have thus far limited our studies to the lower members of the series. The maximal absorptions of the aliphatic polyene azines lie at much shorter wave lengths than those of the aliphatic polyene hydrocarbons with the same number of double bonds (*cf.* Tables I and II). Since one might expect that systems containing the same number of conjugated double bonds and no highly polar groups would absorb at approximately the same positions, the absorption of the azines at much shorter wave lengths than their hydrocarbon analogs must mean that the effective absorbing system is shorter in

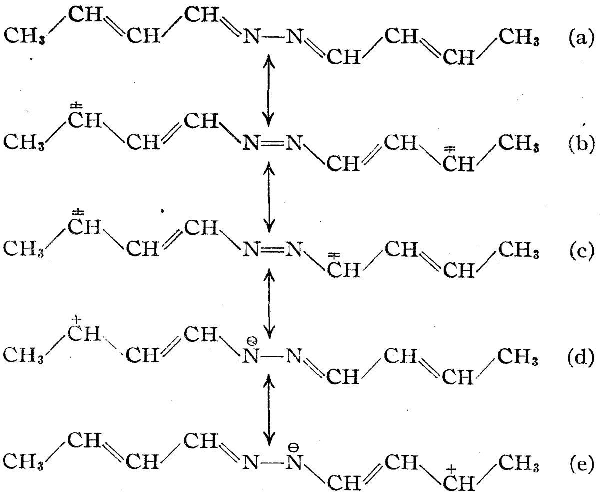
---

(7) Ferguson and Branch, THIS JOURNAL, **66**, 1467 (1944).

the nitrogen-containing compounds. Some of the possible resonance forms of a polyene hydrocarbon are shown in V


V

and of the azine with the same number of double bonds in VI.


VI

The presence of the relatively electronegative nitrogen atoms in the azines leads to an increased contribution of forms such as VId and e to the resonance hybrid VI as compared with the contribution of forms such as Vd to the resonance hybrid V, and this favors absorption at shorter wave lengths.

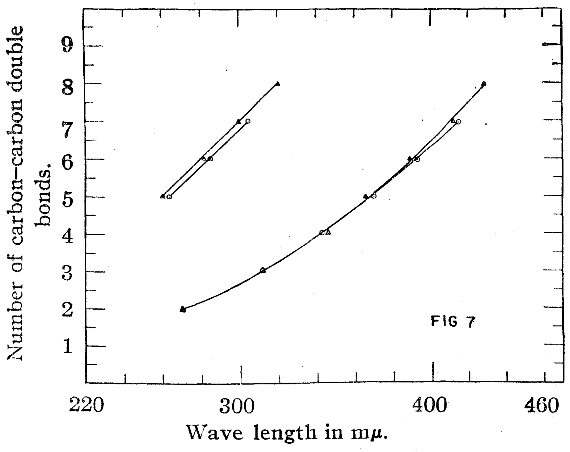


Fig. 7.—Wave lengths of maximum absorption *vs.* number of carbon–carbon double bonds in polyene aldehydes: ⊙—⊙, aliphatic polyene aldehydes; △—△, furyl polyene aldehydes.

The four lowest α-furyl polyene azines have similar absorption spectra (Fig. 6). Comparison of these spectra with those of the aliphatic polyene azines with the same number of double bonds (Fig. 5) shows that the maximal absorptions in the furyl series lie at shorter wave lengths than in the aliphatic series. This is consistent with the generalizations developed above inasmuch as in the furyl series forms containing negatively charged nitrogen atoms should be even larger contributors to the excited state because of the ready acceptance of the positive charge by the oxygen in the furan ring.

The absorption spectra of ω,ω′-diphenyl polyene azines containing as many as six double bonds in the linear portion of the molecule have already been measured by previous workers.[7] On comparing these data with the results of Kuhn's measurements[8] on some of the corresponding diphenylpolyene hydrocarbons, we note that in all cases the azines absorb at shorter wave lengths than the analogous hydrocarbons.

It has already been pointed out by Lewis and Calvin[5] that polyene azines should absorb at shorter wave lengths than the corresponding polyene hydrocarbons because of the greater "strain" of forms (such as VIb and c) which contain the —N=N— group. Our concept of this effect emphasizes the relatively greater contribution of forms containing charged nitrogen atoms as compared with forms in which the nitrogen atoms bear no formal charge. It appears to us that in this fact lies the reason for the differences in the ultraviolet absorption spectra of the polyene azines and the polyene hydrocarbons.

Acknowledgment.—We wish to acknowledge the assistance of Messrs. Marshall Kane and Claude Valle, who prepared many of the compounds, and Miss Adelaide Sutton, who measured the absorption spectra.

Experimental

Aliphatic Polyene Aldehydes.—These aldehydes were all prepared by modifications of the procedures of Kuhn and co-workers who condensed crotonaldehyde with itself or with acetaldehyde in the presence of piperidine acetate. Although the aliphatic polyene aldehydes undergo more or less rapid decomposition under ordinary conditions, they can be stored in vacuum at −50° for several months without change.

Condensation of Crotonaldehyde with Acetaldehyde.[9]—A solution of 380 cc. of acetaldehyde and 280 cc. of crotonaldehyde (Niacet, redistilled, b. p. 100–102°) in a 1-liter flask equipped with a Dry Ice condenser and a gas inlet tube was deaerated with nitrogen for thirty minutes; this precaution appears to be required in these reactions in

---

[8] Hausser, Kuhn and Smakula, *Z. phys. Chem.*, **29B**, 384 (1935).

[9] Kuhn, Badstübner and Grundmann, *Ber.*, **69**, 98 (1936).

order to approximate the yields of condensation products reported by Kuhn and co-workers. After addition of 4 cc. of piperidine and 2.8 cc. of acetic acid, the reaction mixture was allowed to stand under nitrogen for eighteen hours. The clear red solution obtained after extracting the mixture with 1 liter of ether was filtered, washed well with water, dried over anhydrous sodium sulfate and stored at 0° for forty-eight hours. The small quantity of the red 2,4,6,8,10,12-tetradecahexaenal which had separated was filtered, washed with ether, and crystallized from chloroform. The yield of the pure hexaenal, m. p. 194–195°,[10] was 0.29 g.

Distillation of the ether filtrate in vacuum afforded, in three fractions, crude 2,4-hexadienal, 2,4,6-octatrienal and 2,4,6,8-decatetraenal in approximately the quantities reported by Kuhn, Badstübner and Grundmann.[9]

Distillation of the crude dienal fraction through an efficient column afforded 18.1 g. of 2,4-hexadienal, b. p. 62–65° (14 mm.). The sample used for absorption spectra measurements was distilled, retaining the middle fraction, b. p. 63.0–63.5° (15 mm.) (n^{20}_{D} 1.5298), reported 64–66° (11 mm.),[1] n^{22}_{D} 1.5372.

Isolation of pure 2,4,6-octatrienal was most effectively accomplished by cooling the crude fraction in a Dry Ice-butyl cellosolve bath, filtering the crystalline product, and then distilling the residual oil. The distillation of this oil yielded a fraction boiling at 74–85° (1.5 mm.) which afforded a considerable quantity of crystalline trienal upon cooling in a Dry Ice-bath. The crystallization of the total amount of crude cystalline material from its own weight of hexane gave 7.2 g. of octatrienal, m. p. 57–59°. After two more crystallizations from hexane the aldehyde melted at 55.5–57°; reported, 55°.[11]

Distillation of the crude decatetraenal fraction in a manner similar to that described above yielded 0.7 g. of the pure aldehyde, which melted at 105.5–107°, in good agreement with the value reported by Kuhn and co-workers.[9]

Self-Condensation of Crotonaldehyde.—This reaction was performed with deaerated crotonaldehyde essentially as described by Kuhn and Grundmann.[12,13] Although the yields of crude 2,4,6-octatrienal, 2,4,6,8,10-dodecapentaenal, and 2,4,6,8,10,12,14-hexadecaheptaenal were approximately those obtained by the previous workers, the yields of the pure compounds were considerably lower.

Furylpolyene Aldehydes.—Syntheses of these aldehydes were also achieved by condensation reactions as described in the literature.[14,15] The properties of our samples of these compounds, summarized in Table II, correspond with those reported.

Polyene Azines.—Most of the azines studied were known compounds whose preparation was accomplished by refluxing for several hours an ethanol or dioxane solution of 2.1 moles of aldehyde with 1 mole of 85% hydrazine hydrate.

Because of difficulties encountered with the method of Hladík,[16] an improved procedure for the preparation of crotonaldehyde azine had to be developed. One hundred and twenty-six cubic centimeters of 85% hydrazine hydrate was added dropwise at 0° to 300 g. of vigorously stirred crotonaldehyde; extraction of the reaction mixture with hexane yielded a clear yellow extract. Stored overnight at −50°, the washed and dried hexane solution deposited 15 g. of crude crotonaldehyde azine, m. p. 63–94°. After several crystallizations from hexane 5.3 g. of material, m. p. 98–101°, was obtained. Although several more crystallizations failed to sharpen the melting point, the pure azine, m. p. 101.5–102°, was finally obtained with small loss by sublimation followed by one more crystallization from hexane. Crotonaldehyde azine is reported by Hladík to melt at 96°.

2,4,6,8-Decatetraenal Azine.—A satisfactory analytical sample of this azine could not be prepared. The extremely slight solubility of the substance rendered crystallization impracticable and high vacuum sublimation (10^{-4} mm.) was accompanied by considerable decomposition. The compound decomposed without melting at about 250°.

Anal. Calcd. for $C_{20}H_{24}N_2$: C, 82.14; H, 8.27. Found: C, 82.03; H, 8.87.

7-α-Furylheptatrienal Azine.—This substance crystallizes from dioxane in tiny bronze colored needles, m. p 241.5–242.5° dec.

Anal. Calcd. for $C_{22}H_{20}O_2N_2$: C, 76.75; H, 5.86. Found: C, 76.47; H, 6.30.

Spectral Measurements.—The absorption spectra measurements were made on a Beckman Quartz Spectrophotometer Model DU using a 1-cm. quartz cell and a hydrogen discharge tube as an ultraviolet source. Because of the wide variation in the solubilities of the substances investigated it was impossible to make all measurements in a single solvent. When, because of the lower solubility of the higher members of a homologous series it was necessary to change the solvent for spectral measurements, we obtained data for intermediate members in both solvents. Although the magnitude of the shift of the absorption maxima due to changes in solvent was not constant, it was always in the direction of shorter wave lengths when one changed from anisole or ethanol to dioxane (Table II).

Ethanol.—Commercial absolute ethanol was used without purification.

1,4-Dioxane.—The material used in the early phase of the work was purified by the standard method[17]; but when it was found that a commercial product[18] was satisfactory after refluxing for three days over sodium followed by distillation, the abbreviated treatment was adopted. Stored over sodium wire with minimum contact with air, the pure solvent, b. p. 100.5–101.0°, was suitable for spectrophotometric measurements at wave lengths as short as 238 mμ.

Anisole.—Distillation of Eastman Kodak Co. "White Label" grade gave a product, b. p. 152–153°, satisfactory for spectrophotometric measurements at wave lengths greater than 295 mμ.

Tetrachloroethylene.—The commercial product was distilled, retaining the middle fraction, b. p. 120–121°.

Summary

The ultraviolet and visible absorption spectra of certain polyene aldehydes of the type $R-(CH{=}CH)_n-CHO$, where R is methyl or α-furyl, have been determined. The spectra of azines prepared from the lower members of both polyene aldehydes series have been measured. Correlation of these data with those of other polyenic compounds has been attempted.

CAMBRIDGE 39, MASSACHUSETTS RECEIVED APRIL 2, 1947

---

(10) Schmitt and Obermeit, *Ann.*, **547**, 285 (1941).

(11) Kuhn and Hoffer, *Ber.*, **64**, 1977 (1931); Baumgarten and Glatzel, *ibid.*, **59**, 2662 (1926).

(12) Kuhn and Grundmann, *ibid.*, **70**, 1318 (1937).

(13) Kuhn, *Angew. Chem.*, **50**, 706 (1937).

(14) Schmitt, *Ann.*, **547**, 282 (1941).

(15) Hinz, Meyer and Schucking, *Ber.*, **76B**, 676 (1943).

(16) Hladík, *Monatsh.*, **24**, 440 (1903).

(17) Fieser, "Experiments in Organic Chemistry," D. C. Heath Co., Boston, Mass., 1941, p. 368.

(18) Union Carbide and Carbon Corporation.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF POLAROID CORPORATION]

Absorption Spectra. VI. The Infrared Spectra of Certain Compounds Containing Conjugated Double Bonds

BY ELKAN R. BLOUT, MELVIN FIELDS AND ROBERT KARPLUS

This investigation is concerned with the infrared absorption spectra of compounds containing conjugated double bonds, and more particularly with the effects of increased conjugation on the spectra in the region of double bond absorption. It has been shown that in the ultraviolet and visible regions the absorption maxima in a series of polyenic compounds shift toward lower frequencies as the conjugation increases.[1,2,3] The question of whether the frequency of maximum absorption in the visible region approaches a limiting value for molecules with very long conjugated systems has not yet been settled.

Compounds containing isolated double bonds, such as butene[4] and squalene,[5] show in the infrared a characteristic absorption in the region 1640–1660 cm.$^{-1}$ attributed to these bonds. Substances such as butadiene and piperylene[4] which contain two conjugated double bonds have also been measured and show absorption at lower frequencies, generally around 1600 cm.$^{-1}$. 2,5-Dimethylhexatriene also shows an absorption maximum in this region.[4] In this paper we wish to report our results with compounds containing as many as ten non-cyclic conjugated double bonds.

1. Aliphatic Polyene Hydrocarbons

The simplest compounds containing conjugated carbon–carbon double bonds are the aliphatic polyene hydrocarbons. Investigation of the infrared spectra of the lower members of this series (Figs. 1–4) in the region 1440–1900 cm.$^{-1}$ shows in addition to the characteristic strong C–H frequency at 1445–1455 cm.$^{-1}$ several other bands of lower intensities. The symmetry of these molecules probably accounts for the lack of intense absorption in this region. Because of the multiplicity of the absorption maxima shown by these compounds in the general neighborhood of C=C absorption it is not possible at this time to interpret these spectra without mathematical analysis. Perhaps it is significant that in the region examined the diene has two, the triene three, and the tetraene four bands which are doublets or even higher multiplets. The strongest of the bands that may possibly be ascribed to double bond vibrations lies for each compound at or near 1650 cm.$^{-1}$; the simpler compounds containing double bonds, such as *cis*-2-butene,[6] also have a band in this region at 1660 cm.$^{-1}$.

2. Aliphatic Polyene Azines

The aliphatic polyene azine series, the lower members of which can be readily prepared from the corresponding aldehydes, offer an opportunity for the spectral examination of compounds containing a larger number of double bonds. In Figs. 5 through 9 are shown the spectra in the region 1440 to 1900 cm.$^{-1}$ for the aliphatic azines containing, respectively, 2, 4, 6, 8 and 10 double bonds. In addition to the characteristic C–H bending frequency around 1450 cm.$^{-1}$,[7] the strongest absorption band in these compounds occurs in the region 1580–1670 cm.$^{-1}$ and is attributable to motions of doubly bonded atoms. The frequency of maximal absorption decreases with increasing chain length. In Fig. 10 we have plotted this frequency as a function of the number of double bonds in the chain.

3. Furyl Polyene Azines

The general characteristics of the spectra in the region of double bond absorption obtained from the polyene azines having terminal α-furyl groups (Figs. 11–14) are similar to those of the corresponding aliphatic azines. The furyl compounds, however, show the C–H bending frequency around 1475 cm.$^{-1}$ rather than at 1450 cm.$^{-1}$. The frequency of the most prominent band decreases with increasing chain length as may be seen from the plot of the position of this maximum against the number of double bonds (Fig. 10). It is observed that the maxima for these bands may be brought into good superposition with the maxima in the aliphatic polyene azine series if each furan ring is weighted as one double bond. It is perhaps worthy of note that both decatetraenal azine (10 double bonds) and 7-furyl heptatrienal azine (10 "double bond equivalents") have very similar spectra in that each compound shows a secondary less intense band at a frequency slightly higher than that of the main band (*cf.* Figs. 9 and 14).

4. Aliphatic Polyene Aldehydes

All the aldehydes examined have one or more very strong bands in the 1500 to 1800 cm.$^{-1}$ region (Figs. 15–21). In addition, these compounds all show a band about 1450 cm.$^{-1}$.[7] The extinction coefficient at the center of this band is about one-

---

[1] For a summary of the work of Kuhn and his school see Kuhn, *J. Chem. Soc.*, 605 (1938).

[2] Lewis and Calvin, *Chem. Rev.*, **25**, 273 (1939).

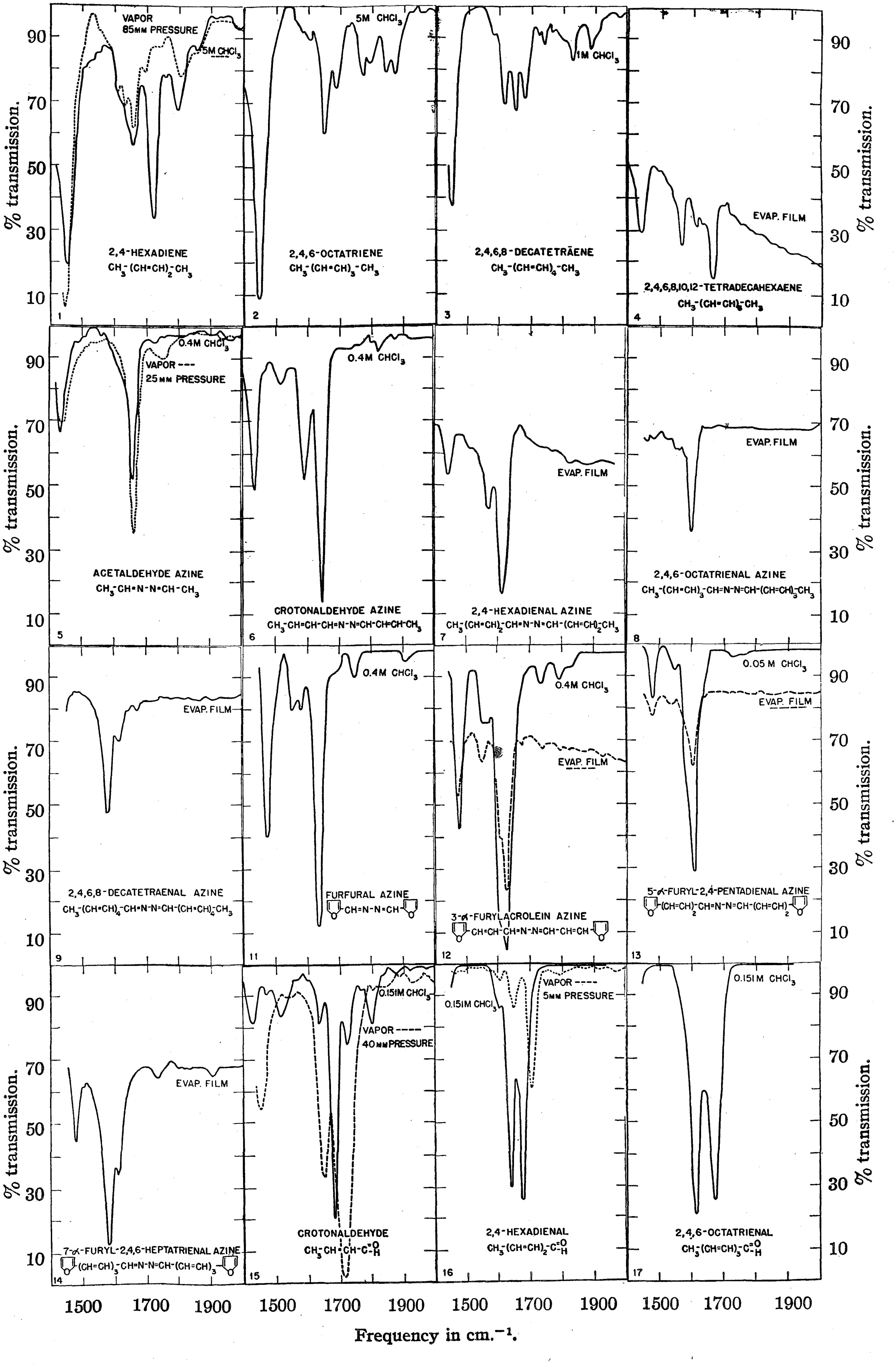
[3] Blout and Fields, THIS JOURNAL, **70**, 189 (1948).

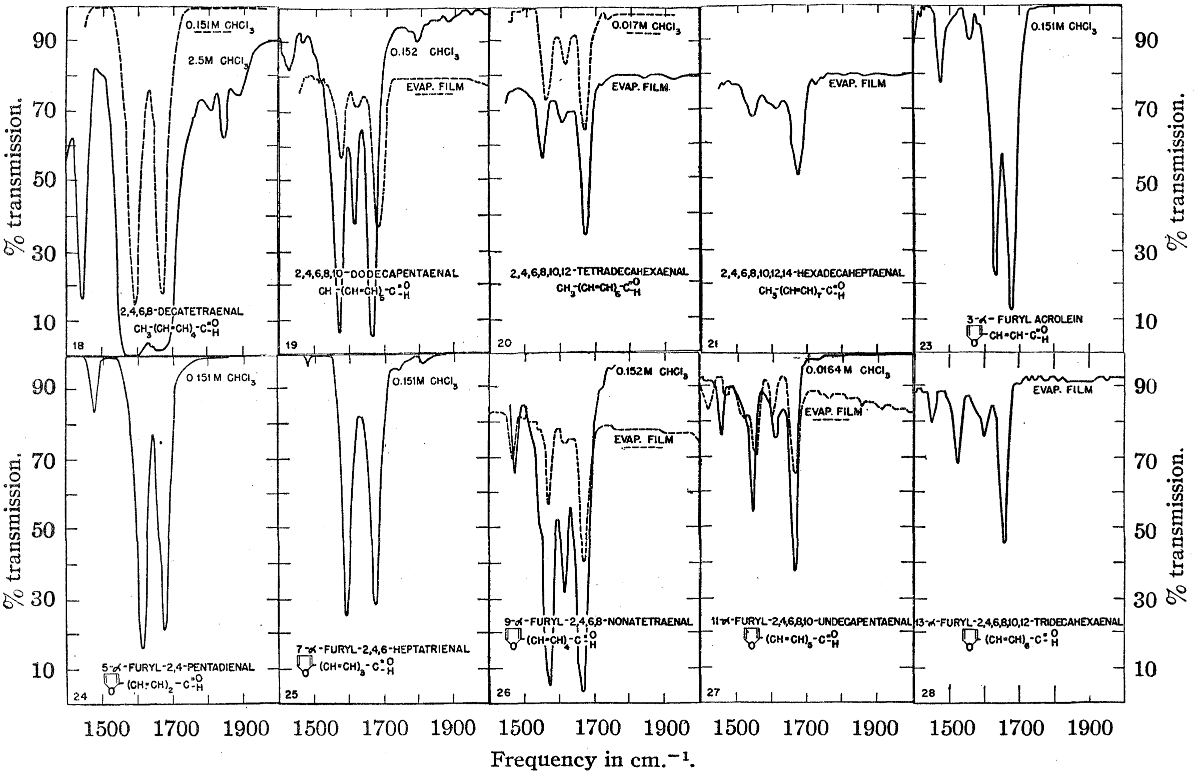
[4] Barnes, Gore, Liddel and Williams, "Infrared Spectroscopy," Reinhold Publishing Co., New York, N. Y., 1944.

[5] Thompson and Torkington, *Trans. Faraday Soc.*, **XLI**, 246 (1945).

[6] A. P. I. Res. Proj. 44, Infrared Absorption Spectrograms, Ser. No. 21, 376.

[7] Although this band is not shown in Figs. 8, 9, 16, 17, 20 and 29, since measurements were not extended to low enough frequencies, it is undoubtedly present.


% transmission.
90
70
50
30
10
1500
1700
1900
Frequency in cm.⁻¹.
1
VAPOR 85MM PRESSURE
5M CHCl3
2,4-HEXADIENE
CH3-(CH=CH)2-CH3
2
5M CHCl3
2,4,6-OCTATRIENE
CH3-(CH=CH)3-CH3
3
1M CHCl3
2,4,6,8-DECATETRAENE
CH3-(CH=CH)4-CH3
4
EVAP. FILM
2,4,6,8,10,12-TETRADECAHEXAENE
CH3-(CH=CH)6-CH3
5
0.4M CHCl3
VAPOR --- 25MM PRESSURE
ACETALDEHYDE AZINE
CH3-CH=N-N=CH-CH3
6
0.4M CHCl3
CROTONALDEHYDE AZINE
CH3-CH=CH-CH=N-N=CH-CH=CH-CH3
7
EVAP. FILM
2,4-HEXADIENAL AZINE
CH3-(CH=CH)2-CH=N-N=CH-(CH=CH)2-CH3
8
EVAP. FILM
2,4,6-OCTATRIENAL AZINE
CH3-(CH=CH)3-CH=N-N=CH-(CH=CH)3-CH3
9
EVAP. FILM
2,4,6,8-DECATETRAENAL AZINE
CH3-(CH=CH)4-CH=N-N=CH-(CH=CH)4-CH3
11
0.4M CHCl3
FURFURAL AZINE
CH=N-N=CH
12
0.4M CHCl3
EVAP. FILM
3-α-FURYLACROLEIN AZINE
CH=CH-CH=N-N=CH-CH=CH
13
0.05 M CHCl3
EVAP. FILM
5-α-FURYL-2,4-PENTADIENAL AZINE
(CH=CH)2-CH=N-N=CH-(CH=CH)2
14
EVAP. FILM
7-α-FURYL-2,4,6-HEPTATRIENAL AZINE
(CH=CH)3-CH=N-N=CH-(CH=CH)3
15
0.151M CHCl3
VAPOR ---- 40MM PRESSURE
CROTONALDEHYDE
CH3-CH=CH-C=O H
16
0.151M CHCl3
VAPOR ---- 5MM PRESSURE
2,4-HEXADIENAL
CH3-(CH=CH)2-C=O H
17
0.151M CHCl3
2,4,6-OCTATRIENAL
CH3-(CH=CH)3-C=O H



sixth as large as those at the centers of the strong bands between 1500 and 1700 cm.$^{-1}$.

If the frequencies of the strong lines are plotted against the total number of double bonds in the molecule (Fig. 22), two different curves are obtained for compounds containing up to five double bonds, whereas three curves are obtained for higher members of the series. The position and intensity of the high frequency band around 1672 cm.$^{-1}$ is essentially constant for aldehydes having more than two double bonds in the chain. The maximum absorption of the lowest frequency band, however, shifts with increasing chain length. It may be seen from Fig. 22 that this shift is always in the same direction (toward lower frequencies with increasing chain length) but the increment per double bond decreases for the longer molecules so that this curve of the lowest frequency band may also become asymptotic with sufficiently long chains of conjugated double bonds.

5. ω-Furyl Polyene Aldehydes

The infrared spectra of these compounds are very similar to those of their aliphatic analogs. They are characterized by the same band system (Figs. 23–28) consisting of a strong band around 1672 cm.$^{-1}$ whose position remains unchanged as the chain length is increased, a second strong band whose frequency decreases as the number of double bonds increases, and a weaker band whose position is constant around 1475 cm.$^{-1}$. In addition, as in the aliphatic series, a third band appears in the higher molecular weight compounds. The salient features of the spectra of this group of compounds can perhaps best be seen by referring to the plot of the frequency of maximal absorption *vs.* the number of double bonds (Fig. 29). It is of interest to observe that the contribution of the furyl group in the aldehyde series as in the azine series is again equivalent to approximately one aliphatic double bond.

Discussion

There are two causes from which one might derive these observations. First, with increasing conjugation, the apparent order[8] or double-bond character[9] of the double bonds decreases. This in turn results in a decrease in the force constants of the vibrations involving the double bonds, while an increase would be expected in the force constants appropriate to vibrations primarily involving single bonds. The decrease in force constants with unchanged or increased reduced masses is then responsible for the decrease in the normal vibration frequency. Second, the normal modes will be different. That is, the frequencies no longer correspond to the vibration of an individual bond as in ethylene; instead, for two identical double bonds, for instance, the normal modes would be in the in-phase and opposite-phase simultaneous vibration of the two bonds. Where there are more double bonds, the interactions become

---

(8) Penney, *Proc. Roy. Soc.* (*London*), **A158**, 306 (1937).

(9) Pauling, Brockway and Beach, THIS JOURNAL, **57**, 2705 (1935); Pauling and Brockway, *ibid.*, **59**, 1223 (1937).

more complicated. Where, finally, the bonds are no longer alike, as is the case with the polyene aldehydes and the polyene azines, the assignment of the vibrations to the oscillation of individual structures, or even to certain combinations of such oscillations, becomes impossible.

One can, however, in the case of the polyene aldehydes, say that the higher frequency band, the one that is almost unaffected by increasing chain length, is associated more with the carbonyl bond, while the other strong bands contain more carbon–carbon double bond vibration. It is sur-

TABLE I

The relative intensities for the different maxima are shown on a 1 to 10 scale by the figures in parentheses. They were calculated by determining the ratios of the absorptions of the less intense peaks to the most intense peak in any compound and multiplying these values by 10.

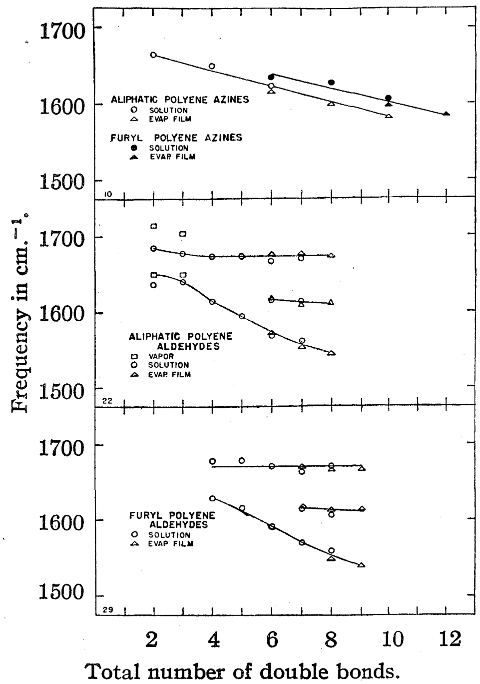
Compound	Physical state of spectral sample	Positions (cm.$^{-1}$) and relative intensities of main absorption maxima								
2,4-Hexadiene	Vapor, 85 mm.	1452			1656	1717		1795		
		(10)			(5)	(8)		(4)		
	5.0 *M* $CHCl_3$ soln.	1445	1608	1635	1656	1693		1805		
		(10)	(3)	(3.5)	(4)	(2)		(2)		
2,4,6-Octatriene	5.0 *M* $CHCl_3$ soln.	1445	1601		1646	1685	1763	1785	1804	1867
		(10)	(1)		(4)	(2)	(1.5)	(1.5)	(2)	(1.5)
2,4,6,8-Decatetraene	7.0×10^{-1} *M* $CHCl_3$ soln.	1450	1615		1646	1677	1733		1825	1890
		(10)	(6)		(5.5)	(5.5)	(3)		(4)	(3.5)
2,4,6,8,10,12-Tetradecahexaene	Evaporated film	1444	1567	1611	1635	1664				
		(8)	(10)	(4)	(4)	(10)				

TABLE II

Compound	Physical state of spectral sample	Positions (cm.$^{-1}$) and relative intensities of main absorption maxima				
Acetaldehyde azine	Vapor, 25 mm. pressure	1442(5)			1664(10)	1755(2)
	4.0×10^{-1} *M* $CHCl_3$ soln.	1432(7)			1664(10)	
Crotonaldehyde azine	4.0×10^{-1} *M* $CHCl_3$ soln.	1439(6)	1521(2)	1592(6)	1650(10)	
2,4-Hexadienal azine	3.8×10^{-1} *M* $CHCl_3$ soln.	1438(4)	1573(4)		1624(10)	
	Evaporated film	1445(6)	1573(7)		1618(10)	
2,4,6-Octatrienal azine	Evaporated film	1443(1.5)	1558(2)		1601(10)	
2,4,6,8-Decatetraenal azine	Evaporated film				1583(10)	1615(4)
Furfural azine	4.0×10^{-1} *M* $CHCl_3$ soln.	1473(7)	1552(2)	1579(2)	1635(10)	1750(1)
3-α-Furylacrolein azine	4.0×10^{-1} *M* $CHCl_3$ soln.	1477(6)	1561(3)		1628(10)	1737(1)
	Evaporated film	1475(3)	1549(1)		1628(10)	
5-α-Furyl-2,4-pentadienal azine	5.0×10^{-2} *M* $CHCl_3$ soln.	1479(2)	1546(1)		1608(10)	
	Evaporated film	1477(2)	1538(1)		1601(10)	
7-α-Furyl-2,4,6-heptatrienal azine	Evaporated film	1477(4)			1583(10)	1611(6)

TABLE III

Compound	Physical state of spectral sample	Positions (cm.$^{-1}$) and relative intensities and main absorption maxima				
Crotonaldehyde	Vapor, 40 mm. pressure	1449(5)		1650(7)		1715(10)
	1.5×10^{-1} *M* $CHCl_3$ soln.	1429(2)	1520(2)	1638(2)		1685(10)
2,4-Hexadienal	Vapor, 5 mm. pressure		1608(1)	1650(4)		1705(10)
	1.5×10^{-1} *M* $CHCl_3$ soln.	1447(7.5)	1608(2)	1642(9.5)		1677(10)
2,4,6-Octatrienal	1.5×10^{-1} *M* $CHCl_3$ soln.	1445		1615(10)		1674(9.5)
2,4,6,8-Decatetraenal	1.5×10^{-1} *M* $CHCl_3$ soln.	1445(6)		1592(10)		1673(9.5)
2,4,6,8,10-Dodecapentenal	1.5×10^{-1} *M* $CHCl_3$ soln.	1429(2)		1570(9.8)	1615(6)	1664(10)
	Evaporated film			1573(5)	1618(3)	1677(10)
2,4,6,8,10,12-Tetradecahexaenal	1.7×10^{-2} *M* $CHCl_3$ soln.			1561(7.5)	1615(4)	1671(10)
	Evaporated film			1555(5.5)	1611(3)	1677(10)
2,4,6,8,10,12,14-Hexadecaheptaenal	Evaporated film			1546(4)	1611(3)	1674(10)
3-α-Furylacrolein	1.5×10^{-1} *M* $CHCl_3$ soln.	1472(3)	1558(1)	1628(9)		1677(10)
5-α-Furyl-2,4-pentadienal	1.5×10^{-1} *M* $CHCl_3$ soln.	1477(2)		1615(10)		1677(9.5)
7-α-Furyl-2,4,6-heptatrienal	1.5×10^{-1} *M* $CHCl_3$ soln.	1477(1)		1591(10)		1672(9.5)
9-α-Furyl-2,4,6,8-nonatetraenal	1.5×10^{-1} *M* $CHCl_3$ soln.	1477(4)		1570(9.5)	1615(7)	1667(10)
	Evaporated film	1467(3)		1570(6)	1618(1.5)	1671(10)
11-α-Furyl-2,4,6,8,10-undecapentaenal	9.6×10^{-2} *M* $CHCl_3$ soln.	1477(4)	1528(6)	1558(8.5)	1608(5)	1671(10)
	Evaporated film	1462(3)		1549(8)	1614(3)	1668(10)
13-α-Furyl-2,4,6,8,10,12-tridecahexaenal	Evaporated film	1463(2)		1539(5)	1613(3)	1668(10)



prising, even in view of the resolving power of the spectrometer used in this investigation, that a greater number of distinct bands are not observed in the region examined. Since one would expect all the double bond vibrations to yield bands of comparable intensity (the molecules have no symmetry), the weak bands that appear above 1700 cm.$^{-1}$ in the more concentrated solutions must be assigned to overtones or combinations. Finally, one must consider the possibility that each of the observed strong bands in the region 1550—1700 cm.$^{-1}$ is actually a group of several unresolved bands. The ultimate solution to this problem awaits mathematical analysis.

Acknowledgment.—We wish to acknowledge the valuable assistance of Messrs. Claude Valle and Marshall Kane in the preparation of many of the compounds, and the aid of Mr. Dwight Merrill and other members of the spectrophotometric group in determining many of the spectra.

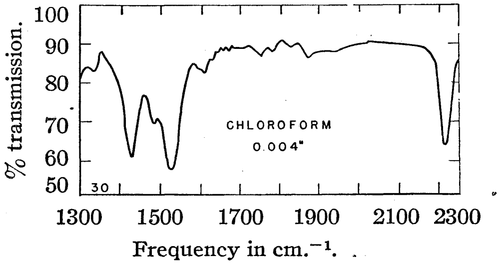
Experimental

The aliphatic polyene hydrocarbons were prepared according to the method of Kuhn and Grundmann.[10] The polyene azines and aldehydes were prepared according to the procedures described or referred to in a previous paper.[3]

The spectral measurements were made on a Perkin–Elmer infrared spectrometer Model 12-A using a 40 cycle chopper, a Strong[11] bolometer, an a.c. amplifier, and a Brown Instrument Company potentiometer. The data were obtained on a point-to-point basis, the points being taken from 5 to 10 cm.$^{-1}$ apart in the 1440 to 1900 cm.$^{-1}$ region. In the vicinity of the absorption maxima points were taken every 2 to 4 cm.$^{-1}$.

The vapor measurements were made in an 80-mm. cell having plane parallel rock salt windows. A second identical cell evacuated to 2 mm. was used to correct for reflection losses.

Chloroform, a useful solvent for spectral measurements in this region,[12] was purified by drying over phosphorus pentoxide followed by distillation; the material used gave the spectral curve shown in Fig. 30. As can be seen from Tables I–III and the figures, the lower members of each series were measured in chloroform solution. The cell used was constructed from two rock salt plates and had a thickness of 0.004″.[13] To correct for reflection and absorption losses the measurements were made against an identical cell containing only C. P. chloroform.



The decrease in solubility with the increasing number of double bonds in the higher molecular weight compounds made it necessary to use films of the less soluble materials which had been evaporated in high vacuum (<10^{-4} mm. of mercury) on rock salt discs. No measurements of film thickness were made. Evaporated films of the more unstable compounds, the aliphatic polyene aldehydes and 2,4,6,8,10,12-tetradecahexaene, were measured in a specially constructed evacuated cell.

Summary

The infrared spectra of twenty-six compounds containing two or more conjugated double bonds were determined in the region of double bond vibrational absorption. Polyene aldehydes and polyene azines show at least one strong absorption maximum which shifts toward lower frequencies as the length of the conjugated system is increased.

CAMBRIDGE 39, MASSACHUSETTS RECEIVED APRIL 2, 1947

---

[10] Kuhn and Grundmann, *Ber.*, **71**, 442 (1938).

[11] The nickel-strip bolometer used was kindly supplied to us by Professor John Strong of Johns Hopkins University.

[12] Torkington and Thompson, *Trans. Faraday Soc.*, **41**, 184 (1945).

[13] Halford and Schaeffer, *J. Chem. Phys.*, **14**, 141 (1946).

[Contribution from the U. S. Bureau of Mines, Central Experiment Station]

Steric Hindrance and Short Wave Length Bands in the Ultraviolet Spectra of Some Naphthalene and Diphenyl Derivatives[1]

By R. A. Friedel,[2] Milton Orchin[3] and Leslie Reggel[3]

Introduction

The aromatic cyclodehydrogenation studies being conducted in this Laboratory have provided a series of compounds that exhibit interesting relationships between ultraviolet absorption spectra and steric hindrance. Most of the work on the correlation of steric hindrance with ultraviolet spectra has been done on diphenyls,[4,5,6] but Jones[7,8,9] has studied more complex aromatic systems. He observed, for example, that in 9-phenylanthracene and 9,10-diphenylanthracene, the phenyl groups cannot be coplanar with the anthracene nucleus because of hindrance between neighboring hydrogen atoms. The resultant lack of coplanarity is manifested by the similarity of the spectra to that of anthracene. Jones[8] has noted the general effects of steric hindrance on the spectra of conjugated ring systems, such as increased fine structure, hypsochromic band shifts, and decreased intensity. The present paper discusses these effects as observed for several naphthalene and diphenyl derivatives, which were investigated down to 206 mμ.

Discussion and Results

Dinaphthyls.—The spectra of the three dinaphthyls[10] are shown in Fig. 1. 1,1′-Dinaphthyl (I) shows the greatest effect of steric hindrance as its spectrum is closest to that of naphthalene (Fig. 3); however, some resonance structures involving coplanarity probably exist, since fine structure is diminished. 2,2′-Dinaphthyl (II) should be free of steric hindrance; its spectrum shows a type of structure radically different from that of naphthalene with a very strong band at 254, a weaker broad band at 305, and a short wave length band at 212 mμ. 1,2′-Dinaphthyl (III) is, as expected, intermediate between the other two. Its spectrum is more similar to that of 1,1′-dinaphthyl (I); however, intensities are greater, fine structure is diminished, and bands are considerably broader than in (I).

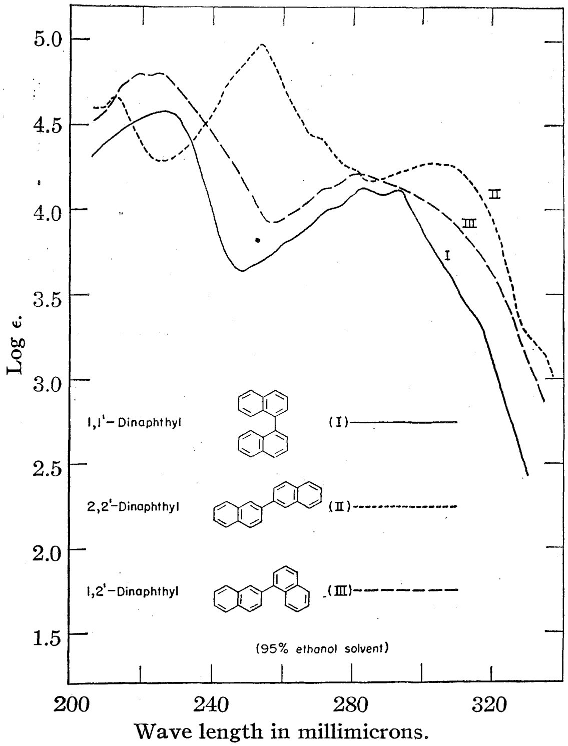


Fig. 1.

The spectrum of a dinaphthyl derivative,[11] 2,2′7,7′-tetramethyl-1,1′-dinaphthyl (IV) (Fig. 2), indicates very strong steric hindrance. Fine structure is developed, including the appearance of the typical naphthalene band at 319 mμ, and intensities are approximately double those of naphthalene. Also shown is the spectrum of a hydrogenated derivative, 3,4,3′,4′-tetrahydro-1,1′-dinaphthyl (V). Coplanarity is probably lacking in this compound also since the spectrum is very similar to that of 1,2-dihydronaphthalene.

Phenylnaphthalenes.—The spectra[12] of naphthalene (VI), 1-phenylnaphthalene (VII), and 2-phenylnaphthalene (VIII) are shown in Fig. 3. The 1-phenylnaphthalene (VII) spectrum resembles that of naphthalene, indicating strong steric hindrance; however, bathochromic shifts and greatly decreased fine structure indicate appreciable contribution from coplanar resonance

---

[1] Published by permission of the Director, U. S. Bureau of Mines. Presented before the Organic Division at Atlantic City, 1947. Not copyrighted.

[2] Physical chemist, Research and Development Division, Office of Synthetic Liquid Fuels, U. S. Bureau of Mines, Central Experiment Station, Pittsburgh, Pennsylvania.

[3] Organic chemist, Research and Development Division, Office of Synthetic Liquid Fuels, U. S. Bureau of Mines, Central Experiment station, Pittsburgh, Pennsylvania.

[4] O'Shaughnessy and Rodebush, This Journal, **62**, 2906 (1940).

[5] Pickett, Walter and France, *ibid.*, **58**, 2296 (1936).

[6] Pestemer and Mayer-Pitsch, *Monatsh.*, **70**, 104 (1937).

[7] R. N. Jones, This Journal, **63**, 313, 1658 (1941).

[8] R. N. Jones, *ibid.*, **67**, 2127 (1945).

[9] R. N. Jones, *Chem. Rev.*, **32**, 1 (1943).

[10] Adams and Kirkpatrick, This Journal, **60**, 2180 (1938), determined the spectra of 1,1′- and 2,2′-dinaphthyl to 230 mμ. They found a band at 297 in 2,2′- which we do not find. Their low wave length band for 1,1′- is at 238, whereas ours lies at 226.

[11] Jones, This Journal, **67**, 2127 (1945), determined the spectrum of 2,2′-diamino-1,1′-dinaphthyl.

[12] Jacobs, Craig and Lavin, *J. Biol. Chem.*, **141**, 51 (1941), determined the spectra of 1- and 2-phenylnaphthalene down to 235 mμ.

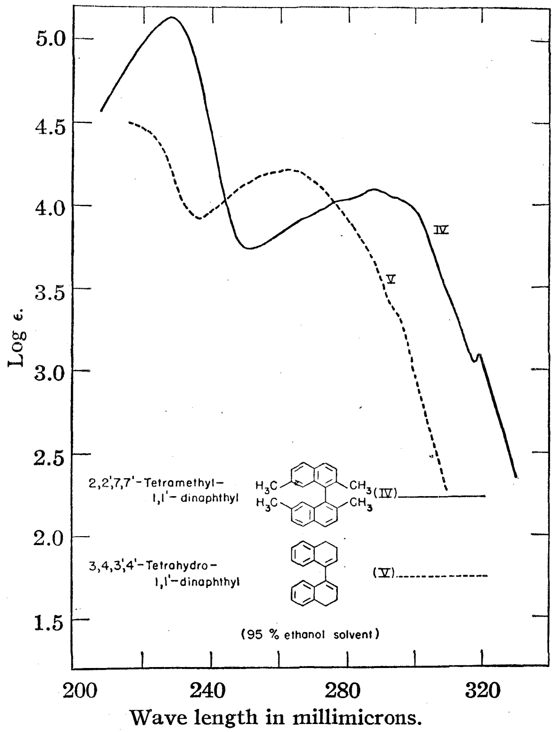


Fig. 2.

structures. The aromatic rings of 2-phenylnaphthalene (VIII), on the other hand, can assume a coplanar structure; accordingly the spectrum of this compound is quite different from that of naphthalene. The same bands observed by Jacobs, *et al.*, for (VIII) are found at 250 and 285; in addition a short wave length band appears at 212 mμ. Thus the general form of the spectrum of (VIII) is the same as that of unhindered 2,2'-dinaphthyl (II) (Fig. 1).

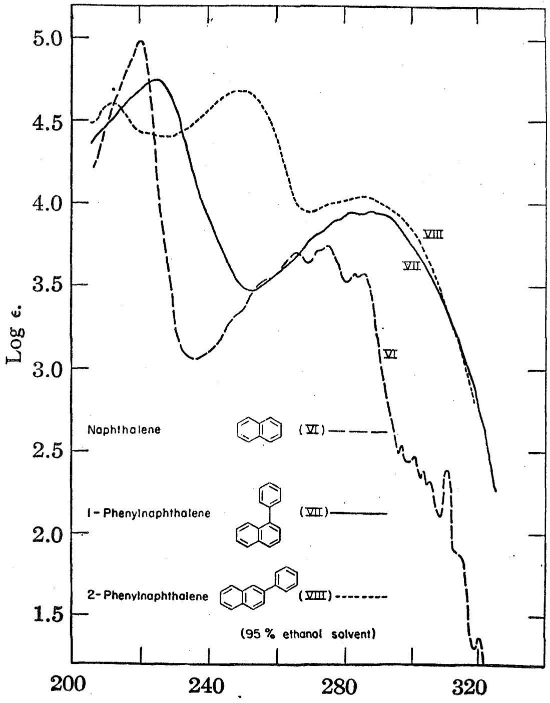


Fig. 3.

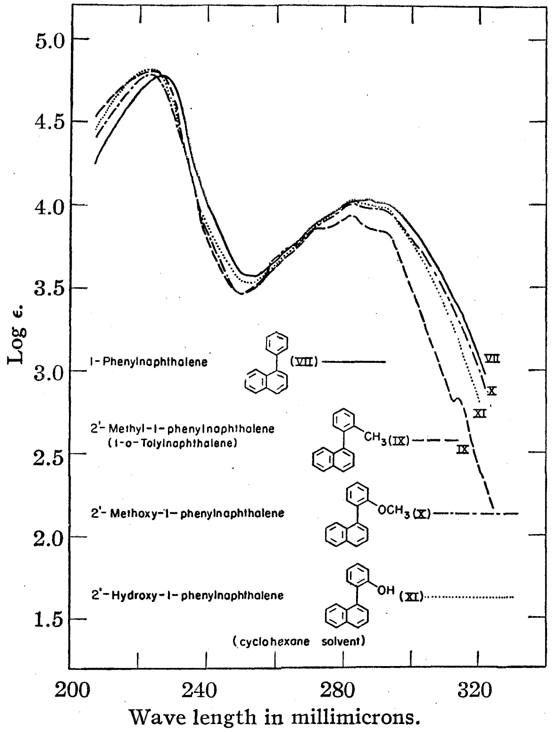


Fig. 4.

The spectra in Fig. 4 of 1-phenylnaphthalene (VII) and three of its derivatives, 2'-methyl-1-phenylnaphthalene (1-*o*-tolylnaphthalene) (IX), 2'-methoxy-1-phenylnaphthalene (X) and 2'-hydroxy-1-phenylnaphthalene (XI), show the effects of substituting the groups —CH_3, —OCH_3 and —OH, respectively, in the ortho position of the phenyl group of 1-phenylnaphthalene (VII). The methyl group in 1-*o*-tolylnaphthalene (IX) appreciably increases steric hindrance since its presence produces in the 280 mμ region a weaker, narrower band with typical naphthalene fine structure, including the band at 314 mμ. The methoxyl (X) and hydroxyl (XI) groups apparently cause only slight additional hindrance over that already present in 1-phenylnaphthalene (VII); the bands as a whole are somewhat narrower and definite peaks are produced at 282 and 283, respectively, giving band structures similar to that of the strongly hindered methyl derivative (IX). All of these spectra were determined in both 95% alcohol and cyclohexane. Differences are very slight if any, but the spectra shown were obtained in cyclohexane in order to remove any effect of a polar solvent.

The spectra of 2-phenylnaphthalene (VIII) and two of its derivatives, 2'-methyl-2-phenylnaptha-

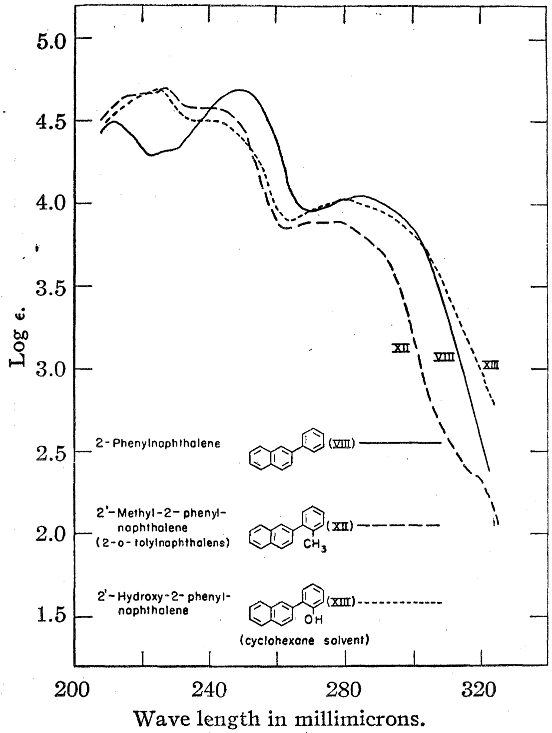


Fig. 5.

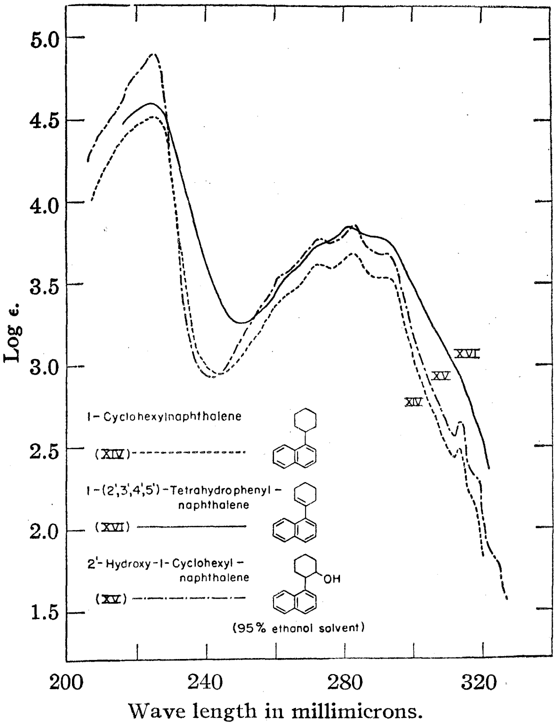


Fig. 6.

lene (2-*o*-tolylnaphthalene) (XII) and 2'-hydroxy-2-phenylnaphthalene (XIII) are given in Fig. 5 to permit comparison of the relative degrees of steric hindrance produced by the groups —CH_3 and —OH, in the ortho position of the phenyl group of unhindered 2-phenylnaphthalene. The methyl group, in 2-*o*-tolylnaphthalene (XII), again causes the greater steric hindrance; instead of the two 2-phenylnaphthalene bands at 250 and 212, one wide band with a doublet splitting occurs around 230 mμ. Further, the long wave length band undergoes a hypsochromic shift from 286 to 274 mμ. The spectrum of the hydroxyl derivative (XIII) exhibits the same spectral structure as (XII) indicating a surprising amount of hindrance due to the hydroxyl group. The wide long wave length band at 280 does not shift with respect to the same band in 2-phenylnaphthalene, probably because of a phenoxy contribution; in a polar solvent, 95% ethanol, this band is shifted 10 mμ to longer wave lengths and is considerably broader.

Other Naphthalene Derivatives.—The spectra of 1-cyclohexylnaphthalene (XIV), 2'-hydroxy-1-cyclohexylnaphthalene (XV) and 1-(2',3',4',5'-tetrahydrophenyl)-naphthalene (XVI) are shown in Fig. 6. The first two compounds produce spectra typical of naphthalene derivatives with one saturated substituent; their spectra are almost identical with that of strongly hindered 1-*o*-tolylnaphthalene (IX). The spectrum of the tetrahydro compound (XVI), in which the naphthalene nucleus is conjugated with one double bond, shows the usual band widening, decreased fine structure, and increased intensity which accompany conjugation.

Diphenyls.—The spectra of diphenyl (XVII) and three of its derivatives, 2-methyldiphenyl (XVIII), 2-methoxydiphenyl (XIX) and 2-hydroxydiphenyl (*o*-phenylphenol) (XX) (Fig. 7) exhibit the effect of —CH_3, —OCH_3 and —OH, in an ortho position of diphenyl. The methyl group in (XVIII) has the greatest effect with the 248 diphenyl band shifting to 235 mμ and the intensity decreasing appreciably. The same band in the spectrum of the methoxy derivative (XIX) shifts only 2 mμ to 246, which indicates very slight hindrance; but the decrease in intensity is significant. The hydroxyl group in *o*-phenylphenol (XX) appears to have an even greater effect; in cyclohexane solvent the 248 band shifts 3 mμ to 245 and the decrease in intensity is quite large. For (XIX) and (XX) in 95% ethanol, however, intensities of the band coincide and band positions are reversed; 2-methoxydiphenyl (XIX) is not affected by the polarity of the solvent, but for *o*-phenylphenol (XX) the band shifts from 245 to 246.5. The bands at 284 in the spectra of both oxygenated compounds are phenoxy bands.

Comparison of Diphenyls and Naphthalenes.—Diphenyl and its derivatives were investigated principally because of the similarity in the 250 mμ region between diphenyl (XVII) and the related unhindered naphthalenes, 2-phenylnaphthalene (VIII) and 2,2'-dinaphthyl (II). Since these compounds also produce bands at 212 mμ, diphenyl was investigated in the same region;

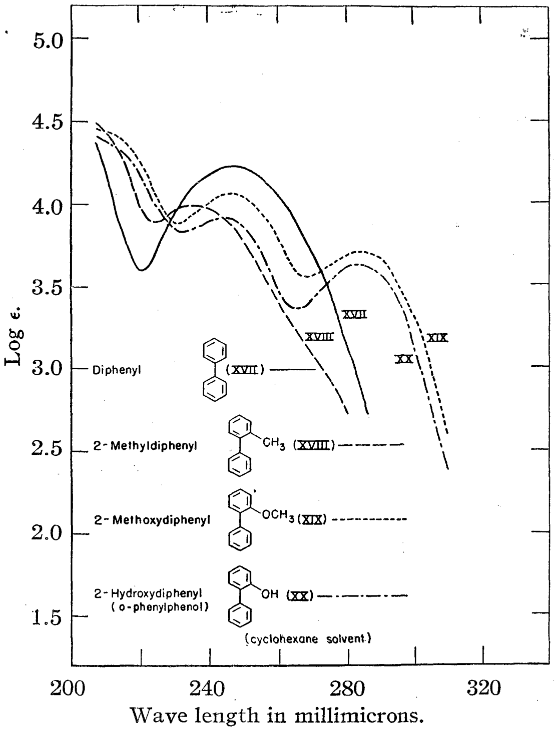


Fig. 7.

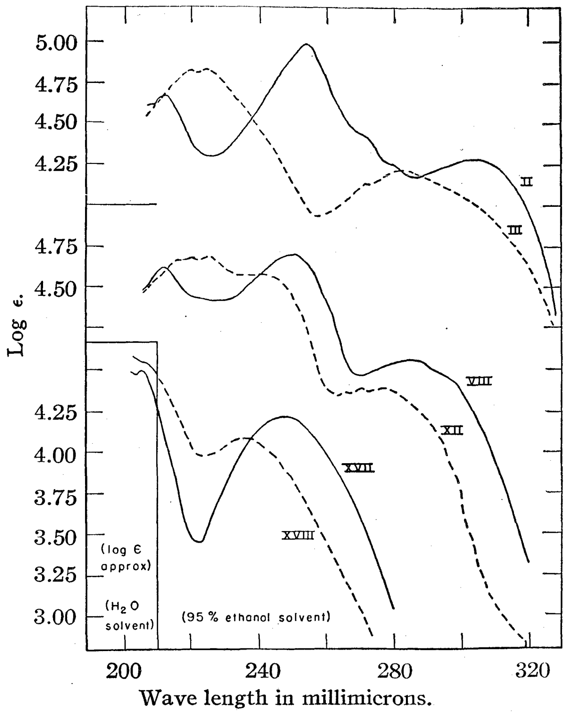


Fig. 8.—Comparison of diphenyls and naphthalenes. Convergence of bands with steric hindrance. Curves: (II) 2,2′-dinaphthyl, (III) 1,2′-dinaphthyl, (VIII) 2-phenylnaphthalene, (XII) 2-*o*-tolylnaphthalene, (XVII) diphenyl and (XVIII) 2-methyldiphenyl.

using water as a solvent at short wave lengths a new small band is found at 205 mμ.[13] The spectrum is given in Fig. 8 together with the spectra of (II) and (VIII).

Similarities in steric hindrance effects for the three compounds, (II), (VIII) and (XVII), are shown by plotting with each of them the spectra of the related sterically hindered derivatives, 2-methyldiphenyl (XVIII), 2-*o*-tolylnaphthalene (XII) and 1,2′-dinaphthyl[14] (III) (Fig. 8). In all three cases the 250 mμ bands of the respective parent compounds undergo hypsochromic shifts and decreased intensities with introduction of hindrance. On the other hand, the short wave length bands in the 210 mμ region appear to sustain bathochromic shifts and thus to converge toward the shifted 250 mμ bands. The effect is greater for the hindered naphthalene derivatives.

Spectrophotometry

The customary limit of the Beckman spectrophotometer used, with good absolute ethanol, is around 220 mμ. As is well known, this solvent always contains troublesome traces of benzene which are difficult to remove. Purification is simplified and the limit of the instrument reduced to 216 mμ by merely using 95% ethanol; this solvent has already come into general use. The limit is further reduced to 206 mμ by substituting for the original 2,000 megohm grid resistor in the phototube amplifier a 20,000 megohm, essentially noise-free, resistor.[15] A 10,000 megohm resistance results in a limit of 208 mμ. Increased resolution also results from these substitutions as seen in the spectra of naphthalene in Fig. 9; the decreased band widths made possible by such resistors are compared at one wave length. It is apparent from these curves, especially in the 305 mμ region that the 20,000 megohm resistor has effected some increased resolution over that obtained with 10,000 megohms. The former resistor was used throughout this investigation but because of the sluggishness of the galvanometer the latter is preferable for general use.

The lowest wave length attained for solutions is 202 mμ, with water as solvent. Water was resorted to in the short wave length measurements of diphenyl and methyldiphenyl since no bands are found down to 206 mμ, the limit of the instrument with 95% ethanol as solvent. Although the solubility of these compounds in water is very slight, it is found to be more than enough to make measurements in this region of intense absorption. For gases the lowest wave length attainable is slightly below 200 mμ, the end of the wave length scale.

In these regions of the spectrum scattered energy is a large percentage of the small total energy transmitted by the glass envelopes on hydrogen

---

[13] Carr and Stücklen, *J. Chem. Phys.*, **4**, 760 (1936), reported a small band for diphenyl vapor in the vacuum ultraviolet at 203 mμ.

[14] 1,2′-Dinaphthyl was used to show this steric effect in lieu of a hindered methyl derivative of 2,2′-dinaphthyl.

[15] Made by Victoreen Instrument Company, Cleveland, Ohio.

tube and phototube. Appropriate corrections for this scattered energy were applied to all spectra. Reliability of the low wave length bands reported is substantiated by the detection of the 207 and 203.5 mμ fine structure bands for benzene solution,[15a] found by Henri.[16] These bands were also observed on a borrowed Beckman which was modified for checking purposes by inserting a 20,000 megohm resistor in the amplifier.

Preparation of Compounds[17]

The preparation of 1,2′-dinaphthyl, 2,2′-dinaphthyl, 1-(2′,3′,4′,5′-tetrahydrophenyl)-naphthalene, 1-cyclohexylnaphthalene, 1-phenylnaphthalene,[18] 1,1′-dinaphthyl,[19] and 2-methyldiphenyl[20] have been described previously. The 2,2′,7,7′-tetramethyl-1,1′-dinaphthyl and 3,3′,4,4′-tetrahydro-1,1′-dinaphthyl were gifts of Professor M. S. Newman. *o*-Phenylphenol was a gift of the Dow Chemical Company and was purified by recrystallization, melting point 56.6–57.8°. The diphenyl was an Eastman Kodak Co. product which was chromatographed to remove fluorescent impurities and then recrystallized, melting point 68.5–69.4°. 2-Methoxydiphenyl[21] was prepared by Mr. E. O. Woolfolk by the methylation of *o*-phenylphenol with diazomethane. It was purified by chromatography, followed by recrystallization from petroleum ether and had melting point 28.8–29.4°. Semimicro methoxyl determination (E. O. W.) gave 16.6% methoxyl (calcd. 16.9). The preparation of 2′-hydroxy- and 2′-methoxy-1-phenylnaphthalene and 2′-hydroxy-2-phenylnaphthalene will be described in a future publication.

2-Phenylnaphthalene.[22]—1-Phenylnaphthalene (5.06 g.) was passed over silica gel at 405–460° during twenty minutes in the apparatus previously described.[23] The product (4.57 g.) was twice crystallized from alcohol and gave 1.0 g. of 2-phenylnaphthalene as colorless crystals, m. p. 102.4–103.8°. The sample used for ultraviolet absorption spectrum measurements was carefully purified by chromatographic adsorption on alumina.

The complex with *s*-trinitrobenzene was obtained from ethanol as yellow plates, m. p. 113.5–115.2° with sintering at 111°. *Anal.*[24] Calcd. for $C_{22}H_{15}N_3O_6$: N, 10.07; for $C_{28}H_{18}N_6O_{12}$: N, 13.33. Found: N, 12.8, 12.7. The analysis indicates that the complex of *s*-trinitrobenzene with 2-phenylnaphthalene is formed in the ratio of 2 moles of the nitro compound to one of the hydrocarbon. The complex is readily dissociated and difficult to purify. 2-Phenylnaphthalene did not form a complex with picric acid when solutions of both components were mixed in the usual fashion.

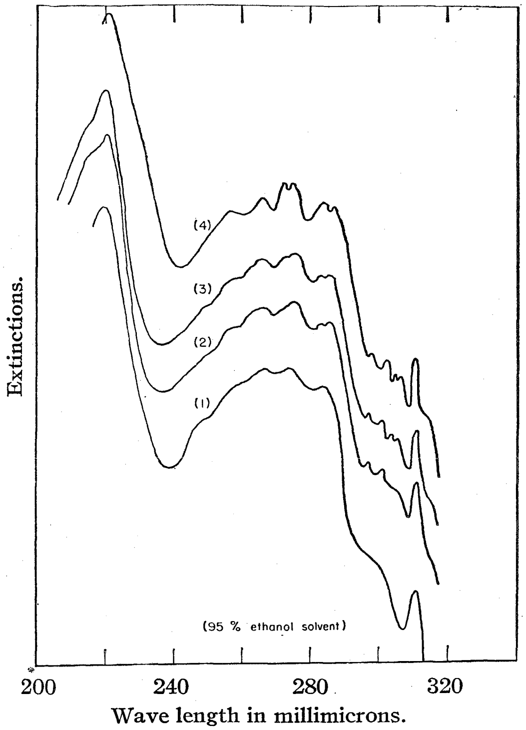


Fig. 9.—Spectra of naphthalene under varying resolving power. Amplifier grid resistance, R, and the usable band widths (B. W.) at 285 mμ are: (1), R = 2000 MΩ, B. W. = 13.6 Å.; (2), R = 10,000 MΩ, B. W. = 6.8 Å.; (3), R = 20,000 MΩ, B. W. = 5.1 Å.; (4), comparison curve from Mayneord and Roe, *J. Chem. Soc.*, 929 (1934).

1-*o*-Tolylnaphthalene.—To the Grignard reagent from 1.1 mole of *o*-bromotoluene and 1.21 moles of magnesium in 725 cc. of ether, there was added 1.0 mole of 1-tetralone[25] in 150 cc. of ether. The mixture was stirred and refluxed for sixteen hours, then decomposed with ammonium chloride solution. The ether layer was separated and dried. Evaporation of the ether left a mixture of crystals and oil which was filtered. The crystalline material was washed with cold petroleum ether and was obtained as colorless needles (34 g.). This material was investigated separately, and the results will be reported later. The filtrate containing the oil and petroleum ether was fractionally distilled. There was collected 64.12 g., b. p. 90–115° (1 mm.), of a first fraction which was nearly all recovered tetralone; 41.97 g., b. p. 115–142° (0.7 mm.); and a third fraction, b. p. 130–230° (0.3 mm.) which was a gum. The second fraction was redistilled from sodium and gave as a main fraction, 31.99 g., b. p. 130–138° (1 mm.). *Anal.*[26] Calcd. for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 91.2; H, 7.5. This crude 1-(*o*-tolyl)-3,4-dihydronaphthalene (29.25 g.) was heated with 1.5 g. of 30% palladium-on-charcoal catalyst.[27] There was evolved 2720 cc. (N. T. P.) of hydrogen (91.3%). The product was distilled and 28.25 g. of material which solidified on cooling was collected. One crystallization from methanol gave 22.73 g. of colorless needles, m. p. 68.8–70.8°. The sample for ultraviolet absorption spectrum measurements was carefully purified by chromatographic adsorption on alumina.

2-*o*-Tolylnaphthalene.—To the lithium compound from 20.0 g. of 2-bromonaphthalene, 1.47 g. of lithium wire, 95 cc. of ether and 25 cc. of benzene there was added 11.9 g. of *o*-methylcyclohexanone in 45 cc. of ether. After four and one-half hours of refluxing with stirring the green mixture was decomposed with ice water. The organic layer was separated, dried and the solvents evaporated. The residual oil was heated at 160–170° for half an hour with 14 g. of potassium bisulfate. The

---

[15a] NOTE ADDED IN PROOF: Detection of these benzene bands in water solution was reported by Doub and Vandenbelt, THIS JOURNAL, **69**, 2714 (1947).

[16] Henri, "International Critical Tables," Vol. V, McGraw-Hill Book Co., Inc., New York, N. Y., 1929, p. 359.

[17] All melting points corrected.

[18] Orchin and Reggel, THIS JOURNAL, **69**, 505 (1947).

[19] Orchin and Friedel, *ibid.*, **68**, 573 (1946).

[20] Orchin, *ibid.*, **67**, 499 (1945).

[21] Hönigschmidt, *Monatsh.*, **22**, 570 (1901).

[22] Mayer and Schiffner, *Ber.*, **67B**, 67 (1934).

[23] Orchin, *Ind. Eng. Chem.*, *Anal. Ed.*, **17**, 673 (1945).

[24] Microanalysis by Dr. T. S. Ma, University of Chicago, Chicago, Illinois.

[25] We wish to thank Dr. Gilbert Thiessen and the Koppers Co. for a generous sample of 1-tetralone.

[26] Macroanalysis by Coal Analysis Section, U. S. Bureau of Mines.

[27] Linstead and Thomas, *J. Chem. Soc.*, 1127 (1940); catalyst-d.

product was taken up in benzene, and the benzene evaporated. Distillation of the residue gave a first fraction which was discarded and a second fraction, b. p. 132–150° (0.4 mm.) weighing 11.13 g. This oil was heated with 1.00 g. of palladium-on-charcoal catalyst[27] at 320–360° for two hours during which time 1513 cc. (N. T. P.) of hydrogen (67.5%) was evolved. The material was distilled, and the distillate dissolved in petroleum ether and chromatographed on alumina. The least strongly adsorbed material was discarded (small amount of naphthalene), and the balance of the product with the exception of some very strongly absorbed material recovered. Crystallization from methanol gave 2.80 g. of colorless crystals, m. p. 44.7–46.6°. The pure sample used for ultraviolet absorption spectrum measurements had m. p. 45.7–48.0°.

Anal.[28] Calcd. for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.5; H, 6.6.

2-*o*-Tolylnaphthalene did not form complexes with picric acid or 2,4,7-trinitrofluorenone[29] when solutions of the two components were mixed in the usual manner. A concentrated solution of the hydrocarbon and *s*-trinitrobenzene in alcohol gave a first crop of *s*-trinitrobenzene. The mother liquor precipitated bright yellow crystals, m. p. 101.2–102.5°, which were shown by analysis to contain one mole of the hydrocarbon to two moles of the nitro compound.

Anal.[29] Calcd. for $C_{29}H_{20}N_6O_{12}$: N, 13.04. Found: N, 13.1.

Acknowledgments.—The authors wish to acknowledge the helpful suggestions of Drs. J. J. McGovern and E. Solomon and the loan of the former's instrument for checking purposes. Thanks are due Lois Pierce and Ruth Borgman, who determined the spectra.

Summary

Steric hindrance effects are discussed in connection with the spectra of 1,1′-, 1,2′- and 2,2′-dinaphthyl, 1- and 2-phenylnaphthalene, diphenyl and various derivatives of some of these compounds. Short wave length peaks are detected in the region 205 to 212 mμ for compounds containing two aromatic ring systems conjugated without steric hindrance. These bands and the longer wave length bands appear to converge toward each other when the coplanarity of the systems is hindered by introduction of interfering groups.

All spectra were determined to 206 mμ on a Beckman spectrophotometer; two spectra were measured to 202 mμ. The simple methods for attaining this limit, as well as increased resolution, are described.

PITTSBURGH, PENNSYLVANIA RECEIVED MAY 29, 1947

---

[28] Microanalysis by Arlington Laboratories, Fairfax, Virginia.

[29] Orchin and Woolfolk, THIS JOURNAL, **68**, 1727 (1946).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Kinetics of Neutralization of Nitroethane with Ammonia and Methylamines

BY RALPH G. PEARSON

The rates of neutralization of the simple nitroparaffins with hydroxyl ion and other charged bases have been measured by several investigators.[1] The reaction is a slow process conveniently

$$R_1R_2CHNO_2 + B^- \longrightarrow R_1R_2CNO_2^- + BH \quad (1)$$

measured at 0° in water solution. This paper reports the rates of neutralization of nitroethane with ammonia, methyl-, dimethyl- and trimethylamine in aqueous solution at 0 and 5.2°. The reactions were followed by the change in conductance as the ions were formed

$$CH_3CH_2NO_2 + B \underset{k_2}{\overset{k_1}{\rightleftarrows}} CH_3CHNO_2^- + BH^+ \quad (2)$$

where B stands for the neutral base and BH^+ for the conjugate acid.

The work was undertaken both to obtain fundamental data on the kinetics of ionization of neutral molecules in a solvent of high dielectric constant and to see how the rates for the various amines correlate with their base strengths. The increased basicity of methylamine and dimethylamine compared with ammonia and the sharp decrease in base strength for trimethylamine have been the subject of several papers.[2]

Experimental

Preparation of Materials.—Commerical Solvents nitroethane was dried with magnesium sulfate, refluxed with urea, dried with phosphorus pentoxide and fractionated through a 10-plate column. Small middle portions boiling within a 0.1° range were taken for use. The organic amines were obtained from Eastman Kodak Co. white label hydrochlorides or amines converted to hydrochlorides. The salts were recrystallized from water and the amines freed by adding measured amounts of sodium hydroxide and distilling in all glass carbon dioxide-free apparatus into conductivity water. For methylamine and dimethylamine, one-third of the amount of sodium hydroxide needed was added and the distillate discarded, another one-third of sodium hydroxide was added and the distillate collected. For trimethylamine the distillate from the first one-third equivalent of sodium hydroxide was collected. Ammonia was obtained by distilling C. P. ammonia into conductivity water. Solutions were made up 0.05 to 0.10 molar as determined by titration and stored in a carbon dioxide-free apparatus connected to a buret. Solutions of nitroethane were made up by direct weighing, adding conductivity water and storing in a cold room until used.

Apparatus.—Conductances were measured with a modified Jones–Josephs bridge[3] using an oscilloscope for a null point indicator. This combination of direct reading

---

(1) (a) Pedersen, *Kgl. Danske Videnskab. Selskab., Math-fys. Medd.*, **12**, No. 1 (1932); (b) Junell, Dissertation, Upsala, 1935; (c) Maron and La Mer, THIS JOURNAL, **60**, 2588 (1938).

(2) (a) Wynne-Jones and Everett, *Proc. Roy. Soc.* (*London*), **A177**, 499 (1941); (b) Brown, THIS JOURNAL, **67**, 374, 378 (1945).

(3) Dike, *Rev. Sci. Inst.*, **2**, 379 (1931).

bridge and rapid visual indicator greatly simplified the following of the resistance with time. A Washburn type cell for medium conductivities was used. Time was followed with a calibrated stop watch. Temperature control was obtained by using ice-water mixtures in a large Dewar flask at 0° and a solid-liquid benzene slush at 5°. With manual stirring temperature could be maintained constant to ± 0.02° during a run using the benzene freezing mixture. Low humidity, however, was essential for good results.

General Procedure.—The quantity of base needed to react with 10 cc. of nitroethane was run into a flask, stoppered and cooled to the reaction temperature. The separately cooled nitroethane solution was added with a pipet and the stop watch started during the course of the addition. After mixing, a sample was drawn into the conductance cell, placed in the bath and vigorously stirred for two or three minutes before readings were begun. The times required for sufficient readings ran from fifteen minutes to an hour. The cell contents and bath were placed in a cold room for a day or two and the equilibrium value of the resistance read after bringing back to the reaction temperature. Wrapping the entire system in aluminum foil greatly aided in preserving the benzene-bath.

Calculations.—The kinetics are complicated by the simultaneous reactions of nitroethane with the amine and hydroxyl ion and by the reversal of reaction (2).

$$\mathrm{CH_3CH_2NO_2 + OH^-} \xrightarrow{k_3} \mathrm{CH_3CHNO_2^- + H_2O} \quad (3)$$

However, the rate constant, k_3, for hydroxyl ion is known.[1c] Also we have sufficient data on the acid ionization constant of $C_2H_5NO_2$,[4] and the basic ionization constants of the amines[2a,5] to get the equilibrium constant for (2). We have

$$K_1 = \frac{k_1}{k_2} = \frac{K_aK_b}{K_w} \quad (4)$$

Since K_a for $C_2H_5NO_2$ is 2.67×10^{-9} at 0°, K_w for water is 1.14×10^{-15} at 0°,[6] and K_b for the amines runs from 10^{-5} to 5×10^{-4} we see that $k_1 > k_2$ by a factor of 30 to 1000 and that we can neglect the reverse reaction provided we do not carry the measurements too far.

The rate expression then becomes

$$d[\mathrm{C_2H_4NO_2^-}]/dt = k_1[\mathrm{C_2H_5NO_2}][\mathrm{B}] + k_3[\mathrm{C_2H_5NO_2}][\mathrm{OH^-}] \quad (5)$$

Now if we assume that the equilibrium

$$\mathrm{B + H_2O} \rightleftarrows \mathrm{BH^+ + OH^-} \quad (6)$$

is always maintained, we can write

$$[\mathrm{OH^-}] = K_b[\mathrm{B}]/[\mathrm{BH^+}] \quad (7)$$

where we now substitute for the activities the molar concentrations and use the thermodynamic equilibrium constant as we shall do throughout. The rate expression then becomes

$$\frac{dx}{dt} = k_1(a - x)^2 + k_3K_b\frac{(a - x)^2}{x} \quad (8)$$

where $x = [\mathrm{C_2H_4NO_2^-}] = [\mathrm{BH^+}]$, $a = [\mathrm{C_2H_5NO_2}]_0 = [\mathrm{B}]_0$, and $(a - x) = [\mathrm{C_2H_5NO_2}] = [\mathrm{B}]$. Equation (8) can be integrated by the use of partial fractions giving

$$t = c + \frac{k_3K_b}{(ak_1 + k_3K_b)^2}\ln\frac{(a - x)}{(k_1x + k_3K_b)} + \frac{1}{(ak_1 + k_3K_b)}\frac{a}{(a - x)} \quad (9)$$

The use of the integration constant, c, eliminates the necessity of matching the start of the reaction with the zero of time.

Assuming that equivalent conductances do not change over the range of ionic concentration encountered in an experiment, it is possible to write (9) in terms of the measured resistance R. It is necessary to allow for the conductance of the hydroxyl ion which is appreciable only during the early part of a run. Thus we have

$$\frac{z}{R} = \Lambda_{\mathrm{OH^-}}\, K_b\frac{(a - x)}{x} \times (\Lambda_{\mathrm{BH^+}} + \Lambda_{\mathrm{C_2H_4NO_2^-}})\, x \quad (10)$$

where z is a constant for the cell and the Λ's refer to the equivalent ionic conductances. This can be converted to

$$\frac{z}{R} = \frac{z(a - x)}{R_0x} + \frac{zx}{R_ca} \quad (11)$$

where R_0 is a quantity estimated from values of K_b, measured conductances of sodium hydroxide solutions in the cell used for the kinetic studies, and the transference numbers of Na^+ and OH^-. R_c is a value of the equilibrium resistance corrected for the incompleteness of reaction (2). If we let R_e be the measured value of the equilibrium resistance, then R_c differs from R_e by a factor of $K_1^{1/2}/(K_1^{1/2} + 1)$. Solving for x in (11)

$$x = \frac{aR_c}{R}\left(1/2 + R/2R_0 + 1/2\sqrt{1 + \frac{R^2}{R_0^2} + \frac{2R}{R_0} - \frac{4R^2}{R_0R_c}}\right) = \frac{aR_c'}{R} \quad (12)$$

Actually the values of R_c' calculated from (12) differ by only a few per cent. from the constant value R_c. Equation (9) now becomes

$$t = c + \frac{k_3K}{(ak_1 + k_3K_b)^2}\ln\frac{(R - R_c')}{\left(k_1R_c' + \frac{k_3K_b}{a}R\right)} + \frac{1}{(ak_1 + k_3K_b)}\frac{R}{(R - R_c')} \quad (13)$$

We have from (13) that t is a function of the resistance and several constants of which only k_1 is unknown. For the three organic amines the log term is only a small correction factor and a good estimate of k_1 can be made by plotting t against $R/(R - R_c')$ and setting the slope equal to $1/(ak_1 + k_3K_b)$. Placing this value of k_1 in the log term it is possible to solve (10) algebraically using pairs of t and R readings and get a better value of k_1. For methylamine and dimethylamine the k_1 values calculated for pairs selected at random usually agree to 1 or 2%. For trimethylamine and ammonia k_1 show a systematic decrease as the reaction proceeds. For ammonia the log term is

---

[4] Turnbull and Maron, THIS JOURNAL, **65**, 212 (1943).

[5] Everett and Wynne-Jones, *Proc. Roy. Soc.* (*London*), **A169**, 190 (1938).

[6] Harned and Owen, "Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1943.

quite important, and it is necessary to try several values of k_1 until the calculated values agree with the starting one.

Another method of analyzing the data is to write (10) as

$$t = c + \frac{1}{ak_1 + k_3K_b} F(R) \qquad (14)$$

where

$$F(R) = \frac{k_3K_b}{(ak_1 + k_3K_b)} \ln \frac{R - R'_e}{(k_1R'_e + (k_3K_bR/a))} + \frac{R}{(R - R'_e)} \qquad (15)$$

and use the estimated value of k_1 to solve for $F(R)$. Then plotting t against $F(R)$ should give a straight line with a slope from which k_1 can be found. Figures 1 and 2 show the results obtained in this way with the four bases in typical runs. The values of the rate constants from the best values of the slopes agree with the one used to get $F(R)$. The falling off of the rate constant for ammonia and trimethylamine is clearly evident. The extent of reaction in the measured portions for various runs was approximately from 10 to 25% for ammonia, from 20 to 40% for trimethylamine, and from 25 to 75% for methylamine and dimethylamine. Table I is a tabulation of the rate constants k_1 obtained at 0 and 5.2°. The units of

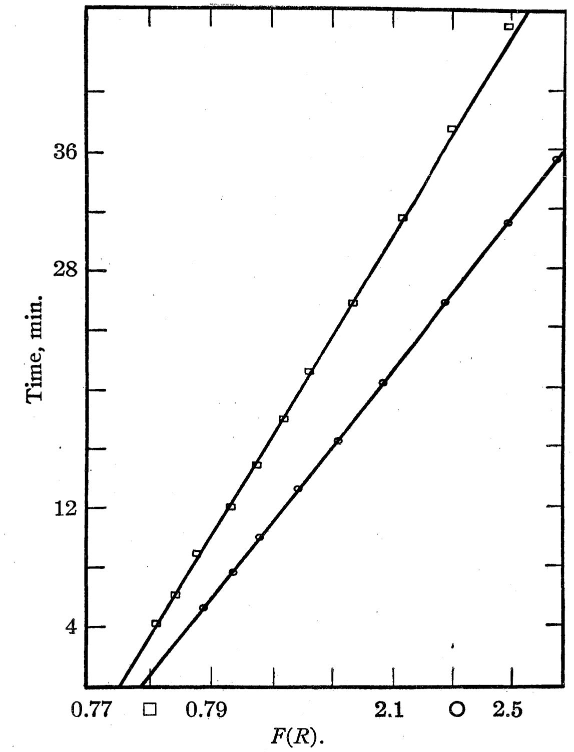


Fig. 1.—□, 0.0212 M ammonia, 0°, slope = 585; ○, 0.0258 M methylamine, 0°, slope = 28.2.

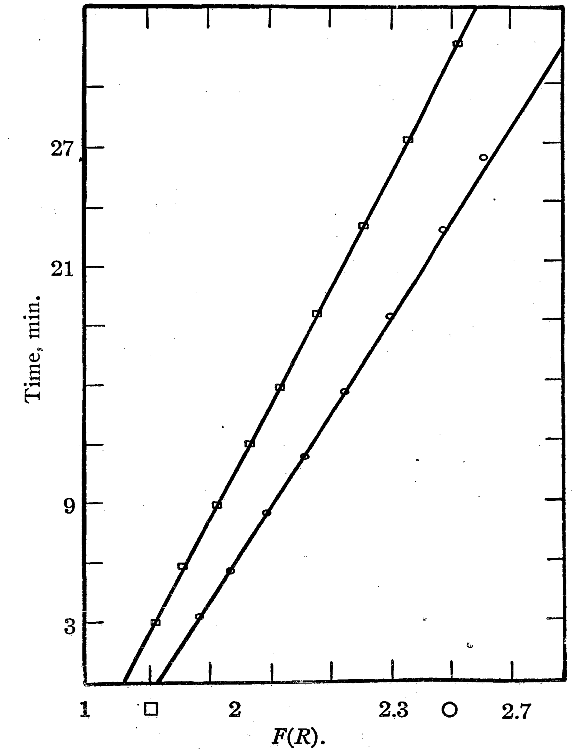


Fig. 2.—□, 0.0252 M dimethylamine, 0°, slope = 12.30; ○, 0.0333 M trimethylamine, 0°, slope = 14.35.

TABLE I

KINETICS OF B + $C_2H_5NO_2$

Temp., °C.	Base	Concentration moles/liter	k_1 liters/mole-minute
0	Ammonia	0.0212	0.057
0	Ammonia	.0218	.057
0	Ammonia	.0650	.047
5.2	Ammonia	.0206	.097
5.2	Ammonia	.0218	.097
5.2	Ammonia	.0650	.079
0	Methylamine	.0214	.86
0	Methylamine	.0258	.84
0	Methylamine	.0325	.85
0	Methylamine	.0440	.78
5.2	Methylamine	.0258	1.47
5.2	Methylamine	.0325	1.45
5.2	Methylamine	.0416	1.41
0	Dimethylamine	.0173	2.60
0	Dimethylamine	.0232	2.50
0	Dimethylamine	.0249	2.67
0	Dimethylamine	.0359	2.60
0	Dimethylamine	.0430	2.54
0	Dimethylamine	.0510	2.44
5.2	Dimethylamine	.0228	4.50
5.2	Dimethylamine	.0252	4.60
5.2	Dimethylamine	.0458	4.42
0	Trimethylamine	.0320	2.04
0	Trimethylamine	.0333	2.08
0	Trimethylamine	.0448	2.04
5.2	Trimethylamine	.0198	3.68
5.2	Trimethylamine	.0314	3.64
5.2	Trimethylamine	.0448	3.60
0	Hydroxyl ion		39.1
5.2	Hydroxyl ion		59.5

all rate constants are liters/mole-minute. The corresponding data for hydroxyl ion have been included for comparison using the results of Maron and LaMer.[1c]

From the relationship indicated in (4) we can calculate k_2 also, the rate constant for the recombination of the ions. Unfortunately the constants k_1 are seen to be not quite independent of concentration, decreasing somewhat in solutions more concentrated than 0.04 molar. Neglecting the results for these more concentrated solutions where the interionic effects will be greatest, we can calculate the values of k_2 for the range 0.02 to 0.04 molar which will be at least comparable for the several bases. From the variation of k_1 with temperature the activation energy, E_{act}, can be found. Also using the transition state theory of reaction velocity[7]

$$k = \frac{RT}{Nh} e^{\Delta S^{\neq}/R} \, e^{-\Delta H^{\neq}/RT} \qquad (16)$$

and

$$E_{\text{act}} = \Delta H^{\neq} + RT$$

we can calculate the heats and entropies of activation for the reaction (2). Then the corresponding quantities for the reverse reaction can be obtained from

$$\Delta H^0 = \Delta H_1^{\neq} - \Delta H_2^{\neq} \qquad (17)$$

and

$$\Delta S^0 = \Delta S_1^{\neq} - \Delta S_2^{\neq} \qquad (18)$$

where the subscripts 1 and 2 refer to the forward and reverse processes. The standard state is unit activity though actually we are neglecting the difference between activity and concentration for reactants, products and activated complex alike. Table II summarizes all of this information calculated at 0°. The source of the thermodynamic data is from references (2a), (4) and (5). Since the data on nitroethane do not go down to 0°, it was assumed that $\Delta C_p^0 = -40$ cal./degree for the ionization of nitroethane in computing ΔH^0 and ΔS^0 at 0° from the data at 10 and 25°. According to Pitzer[8] this is a reasonable value for the heat capacity change in the ionization of a weak acid if the change in entropy is negative. The correction involved is small and will not affect the relative values for the four bases.

TABLE II

EQUILIBRIA $B + C_2H_5NO_2 \rightleftarrows BH^+ + C_2H_4NO_2^-$ AT 0°

Base	K_1	ΔH°, kcal.	ΔS°, E. U.	$\Delta H_1^{\neq}$, kcal.	$\Delta S_1^{\neq}$, E. U.
Ammonia	29.8	−10.0	−32.4	14.9	−17.9
Methylamine	836	−10.5	−27.9	15.0	−12.0
Dimethylamine	951	− 8.9	−21.5	15.9	− 6.6
Trimethylamine	60.4	− 5.4	−14.1	15.8	− 7.3
Hydroxyl ion	2.35×10^6	−12.2	−18.3	12.1	−15.5

Kinetics of $BH^+ + C_2H_4NO_2^-$ at 0°

Acid	k_2, liters-mole-min.	$\Delta H_2^{\neq}$, kcal.	$\Delta S_2^{\neq}$, E. U.
Ammonium ion	1.91×10^{-3}	24.9	+14.5
Methylammonium ion	1.02×10^{-3}	25.5	+15.9
Dimethylammonium ion	2.74×10^{-3}	24.8	+14.9
Trimethylammonium ion	3.44×10^{-2}	21.1	+ 6.8
Water	1.66×10^{-5}	24.3	+ 3.0

Discussion

It is evident that there is no linearity between the rates of neutralization and the base strengths of the amines, dimethylamine and particularly trimethylamine, reacting more rapidly than their basicities would warrant. This is in accord with previous observations that substitutions close to the center of reaction destroy any linear free energy relationships between rates and equilibria.[9] It is interesting also to compare the values of k_2 determined in these experiments with those calculated from an equation due to Junell,[1b] who measured the rates of combination of a number of neutral acids with the anion of nitroethane. Junell found that k_2 would be calculated from K_a, the acid ionization constant by the equation

$$\log k_2 = 1.54 + 0.37 \log K_a \qquad (18)$$

Taking K_a for the ammonium ions as K_w/K_b, we find for k_2 6.6×10^{-3}, 1.95×10^{-3}, 1.90×10^{-3} and 5.2×10^{-3} for NH_4^+, $CH_3NH_3^+$, $(CH_3)_2NH_2^+$ and $(CH_3)_3NH^+$, respectively. We see from Table II that NH_4^+ and $CH_3NH_3^+$ react more slowly and $(CH_3)_2NH_2^+$ and $(CH_3)_3NH^+$ react more rapidly. In fact, the reason for the low basicity of trimethylamine, judging from this one reaction, is the abnormally high rate of conversion of the ion to the neutral base.

The heats of activation for the forward reaction appear to be normal for bimolecular reactions in solution. The entropies of activation, while fairly large and negative, compare with that for the hydroxyl ion reaction. For the reverse process $\Delta H^{\neq}$ is high, in agreement again with the hydroxyl ion reaction. The trimethylammonium ion has a conspicuously low heat of activation. The entropies of activation for the reverse reaction are large and positive. The interpretation of this in terms of the transition state theory is as follows: if we identify the entropy decrease in ionization with the electrostriction of the solvent or the binding of solvent molecules around the ions, the activated complex is solvated more than the neutral reactants but less than the product ions. Hence there is a loosening of structure in going from the ions to the complex and $\Delta S_2^{\neq}$ is positive. The desolvation of the ions accounts for the high energy barrier in forming the complex. Trimethylammonium ion does not appear to be as strongly solvated then as the other ions. This would be expected in view of the hydrophobic nature of the

---

[7] Glasstone, Laidler and Eyring, "Theory of Rate Processes," McGraw-Hill Book Co., New York, N. Y., 1941, Chapt. IV.

[8] Pitzer, THIS JOURNAL, **59**, 2365 (1937).

[9] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, Chapt. VII.

methyl groups compared with the hydrogen atoms that they displace.

Summary

1. The second order rate constants for the reaction of nitroethane with ammonia, methyl-, dimethyl- and trimethylamine in water at 0 and 5.2° are reported.

2. The values of the rate constants at 0° are calculated from equilibrium data for the reaction of ammonium ion, methyl-, dimethyl- and trimethylammonium ions with the anion of nitroethane.

3. The heats and entropies of activation for the above reactions are computed.

4. The interpretation of the data indicates that the activated complex is not as strongly solvated as the product ions but more solvated than the reactants.

5. The decreased base strength of trimethylamine appears to be due to the decreased solvation energy and hence increased reactivity of the trimethylammonium ion.

EVANSTON, ILLINOIS RECEIVED FEBRUARY 24, 1947

CONTRIBUTION FROM THE ARMOUR RESEARCH FOUNDATION OF THE ILLINOIS INSTITUTE OF TECHNOLOGY]

Crystallization of *p,p'*-DDT from Binary Melts

BY VICTOR GILPIN,[1] WALTER MCCRONE, ANNETTE SMEDAL AND HELEN GRANT

Introduction

Little work has been reported in recent years on the linear crystallization velocity (C.V.) of supercooled melts of organic compounds. Undoubtedly, part of this lack of interest has been due to the belief that C.V. measurements have no physical significance, because the problem of conducting the heat of crystallization away from the solid-liquid interface has made true temperature measurements difficult.[2,3] This difficulty has arisen in two ways. In the first place, the majority of investigators have been interested in the maximum C.V.; as Michel[4] has shown, this quantity is of value as a criterion of purity, but, due to the rapid movement of the crystal front, the temperature recorded is that of the thermostat, not that of the interface. In the second place, most previous workers employed capillary tubes of several millimeters bore; the crystal front accordingly had only a small portion of its surface exposed to the thermostat.

It is believed that the method recently developed for microscopic quantitative analysis of *p,p'*-DDT[5] avoids both these difficulties, and permits the measurement of true equilibrium temperatures over a limited range. The method employs thin films of the melt (less than 0.1 mm.) which have a correspondingly larger fraction of the interface in contact with the thermostat. Measurements are made on the lower temperature branch of the C.V. *vs.* temperature curve, in which region the rates are relatively slow, and where, moreover, rate measurements are uncomplicated by the transition in the reverse direction. It should be possible to attempt theoretical interpretation of data obtained in this way. The aim of the present and future work is to provide such data.

No claim of originality is made for the method of measuring such rates under the microscope. Dreyer[6] appears to have been the first to measure the C.V. on microscope slides.

Experimental Results

Effect of Temperature.—The technique described previously for *o,p*-DDT/*p,p'*-DDT mixtures[5] was used to establish C.V. *vs.* temperature curves for various mixtures of *p,p'*-DDT with 1,3,5-triphenylbenzene (TPB) and with 5-methyl-2-isopropylphenol (thymol). Figure 1 shows the general form of such curves. To avoid crowding, some experimental curves were omitted. In agreement with much earlier work on binary melts[7] the scatter of experimental points becomes considerable for *p,p'*-DDT mixtures containing more than about twenty-five weight per cent. of a second component. Thymol results are indicated in the smoothed curves of Fig. 2, in the rate *vs.* composition form used previously,[5] because a rate *vs.* temperature plot leads to undue crowding here. A similar increase in C.V. on addition of certain types of impurities was first noted by Dreyer.[8]

In Fig. 4 of the previous publication,[5] the Arrhenius lines were drawn through the raw experimental data. Because of the scatter of experimental points, it is now believed that a better representation of the true trend of the Arrhenius lines is achieved by using smoothed data from the C.V. *vs.* temperature curves. In Fig. 3, the best line was drawn through the smoothed data for pure *p,p'*-DDT, and the other lines were drawn parallel (except for thymol). The same procedure was used in constructing the graph for TPB mixtures (Fig. 4). Only one point of the one per cent. thymol line has been included, and several thymol

---

[1] Present address: School of Chemistry & Physics, Pennsylvania State College, State College, Pa.

(2a) Tammann, "Kristallisieren and Schmelzen," Leipzig, 1903; (2b) Frenkel, "Kinetic Theory of Liquids," Oxford University Press, London, 1947.

(3) Luyet, *Biodynamica*, No. 48, 28 (1939).

(4) Michel, *Bull. soc. chim. Belg.*, **48**, 105 (1939).

(5) McCrone, Smedal and Gilpin, *Ind. Eng. Chem., Anal. Ed.*, **18**, 578 (1946).

(6) Dreyer, quoted in (1).

(7) Bogojawlensky, *Z. physik. Chem.*, **27**, 585 (1898).

(8) Dreyer, *ibid.*, **48**, 467 (1940).

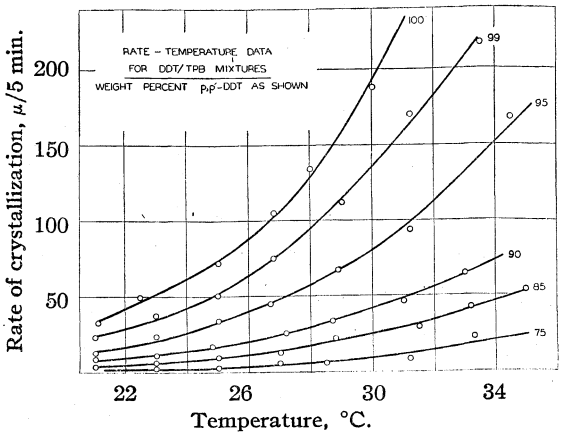


Fig. 1.—The effect of temperature on C.V. of p,p'-DDT/TPB mixtures.

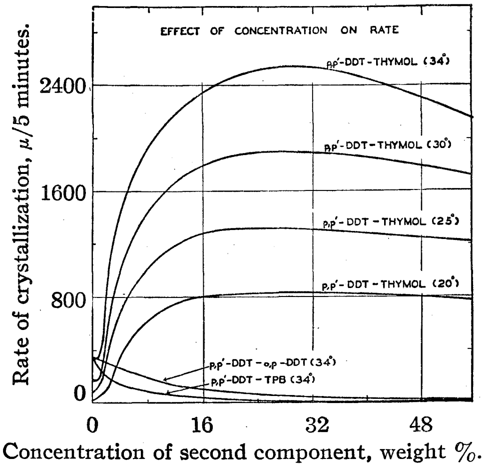


Fig. 2.—The effect of concentration on C.V. of p,p'-DDT/thymol mixtures.

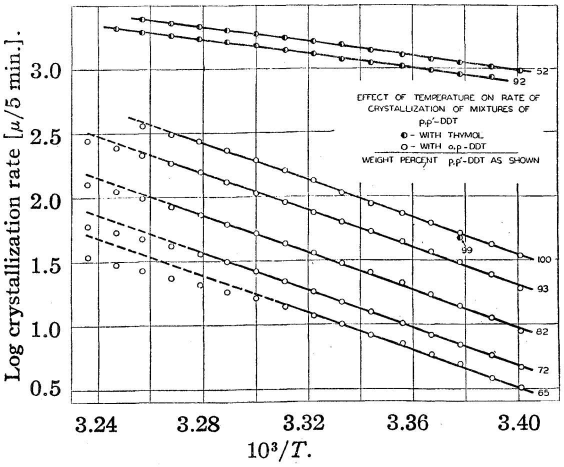


Fig. 3.—Arrhenius-type relations for mixtures of p,p'-DDT with o,p-DDT and thymol.

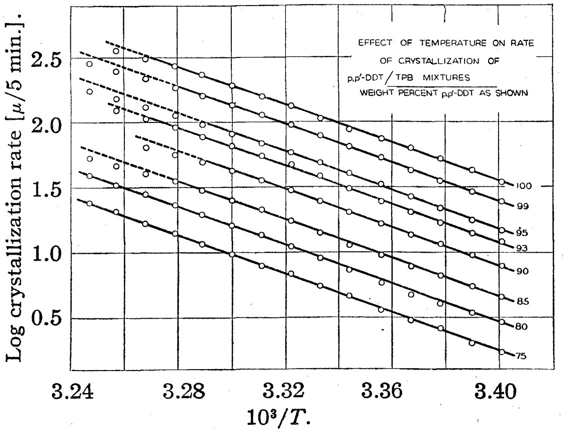


Fig. 4.—Arrhenius-type relations for p,p'-DDT/TPB mixtures.

lines have been omitted, to avoid crowding the graph. Because of very poor reproducibility of results for thymol mixtures, of compositions between 99 and 92% DDT, no data were recorded in this range.

Figures 3 and 4 show the Arrhenius-type relation.

$$\text{C.V.} = Be^{-E_c/RT}$$

holding remarkably well at lower temperatures. At these lower temperatures, the apparent activation energy of crystallization (E_c) for p,p'-DDT is 33.4 kcal., and this does not change when this compound is growing from mixtures containing TPB, o,p-DDT, or very small amounts of thymol. In other words, these compounds do not make it easier or harder for p,p'-DDT to crystallize. They do decrease the rate, however by lowering the value of B. The importance of B, which may include an entropy term, suggests that structural symmetry of the second component may play some part in the rate determining process in these mixtures. Larger concentrations of thymol, however, do lower the apparent activation energy to 12.1 kcal., and do appear to make it easier for p,p'-DDT to crystallize in thymol mixtures.

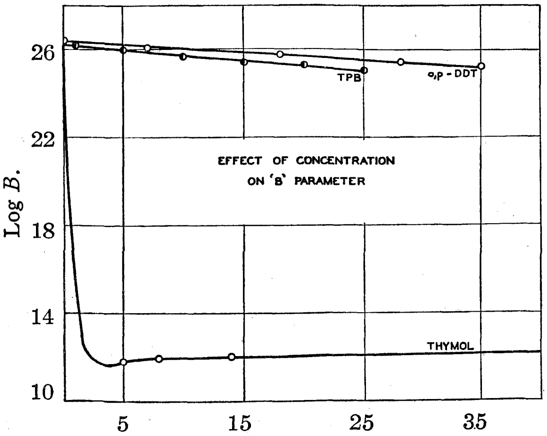
A survey of earlier work reveals only three compounds for which enough of the lower temperature branch of the C.V. *vs.* temperature curve has been reported to make possible a calculation of E_c. Dreyer's figures[6] for benzil-o-carboxyllic acid yield a value of 32.9 kcal. From the data of Michel[4] on cholesterol methyl carbonate, E_c is calculated to be 13.2 kcal. The glycerol data of Volmer and Marder[9] give a value of 10.2 kcal. for E_c. A theoretical interpretation of these activation energies must await further experimental work.

The B parameter bears a linear relation to the concentration of o,p-DDT and TPB, as shown in Fig. 5. If mole fraction is plotted, instead of weight fraction, the lines for o,p-DDT and TPB do not coincide. This disagrees with von Pickardt[10] but agrees with Dreyer.[8]

It is possible to derive equations relating the

[9] Volmer and Marder, *Z. physik. Chem.*, **A154**, 97 (1931).

[10] Von Pickardt, *ibid.*, **42**, 17 (1902).



Concentration of second component, weight per cent.

Fig. 5.—Relation of the concentration to Arrhenius "B" parameter.

variables for crystallization of mixtures containing *o,p*-DDT or TPB. These equations are more accurate in predicting rates, over a wider variety of conditions, than the equation developed previously.[5] For *p,p'*-DDT, or for mixtures in which E_c does not change

$$\text{C.V.} = Be^{-33,400/RT}$$
$$\text{or } \log \text{C.V.} = \log B - 7.30 \times 10^3/T$$

From Fig. 5

$$\log B = 26.36 - 3.06 \times 10^{-2}C \text{ (for } o,p\text{-DDT mixtures)}$$
$$\log B = 26.27 - 5.05 \times 10^{-2}C \text{ (for TPB mixtures)}$$

where C.V. is in microns per five minutes, and C is the weight per cent. impurity.

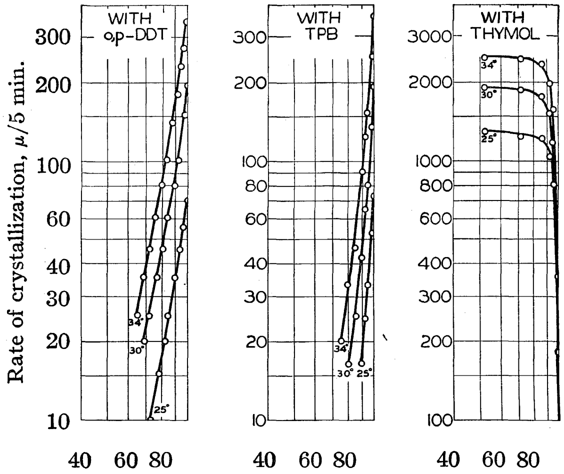
Table I compares rates predicted by these equations with the observed values. The deviation of calculated from observed values becomes considerable at the highest experimental temperatures, where the Arrhenius equation ceases to hold accurately.

TABLE I

COMPARISON OF OBSERVED AND CALCULATED VALUES OF C.V.

	o,p-DDT mixtures			TPB mixtures		
T, °C.	*C*, wt.%	C. V., obs.	C. V., calcd.	*C*, wt.%	C. V., obs.	C. V., calcd.
21	2	29	30	1	24.5	25.0
21	10	15	16	5	14.5	15.0
21	26	5	5	10	7.8	8.5
25	4	55	55	1	53	53
25	10	37	36	10	17	18
25	28	10	10	20	5.8	6.5
29	1	145	145	1	113	132
29	11	70	71	10	36	39
29	30	19	19	25	7.9	6.9
33	2	277	295	1	215	230
33	24	55	58	7	106	115
33	33	28	31	25	16.6	14.2

Effect of Concentration.—The nature of the crystallization of *p,p'*-DDT is such that the crystal front advances, apparently, into a melt of nearly constant composition. Consequently, the isothermal rates measured for a given concentration are constant, unless the second component exceeds about 25%, when irregularities begin to appear. The same phenomenon occurs for many organic compounds if the capillary method is used. Were this not so, it would be impossible to measure the C.V. at different concentrations, for the C.V. of the major component of the mixture would change as the impurity concentration increased ahead of the crystal front.



Concentration–weight per cent. of *p,p'*-DDT.

Fig. 6.—Effect of second component on C.V. of *p,p'*-DDT.

The apparent "order" of the crystallization process in mixtures may thus be calculated, using the van't Hoff method (Fig. 6). From the slopes of the isothermal curves it is found that the order falls with decreasing *p,p'*-DDT concentration. For *o,p*-DDT mixtures, the order falls from about seven to nearly five; for TPB mixtures the corresponding decrease is approximately from twelve to seven. Rawitzer[11] applied essentially the same method to the data of Tammann[12] for benzil/azobenzene and dinitrophenol/acetanilide mixtures. The lines plotted by Rawitzer, however, were straight, and values of the apparent order varied between six and nine, according to the isotherm and mixture chosen. It is hard to understand why the present work and Rawitzer should disagree on the constancy of the order for a given isotherm, unless it be that the nature of the process differs for different compounds and mixtures.

By curve fitting methods it is possible to straighten the curving isotherms. For example, the *o,p*-DDT mixture yields the relation

$$\text{C.V.} = K(C + 100)^{13.7} = K'\ (c + 1)^{13.7}\ (c = \text{weight fraction } p,p'\text{-DDT})$$

Adequate discussion of these kinetics must await further experimental studies.

---

[11] Rawitzer, *Z. anorg. allgem. Chem.*, **175**, 321 (1928).

[12] Tammann and Botschwar, *ibid.*, **157**, 27 (1926).

Acknowledgments.—The authors wish to thank A. Van Hook and C. A. Winkler for reading the manuscript.

Summary

The linear rate of crystallization of p,p-DDT from some supercooled binary melts has been determined, as a function of temperature and melt concentration. The second component of the melt may increase or decrease the rate. The apparent activation energy for the crystallization of pure p,p'-DDT is 33.4 kcal.

CHICAGO, ILL. RECEIVED JULY 7, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN, AND THE DEPARTMENT OF MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, THE PRESBYTERIAN HOSPITAL]

Fractionation and Physical–Chemical Studies of a Commercial Preparation of the Specific Polysaccharide of Type I Pneumococcus[1]

BY ROBERT A. ALBERTY AND MICHAEL HEIDELBERGER

The specific polysaccharide of Type I pneumococcus (SI)[2] is similar to the proteins in its electrochemical and solubility characteristics because it is also an amphoteric colloidal electrolyte. For this reason an attempt was made to apply the alcohol fractionation techniques which have been developed in the purification and separation of plasma proteins[3,4] to the purification of this polysaccharide. As with proteins, electrophoresis has proved a useful method for analyzing crude products[5] and those obtained by fractionation and in determining the isoelectric points of the components.

Experimental

The electrophoresis experiments were carried out in the usual Tiselius apparatus equipped with a cylindrical lens schlieren optical system. The mobilities were calculated by using the conductivity of the buffer in Donnan equilibrium with the electrophoresis sample determined at the temperature of the thermostat, 1°. Because of the high viscosity of the polysaccharide solutions the concentrations of the electrophoresis samples were made 0.5% or less.[6] Throughout the paper, mobilities on the descending side are given, as well as analyses obtained by averaging the results from the ascending and descending patterns.

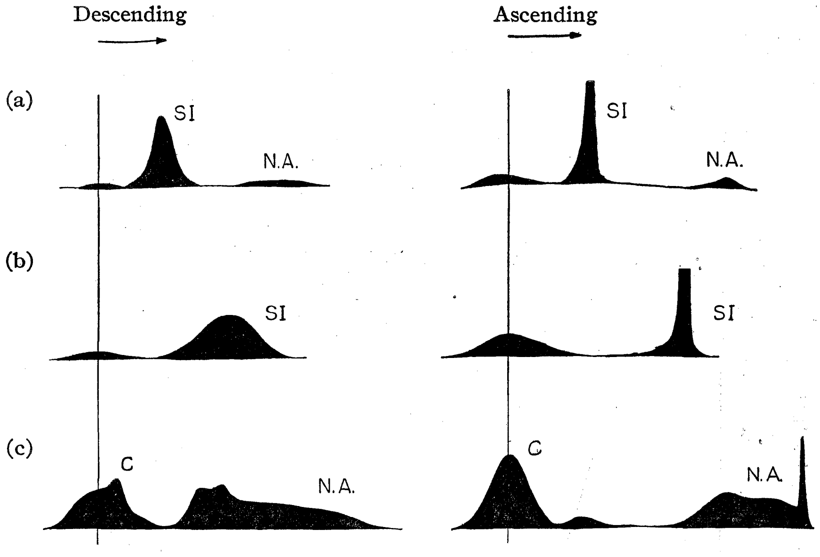


Fig. 1.—Electrophoresis diagrams: (a) commercial preparation, pH 3.90, $\Gamma/2 = 0.10$, after 144 minutes at 3.60 volts/cm.; (b) fraction A, pH 6.90, $\Gamma/2 = 0.10$, after 79 minutes at 3.28 volts/cm.; (c) fraction C, pH 6.90, $\Gamma/2 = 0.10$, after 80 minutes at 3.26 volts/cm.

The SI polysaccharide used as starting material was prepared by E. R. Squibb and Sons and supplied by the Commission on Pneumonia of the U. S. Army Epidemiological Board. The electrophoresis pattern for this preparation at pH 3.9, 0.10 ionic strength acetate buffer, is shown in Fig. 1a. The fast component which makes up 19% of the area of the moving peaks in the pattern contains nucleic acid, and the largest peak represents the SI polysaccharide. These components were identified after electrophoresis by withdrawal of small samples from various levels in the electrophoresis cell by means of a syringe with a long needle. The sample taken just below the fastest ascending peak showed the typical ultraviolet absorption of nucleic acid, with a

---

(1) Presented before the Symposium on Sugars and Amino Sugars in Biochemistry, American Chemical Society Meeting, Atlantic City, April, 1947.

(2) (a) Avery and Heidelberger, *J. Exptl. Med.*, **42**, 367 (1925); (b) Heidelberger, Goebel and Avery, *ibid.*, **42**, 727 (1925); (c) Heidelberger, Kendall and Scherp, *ibid.*, **64**, 559 (1936).

(3) Cohn, Strong, Hughes, Mulford, Ashworth, Melin and Taylor, THIS JOURNAL, **68**, 459 (1946).

(4) Deutsch, Gosting, Alberty and Williams, *J. Biol. Chem.*, **164**, 109 (1946).

(5) As indicated in preliminary tests carried out several years ago with Dr. Dan H. Moore at Columbia University.

(6) The relative viscosity of a 0.1% solution of SI in 0.9% sodium chloride is 1.69; ref. 2c.

maximum at 255 mμ. Samples tested serologically showed that the slower moving component was SI and that the C polysaccharide (the somatic polysaccharide common to all types of pneumococci) did not move in the electrical field or moved so slowly it was not resolved from the salt boundary. The C substance had previously been observed[7] to move with a low mobility (-2.2×10^{-5} at *p*H 7.85 and -1.2×10^{-5} at *p*H 6.20) at 0.05 ionic strength. Since there was no resolution at 0.10 ionic strength it was difficult to estimate the amount of C substance present, but it could not exceed 10% because the area of the stationary boundary was 10–15% of the total area of the electrophoretic pattern in experiments at various *p*H and ionic strengths (see Fractionation). The areas in the electrophoresis pattern were not weighted for differences in refractive index increment for the polysaccharide and nucleic acid since the increments are presumably about the same.[8] Although a trace of nucleoprotein was believed present, it did not appear in the electrophoresis patterns because of the small amount or because its mobility was close to that of one of the other components.

In spite of the high viscosity of the polysaccharide solutions the velocity of the nucleic acid boundary on the ascending side where it moves up into buffer was only slightly higher (about 15%) than on the descending side where it moved into the viscous polysaccharide solution. This difference is caused by the presence of the conductivity gradient at the stationary boundary, the nature of which is understood[9] so that the mobility of the nucleic acid is relatively independent of the viscosity due to the polysaccharide.

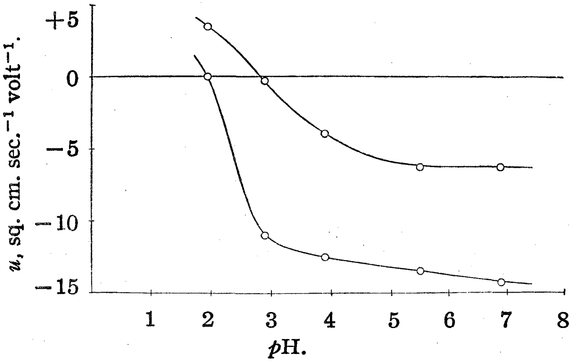


Fig. 2.—Determination of isoelectric points at $\Gamma/2 = 0.10$; upper curve, SI polysaccharide; lower curve, nucleic acid.

Results and Discussion

1. Determination of Isoelectric Point.—The isoelectric point of the SI and nucleic acid in the crude mixture were determined at 0.10 ionic strength from mobility determinations at several *p*H with sodium glycinate, acetate and cacodylate buffers. Figure 2 is a plot of mobility *vs.* *p*H for the two moving components in this material. The isoelectric point for the SI at this ionic strength is *p*H 2.8, and that for the nucleic acid is *p*H 2.0. Since the experiments were performed on mixtures, there is the possibility of some interaction between the components, although this was not evidenced by the electrophoretic patterns.[10] The isoelectric point for the nucleic acid is in agreement with earlier values.[11] The presence of basic groups in the SI polysaccharide is confirmed by the positive mobility at *p*H 2.0.

A sample of SI prepared by earlier methods[2] had a mobility of -5.5×10^{-5} at *p*H 6.9, $\Gamma/2 = 0.10$, in agreement with the mobility of the commercial preparation. Another sample prepared from cultures concentrated by heat and purified in part by precipitation from alkaline solution showed a mobility of -6.5×10^{-5} at *p*H 5.5 in agreement with that obtained for the undegraded SI in spite of the known removal, under these conditions, of an O-acetyl group.[12]

2. Fractionations.—Several fractionations with alcohol were performed on the commercial preparation in the cold in attempts to obtain SI free from nucleic acid and C substance. Addition of ethyl alcohol to dilute solutions (0.5%) at the low ionic strengths ($\Gamma/2 = 0.01$ to 0.1) most suitable for the fractionation of proteins at 0° produced voluminous gels which were not suitable for fractionation. With isopropyl and *n*-propyl alcohols and the much higher ionic strengths customarily used in the precipitation of carbohydrates (3% sodium acetate), there was less tendency to form gels. Figure 3 shows the flow sheet for a fractionation with the electrophoretic analysis (electro.) and serological assay (serol.) of the various fractions. The analytical electrophoresis experiments were carried out at *p*H 6.9 in a cacodylate buffer of 0.10 ionic strength (0.02 *N* sodium cacodylate, 0.08 *N* sodium chloride). The percentage given for the "fast" component includes material with a more negative mobility than -10×10^{-5}. Fraction C contained a large amount of such material (Fig. 1c), although only a portion was nucleic acid as determined with the Beckman spectrophotometer at a wave length of 255 mμ and the extinction values given by Kunitz.[13] Fraction A showed a single symmetrical gradient in electrophoresis and precipitated 90% as much antibody[14] as the same amount of the most active sample of SI available. The electrophoresis pattern is given in Fig. 1b.

Fraction C showed an abnormally large stationary boundary in electrophoresis because of the

---

(7) Goebel, Shedlovsky, Lavin and Adams, *J. Biol. Chem.*, **148**, 1 (1943).

(8) Seibert and Watson, *ibid.*, **140**, 55 (1941), obtained 0.0013 for the specific refractive increment for nucleic acid.

(9) Longsworth and MacInnes, THIS JOURNAL, **62**, 705 (1940).

(10) Longsworth and MacInnes, *J. Gen. Physiol.*, **25**, 507 (1942).

(11) Stenhagen and Teorell, *Trans. Faraday Soc.*, **35**, 743 (1939).

(12) Enders and Pappenheimer, *Proc. Soc. Exptl. Biol. Med.*, **31**, 37 (1933); Avery and Goebel, *J. Exptl. Med.*, **58**, 731 (1933).

(13) Kunitz, *J. Biol. Chem.*, **164**, 563 (1946).

(14) For the method, *cf.* Heidelberger and Kendall, *J. Exptl. Med.*, **55**, 555 (1932).

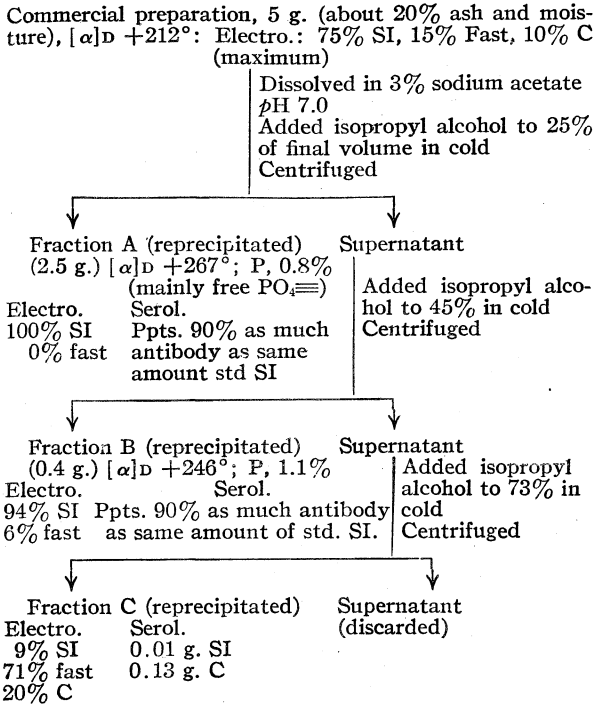


Fig. 3.—Fractionation flow sheet

presence of C substance (see Fig. 1c). The buffer dilution factor at the stationary boundary was calculated from the area of the rising and descending moving peaks. The portion of the area of the ϵ boundary due to salt was calculated by assuming the buffer dilution factor to be equal to the dilution factor for the fast peak. The values indicate that Fraction C contains approximately 20% C.[15] Electrophoresis indicated more SI in Fraction C than did serological assay, but the serological activity of SI may possibly be partially inhibited by excess C substance. Isopropyl alcohol has been found to be a useful reagent in the fractionation and purification of other specific bacterial polysaccharides.

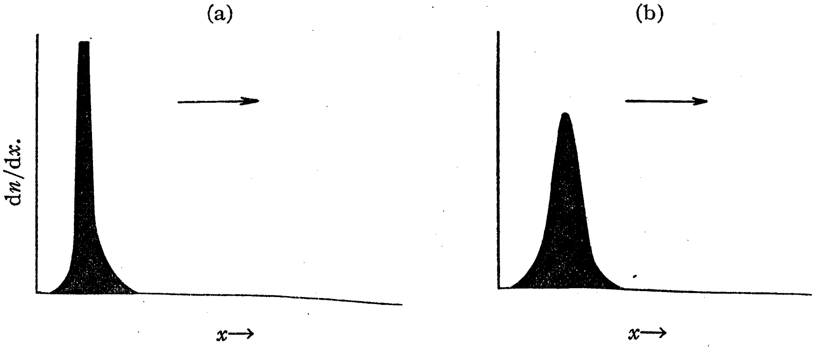


Fig. 4.—Sedimentation diagrams for purified SI (Fraction A) at 50,400 r. p.m. (pH 5.5, acetate buffer, Γ/2 = 0.10): (a) 0.5% solution after 119 minutes, s_{20_w} = 1.2S; (b) 0.15% solution after 119 minutes, s_{20_w} = 2.3S.

3. **Sedimentation Velocity.**—Several sedimentation experiments with the purified SI were carried out at 50,400 r. p. m. in the standard Svedberg oil turbine velocity ultracentrifuge with a cell having a 12-mm. optical path. Both the sedimentation constant and the rate of boundary spreading are quite dependent on concentration as shown in Fig. 4. However, as shown by Gralén,[16] the calculated value of s taken from the apex of the peak does not correspond to the same molecules in experiments at different concentrations. Information as to homogeneity and molecular weight of this material may be obtained only by extrapolation of sedimentation constants and rate of boundary spreading to infinite dilution.

Acknowledgment.—The authors wish to express their appreciation for the interest and helpful suggestions of Dr. J. W. Williams.

Summary

Fractionation procedures with isopropyl alcohol have been applied to the purification of the specific polysaccharide of Type I pneumococcus (SI). Electrophoretic and serological assays were used for the analysis of products. The isoelectric points of the SI and nucleic acid in the crude preparation have been determined by electrophoresis.

MADISON, WISCONSIN
NEW YORK, NEW YORK

RECEIVED JULY 22, 1947

---

[15] The calculation of the protein dilution factor across the stationary boundaries in electrophoresis has been described by Longsworth and MacInnes, ref. 9, and by Longsworth, *Chem. Rev.*, **30**, 323 (1940). The application of these calculations to the determination of immobile components in electrophoresis will be described in a future publication.

[16] Gralén, Sedimentation and Diffusion Measurements on Cellulose and Cellulose Derivatives, Inaugural Dissertation, Upsala, 1944.

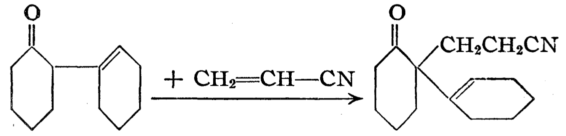
[CONTRIBUTION FROM ROHM AND HAAS CO., INC., AND RESINOUS PRODUCTS AND CHEM. CO.]

The Chemistry of Acrylonitrile. VII. Cyanoethylation of Ketones and Sulfones

BY HERMAN A. BRUSON AND THOMAS W. RIENER

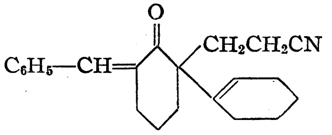
During the course of an investigation on the reactions of acrylonitrile in the presence of alkalies with various types of active methylene compounds,[1] the behavior of 2-cyclohexenylcyclohexanone (I) toward cyanoethylation was examined.

It was found that with one molecular equivalent of acrylonitrile, monocyanoethylation first occurs largely on the methenyl group to give 2-(β-cyanoethyl)-2-cyclohexenylcyclohexanone (II) in about 50% yield, together with unchanged 2-cyclohexenyl-cyclohexanone and higher cyanoethylation products.



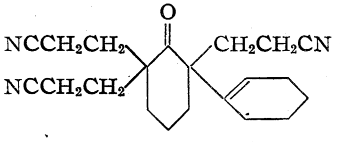
(I) (II)

That the methylene group adjacent to the carbonyl in (II) is intact, is shown by the fact that (II) readily yields a crystalline mono-benzylidene derivative (II) with benzaldehyde.



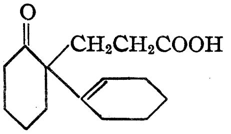
(III)

Further cyanoethylation of (II) with two additional molecular equivalents of acrylonitrile yields the *tri*-cyanoethylation product (IV).

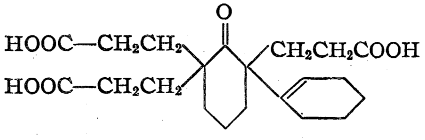


(IV)

Upon alkaline hydrolysis (II) and (IV) yield the respective carboxylic acids (V) and (VI).

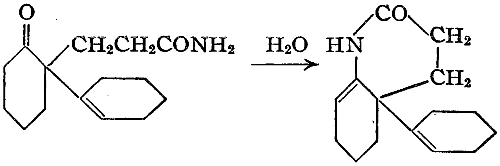


(V)



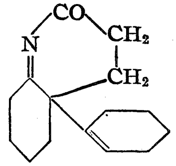
(VI)

When (II) is treated with aqueous sulfuric acid (1 mole sulfuric acid plus 1 mole water per mole of II) a product is obtained which is not the anticipated amide (VII), but a dehydration product thereof, presumably a cyclohexenyl hexahydroquinolone (VIII)



(VII) (VIII)

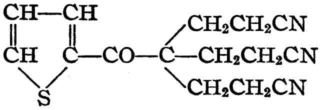
or



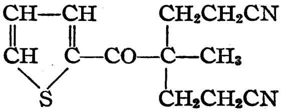
(VIII)

such as would be expected to form when a δ-ketonic amide (VII) or nitrile (II) reacts with aqueous mineral acids.[2]

The reaction of acrylonitrile with 2-acetylthiophene and 2-propionylthiophene gave good yields of the corresponding *tri*- and *di*-cyanoethylation products (IX) and (X), respectively.

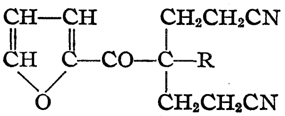


(IX)



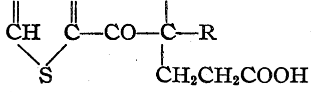
(X)

In a similar manner, acrylonitrile added to 2-acetylfuran, 2-propionylfuran and 2-butyrylfuran to give the crystalline cyanoethylation products (XI), (XII) and (XIII), respectively.



(XI) R = —CH_2CH_2CN
(XII) R = CH_3—
(XIII) R = CH_3CH_2—

Upon alkaline hydrolysis of the cyano groups, (IX) and (X) gave the corresponding carboxylic acids, (XIV) and (XV), respectively.



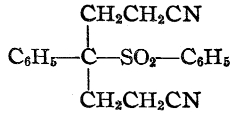
(XIV) R = —CH_2CH_2COOH
(XV) R = CH_3—

The cyanoethylation reaction was also applied to an active methylene sulfone, namely, benzyl phenyl sulfone $C_6H_5CH_2—SO_2—C_6H_5$. This reacted smoothly with two equivalents of acrylonitrile in the presence of "Triton B" to give (XVI)

---

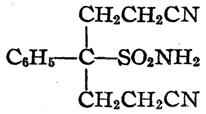
[1] Bruson and Riener, THIS JOURNAL, **64**, 2850 (1942).

[2] Allan and Ball, *ibid.*, **59**, 686 (1937); Kohler, Graustein and Merrill, *ibid.*, **44**, 2536 (1922); Kohler and Souther, *ibid.*, **44**, 2903 (1922); Kohler and Allen, *ibid.*, **46**, 1522 (1924).



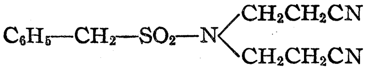
$$C_6H_5-\overset{CH_2CH_2CN}{\underset{CH_2CH_2CN}{C}}-SO_2-C_6H_5 \qquad (XVI)$$

In a previous article[5] it was reported that the cyanoethylation of α-toluene sulfonamide yielded γ-phenyl-γ-(sulfonamido)-pimelonitrile (XVII).



$$C_6H_5-\overset{CH_2CH_2CN}{\underset{CH_2CH_2CN}{C}}-SO_2NH_2 \qquad (XVII)$$

A reinvestigation of this reaction indicates however that the two cyanoethyl groups are attached to the nitrogen atom of the sulfonamido group instead of on the methylene carbon atom, and that the compound is therefore N,N-bis-(2-cyanoethyl)-α-toluenesulfonamide (XVIII).



$$C_6H_5-CH_2-SO_2-N\begin{smallmatrix}\diagup CH_2CH_2CN\\ \diagdown CH_2CH_2CN\end{smallmatrix} \qquad (XVIII)$$

This was established by the synthesis of (XVIII) from the reaction of benzylsulfonyl chloride with bis-(β-cyanoethyl)-amine, $HN(CH_2CH_2CN)_2$.

Upon alkaline hydrolysis of (XVIII) one of the cyanoethyl groups is eliminated with the formation of benzylsulfonamidopropionic acid $C_6H_5CH_2SO_2NHCH_2CH_2COOH$ (XIX).

Experimental

All melting points are uncorrected.

2-(β-Cyanoethyl)-2-cyclohexenylcyclohexanone (II).—To a stirred mixture of 100 g. of *t*-butyl alcohol, 5 g. of aqueous 40% benzyltrimethylammonium hydroxide ("Triton B") and 178 g. of 2-cyclohexenylcyclohexanone[3] (1 mole), there was added dropwise 53 g. of acrylonitrile (1 mole) during the course of thirty minutes. The exothermic reaction was maintained at 25–30° by cooling. The mixture was stirred for two hours at room temperature after the addition of the acrylonitrile, and was then acidified to congo with dilute hydrochloric acid. The mixture was washed twice with water, dried *in vacuo* to remove moisture and solvent, and the residual oil was distilled under high vacuum (0.2 mm.) to give the following cuts: (a) 25 g., b. p. 110–138°; (b) 44 g., 138–162°; (c) 103 g. 162–172°; (d) 7 g., 172–245°; (e) 16 g., 245–255°; (f) 32 g. residue. Fraction (c) was redistilled to give 91 g. of product which came over as a colorless oil at 152–156° (0.1 mm.), and which solidified to a crystalline solid on standing. Upon recrystallization from petroleum ether it formed white crystals, m. p. 61–62°. An additional 19 g. was obtained by redistilling fraction (b); total yield of product, 110 g. or 47.6%.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.92; H, 9.09; N, 6.06. Found: C, 77.90; H, 9.18; N, 6.12.

6-Benzylidene-2-(β-cyanoethyl)-2-cyclohexenylcyclohexanone (III).—Freshly distilled benzaldehyde (10.6 g.) was added to a stirred solution of 23.1 g. of II, 50 g. of ethanol and 2 g. of 35% methanolic potassium hydroxide solution. The solution was allowed to stand for forty-eight hours during which time a crystalline deposit formed. The filtered crystals (26 g.) were recrystallized first from methanol and three times from ethanol to give white crystals m. p. 169–170°, which apparently contained a trace of amide.

Anal. Calcd. for $C_{22}H_{25}NO$: N, 4.39. Found: N, 4.04.

2-Cyclohexenyl-2,6,6-tri-(β-cyanoethyl)-cyclohexanone (IV).—A mixture of 57.8 g. of II, 100 g. of *t*-butyl alcohol and 3 g. of "Triton B" was stirred, and 29 g. of acrylonitrile was added dropwise thereto during the course of thirty minutes at 40–45°. The mixture was stirred thereafter for ten hours at room temperature, and then made faintly acid to congo with dilute hydrochloric acid. The product was washed with water, taken up in ethylene dichloride, washed with water several more times and the ethylene dichloride layer was evaporated to dryness *in vacuo* on the steam-bath.

The residual thick oil was mixed with about three times its volume of methanol and set aside in the refrigerator at 4° to crystallize. After a few hours the light tan crystalline deposit was filtered off; yield was 48.5 g. Upon recrystallization from methanol with a little Norite, the sample for analysis was obtained in white crystals, m. p. 111°.

Anal. Calcd. for $C_{21}H_{27}N_3O$: C, 74.78; H, 8.01; N, 12.46. Found: C, 74.73; H, 8.12; N, 12.34.

2-(β-Carboxyethyl)-2-cyclohexenylcyclohexanone (V).—A mixture of 11.5 g. of II, 11.5 g. of potassium hydroxide and 90 g. of water was boiled under reflux until an almost clear solution was formed. This required about twenty hours. The filtered solution was acidified with hydrochloric acid and the taffy-like mass which precipitated was taken up in benzene. The benzene solution was evaporated to dryness *in vacuo* and the residual oil was distilled under high vacuum to give 9 g. of colorless, very viscous oil boiling at 175–180° (0.2 mm.) which crystallized upon rubbing with petroleum ether in the cold. Upon recrystallization from petroleum ether it formed white crystals, m. p. 60–61°.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 72.00; H, 8.80. Found: C, 71.78; H, 8.81

2-Cyclohexenyl-2,6,6-tri-(β-carboxyethyl)-cyclohexanone (VI).—A mixture of 6 g. of IV, 72 g. of water and 8 g. of sodium hydroxide was boiled under reflux for ten hours, until practically all the oily material had dissolved. The solution was filtered and acidified with hydrochloric acid to precipitate the crude tricarboxylic acid as a dough-like mass which hardened on standing It was dried in the air and crystallized twice from nitroethane to form white crystals, m. p. 158–159°.

Anal. Calcd. for $C_{21}H_{30}O_7$: C, 63.96; H, 7.61. Found: C, 63.50: H, 7.76.

Cyclohexenylhexahydroquinolone (VIII).—To a stirred solution of 23.1 g. of II and 50 g. of ethylene dichloride there was added dropwise with cooling, a solution of 10 g. of 98% sulfuric acid and 1.8 g. of water during the course of ten minutes. The reaction temperature was between 30 and 40°. After all had been added the mixture was stirred for fifteen minutes at room temperature and then heated for five hours at 45–50° with constant stirring, and allowed to stand overnight. Water (200 cc.) was then added and the mixture stirred. The white solid which separated was filtered off, washed and dried. Yield was 5 g. Upon crystallization from nitromethane it formed white needles m. p. 213–214°. The analytical sample was dried at 100° in high vacuum.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.92; H, 9.09; N, 6.06. Found: C, 77.70; H, 9.10; N, 6.13.

From the ethylene dichloride layer there was obtained upon evaporation an additional 10 g. of product, m. p. 212–214° after crystallization from nitromethane. Total yield was 15 g. or 64.9%.

1,1,1-Tri-(β-cyanoethyl)-methyl 2-Thienyl Ketone (IX).—Acrylonitrile (31.8 g.) was added dropwise to a stirred solution of 25.2 g. of 2-acetylthiophene, 25 g. of *t*-butyl alcohol and 2 g. of "Triton B" while maintaining the reaction mixture at 25–30° by cooling. The addition required about thirty minutes during which time crystals began to separate and clog the stirrer so that 50 cc. of additional *t*-butyl alcohol had to be added to form a thinner

---

[3] Hückel, Neunhoeffer, Gerche and Frank, *Ann.*, **477**, 119 (1930).

suspension. After the addition, the mixture was stirred for two hours, then acidified with dilute hydrochloric acid and the crystalline product filtered off. Yield was 50 g. of a tan-colored, air-dried product or 87.7%. Upon recrystallization from ethanol the sample for analysis formed white, feathery crystals, m. p. 146–147°.

Anal. Calcd. for $C_{15}H_{15}N_3OS$: C, 63.15; H, 5.26; N, 14.73; S, 11.22. Found: C, 63.04; H, 5.20; N, 14.77; S, 11.28.

γ-Methyl-γ-thienoyl-pimelonitrile (X).—To a stirred solution of 55 g. of 2-propionylthiophene, 50 g. of *t*-butyl alcohol and 3 g. of "Triton B," there was added dropwise 42.4 g. of acrylonitrile while cooling the mixture to 25–30°. After the addition the mixture was stirred for twenty-four hours during which time the product separated in crystalline form. The mixture was neutralized with dilute hydrochloric acid and the crystals filtered off. Yield was 94 g. of air dried product or 98%. Upon crystallization from ethanol the sample for analysis formed white flaky crystals, m. p. 81–82°.

Anal. Calcd. for $C_{13}H_{14}N_2OS$: C, 63.41; H, 5.69; N, 11.38; S, 13.00. Found: C, 63.34; H, 5.65; N, 11.31; S, 13.27.

Tri-(β-cyanoethyl)-2-acetylfuran (XI).—To a stirred mixture of 6 g. of "Triton B," 200 g. of *t*-butyl alcohol and 99 g. of 2-acetylfuran[4] there was added dropwise 143 g. of acrylonitrile during the course of an hour while cooling the mixture to 22–28°. During the addition a heavy crystalline mush formed. To assist the stirring, 150 g. more of *t*-butyl alcohol was added, and the mixture was stirred for eighteen hours at room temperature. The catalyst was then neutralized with dilute hydrochloric acid and the crystalline product filtered off sharply by suction. Yield was 216 g. After recrystallization from ethanol it formed white crystals, m. p. 121–122°.

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.91; H, 5.57; N, 15.61. Found: C, 66.77; H, 5.68; N, 15.52.

γ-Furoyl-γ-methylpimelonitrile (XII).—The 2-propionylfuran used was prepared from furan, propionic anhydride and hydrogen iodide by the method of Hartough and Kosak.[4] It was thoroughly freed from traces of acidity (which poison the catalyst), by several washings with soda solutions and two distillations.

Acrylonitrile (32.4 g.) was added dropwise to a stirred solution of 38 g. of 2-propionylfuran, 50 g. of *t*-butyl alcohol and 3 g. of "Triton B" at 24–28°. The mixture was stirred for twenty-four hours thereafter at room temperature, then neutralized with dilute hydrochloric acid and washed with water. The oil layer was separated and dried *in vacuo* at 90°. The product formed a thick oil (69 g.) which crystallized slowly on scratching and standing eventually forming a solid, waxy mass. After several recrystallizations from ethanol, the sample for analysis formed white crystals, m. p. 49°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.83; H, 6.09; N, 12.17. Found: C, 67.89; H, 6.11; N, 12.06.

γ-Furoyl-γ-ethylpimelonitrile (XIII).—The 2-butyrylfuran used was prepared from furan, hydrogen iodide and butyric anhydride.[4] It boiled at 83–84° (10 mm.). It must be freed from traces of acidity which poison the catalyst.

A mixture of 30 g. of 2-butyrylfuran, 30 g. of *t*-butyl alcohol and 2 g. of "Triton B" was treated with 23 g. of acrylonitrile as described above. The dark resinous sirup obtained gradually crystallized to yield 36 g. of white crystalline product after washing with a little *t*-butyl alcohol. The sample for analysis was recrystallized twice from ethanol to give large prisms, m. p. 102°.

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.85; H, 6.56; N, 11.47. Found: C, 68.70; H, 6.58; N, 11.39.

1,1,1-Tri-(β-carboxyethyl)-methyl 2-Thienyl Ketone (XIV).—A mixture of 14.3 g. of IX, 100 g. of water and 12 g. of sodium hydroxide was boiled under reflux for twelve hours. The filtered solution was acidified with hydrochloric acid. A heavy oil separated which solidified to a crystalline mass. Yield was 14 g. of air-dried product. Upon crystallization from nitromethane it formed white crystals, m. p. 183–184°. The sample for analysis was dried in high vacuum at 100°.

Anal. Calcd. for $C_{15}H_{18}O_7S$: C, 52.63; H, 5.26; S, 9.35. Found: C, 52.65; H, 5.34; S, 9.23.

γ-Methyl-γ-thienoylpimelic Acid (XV).—A mixture of 12.3 g. of (X), 100 g. of water and 12 g. of sodium hydroxide was boiled under reflux for eight hours. The filtered solution was acidified with hydrochloric acid. An oil precipitated which gradually solidified to a crystalline mass. Yield of air-dried product was 12 g. Upon crystallization from nitromethane, the product formed white crystals, m. p. 137–138°.

Anal. Calcd. for $C_{13}H_{16}O_5S$: C, 54.92; H, 5.63; S, 11.26. Found: C, 54.44; H, 5.83; S, 11.23.

γ-Phenyl-γ-phenylsulfonylpimelonitrile (XVI).—To a stirred solution of 5.8 g. of benzyl phenyl sulfone, 40 g. of acetonitrile and 0.5 g. of "Triton B" there was added dropwise 2.7 g. of acrylonitrile while the reaction mixture was maintained at 32–38° by occasional cooling. The mixture was then stirred for eighteen hours at room temperature, neutralized with dilute hydrochloric acid and the product washed with water and dried *in vacuo*. The residual oil (5 g.) crystallized when rubbed with ethanol. After recrystallization from ethanol the product formed white crystals, m. p. 180°.

Anal. Calcd. for $C_{19}H_{18}N_2O_2S$: C, 67.45; H, 5.32; N, 8.29; S, 9.47. Found: C, 67.80; H, 5.53; N, 8.26; S, 9.25.

N,N-bis-(2-Cyanoethyl)-α-toluenesulfonamide (XVIII).—To a solution of 6.2 g. of bis-β-cyanoethylamine in 50 g. of benzene, there was added 8.5 g. of benzylsulfonyl chloride (obtained from Eastman Kodak Co.). The clear solution gradually deposited a slimy precipitate. After standing two hours, the mixture was filtered free from this material and the filtrate allowed to stand overnight. The white crystalline deposit which separated therefrom was filtered off and recrystallized from ethanol. It melted at 103° and was identical with the product obtained from the cyanoethylation of α-toluenesulfonamide.[5]

A mixed melting point of the two products showed no depression.

β-(Benzylsulfonamido)-propionic Acid (XIX).—A mixture of 10 g. of (XVIII), 12 g. of sodium hydroxide and 80 cc. of water was boiled under reflux for six hours. The clear solution obtained was acidified with hydrochloric acid and the crystalline precipitate filtered off and dried. Yield was 9 g. After recrystallization from hot water the product formed white flaky crystals, m. p. 151–152°, having an acid no. 230 (calcd., 230).

Anal. Calcd. for $C_{10}H_{13}NO_4S$: C, 49.38; H, 5.35; N, 5.76; S, 13.16. Found: C, 49.13; H, 5.64; N, 5.68; S, 13.26.

Acknowledgment.—To Mr. Clyde W. Nash for all analyses and to Mr. Raymond Luckenbaugh for preparing several of the intermediates.

Summary

1. Acrylonitrile reacts with 2-cyclohexenylcyclohexanone to yield a *mono-* and a *tri-*cyanoethylation product from which the corresponding carboxylic acids were prepared.

2. Mono-cyanoethylcyclohexenylcyclohexanone yields a cyclohexenylhexahydroquinolone upon treatment with sulfuric acid.

3. Cyanoethylation products of 2-acylthiophenes and 2-acylfurans were prepared.

4. Cyanoethylation of benzyl phenyl sulfone

---

[4] Hartough and Kosak, This Journal, 68, 2641 (1946). The product should be free from traces of acidity.

[5] Bruson and Riener, *ibid.*, 65, 25 (1943).

introduced two cyanoethyl groups on the methylene carbon atom. Cyanoethylation of α-toluenesulfonamide introduced two cyanoethyl groups on the nitrogen atom of the sulfonamido group instead of on the methylene carbon atom.

PHILADELPHIA, PA. RECEIVED JUNE 25, 1947

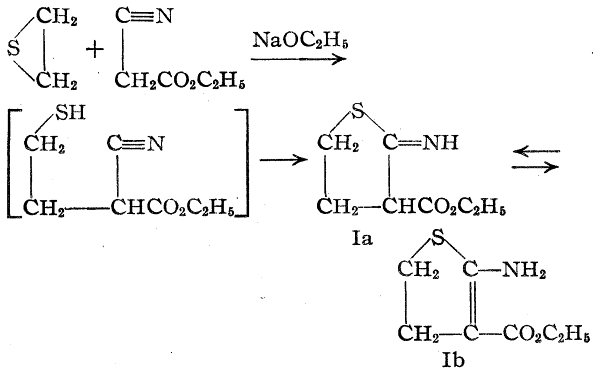
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of 2-Iminothiophanes from Ethyl Cyanoacetate and Alkene Sulfides

BY H. R. SNYDER AND WYVONA ALEXANDER[1]

The structural similarity of alkene sulfides to alkene oxides suggests that these sulfur compounds may be useful in the alkylation of active methylene compounds. Such alkylations with the alkene oxides have become important synthetic methods[2] and they appear to be of quite general application.[3]

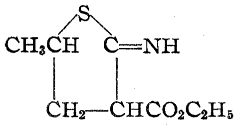
Preliminary tests of reactions between simple olefin sulfides and ethyl malonate, ethyl acetoacetate and ethyl cyanoacetate in the presence of sodium ethoxide indicated that alkylation occurred readily only with the last-named ester. The yield of the condensation product from ethylene sulfide and ethyl cyanoacetate was not large (23%), much of the cyclic sulfide being lost through polymerization. As might have been expected, the yields from propylene sulfide and isobutylene sulfide, which have less tendency toward polymerization, were higher (30 and 60%, respectively). The products of the reactions were solid basic esters which could be converted to hydrochlorides and acetyl derivatives. The presence of a basic group and an ester group in the molecule from ethylene sulfide and the cyanoacetate suffices to establish the structure of the substance as I. The structure is confirmed by the conversion of the product to γ-thiobutyrolactone[4] by alkaline hydrolysis and decarboxylation, and to γ,γ'-dithio-bisbutyric acid[4] by alkaline hydrolysis, decarboxylation and oxidation.



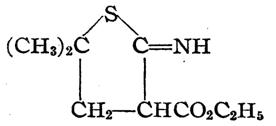
Ia

Ib

In the alkylation of ethyl cyanoacetate with propylene oxide and isobutylene oxide the less highly alkylated carbon atom of the oxide becomes attached to the active methylene carbon atom.[3] Accordingly, one would expect the products from propylene sulfide and isobutylene sulfide to have the structures II and III. The properties of the compounds are compatible only with these structures (or their tautomers). Hydrolysis, decarboxylation and oxidation of II gave the known γ,γ'-dithio-bis-valeric acid, and similar treatment of III gave a disulfide which proved identical with γ,γ'-dithio-bis-isocaproic acid synthesized by another method. An independent proof of the orientation of the methyl groups in III resulted from the desulfurization with Raney nickel alloy.[5,6] The desulfurization was carried out in aqueous alkali under conditions such that hydrolysis first occurred; the product unquestionably was isobutylmalonic acid.



II



III

When the condensations of propylene sulfide and isobutylene sulfide with ethyl cyanoacetate were carried out in methanol solution ester interchange occurred and the methyl esters corresponding to II and III were obtained.

Experimental

The Preparation of the Alkene Sulfides.—The ethylene, propylene and isobutylene sulfides used in this investigation were obtained from the oxides through treatment with aqueous potassium thiocyanate as described in an earlier paper.[7]

Condensation of Ethyl Cyanoacetate with Ethylene Sulfide.—No entirely satisfactory procedure was found for this condensation; the best results were obtained by the following method. To a solution prepared by dissolving 2.3 g. of sodium in 250 ml. of absolute ethanol was added 20 g. of ethyl cyanoacetate; this mixture was refluxed while 6 g. of ethylene sulfide was added dropwise over a period of one hour. Refluxing was continued for one hour, after which time the ethanol was distilled. The residue was extracted with ether, leaving large amounts of insoluble, probably polymeric, material. The sirup remaining

---

[1] Present address: Calco Chemical Division, American Cyanamid Co., Bound Brook, N. J.

[2] For an application to the synthesis of thiamin see Buchman, THIS JOURNAL, **58**, 1803 (1936).

[3] Glickman and Cope, *ibid.*, **67**, 1012 (1945).

[4] Holmberg and Schjånberg, *Arkiv. Kemi, Mineral Geol.*, **14A**, No. 7 (1940) [*C. A.*, **35**, 2113 (1941)].

[5] Mozingo, Wolf, Harris and Folkers, THIS JOURNAL, **65**, 1013 (1943).

[6] Schwenk, Papa, Whitman and Ginsberg, *J. Org. Chem.*, **9**, 1 (1944); **7**, 587 (1942).

[7] Snyder, Stewart and Ziegler, THIS JOURNAL, **69**, 2672 (1947).

after evaporation of the ether crystallized very slowly. A solution of this material in about 5 ml. of ethanol was diluted to turbidity with water, chilled and seeded to yield about 4 g. (23%) of 2-imino-3-carbethoxythiophane, melting at 74–78°. Further recrystallization of a sample raised the melting point to 79.5–80°.

Anal. Calcd. for $C_7H_{11}O_2NS$: C, 48.55; H, 6.41. Found: C, 48.59; H, 6.62.

The **hydrochloride** precipitated as a colorless hygroscopic solid when dry hydrogen chloride was passed into an ether solution of the imino ester. The neutralization equivalent of the salt, determined by titration with sodium hydroxide in the presence of phenolphthalein, was 212 (calcd., 210).

The **acetyl derivative** was prepared by heating the imino ester with about 10% excess of acetic anhydride; after recrystallization from ethanol it melted at 73–74°.

Anal. Calcd. for $C_9H_{13}O_3NS$: C, 50.22; H, 6.09. Found: C, 50.58; H, 6.21.

Condensation of Ethyl Cyanoacetate with Propylene Sulfide.—The reaction mixture prepared as described for the ethylene sulfide reaction, except that the propylene sulfide (7.4 g.) was added in one lot, was refluxed one hour and then concentrated to 20 ml. The ethanol solution was decanted from the viscous sirup and poured into ice water. Recrystallization (from aqueous ethanol) of the resulting solid yielded 6 g. (30%) of 2-imino-3-carbethoxy-5-methylthiophane melting at 50–51°.

Anal. Calcd. for $C_8H_{13}O_2NS$: C, 51.31; H, 7.00. Found: C, 51.34; H, 7.06.

From a similar reaction carried out in methanol 2-imino-3-carbomethoxy-5-methylthiophane, m. p. 96–98°, was isolated; the acetyl derivative, m. p. 87–88°, was analyzed.

Anal. Calcd. for $C_9H_{13}O_3NS$: C, 50.22; H, 6.09. Found: C, 50.45; H, 6.28.

Condensation of Ethyl Cyanoacetate with Isobutylene Sulfide.—To a solution prepared from 2.3 g. of sodium and 300 ml. of ethanol was added 15 g. of ethyl cyanoacetate and this mixture was refluxed while 9 g. of isobutylene sulfide was added over a period of one hour. Refluxing was continued for one hour after completion of the addition, and the solution was concentrated to a volume of about 50 ml. The concentrated solution, filtered if not clear, was poured into ice-water to precipitate the product. After recrystallization from aqueous ethanol the 2-imino-3-carbethoxy-5,5-dimethylthiophane, weight 12 g. (60%), melted at 53–54°.

Anal. Calcd. for $C_9H_{15}O_2NS$: C, 53.65; H, 7.51. Found: C, 53.88; H, 7.67.

The **hydrochloride** melted at 122–124° and had a neutralization equivalent of 244 (calcd., 238).

The **acetyl derivative** melted at 69–70°.

Anal. Calcd. for $C_{11}H_{17}O_3NS$: C, 54.30; H, 7.05. Found: C, 54.12; H, 7.26.

2-Imino-3-carbomethoxy-5,5-dimethylthiophane, prepared by the use of methanol instead of ethanol in the above procedure, melted at 137.5–139°.

Anal. Calcd. for $C_8H_{13}O_2NS$: C, 51.31; H, 7.00. Found: C, 51.53; H, 7.19.

Hydrolysis of Condensation Products with Strong Alkali.—Hydrolysis by ten per cent. sodium or potassium hydroxide was brought about by refluxing for an hour. The γ-thiolactone of the corresponding dicarboxylic acid was formed. From 2-imino-3-carbethoxythiophane a liquid acid was obtained which was readily decomposed to γ-thiobutyrolactone (n^{20}D 1.5241) (lit.[4] n^{20}D 1.5242). Hydrolysis of 2-imino-3-carbethoxy-5,5-dimethylthiophane yielded a solid acid (2-keto-5,5-dimethylthiophane-3-carboxylic acid) which melted with decomposition at 90–91°.

Anal. Calcd. for $C_7H_{10}O_3S$: C, 48.26; H, 5.79; neutralization equivalent, 174. Found: C, 48.31 H, 6.09; neut. equiv., 174.

Hydrolysis and Oxidation of the Condensation Products.—The products of condensation were hydrolyzed by refluxing for about six hours with an excess of 10% sodium carbonate solution. The hydrolysis mixture was cooled, acidified and extracted with ether. Evaporation of the ether left a residue of a liquid mercapto acid which was readily oxidized to the solid disulfide by the addition of aqueous iodine-potassium iodide solution.

Compound I yielded γ,γ'-dithio-bisbutyric acid, melting at 108–109° (lit.[4] 109–110°). Compound II yielded γ,γ' dithio-bis-valeric acid melting at 117–118° (lit.[8] 118–121°). The neutral equivalent was determined as 132 (calcd. 133). The liquid mercapto acid obtained by the hydrolysis of compound III had the reactions of a tertiary mercaptan; it distilled at 110° (10 mm.).

Anal. Calcd. for $C_6H_{12}O_2S$: C, 48.62; H, 8.16. Found: C, 49.52 H, 8.30.

The solid acid obtained by oxidation melted at 84–85°.

Anal. Calcd. for $C_{12}H_{22}O_4S_2$: C, 48.95; H, 7.53; neut. equiv., 147. Found: C, 49.26; H, 7.79; neut. equiv., 144.

This acid showed no depression in melting point when mixed with a sample of γ,γ'-dithio-bis-isocaproic acid prepared by the method described below.

Preparation of γ,γ'-Dithio-bis-isocaproic Acid.—Fifteen grams of Δ^{β}-isohexenoic acid, prepared according to Goldberg and Linstead,[9] was mixed with about 15 ml. of liquid hydrogen sulfide and 2 g. of flowers of sulfur in a steel bomb and heated at 180° for ten hours. Addition of hydrogen sulfide to olefinic compounds under these conditions has been shown to follow Markownikoff's rule.[10] The residue, after evaporation of the hydrogen sulfide, was dissolved in 100 ml. of ether and washed several times with sodium bicarbonate solution. No γ-mercaptoisocaproic acid was found in the aqueous extract, presumably because of thiolactone formation. The residue from the removal of the ether was refluxed for sixteen hours with 8 g. of sodium carbonate in 100 ml. of water. The mixture was cooled, acidified and extracted with ether. From the ether extract, 7 g. (44%) of γ-mercaptoisocaproic acid, boiling at 107–109° (10 mm.), was obtained. Oxidation by aqueous iodine yielded γ,γ'-dithio-bis-isocaproic acid, melting at 84–85°.

Isocaproic Acid from Compound III.—A Raney nickel-aluminum alloy reduction of 2-imino-3-carbethoxy-5,5-dimethylthiophane by the procedure described by Papa, Schwenk and Whitman[6] gave isobutylmalonic acid which melted at 105–106.5° (lit.[11a] 108°). No depression of melting point was noted when this compound was mixed with an authentic sample. The neutralization equivalent was determined as 80 (calcd. 80). Bromination yielded α-bromoisobutylmalonic acid which decomposed at 134.5–136° (lit.[11b] 139–141°). Isobutylmalonic acid was readily decarboxylated. The resulting isocaproic acid boiled at 198° (lit.[11c] 199.7° at 732 mm.); the anilide melted at 110–111° (lit.[12] 112°), and the *p*-bromophenacyl ester melted at 76–77° (lit.[13] 77°).

Summary

In the presence of sodium ethoxide ethylene sulfide reacts with ethyl cyanoacetate to give 2-imino-3-carbethoxythiophane, the reaction evidently consisting in alkylation followed by cyclization through interaction of the thiol and cyano groups. Propylene sulfide and isobutylene sulfide react similarly to give 2-imino-3-carbethoxy-5-methylthiophane and 2-imino-3-carbethoxy-5,5-dimethylthiophane, respectively.

Urbana, Illinois Received July 17, 1947

---

(8) Schjanberg, *Ber.*, **74**, 1751 (1941).

(9) Goldberg and Linstead, *J. Chem. Soc.*, 2343 (1928).

(10) Jones and Reid, This Journal, **60**, 2452 (1938).

(11) Beilstein, "Handbuch der organische Chemie," 4th ed., Julius Springer, Berlin, 1920, (a) Vol. II, p. 683; (b) Vol. II, p. 684; (c) Vol. II, p. 328.

(12) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, 2nd ed., p. 181.

(13) Karrer and Geiger, *Helv. Chim. Acta*, **24**, 289 (1941).

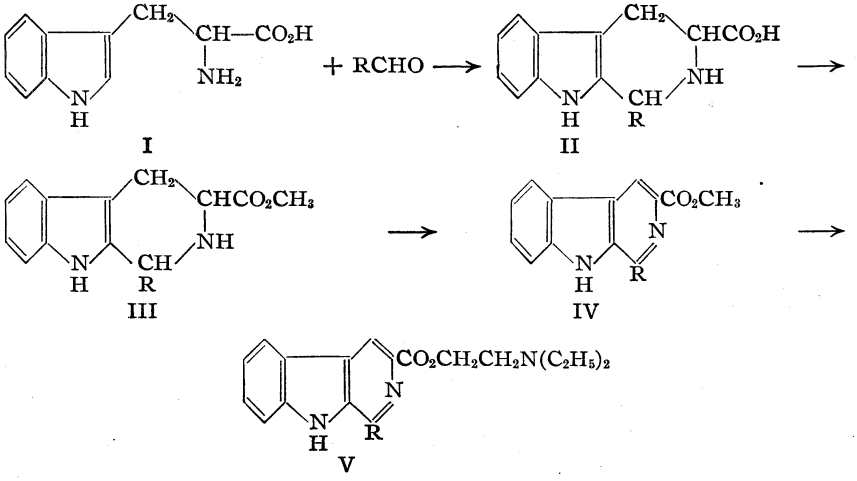
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Derivatives of β-Carboline. II. Syntheses from *dl*-Tryptophan and Aldehydes[1]

BY H. R. SNYDER, CORWIN H. HANSCH,[2] LEON KATZ,[3] STANLEY M. PARMERTER[4] AND EARL C. SPAETH[5]

Although compounds containing the β-carboline nucleus have been of great interest in connection with their occurrence in certain alkaloids, particularly in *Peganum harmala*[6] and *Alstonia constricta*,[7] relatively few synthetic members of this class have been prepared in quantity sufficient for physiological studies. Methods of synthesis have been devised,[6] but comparatively inaccessible raw materials such as *l*-tryptophan and tryptamine have been employed. Since *dl*-tryptophan is now readily available[8] it is of interest to consider its use in the preparation of derivatives of β-carboline.

The condensation of *l*-tryptophan with aldehydes, including formaldehyde, acetaldehyde and benzaldehyde,[9–11] has been extended to the racemic amino acid. The aldehydes which have been employed in the condensation are acetaldehyde, benzaldehyde, phenylacetaldehyde, homoanisaldehyde, *p*-nitrobenzaldehyde, *p*-dimethylaminobenzaldehyde and hydratropic aldehyde (see Table I). The products (formula II) were obtained as mixtures of two racemic modifications in yields of 63–90%. The products from *dl*-tryptophan would not be expected to be identical with those from the natural amino acid. It is of interest that one of the isomers obtained from benzaldehyde and the racemic acid had a melting point (225–226°) near that reported (223–226°) for the product from the optically active amino acid,[9] whereas the products from acetaldehyde differed widely in melting points (247–248 and 258° for the racemic compounds, as compared to 290[10] or 297°[9] for the optically active substance).



The formation of isomers and the tendency to hydration often made the isolation of analytically pure specimens of the tetrahydro acids (II) extremely difficult, but did not interfere with the utilization of the substances in further syntheses. The condensation was unsuccessful when applied to chloral hydrate, chloroacetal or formamide.

The methyl esters, obtained by esterification of the crude acids with methanol and dry hydrogen chloride, also formed hydrates, but in several instances analytically pure samples of the esters were obtained with much less difficulty than had been experienced with the acids. However, the separation of the diastereoisomeric forms proved no less difficult with the esters than with the acids.

The products from acetaldehyde, phenylacetaldehyde and benzaldehyde were dehydrogenated to the fully aromatic compounds (IV, R = CH_3, $C_6H_5CH_2$ and C_6H_5, respectively). Various dehydrogenation procedures were tested on these and other tetrahydro esters, but no satisfactory general procedure was evolved. Methyl 1-methyl-β-carboline-3-carboxylate (IV, R = CH_3) and methyl 1-benzyl-β-carboline-3-carboxylate (IV, R = $C_6H_5CH_2$) were prepared by dehydrogenation with sulfur in refluxing xylene, and methyl 1-phenyl-β-carboline-3-carboxylate was prepared by dehydrogenation with chloranil[12,13] in refluxing tetrachloroethane.

The aromatic acids corresponding to IV were prepared by saponification of the esters. Thionyl

---

[1] For the preceding paper, see Snyder and Katz, THIS JOURNAL, **69**, 3190 (1947).

[2] Wm. S. Merrell Post-Doctorate Fellow, 1944. Present address: Pomona College, Pomona, California.

[3] Present address: Calco Chemical Division, American Cyanamid Co., Bound Brook, New Jersey.

[4] Wm. S. Merrell Post-Doctorate Fellow, 1944–1945. Present address: Eastman Kodak Co., Rochester, N. Y.

[5] Wm. S. Merrell Post-Doctorate Fellow, 1946. Present address: The Department of Chemistry, the University of Connecticut, Storrs, Conn.

[6] "Thorpe's Dictionary of Applied Chemistry," Vol. VI, Longmans Green and Co., London, 1943, p. 186.

[7] Elderfield and Leonard, *J. Org. Chem.*, **7**, 556 (1942).

[8] Howe, Zambito, Snyder and Tishler, THIS JOURNAL, **67**, 38 (1945).

[9] Jacobs and Craig, *J. Biol. Chem.*, **113**, 759 (1936).

[10] Harvey and Robson, *J. Chem. Soc.*, 97 (1938).

[11] Harvey, Miller and Robson, *ibid.*, 153 (1941).

[12] Clar and John, *Ber.*, **63**, 2967 (1930); *ibid.*, **64**, 981 (1931).

[13] Arnold and Collins, THIS JOURNAL, **61**, 1407 (1939); Arnold, Collins and Zenk, *ibid.*, **62**, 983 (1940).

TABLE I

1,2,3,4-TETRAHYDRO-β-CARGOXYLIC ACIDS AND METHYL ESTERS

	Acids								Methyl esters							
	Crude acids			Isomeric acids					Crude esters			Pure esters				
					Analyses, %								Analyses, %			
					Calcd.		Found						Calcd.		Found	
Substituent in 1 position	M. p., °C. (dec.)	Yield, %	Recrys. solvent[a]	M. p., °C. (dec.)	C	H	C	H	M. p., °C.	Yield, %	Recrys. solvent	M. p., °C.	C	H	C	H
CH_3	242–243	66	E-W	247–248	67.81[b]	6.13	66.89[c]	6.55	105–110	81	M	129–130	68.81	6.60	69.31	6.78
					62.87[d]	6.50	61.84[e]	6.45								
			W	258			64.73	6.38								
C_6H_5	254–257	71	E-W	260–261	....	..	...[f]	..	152–156	96	I	169–170	74.49	5.92	74.41	5.95
			M	225–226	....	..	...[f]	..								
$C_6H_5CH_2$	241–243	81	E-W	247–248	70.35[d]	6.22	70.38[c]	6.48	70–80	96						
			E-W	180			70.54[c]	6.32								
p-$CH_3OC_6H_4CH_2$	175–178	92	E	219–220	71.43[b]	5.95	68.77[c]	6.69	147–148	82						
					67.79[d]	6.21										
			E	180–181			68.47[c]	6.34								
p-$NO_2C_6H_4$	190–195	88	M-W	196–197					.....	93	M	173–174	64.95	4.88	64.85	4.72
p-$(CH_3)_2NC_6H_4$	238–239	85	E-W	242–243	71.64[b]	6.31	71.61[c]	6.40	225–227	80						
$C_6H_5CH(CH_3)$	185–190	62	E-W	230–232	74.95[b]	6.29	74.91[c]	6.43								

[a] W, water; E, ethanol; M, methanol; I, isopropyl alcohol. [b] Calculated for the anhydrous product. [c] Samples were dried at 100° or above *in vacuo* for many hours. [d] Calculated for the monohydrate. [e] Samples were dried *in vacuo* usually at room temperature. [f] The analytical samples evidently contained varying amounts of water. However, either isomeric acid could be converted to the pure completely aromatized derivative (see text).

chloride proved satisfactory for the conversion of the acids to the chlorides, two of which were treated with β-diethylaminoethanol to give the esters (V, R = CH_3 and C_6H_5, respectively).

The analogy to the conversion of amides of tryptamine to 3,4-dihydro-β-carbolines[14–17] suggested that some of the intermediates of the tryptophan synthesis might be converted directly to β-carboline derivatives. Accordingly, numerous attempts to effect the cyclization of acetyltryptophan and of ethyl α-acetamino-α-carbethoxy-β-(3-indole)-propionate were made. Each substance was heated alone in phenyl ether, with phosphorus oxychloride in benzene, with zinc chloride in acetic anhydride, and with acetaldehyde in water, and the second substance was also heated with phosphorus pentoxide in phenyl ether. The methyl ester of acetyltryptophan also was heated with phosphorus oxychloride in benzene. All these experiments were unsuccessful.

Experimental

A. Preparation of the 1,2,3,4-Tetrahydro-β-carboline-3-Carboxylic Acids (see Table I).—1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid was prepared according to the following modification of the method of Jacobs and Craig.[9] In a one-liter flask connected to a Dry Ice condenser with ground-glass joints were placed 26.39 g. of *dl*-tryptophan (0.13 mole), 132 ml. of 1 *N* sulfuric acid, 350 ml. of water and 70 ml. of freshly-distilled acetaldehyde. This suspension was heated in a water-bath at 50–60° for one hour. The resulting clear solution was then heated directly on the steam-bath for one and one-half hours. The Dry Ice condenser was now removed and heating was continued for four and one-half hours to remove the excess acetaldehyde (hood). The solution was made strongly basic with concentrated ammonium hydroxide, heated for one-half hour on the steam-bath with decolorizing carbon and filtered. The clear yellow filtrate was concentrated to a volume of about 150 ml., and the resulting mixture was cooled at 5° for nine hours. The white to cream-colored crystals were filtered by suction, washed with cold water and dried at 80°. The dry crystals were allowed to stand in the air for thirteen hours until the weight had become constant and the material existed principally as the monohydrate. Concentration of the mother liquor usually caused the separation of additional small quantities of the same material. However, occasionally the material obtained by concentration proved to be higher-melting, and the high-melting isomer (m. p. 258°) was obtained by recrystallization of such samples from water.

1-Phenyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid was prepared according to the general procedure outlined above. It was not necessary to use a Dry Ice condenser, but it was found helpful to stir the reaction mixture with a Hershberg-type stirrer. The reaction mixture consisting of 0.10 mole of tryptophan, 0.11 mole of benzaldehyde, 100 ml. of 1 *N* sulfuric acid, 300 ml. of water and 40 ml. of ethanol (95%) was stirred and heated for four hours. After the addition of 100 ml. of concentrated ammonium hydroxide the mixture was heated with decolorizing carbon for twenty minutes, diluted with 50 ml. of concentrated ammonium hydroxide and filtered. The pale yellow solution was cooled in an ice-bath and extracted with two 75-ml. portions of ether. The aqueous solution was then concentrated and the product isolated as described for the 1-methyl tetrahydro acid. The main product was a methanol-insoluble portion which could be purified by extraction with methanol and recrystallization from dilute ammonia and then from 50% ethanol. The methanol extracts contained small amounts of the low-melting isomer, which was purified by recrystallization from methanol.

1-Benzyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid was prepared from phenylacetaldehyde by the procedure described for the 2-phenyl tetrahydro acid. Fifty per cent. ethanol was used as the solvent for the reaction, and a reaction time of seventeen hours was necessary. Most of the alcohol was removed by distillation at the end of the reflux period prior to purification and isolation of the product.

The preparation of the 1-homoanisyl-, 1-*p*-nitrophenyl-, 1-*p*-dimethylaminophenyl- and 1-α-phenylethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acids was carried out with essentially the same procedure described for the 1-phenyl tetrahydro acid. The bisulfite addition product of homoanisaldehyde was used satisfactorily in place of the free aldehyde.

B. Preparation of the Methyl 1,2,3,4-Tetrahydro-β-carboline-3-carboxylates (see Table I).—Ten grams of 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid was suspended in 75 ml. of dry methanol, and the mixture was saturated with dry hydrogen chloride.

---

(14) Akabori and Saito, *Ber.*, **63**, 2245 (1930).

(15) Spath and Lederer, *ibid.*, **63**, 124, 2102 (1930).

(16) Asahina and Osada, *Chem. Zentr.*, **98**, I, 1479 (1927).

(17) Tatsui, *ibid.*, **99**, II, 668 (1928).

After a one-hour reflux period, the solution was concentrated and cooled in an ice-bath. The solid ester hydrochloride was filtered, suspended in water, and treated with an excess of saturated sodium bicarbonate solution. The ester was taken up in ether, and the resulting solution, after drying over magnesium sulfate, was evaporated to yield the crude methyl 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate.

The other esters in this series are not very soluble in ether, so the procedure was modified slightly. After the reflux period (two to three hours) the reaction mixture was cooled and poured onto ice and carefully made basic by the slow addition of ammonium hydroxide. The crude ester was then separated and allowed to stand under cold water for one hour. The solid was then filtered by suction, washed well with water, and dried to constant weight at room temperature in a vacuum desiccator.

It has been found that sulfuric acid can be used in place of hydrogen chloride for these esterifications.

C. Dehydrogenation of the Methyl 1,2,3,4-Tetrahydro-β-carboline-3-carboxylates. Preparation of Methyl 1-Methyl-β-carboline-3-carboxylate.—In a 250-ml. flask equipped with a reflux condenser were placed 15.28 g. of methyl 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate, 4.16 g. of sulfur and 100 ml. of dry xylene. This mixture was refluxed for four and one-half hours. The evolution of hydrogen sulfide was noted throughout most of the reflux period. A red crystalline solid precipitated on the walls of the flask. The mixture was cooled overnight at 5° and the pink solid was filtered by suction, washed with 40 ml. of cold xylene and then liberally with low-boiling petroleum ether. The yield was 12.69 g. (85%), m. p. 246–248° (dec.). A sample recrystallized from methanol melted at 245°.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.96; H, 5.04; N, 11.66. Found: C, 69.86; H, 5.12; N, 11.67.

Methyl 1-Benzyl-β-carboline-3-carboxylate was prepared by the same method, but in poor yield; m. p. (after three recrystallizations from *n*-butanol) 237–238°.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10. Found: C, 76.19; H, 5.14.

Methyl 1-Phenyl-β-carboline-3-carboxylate.—In a 100-ml. flask equipped with a reflux condenser were placed 5.88 g. of methyl 1-phenyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate,[18] 9.91 g. of chloranil, and 80 ml. of purified *s*-tetrachloroethane. This mixture was heated under reflux for one hour and twenty minutes. The clear dark-colored solution was stored at 5° overnight and the dark crystals which formed were filtered and washed with *s*-tetrachloroethane, the washings being added to the mother liquor. The solid was discarded. The mother liquor was diluted with a large amount of low-boiling petroleum ether (until no further cloudiness resulted) and the solid was collected and washed with low-boiling petroleum ether. The dried material was extracted with 225 ml. of boiling 1 *N* hydrochloric acid in five portions. A small amount of tar remained undissolved. The combined acid extracts were cooled and treated with an excess of solid sodium bicarbonate, and, after cooling for an hour in an ice-bath, the product was filtered, washed well with water, and dried overnight at 80°. The yield was 5.26 g. (91%), m. p. 233–238° (dec.). The melting point could be raised to 252–253° by one recrystallization from *n*-butyl alcohol. After four such recrystallizations the melting point was constant at 254–255°.

Anal. Calcd. for $C_{19}H_{14}O_2N_2$: C, 75.48; H, 4.67. Found: C, 75.21; H, 4.76.

D. Preparation of the β-Carboline-3-carboxylic Acids, their Chlorides and β-Diethylaminoethyl Esters.—The esters were saponified by heating for three to seven hours with 1 *N* aqueous sodium hydroxide (25 ml. per gram of ester). The solutions were decolorized, cooled and acidified with acetic acid, and allowed to stand in the cold until crystallization was complete. 1-Methyl-β-carboline-3-carboxylic acid, m. p. 305–306° after recrystallization from 50% ethanol, apparently retained some water of crystallization even after drying *in vacuo* at 100° for twelve hours.

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.45. Found: C, 66.45, 67.17; H, 4.74, 4.91.

1-Phenyl-β-carboline-3-carboxylic acid melted at 283.5–284° after recrystallization from aqueous dioxane.

Anal. Calcd. for $C_{18}H_{12}O_2N_2$: C, 74.99; H, 4.20. Found: C, 74.86; H, 4.19.

For the preparation of the β-diethylaminoethyl ester of 1-methyl-β-carboline-3-carboxylate the crude acid chloride (made by refluxing for one and one-fourth hours a solution of 1 part of the acid with 10 volumes of purified thionyl chloride, distillation of most of the excess reagent at atmospheric pressure and removal of the last traces by distillation at 25 mm. followed by addition and distillation of benzene) was employed. The acid chloride was stirred on a steam-bath with a large excess (9 ml. per gram of acid used in the preparation of the chloride) of freshly distilled diethylaminoethanol for five hours. The mixture was poured on ice, treated with concentrated ammonia, and diluted with water to a volume of ten times that of the diethylaminoethanol. The mixture was allowed to stand in an ice-bath for three hours, after which the solid was collected. It was recrystallized from a mixture of benzene and low-boiling petroleum ether to give a product of m. p. 168.5–170° in 74% yield. Samples purified by recrystallization from benzene–petroleum ether or from alcohol–water appeared to retain water of crystallization. A sample (m. p. 169.5–170°) dried by distillation of most of the benzene from a dilute benzene solution of the substance, followed by precipitation with petroleum ether, was anhydrous.

Anal. Calcd. for $C_{19}H_{23}O_2N_3$: C, 70.13; H, 7.12. Found: C, 69.92; H, 7.05.

β-Diethylamino 1-phenyl-β-carboline-3-carboxylate, m. p. 185–186.5°, was obtained in 86% yield by the same procedure. Recrystallization from benzene and low-boiling petroleum ether raised the melting point to 186–187°. Traces of colored materials which resisted the action of Darco on the benzene solution could be removed by decolorization of a solution in 95% ethanol. The last traces of water were removed from the analytical sample by distillation with benzene as described above.

Anal. Calcd. for $C_{24}H_{25}O_2N_3$: C, 74.39; H, 6.50. Found: C, 74.17; H, 6.36.

Summary

The preparation of a number of 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acids by the condensation of *dl*-tryptophan with aldehydes is described. Certain carboline-3-carboxylic acids are prepared by dehydrogenation of the aldehyde-tryptophan condensation products, and the β-diethylaminoethyl esters of 1-methyl and 1-phenyl-β-carboline-3-carboxylic acid are described.

URBANA, ILLINOIS RECEIVED JULY 17, 1947

---

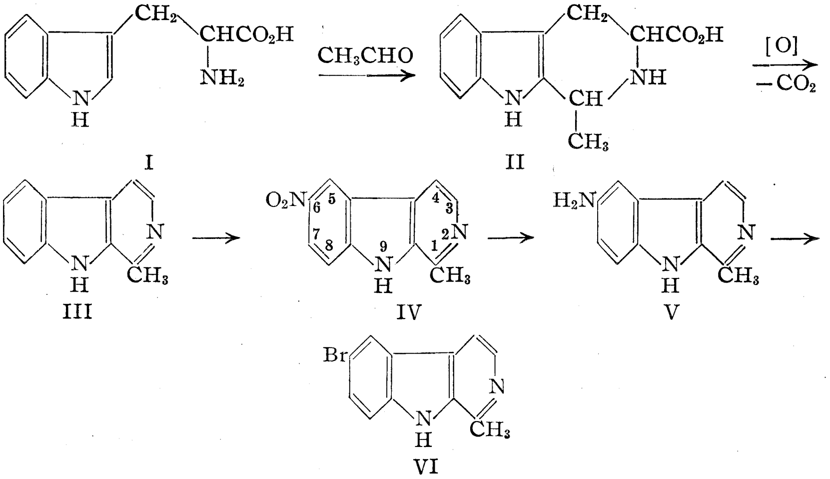
[18] The ester prepared from the crude acid or from either of the separated diastereoisomeric acids could be used.

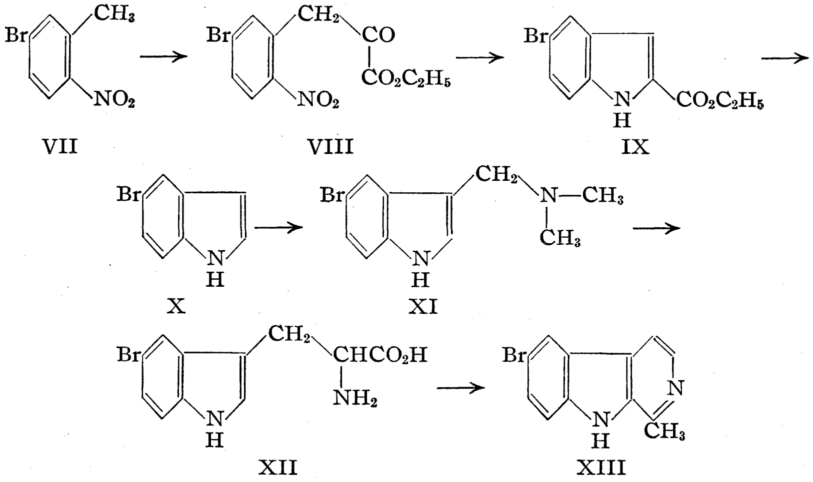
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Derivatives of β-Carboline. III. The Nitration of Harman[1]

BY H. R. SNYDER, STANLEY M. PARMERTER[2] AND LEON KATZ[3]

The preparation of harman (III) by the condensation of tryptophan (I) with acetaldehyde, followed by aromatization, oxidation and decarboxylation in a single step through the action of potassium dichromate,[4] becomes a practical synthetic method when the readily available *dl*-tryptophan is employed as the raw material.[1] It is therefore desirable to examine the substitution reactions of harman, some of which might be expected to lead to compounds of physiological interest. The present report is concerned with the preparation of two isomeric nitroharmans by direct nitration and with the proof of the structure of one of them (IV).





The preparation of harman (III) was carried out according to the method of Harvey and Robson,[4] except for the use of the racemic amino acid, without isolation of any of the intermediates and in 67% yield. The nitration was effected with the aid of concentrated nitric acid at temperatures of 40° or below. The higher-melting nitro derivative, now shown to be 6-nitroharman (IV), was formed in the larger amount (57%); the lower-melting isomer, presumably 8-nitroharman, was isolated in a yield of about 20%.

The higher-melting nitro compound (IV) was reduced to the amine (V) which proved not to be identical with the known 7-aminoharman.[5] Diazotization of the amine (V) was accomplished, and since both 6- and 8-methoxyharman are known, the conversion of the diazonium compound to the methyl ether should have sufficed to demonstrate the structure of IV. However, attempts to replace the diazonium group by methoxyl, either directly or by way of the hydroxy compound, have been unsuccessful.

It was possible to convert the diazonium compound to the bromo compound (VI), so an unequivocal synthesis of any of the compounds IV, V or VI would serve to confirm the identity of the high-melting nitro compound. The bromoharman (VI) was synthesized by the series of reactions shown in the accompanying chart. The 2-nitro-5-bromotoluene condensed readily with ethyl oxalate in the presence of potassium ethoxide to give the potassium salt of VIII, and this salt was reduced directly to the bromoindolecarboxylic ester (IX). The acid obtained by saponification of the ester IX proved unexpectedly resistant to decarboxylation. Of a number of decarboxylation procedures tested only vigorous heating with copper

---

(1) For the preceding paper see Snyder, Hansch, Katz, Parmerter and Spaeth, THIS JOURNAL, **70**, 219 (1948).

(2) Wm. S. Merrell Post-Doctorate Fellow, 1944–1945. Present address: Eastman Kodak Co., Rochester, N. Y.

(3) Present address: Calco Chemical Division, American Cyanamid Co., Bound Brook, New Jersey.

(4) Harvey and Robson. *J. Chem. Soc.*, 97 (1938).

(5) Fischer, *Ber.*, **47**, 99 (1914).

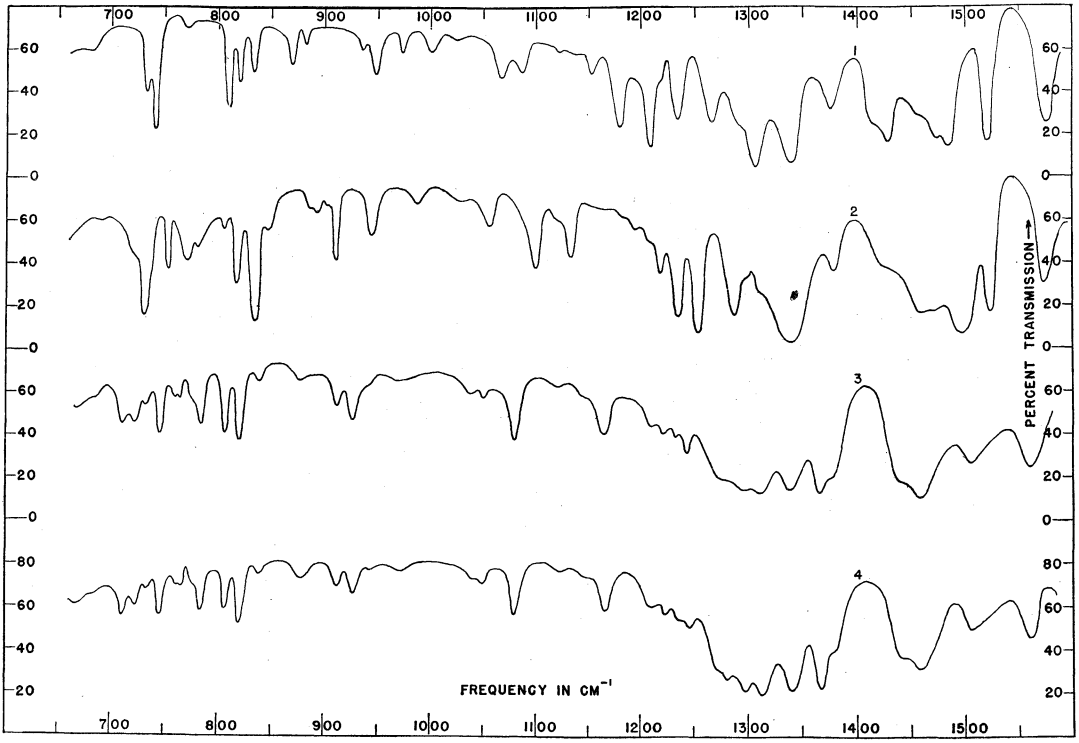


Fig. 1.—1, Nitroharman; m. p. 210°; 2, nitroharman; m. p. 301°; 3, picrate of 6-bromoharman; 4, picrate of bromoharman prepared from high-melting nitro isomer.

and copper chromite catalyst gave yields (*ca.* 20%) high enough to permit continuation of the projected series of reactions. This treatment apparently resulted in removal of bromine from some of the product, and the 5-bromoindole (X) so prepared could not be purified sufficiently for a satisfactory combustion analysis. 5-Bromoindole (X) of high purity could be obtained, but in very poor yield, by heating the ammonium salt of the acid in glycerol. It was found that the picrate of 5-bromogramine, prepared from the crude 5-bromoindole, could be obtained in the analytically pure state, so the synthesis was continued and the picrate of the 6-bromoharman (XIII) was prepared. This picrate was obtained in analytically pure state. The melting point of the picrate of the 6-bromoharman so obtained was identical with that of the picrate of the bromoharman prepared from the nitro compound (IV). A much more striking proof of the identity of the two picrates was obtained by comparison of the infrared absorption spectra of the two samples. The absorption curves[6] (Figs. 1 and 2) were identical in every detail.

Experimental

Harman (2-Methyl-β-carboline) (III).—The general procedure of Harvey and Robson[4] was followed. Twenty-five grams of *dl*-tryptophan and 50 ml. of freshly distilled acetaldehyde were added to 1 liter of water. The suspension was heated at 50–60° in a loosely-stoppered flask for three hours and then left at room temperature overnight. The resulting suspension was heated on a steam-bath to remove excess acetaldehyde, diluted to a volume of 6 l. and heated to boiling. To the hot solution was added 1200 ml. of 10% aqueous potassium dichromate and 240 ml. of glacial acetic acid. The brown suspension was heated for two to three minutes and then cooled under the tap. After treating the cold solution with sodium sulfite to remove the excess oxidizing agent, the mixture was made definitely alkaline with solid sodium carbonate. The solution was extracted exhaustively with ether (5–6 liters), the extracts dried over magnesium sulfate, and the solvent removed. The residue of crystalline harman, m. p. 228–230°, weighed 15.1 g. (67%).

6-Nitroharman (IV).—Crude harman was added slowly with stirring to concentrated nitric acid (10 ml. per g.). The temperature was held below 40° by occasional cooling. Most of the harman dissolved, and a light yellow solid separated. The mixture was stirred for one hour and filtered. The solid was suspended in dilute ammonium hydroxide to neutralize the nitric acid. The crude nitroharman was collected and dissolved in the minimum amount of hot pyridine. As the pyridine cooled, yellow needles separated. Concentration of the pyridine solution to half its original volume yielded an additional crop of needles. The total yield of nitroharman, m. p. 293–295°, was 57.1%. A sample recrystallized from 95% ethanol separated as clusters of yellow needles, m. p. 299–300°. The compound was soluble in acetic acid and pyridine, somewhat soluble in methanol and ethanol, and insoluble in water.

Anal. Calcd. for $C_{12}H_9N_3O_2$: C, 63.45; H, 3.99. Found: C, 63.66; H, 4.09.

Addition of water to the nitric acid used in the nitration gave additional quantities of yellow solid. This was collected and treated with ammonia to yield a lower-melting nitroharman. After recrystallization from 95% ethanol, it melted at 209–210°. It separated as octahedra or short needles. Dilution of the pyridine mother liquor

---

[6] The authors are indebted to Mrs. Agatha Roberts Johnson for the infrared study.

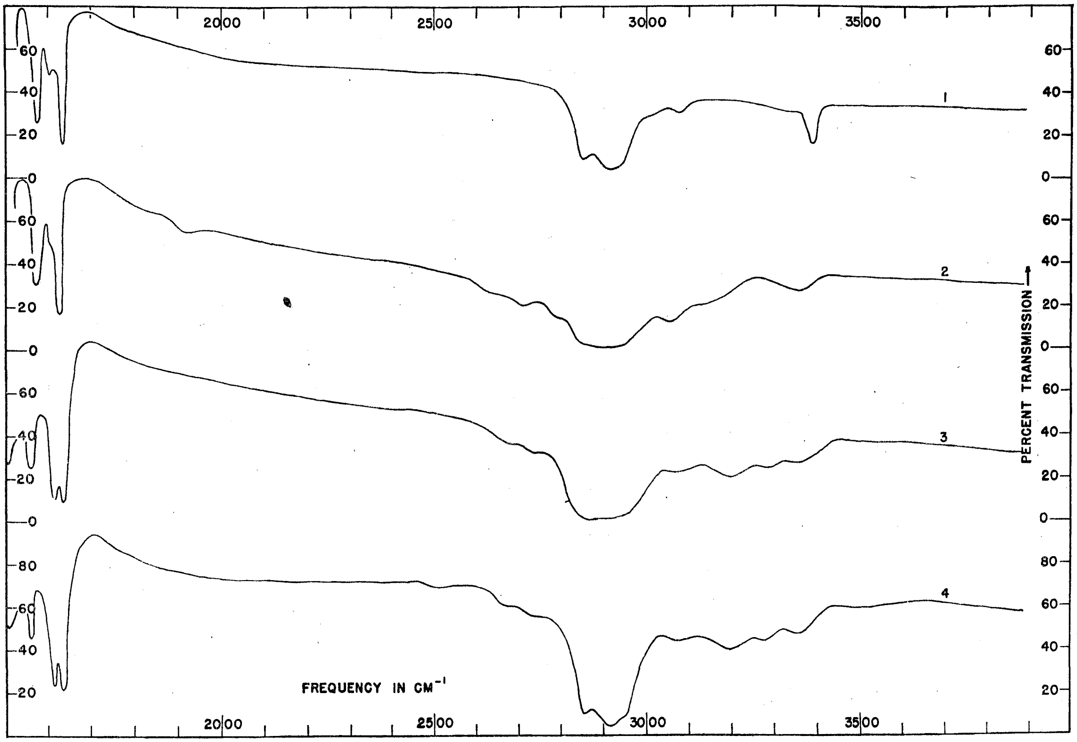


Fig. 2.—1, Nitroharman; m. p. 210°; 2, nitroharman; m. p. 301°; 3, picrate of 6-bromoharman; 4, picrate of bromoharman prepared from high-melting nitro isomer.

yielded additional amounts of this isomer, the total yield being 19.5%.

Anal. Calcd. for $C_{12}H_9N_3O_2$: C, 63.45; H, 3.99. Found: C, 63.59; H, 4.27.

6-Aminoharman (V).—To a solution of 2.2 g. of stannous chloride dihydrate in 2.5 ml. of concentrated hydrochloric acid and 10 ml. of water was added 0.5 g. of high-melting nitroharman. The solution was refluxed two hours and cooled in ice. The yellowish-green salt was collected and suspended in excess 10% aqueous sodium hydroxide to free the base. The solid was collected and washed with water. The yield of crude amine melting at 265–267° was 0.35 g. or 80% of the theoretical amount. After a second recrystallization, the light tan crystals melted at 269–271°. The base slowly darkens on exposure to air, and its solutions rapidly become deep red in color.

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.09; H, 5.62. Found: C, 73.12; H, 5.57.

6-Bromoharman (VI).—A cold solution of 0.394 g. of aminoharman in 1.5 ml. of water and 1 cc. of 40% hydrobromic acid was diazotized by the addition of a solution of 0.15 g. sodium nitrite in 0.5 ml. of water. The diazonium salt partially crystallized. The suspension of diazonium salt was transferred to a hot solution of 0.158 g. of cuprous bromide in 0.3 ml. of 40% hydrobromic acid. Heating on a steam-bath for ten minutes caused evolution of gas and the separation of a green solid, which was collected and suspended in dilute ammonium hydroxide. The free amine was then recrystallized from 25 ml. of 50% ethanol. Pale yellow needles melting at 241–244° separated. When these were recrystallized from benzene, they separated as needles which slowly changed to pale yellow plates. Both crystalline forms melted at 246–247°.

Anal. Calcd. for $C_{12}H_9N_2Br$: C, 55.20; H, 3.47. Found: C, 55.40; H, 3.69.

The picrate, prepared for analysis by recrystallization from absolute ethanol, melted at 291–293° (dec.).

Anal. Calcd. for $C_{12}H_9N_2Br{\cdot}C_6H_3N_3O_7$: C, 44.08; H, 2.45. Found: C, 44.39; H, 2.73.

2-Nitro-5-aminotoluene.—The procedure of Fieser[7] for acetylation, nitration and deacetylation of aniline was followed, with *m*-toluidine obtained from Eastman Kodak Company. From 102 g. of *m*-toluidine, 79.5 g. of 2-nitro-5-aminotoluene, m. p. 130–132° (lit.,[8] 137–138°) was obtained.

2-Nitro-5-bromotoluene (VII).—A modification of the method of Geerling and Wibaut[9] was employed. To a finely divided suspension of 25 g. of 2-nitro-5-aminotoluene in a cold solution of 80 ml. of 48% hydrobromic acid and 150 ml. of water, was added a solution of 11.5 g. of sodium nitrite in 30 ml. of water. The solution of the diazonium salt was filtered and run rapidly into a hot (75°) cuprous bromide solution prepared by boiling 20 g. of copper oxide, 20 g. of copper powder, 100 ml. of 48% hydrobromic acid and 80 ml. of water. The solution was stirred manually and then heated on a steam-bath for one-half hour. The 2-nitro-5-bromotoluene was isolated by steam distillation. The yield was 26 g. (75%); m. p. 55–56° (lit.,[10] 56°).

Potassium Salt of Ethyl 2-Nitro-5-bromophenylpyruvate (VIII).—A strong solution of potassium ethoxide was prepared by cautiously adding 3.2 g. of crust-free potassium to a mixture of 5 ml. of dry ether and 10 ml. of absolute alcohol; when the first violent reaction had subsided, 17 ml. of absolute alcohol was added and the solution was heated gently, if necessary, to effect complete solution of the metal. The solution was then cooled and diluted with 125 ml. of dry ether, and to this solution was added 12.3 g. of ethyl oxalate, followed fifteen minutes later by 15 g. of 2-nitro-5-bromotoluene. The solution was shaken gently and allowed to stand overnight. The red salt was collected, washed with dry ether, and used immediately. The yield was almost quantitative (24.5 g.).

---

[7] Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, pp. 163–170.

[8] Noelting and Stocklin, *Ber.*, **24**, 564 (1891).

[9] Geerling and Wibaut, *Rec. trav. chim.*, **53**, 1012 (1934).

[10] Gibson and Johnson, *J. Chem. Soc.*, 1229 (1929).

5-Bromoindole-2-carboxylic Acid.—The above salt, 28 g., was suspended in a solution of 170 ml. of concentrated aqueous ammonia (sp. gr., 0.880) and 200 ml. of water. To the bright red suspension was added, with stirring, a hot solution of 180 g. of ferrous sulfate heptahydrate in 200 ml. of water. The mixture was heated on a steam-bath for one-half hour and then boiled for one-half hour. The suspension was filtered while hot, and the sludge was extracted three times by boiling the filter cake with 500 ml. of water and filtering. The filtrates were cooled and acidified with concentrated hydrochloric acid. A voluminous white precipitate was formed, but the solution was allowed to stand in a refrigerator at 5° overnight before filtration. The yield of white solid, m. p. 270–273°, was 9 g., 42.5%. A sample was sublimed for analysis; m. p. 279–280°.

Anal. Calcd. for $C_9H_6NO_2Br$: C, 44.98; H, 2.53. Found: C, 44.71; H, 2.73.

The ethyl ester (IX) was obtained by extraction of the dried ferric oxide sludge with ether in a Soxhlet extractor for seventy-two hours. Removal of the solvent yielded 2.7 g. of material; m. p. 162–164°. A sample was prepared for analysis by recrystallization from 95% ethanol; m. p. 165°.

Anal. Calcd. for $C_{11}H_{10}NO_2Br$: C, 49.25; H, 3.76. Found: C, 49.42; H, 3.75.

5-Bromoindole (X).—Two grams of 5-bromoindole-2-carboxylic acid, 1 g. of copper bronze and 1 g. of copper chromite catalyst were intimately mixed and placed in a large test-tube. The test-tube was flushed three times with nitrogen, placed in a metal block, and heated at 247 ± 10° for one and one-half to two hours. A white sublimate of fine needles collected in the upper portion of the tube which was kept cool throughout the heating period. The yield of 5-bromoindole, m. p. 77–82°, was 0.35–0.4 g. (21–24%). Small amounts of sublimed acid were present as an impurity. The use of amounts larger than 3 g. resulted in lowered yields. A sample was resublimed for analysis; m. p. 85.5–86°.

Anal. Calcd. for C_8H_6NBr: C, 48.98; H, 3.06. Found: C, 50.75; H, 3.22.

When the ammonium salt was decarboxylated by heating in glycerol, a small amount of material sublimed into the condenser. This was collected and recrystallized from 50% ethanol; m. p. 88.5–89°.

Anal. Calcd. for C_8H_6NBr: C, 48.98; H, 3.06. Found: C, 49.34; H, 3.29.

5-Bromogramine (XI).—To 7.6 g. of dimethylamine (25%) at 5° was added 6 g. of glacial acetic acid. To this solution, cooled to 5°, was added 3.2 g. of formalin (40%). The solution was agitated mildly and added to 7.5 g. of crude 5-bromoindole. A slight exothermic reaction occurred. The resulting straw-colored solution was kept at room temperature for ten hours and poured into 40 ml. of 10% sodium hydroxide, cooled in an ice-bath. The white precipitate was filtered, yielding 7.8 g. (79%) of crude XI; m. p. 143–145°. A sample subjected to repeated recrystallization from acetone–water melted sharply at 149.5–150°, but still evidently contained bromine-free impurities.

Anal. Calcd. for $C_{11}H_{13}N_2Br$: C, 52.17; H, 5.18. Found: C, 54.12; H, 5.28.

The picrate prepared from the crude 5-bromogramine was purified by recrystallization from ethanol; it melted at 174°.

Anal. Calcd. for $C_{11}H_{13}N_2Br \cdot C_6H_3N_3O_7$: C, 42.32; H, 3.33. Found: C, 42.52; H, 3.42.

Condensation of the Crude 5-Bromogramine with Acetamidomalonic Ester.—The condensation was run in xylene according to the procedure of Howe, Zambito, Snyder and Tishler,[11] and the condensation product was converted to the amino acid by the method of Snyder and Smith.[12] The carbon and hydrogen contents of the intermediates and of the 5-bromotryptophan all were high (see the analysis of the bromogramine above).

6-Bromoharman.—Sixty-five milligrams of 5-bromotryptophan (m. p. 264–267°, dec.) was suspended in 7 ml. of hot water and treated with 20 drops of freshly distilled acetaldehyde and 3 drops of 6 *N* sulfuric acid. The solution was heated on a water-bath for one hour, cooled, treated with 5 drops of acetaldehyde and left at room temperature for twelve hours. The cloudy solution was concentrated on a steam-bath and cooled. Opaque crystals, m. p. 218–220°, were deposited. This acid was dissolved in 15 cc. of hot water and treated with 3.5 cc. of 10% potassium dichromate and 0.5 cc. of glacial acetic acid. The solution was boiled for two minutes, made alkaline with solid sodium carbonate, and extracted with ether. Removal of ether yielded 35 mg. of solid; m. p. 227–230°. Repeated crystallization from benzene raised the melting point to 234–235°.

The picrate was prepared and recrystallized repeatedly from absolute ethanol. The analytical sample thus prepared melted with decomposition at 291–293°, alone or mixed with the picrate of 6-bromoharman (VI) prepared from the nitroharman (IV).

Anal. Calcd. for $C_{12}H_9N_2Br \cdot C_6H_3N_3O_7$: C, 44.08; H, 2.45. Found: C, 44.29; H, 2.76.

Summary

Harman is conveniently prepared by the condensation of *dl*-tryptophan with acetaldehyde, followed by aromatization and decarboxylation of the condensation product. The nitration of harman by concentrated nitric acid at moderate temperatures leads to two isomeric mononitro derivatives; the nitro derivative produced in the larger amount is shown to be 6-nitroharman.

URBANA, ILLINOIS RECEIVED JULY 17, 1947

---

[11] Howe, Zambito, Snyder and Tishler, THIS JOURNAL, **67**, 38 (1945).

[12] Snyder and Smith, *ibid.*, **66**, 350 (1944).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE GEORGIA SCHOOL OF TECHNOLOGY]

The Synthesis of Quinolines from Aryloxyketones by the Method of Pfitzinger

BY ARTHUR M. DOWELL, JR.,[1] HOWARD S. MCCULLOUGH AND PAUL K. CALAWAY

In a recent investigation[2] in this Laboratory we have utilized the tolylthiopropanones in the preparation of substituted quinoline acids by the method of Pfitzinger.[3] The availability of the cresols suggested the preparation of the toloxypropanones[4] and their ultimate condensation with isatin and 5-methylisatin, respectively, to produce six substituted cinchoninic acids. We have studied also the condensation of 5-methylisatin with both α- and β-naphthoxyacetone.[5]

In previous papers[6,7] it has been demonstrated that the product of condensation of isatin with aryloxy ketones has been the 3-aryloxy-4-quinaldinecarboxylic acid rather than the isomeric 2-aryloxymethylcinchoninic acid.

The aryloxy ketones used in this investigation were prepared from the corresponding phenols and chloroacetone by the method of Hurd and Perletz.[8] The yields ranged from 57% of the theoretical, in the case of the *m*-toloxyacetone, to 97% for the β-naphthoxyacetone.

The potassium salts of the quinaldinecarboxylic acids prepared showed a tendency to foam in water solution and were salted out by high concentrations of potassium hydroxide. All of the acids exhibited a tendency to hold water of crystallization.[2] This water was removed by drying for several days in a vacuum desiccator over phosphorus pentoxide. Decarboxylation of the compounds was observed to start around 175°; hence melting point values varied with the rate of heating.

Experimental

Preparation of Aryloxyacetones.—The procedure used for the condensation of chloroacetone with phenols was based on the method of Hurd and Perletz.[8]

To a vigorously stirred and refluxing suspension of 0.41 mole of the phenol and 57 g. (0.41 mole) of anhydrous potassium carbonate in 150 ml. of dry acetone was added over a period of one hour a solution of 50 g. (0.54 mole) of chloroacetone and 3 g. of powdered potassium iodide in 50 ml. of dry acetone. The chloroacetone solution had been allowed to stand for twenty-four hours prior to addition. After refluxing for six hours, stirring was continued at room temperature for an additional twenty hours. The mixture was subjected to filtration, the precipitate washed well with dry acetone and the filtrate and washings combined. The solvent was distilled off and the residue distilled under diminished pressure. Table I contains the data on these preparations.

TABLE I

ARYLOXYACETONES, $ArOCH_2COCH_3$

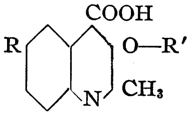
ArO	B. p. or m. p., °C.	Pressure, mm.	Yield, %
p-Toloxy	108–112	6	58
m-Toloxy	110–111	5	57
o-Toloxy	105–106	5	71
α-Naphthoxy	156–165	9	31
β-Naphthoxy	72–73		97

Preparation of 3-*m*-Toloxy-4-quinaldinecarboxylic Acid.—Seven and thirty-five hundredths grams (0.05 mole) of isatin was dissolved in 125 ml. of 33% aqueous potassium hydroxide solution, and 8.2 g. (0.05 mole) of *m*-toloxyacetone was added. The resulting mixture was heated under reflux on the steam-bath for six hours, and, upon cooling, a solid cake of potassium 3-*m*-toloxy-4-quinaldinecarboxylate separated. The latter was disintegrated and dissolved in 500 ml. of hot water. The resulting solution was boiled with Nuchar, filtered, cooled in ice and the crude acid precipitated by the addition of acetic acid (1:1). The quinoline acid was separated by filtration, suspended in 500 ml. of hot water, and converted into the soluble potassium salt by the addition of the calculated amount of 33% potassium hydroxide solution. The solution was again treated with Nuchar, filtered, and made barely acidic by the addition of acetic acid. The quinoline acid was separated by filtration, washed twice with 100-ml. portions of cold water, suspended in 400 ml. of boiling water for forty-five minutes, and filtered while hot. Nine and eight-tenths grams (67% yield) of the 3-*m*-tolyloxy-4-quinaldinecarboxylic acid was obtained. The product melted with decomposition at 224°. Dried over anhydrous calcium chloride the acid retained two molecules of water of hydration (as indicated by analytical data for nitrogen content). This water was removed by drying over phosphorus pentoxide in a vacuum desiccator.

The remaining 3-toloxy-4-quinaldinecarboxylic acids were formed in essential accordance with this general procedure. Table II contains the data on these preparations.

TABLE II

3-ARYLOXY-4-QUINALDINECARBOXYLIC ACIDS



R—	R′—	Yield, %	M. p., °C. (cor.)	Nitrogen, % Calcd.	Nitrogen, % Found
H	*p*-Tolyl	58	206	4.77	4.91
H	*m*-Tolyl	67	224	4.77	4.24
H	*o*-Tolyl	64.8	229	4.77	4.73
CH_3	*p*-Tolyl	72.6	202	4.54	4.42
CH_3	*m*-Tolyl	73.2	231	4.54	4.35
CH_3	*o*-Tolyl	81	225	4.54	4.24
CH_3	α-Naphthyl	40	238	4.08	3.90
CH_3	β-Naphthyl	46.8	233	4.08	3.59

Summary

1. Pfitzinger's method has been extended to include the utilization of the toloxypropanones in the synthesis of six substituted quinoline acids from isatin and 5-methylisatin, respectively.

---

[1] A part of this paper is taken from the thesis presented to the graduate faculty of the Georgia School of Technology by Arthur M. Dowell, Jr., in partial fulfilment of the requirements for the degree of Master of Science, June, 1947.

[2] Newell and Calaway, THIS JOURNAL, **69**, 116 (1947).

[3] (a) Pfitzinger, *J. prakt. Chem.*, **33**, 100 (1886); (b) **38**, 582 (1888); (c) **56**, 283 (1897).

[4] Stoermer, *Ber.*, **28**, 1253 (1895).

[5] Stoermer, *Ann.*, **312**, 313 (1900).

[6] Calaway and Henze, THIS JOURNAL, **61**, 1355 (1939).

[7] Knight, Porter and Calaway, *ibid.*, **66**, 1893 (1944).

[8] Hurd and Perletz, *ibid.*, **68**, 38 (1946).

2. The naphthoxypropanones have been condensed with 5-methylisatin to produce two substituted quinoline acids.

ATLANTA, GEORGIA RECEIVED JULY 8, 1947

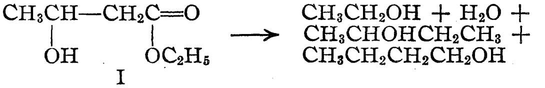
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK AND CO., INC.]

Hydrogenolysis of β-Oxygenated Esters to Glycols

BY RALPH MOZINGO AND KARL FOLKERS

Under the usual conditions for ester reduction,[1] esters containing negative substituents in the β-position to the carboalkoxy group do not give rise to the corresponding alcohols when submitted to hydrogenolysis[2] over copper–chromium oxide catalyst.[3] Under these conditions cleavage products result. However, it has now been found that with these compounds satisfactory ester hydrogenolysis, without additional cleavage at other points, may be accomplished when modified conditions are used.

When ethyl β-hydroxybutyrate is hydrogenated at 250° over copper–chromium oxide under hydrogen at 150–400 atmospheres, the final products obtained are ethyl alcohol, *n*-butyl alcohol and *s*-butyl alcohol,[4] according to the following scheme in which the bonds undergoing hydrogenolysis are indicated by lines.



$$\underset{\text{I}}{\underset{|\atop OH}{CH_3CH}-CH_2\underset{|\atop OC_2H_5}{C}{=}O} \longrightarrow \begin{array}{l} CH_3CH_2OH + H_2O + \\ CH_3CHOHCH_2CH_3 + \\ CH_3CH_2CH_2CH_2OH \end{array}$$

It would appear, however, that the reaction may take the course

$$\begin{array}{l} CH_3CHOHCH_2CO_2C_2H_5 \longrightarrow CH_3CHOHCH_2CH_2OH + C_2H_5OH \\ CH_3CHOHCH_2CH_2OH \longrightarrow CH_3CHOHCH_2CH_3 \text{ or } CH_3CH_2CH_2CH_2OH + H_2O \\ \qquad\qquad\qquad\qquad\quad \text{or} \\ \qquad\qquad\qquad\qquad\quad \longrightarrow 2C_2H_5OH \end{array}$$

If the reaction does proceed stepwise and the glycol is not isolated because the second reaction is the more rapid under the conditions which have been used and if sufficiently mild conditions can be found for the hydrogenation, it seems reasonable to expect that some of the glycol might be isolated. Such conditions were found and it was possible to isolate the glycol in reasonable yields.

Since, at any pressure above a certain minimum which is characteristic of the compound being hydrogenated, the effect of temperature is probably the greatest factor in controlling the hydrogenation products, lower temperatures of reaction seemed desirable. It had been demonstrated[5] that the hydrogenation of esters of certain sugar acids at 75° gives rise to the corresponding sugar alcohols. Ethyl α-hydroxyisobutyrate is hydrogenated at 200°.[6] Further, it had been shown that ethyl benzilate is hydrogenated rapidly to the corresponding 1,2-glycol at 125°.[7] In the last case this has been postulated to be due to tautomerization, and the same might be the controlling factor in all of these cases, since each ester contains an α-hydroxyl. The β-hydroxy esters cannot undergo such enolization, but must be hydrogenated in the ester form.

The hydrogenation of β-oxygenated esters was found to proceed smoothly at temperatures between 150 and 180° when relatively large amounts of copper–chromium oxide catalyst[3] were used. The hydrogenation of the β-oxygenated esters appears to be more satisfactory at higher hydrogen pressures (250–400 atmospheres) since the reactions are rather slow. The hydrogenolysis was carried out most successfully in methyl alcohol, which is quite contrary to the general practice when temperatures in excess of 220° are used for ester reduction.[8] For example, ethyl β-hydroxybutyrate (I) (or ethyl acetoacetate)[9] was hydrogenated to 1,3-butylene glycol (II) in 30% yield and ethyl β-ethoxypropionate (III) was converted into 3-ethoxy-1-propanol (IV) in 78% yield.

$$\underset{\text{I}}{CH_3CHOHCH_2CO_2C_2H_5} \longrightarrow \underset{\text{II}}{CH_3CHOHCH_2CH_2OH + C_2H_5OH}$$

$$\underset{\text{III}}{C_2H_5OCH_2CH_2CO_2C_2H_5} \longrightarrow \underset{\text{IV}}{C_2H_5OCH_2CH_2CH_2OH + C_2H_5OH}$$

Likewise, α-alkyl and α-alkylidine acetoacetic esters gave rise to the corresponding 1,3-glycols. Ethyl α-isobutylideneacetoacetate (V) and ethyl ethylacetoacetate (VI) were converted under these conditions into 2-isobutyl-1,3-butylene glycol (VII) and 2-ethyl-1,3-butylene glycol (VIII), respectively. Both of the racemic forms of these two glycols were formed in the reduction and were separated through their *p*-nitrobenzoyl derivatives.

---

[1] Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wis., 1937, p. 97.

[2] Connor and Adkins, THIS JOURNAL, **54**, 4678 (1932).

[3] Connor, Folkers and Adkins, *ibid.*, **53**, 2012 (1931).

[4] Adkins, ref. 1, p. 103.

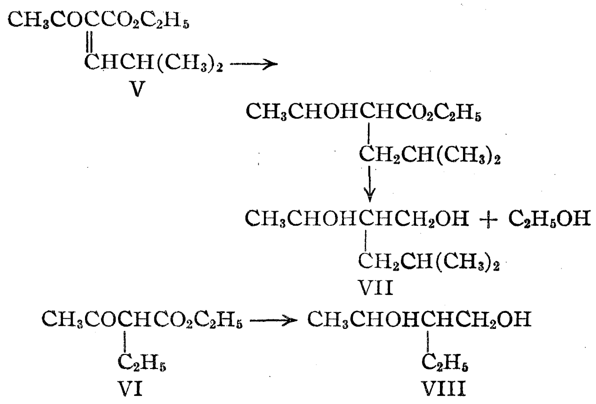
[5] Levene, Meyer and Kuna, *J. Biol. Chem.*, **125**, 703 (1938).

[6] Lazier, U. S. Patent 2,094,611 (October 5, 1937).

[7] Wojcik, Covert and Adkins, THIS JOURNAL, **55**, 1669 (1933).

[8] Lazier, U. S. Patent 2,079,414 (May 4, 1937.)

[9] Since it has been demonstrated that the β-keto esters are converted rapidly to β-hydroxy esters below the temperature used here, the keto esters may be used (see Connor and Adkins, THIS JOURNAL, **53**, 1091 (1931)).



$$\underset{\text{V}}{CH_3COC(=CHCH(CH_3)_2)CO_2C_2H_5} \longrightarrow CH_3CHOHCH(CH_2CH(CH_3)_2)CO_2C_2H_5 \longrightarrow \underset{\text{VII}}{CH_3CHOHCH(CH_2CH(CH_3)_2)CH_2OH} + C_2H_5OH$$

$$\underset{\text{VI}}{CH_3COCH(C_2H_5)CO_2C_2H_5} \longrightarrow \underset{\text{VIII}}{CH_3CHOHCH(C_2H_5)CH_2OH}$$

The esters of the alkylmalonic acids (IX) were hydrogenated to 2-alkyl-1,3-propanediols (X).

$$\underset{\text{IX}}{C_2H_5O_2CCHRCO_2C_2H_5} \longrightarrow HOCH_2CHRCO_2C_2H_5 \longrightarrow \underset{\text{X}}{HOCH_2CHRCH_2OH}$$

Ethyl benzylmalonate, ethyl *s*-butylmalonate and ethyl ethylmalonate were converted into the corresponding 1,3-glycols in 26, 24 and 49% yields, respectively.

These results indicate that the β-oxygenated esters, such as acetoacetic esters, malonic esters and the like, may be converted into the corresponding 1,3-glycols (or their esters) as a general convenient preparative method. While many of the yields reported are low, the method offers a convenient way for the preparation of glycols. The yields reported are usually based upon a single run on each of the esters; no attempt has been made to obtain the maximum yield. The present experiments were merely intended to show that such products can be obtained.

Experimental

Copper–Chromium–Barium Oxide Catalyst.—The catalyst was prepared in the usual way.[3] The decomposition of the ammonium salts was done at the minimum temperature. The catalyst contained barium.

Purification of the Esters.—The esters were distilled over Raney nickel catalyst[10] before use.

Ethyl Isobutylideneacetoacetate.—This ester was prepared in 49% yield by a method for the preparation of ethyl butylideneacetoacetate.[11] The ester boiled at 79–80° at 2 mm.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.46; H, 9.21.

Hydrogenation of β-Oxygenated Esters.—The various esters were each hydrogenated in methyl alcohol over copper–chromium oxide under 250–400 atmospheres of hydrogen at about 160–180° in a manganese steel bomb. The exact temperature, amount of reactants, time, etc., are listed for each ester.

The product was isolated in each case by a standard method. The contents of the bomb was washed out with methyl alcohol and filtered. To the filtrate was added 1.5 equivalents of sodium or potassium hydroxide based on the amount of ester submitted to reduction and about 100 ml. of water. The mixture was then refluxed several hours to saponify any unconverted ester. The methyl alcohol was distilled. The aqueous solution was extracted with chloroform in a continuous extractor to remove the glycol. The chloroform solution was concentrated, and the residue was fractionated.

The liquid glycols and alcohols were converted into their *p*-nitrobenzoates for characterization.

Hydrogenation of Ethyl Acetoacetate.—Sixty-five grams of ethyl acetoacetate in 200 ml. of methyl alcohol was reduced to ethyl β-hydroxybutyrate at 125–140° with 30 g. of copper–chromium oxide for fifteen minutes under 100 atmospheres of hydrogen. The bomb was then cooled, and the pressure drop was the expected amount for one mole of hydrogen. The pressure was then increased to 250 atmospheres and the hydrogenation allowed to proceed at 166–170° for nine hours.

The 1,3-butylene glycol, b. p. 115–120° at 21 mm., obtained after saponification, weighed 13.6 g. (30%). The *p*-nitrobenzoate of the 1,3-butylene glycol melted at 101–102°.

Anal. Calcd. for $C_{18}H_{16}O_8N_2$: C, 55.67; H, 4.12; N, 7.21. Found: C, 55.75; H, 4.13; N, 7.18.

Hydrogenation of Ethyl Isobutylideneacetoacetate.—A solution of 43 g. of ethyl isobutylideneacetoacetate in 100 ml. of methyl alcohol was hydrogenated at 160° and 3400–4600 p. s. i. for thirty hours.

The 2-isobutyl-1,3-butylene glycol, b. p. 142–143° at 22 mm., weighed 6 g. (17%).

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.62; H, 12.32.

The di-*p*-nitrobenzoate of this glycol was prepared and found to be a mixture of the two racemic modifications. The product was repeatedly extracted with hot methyl alcohol. The methyl alcohol extracts were concentrated and then cooled. After several recrystallizations from methyl alcohol, this *p*-nitrobenzoate melted at 129–130°.

Anal. Calcd. for $C_{22}H_{24}O_8N_2$: C, 59.45; H, 5.45; N, 6.30. Found: C, 59.69; H, 5.54; N, 6.49.

The methyl alcohol insoluble residue was recrystallized from acetone to give the second form of the *p*-nitrobenzoate, m. p. 158–159°.

Anal. Calcd. for $C_{22}H_{24}O_8N_2$: C, 59.45; H, 5.45. Found: C, 59.31; H, 5.62.

From the water solution, there was isolated 23.8 g. of acidic material which was fractionated to give 16.1 g. (43%) of β-hydroxy-α-isobutylbutyric acid which after crystallization melted at 68–70°.

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 60.28; H, 10.30.

In another similar run, 8.4 g. (25%) of the glycol was obtained from 27.6 g. of the ester.

Hydrogenation of Ethyl Ethylacetoacetate.—A solution of 23.7 g. of ethyl ethylacetoacetate in 100 ml. of methyl alcohol was hydrogenated at 160–168° and 5000–5300 p. s. i. over 5 g. of copper–chromium oxide for eleven hours.

Fractionation of the chloroform extract gave 2.6 g. (15%) of 2-ethyl-1,3-butylene glycol, b. p. 110–120° at 21 mm., which was identified by conversion into its di-*p*-nitrobenzoate. The glycol was a mixture of both of the racemic modifications since it gave two *p*-nitrobenzoyl derivatives. These were separated by extraction with methyl alcohol as above. The methyl alcohol soluble fraction melted at 124–125° (from methyl alcohol).

Anal. Calcd. for $C_{20}H_{20}O_8N_2$: C, 57.69; H, 4.84; N, 6.73. Found: C, 57.60; H, 4.79; N, 6.98.

The second *p*-nitrobenzoate was recrystallized from acetone and melted at 139–140°.

Anal. Calcd. for $C_{20}H_{20}O_8N_2$: C, 57.69; H, 4.84; N, 6.73. Found: C, 58.05; H, 5.17; N, 7.05.

Hydrogenation of Ethyl β-Ethoxypropionate.—A solution of 146 g. of ethyl β-ethoxypropionate in 100 ml. of methyl alcohol was hydrogenated over 30 g. of copper–chromium oxide at 168–172° and 4200–6350 p. s. i. for twenty-three hours.

The 3-ethoxy-1-propanol, b. p. 160–161°, obtained as above, weighed 81.2 g. (78%). The usual esters of this

---

(10) "Organic Syntheses," **21**, 15 (1941).

(11) Cope and Hofmann, THIS JOURNAL, **63**, 3456 (1941).

glycol appear to be liquids, but its boiling point agrees with the recorded value.[12]

Hydrogenation of Ethyl Benzylmalonate.—Nineteen grams of the ester in 100 ml. of methyl alcohol was hydrogenated over 8 g. of copper–chromium oxide at 160° and 4900–5600 p. s. i. for six hours. The 2-benzyl-1,3-propanediol was collected by distillation and boiled at 143–145° at 0.5 mm. After standing, the glycol crystallized and was recrystallized from benzene, after which it melted at 68–70°. The yield was 3.3 g. (26%).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 72.26; H, 8.49. Found: C, 72.52; H, 8.44.

The *p*-nitrobenzoate of this glycol melted at 130–131° (from chloroform–ether).

Anal. Calcd. for $C_{24}H_{20}O_8N_2$: C, 62.06; H, 4.35; N, 6.03. Found: C, 61.88; H, 4.27; N, 6.06.

Hydrogenation of Ethyl *s*-Butylmalonate.—A solution of 53.7 g. of ethyl *s*-butylmalonate in 85 ml. of methyl alcohol was hydrogenated over 12.5 g. of copper–chromium oxide catalyst at 157–162° and 4700–6400 p. s. i. for ten hours.

The 2-*s*-butyl-1,3-propanediol, isolated as above, boiled at 92–105° at 0.5 mm. and weighed 7.9 g. The *p*-nitrobenzoate of this glycol melted at 101–102°.

Anal. Calcd. for $C_{21}H_{22}O_8N_2$: C, 58.60; H, 5.15; N, 6.51. Found: C, 58.68; H, 5.03; N, 6.55.

Hydrogenation of Ethyl Ethylmalonate.—A solution of 28.2 g. of ethyl ethylmalonate in 100 ml. of methyl alcohol was reduced at 160–162° for nine hours and then at 180° for fifteen hours at 4100–5500 p. s. i. over 8 g. of copper–chromium oxide. The 2-ethyl-1,3-propanediol, b. p. 86–87° at 0.5 mm., weighed 7.7 g. (49%).

Anal. Calcd. for $C_5H_{12}O_2$: C, 57.66; H, 11.62. Found: C, 57.02; H, 10.99.

The *p*-nitrobenzoate prepared from this glycol was recrystallized from methyl alcohol and melted at 88–89°.

Anal. Calcd. for $C_{19}H_{18}O_8N_2$: C, 56.72; H, 4.51; N, 6.96. Found: C, 56.81; H, 4.44; N, 7.09.

Acknowledgment.—The authors wish to express their appreciation to Mr. William B. Wright for technical assistance and Messrs. R. N. Boos, D. F. Hayman, Wilhelm Reiss, W. K. Humphrey, E. Thornton and Leonard Rosalsky, and Mrs. E. H. Meiss for carrying out the analyses.

Summary

Hydrogenation of β-oxygenated esters has been found to give rise to 1,3-glycols or their ethers by a lower temperature ester reduction method. When the malonic esters, acetoacetic ester, the β-hydroxy esters and β-alkoxy esters are hydrogenated at 160–180° over copper–chromium oxide, the corresponding glycols and their derivatives are produced.

By this method, ethyl acetoacetate, ethyl ethylacetoacetate and ethyl isobutylideneacetoacetate were converted into 1,3-butylene glycol, 2-ethyl-1,3-butylene glycol and 2-isobutyl-1,3-butylene glycol. Ethyl β-ethoxypropionate gave 3-ethoxy-1-propanol. The ethyl alkylmalonates (ethyl, *s*-butyl and benzyl) give the corresponding 2-alkyl-1,3-propanediols. The yields were 15–78%.

RAHWAY, NEW JERSEY RECEIVED JULY 9, 1947

---

[12] Bouveault and Blanc, *Bull. soc. chim.*, [3] **31**, 1211 (1904).

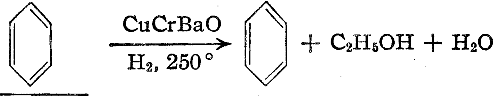
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK AND CO., INC.]

Hydrogenolysis of Aromatic Esters to Alcohols

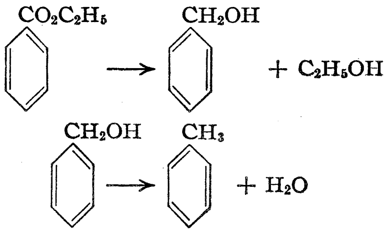
BY RALPH MOZINGO AND KARL FOLKERS

The hydrogenolysis of β-oxygenated esters and their ethers to 1,3-glycols and 1,3-glycol ethers[1] has lead to a reinvestigation of the hydrogenolysis of aromatic esters. While the hydrogenation of aromatic esters under the usual conditions[2] for ester hydrolysis leads to products in which the carboalkoxy group has been converted to a methyl group, it is possible by the low temperature technique previously described[1] to isolate the intermediate alcohol.

When an aromatic ester is hydrogenated at temperatures between 200 and 250° over a copper–chromium oxide catalyst[3] under 200 atmospheres of hydrogen it is converted rapidly into the corresponding methyl derivative. For example, ethyl benzoate gives toluene, ethanol and water.[2]



None of the corresponding alcohol has been obtained under these conditions and it has been suggested that the hydrogenolysis proceeds preferentially to the hydrocarbon.[4] However, it seems equally reasonable that the hydrogenation of an aromatic ester to the hydrocarbon may proceed stepwise.



This has now been found to be the case.

When hydrogenation is carried out between 125 and 175°, the exact temperature depending somewhat upon the ester, hydrogenolysis to the alcohol can be effected. For example, under these conditions ethyl benzoate (I, R = H) and its alkyl derivatives (I, R = CH_3, and II) and its

---

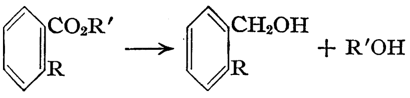
[1] Mozingo and Folkers, THIS JOURNAL, **70**, 227 (1948).

[2] Adkins, "Reaction of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 97–104.

[3] Connor, Folkers and Adkins, THIS JOURNAL, **53**, 2012 (1931).

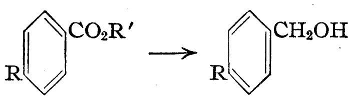
[4] Lazier, U. S. Patent 2,079,414 (May 4, 1937).

3,4-dimethyl derivative (III) are converted into benzyl alcohol (IV, R = H) and its alkyl derivatives (IV, V and VI).



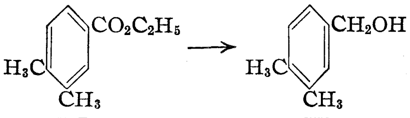
I IV

(R = H, CH_3; R′ = CH_3 or C_2H_5)

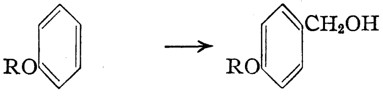


II V

(R = H, CH_3 or $(CH_3)_2CH$; R′ = CH_3 or C_2H_5)



III VI



VII VIII

(R = H or CH_3; R′ = CH_3 or C_2H_5)

Similarly, the oxygenated derivatives may be converted into corresponding alcohols. Methyl anisate (VII, R = CH_3) is converted into *p*-methoxybenzyl alcohol (VIII, R = CH_3) and ethyl *p*-hydroxybenzoate (VII, R = H) is converted into *p*-hydroxybenzyl alcohol (VIII, R = H).

The hydrogenolysis was carried out most successfully in methyl alcohol and, at the temperatures used here, decomposition of the methyl alcohol[4] apparently does not occur. With the aromatic esters the reduction is satisfactory, when pressures of 300 atm. or greater are used at temperatures in the range 125–175° with, in general, those near 160° giving the best yields of the alcohol. The yield of alcohol is greater when the reduction proceeds rapidly at a given temperature. Likewise, the amount of alcohol is usually greater when the reaction is interrupted at the point where its rate decreases markedly or the theoretical quantity of hydrogen has been consumed rather than when the reaction is allowed to proceed longer. Presumably, when the reaction is allowed to proceed beyond this point the benzyl alcohol is converted to the toluene derivative more rapidly than it is formed from the ester in the latter stages of the process.

Experimental

Copper-Chromium Oxide Catalyst.—The catalyst was prepared according to the usual method.[3] The thermal decomposition was carried out at the lowest possible temperature. The catalyst contained barium, except in one case noted.

Purification of Esters.—The esters were heated in a solvent with, or distilled over, Raney nickel catalyst[5] before use.

Hydrogenation of Aromatic Esters.—A solution of the ester in reagent methyl alcohol was hydrogenated over copper–chromium–barium oxide at 125–165° and under 300–400 atm. of hydrogen until the rate of hydrogen absorption became slow or the theoretical amount had been taken up. The amount of material, time, etc., are listed under each ester.

The products were isolated, after removing the catalyst, in the following way. To the solution of products in methyl alcohol were added 1.5 equivalents of potassium hydroxide (based on the original amount of ester) and 100 ml. of water. After refluxing the mixture for five hours or longer, most of the methyl alcohol was distilled. The residue was diluted with 150 ml. of water and extracted repeatedly with chloroform or benzene to remove the aromatic alcohol. The water solution from the chloroform extraction was made strongly acid with concentrated hydrochloric acid, cooled to 0°, and the acid removed by filtration.

The chloroform extract was combined with the methyl alcohol distillate, dried over anhydrous magnesium sulfate and fractionated. For complete identification of the liquid alcohols a solid ester, usually the *p*-nitrobenzoate, was prepared in each case by the pyridine method.[6]

Hydrogenation of Ethyl Benzoate.—A solution of 50 g. of the ester in 75 ml. of methyl alcohol was hydrogenated at 155–160° over 7 g. of copper–chromium–barium oxide for three and one-quarter hours. Eleven grams (25%) of benzoic acid, m. p. 121–122°, and 22.7 g. (63%) of benzyl alcohol, b. p. 103–104° at 23 mm., were isolated as above. The *p*-nitrobenzoate of the benzyl alcohol melted at 84–85° (from methyl alcohol), its recorded melting point.[7]

Another reduction, using 150 g. of ethyl benzoate in 100 ml. of methyl alcohol with 30 g. of catalyst, was carried out at 125–132° for ten and one-third hours. The yield in this case was 53.4 g. (49%) of benzyl alcohol.

In one experiment, barium-free copper–chromium oxide catalyst was used. In this case 75 g. of ethyl benzoate in 75 ml. of methyl alcohol was hydrogenated at 125–134° over 7.5 g. of copper–chromium oxide catalyst containing no barium for fourteen and one-half hours. The yield of benzyl alcohol, b. p. 106–108° at 25 mm., was 12.1 g. (22%) together with 17 g. of liquid boiling at 191–193° at 25 mm. presumably benzyl benzoate since in this case the esters were not saponified before distillation of the reaction mixture.

Hydrogenation of Methyl *o*-Toluate.—A solution of 23 g. of the ester in 120 ml. of methyl alcohol was hydrogenated over 5 g. of copper–chromium–barium oxide for two hours at 159–162°, then was worked up as above.

The products were 13 g. (70%) of *o*-methylbenzyl alcohol,[8] b. p. 120–122° at 23 mm., and 1.3 g. (6%) of *o*-toluic acid, m. p. 104–105°.

The *p*-nitrobenzoate of *o*-methylbenzyl alcohol, m. p. 100–101° (from methyl alcohol), was analyzed.

Anal. Calcd. for $C_{15}H_{13}O_4N$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.49; H, 4.85; N, 4.95.

Hydrogenation of Methyl *p*-Toluate.—A mixture of 50 g. of methyl *p*-toluate, 200 ml. of methyl alcohol and 10 g. of copper–chromium–barium oxide catalyst was agitated under hydrogen at 126–130° for eleven and one-quarter hours. The *p*-methylbenzyl alcohol,[9] m. p. 57–58° (from petroleum ether, b. p. 30–60°), weighed 28.4 g. (70%). The 3,5-dinitrobenzoate of the *p*-methylbenzyl alcohol melted at 117–118° (from ethyl alcohol).

Anal. Calcd. for $C_{15}H_{12}O_6N_2$: C, 56.96; H, 3.80; N, 8.86. Found: C, 57.00; H, 4.07; N, 8.91.

Hydrogenation of Methyl *p*-Isopropylbenzoate.[10]—When 26.9 g. of this ester, 120 ml. of methyl alcohol and 5 g. of copper–chromium–barium oxide catalyst were allowed to react with hydrogen at 156–160° for eight hours, the amount of *p*-isopropylbenzoic acid, m. p. 109–110°, isolated after hydrolysis was 4.0 g. (16%). The *p*-isopro-

---

(5) "Organic Syntheses," **21**, 15 (1941).

(6) Einhorn and Hollandt, *Ann.*, **301**, 95 (1898).

(7) Kothe, *ibid.*, **266**, 313 (1891).

(8) Law, *J. Chem. Soc.*, **91**, 748 (1907).

(9) Cannizzaro, *Ann.*, **124**, 252 (1862).

(10) Bert, *Bull. soc. chim.*, **37**, 1397 (1925).

pylbenzyl alcohol,[11] b. p. 135–136° at 26 mm., weighed 18.4 g. (81%) and gave a 3,5-dinitrobenzoate melting at 91–92°[12] (from petroleum ether, b. p. 60–70°).

Anal. Calcd. for $C_{17}H_{16}O_6N_2$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.20; H, 4.57; N, 8.37.

Hydrogenation of Ethyl 3,4-Dimethylbenzoate.—A solution of 89 g. of ethyl 3,4-dimethylbenzoate in 60 ml. of methyl alcohol was allowed to react with hydrogen over 10 g. of copper–chromium–barium oxide catalyst at 128–132° for twenty-four hours. The 3,4-dimethylbenzoic acid,[13] m. p. 165–166°, weighed 17.3 g. (23%). The 3,4-dimethylbenzyl alcohol,[14] m. p. 61–62° (from ethyl alcohol) amounted to 43.2 g. (64%).

Anal. Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.24; H, 8.79.

The *p*-nitrobenzoate of this alcohol melted at 78–79° (from methyl alcohol).

Anal. Calcd. for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.38; H, 5.57; N, 4.81.

Hydrogenation of Methyl *o*-Methoxybenzoate.—A solution of 36 g. of the ester in 90 ml. of methyl alcohol was reduced over 5 g. of copper–chromium–barium oxide for six and one-third hours at 160–162°. The products were 4.5 g. (14%) of *o*-methoxybenzoic acid, m. p. 100–102°, and 16.7 g. (56%) of *o*-methoxybenzyl alcohol,[15] b. p. 134–135° at 20 mm. The *p*-nitrobenzoate of this alcohol melted at 81–82° (from methyl alcohol).

Anal. Calcd. for $C_{15}H_{13}O_4N$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.90; H, 4.77; N, 5.02.

When reduction of 33.2 g. of methyl *o*-methoxybenzoate, with the same amounts of other reactants as above, was carried out for three and one-third hours, 8 g. (26%) of the acid and 15.6 g. (57%) of the alcohol were isolated.

Hydrogenation of Methyl Anisate.—Eighty-three grams of methyl anisate in 60 ml. of methyl alcohol was hydrogenated over 10 g. of copper–chromium–barium oxide at 130–140° for twenty-three hours. A fore-run in the distillation, b. p. 84–85° at 27 mm., consisted of *p*-cresol methyl ether and weighed 4.0 g. (6.6%). The yield of anisyl alcohol, b. p. 150–151° at 27 mm., was 61.3 g. (89%). The *p*-nitrobenzoate of the anisyl alcohol melted at 93–94° (from 95% ethyl alcohol).

Anal. Calcd. for $C_{15}H_{13}O_5N$: C, 62.72; H, 4.53; N, 4.88. Found: C, 62.81; H, 4.65; N, 4.90.

Hydrogenation of Methyl Veratrate.[16]—A solution of 19.6 g. of methyl veratrate in 130 ml. of methyl alcohol was hydrogenated for three and two-thirds hours at 155–160° over 5 g. of copper–chromium–barium oxide. The recovered acid, m. p. 179–180°, amounted to 0.4 g. (2%). The 3,4-dimethoxybenzyl alcohol,[17] b. p. 135–140° at 1 mm., amounted to 14.4 g. (86%) and gave a *p*-nitrobenzoate melting at 108–109° (from methyl alcohol).

Anal. Calcd. for $C_{16}H_{15}O_6N$: C, 60.56; H, 4.77; N, 4.41. Found: C, 60.57; H, 4.76; N, 4.46.

Hydrogenation of Ethyl *p*-Hydroxybenzoate.—A mixture of 49.8 g. of ethyl *p*-hydroxybenzoate, 75 ml. of methyl alcohol and 10 g. of copper–chromium–barium oxide catalyst was submitted to hydrogenation at 155–160° for nineteen hours. In this case the phenol was separated from the acid by extracting the acid from a chloroform solution of the two with bicarbonate solution. The *p*-hydroxybenzoic acid, m. p. 205–207°, amounted to 7 g. (17%). The solid phenol after recrystallization from benzene weighed 22.5 g. (60%) and melted at 124–125°; the recorded melting point of *p*-hydroxybenzyl alcohol is 124–125°.[18]

Acknowledgment.—The authors wish to express their appreciation to Mr. William Wright for technical assistance and to Messrs. Richard Boos, D. F. Hayman, Wilhelm Reiss, H. S. Clark, W. K. Humphrey and E. Thornton for carrying out the microanalyses.

Summary

Several aromatic esters have been converted into the corresponding benzyl alcohols by catalytic hydrogenation over copper–chromium–barium oxide at 125 to 160° in 50–90% yield. Methyl alcohol has been found to be a suitable solvent for these reductions.

Using this method, it has been found that alkyl and alkoxy benzoic acid esters containing one or more substituents as well as the unsubstituted benzoic esters can be converted into the corresponding alcohols. Likewise, ethyl *p*-hydroxybenzoate gives *p*-hydroxybenzyl alcohol.

RAHWAY, NEW JERSEY RECEIVED JULY 9, 1947

---

[11] Bert, *Bull. soc. chim.*, **37**, 1252 (1925).

[12] Cooke, Gillespie and Macbeth (*J. Chem. Soc.*, 1825 (1938)) report the melting point of this derivative as 107° (from methyl alcohol). The melting point of the compound obtained here could not be raised by repeated recrystallization of the pure material from methyl alcohol. Recrystallization of the crude ester from methyl alcohol gave methyl 3,5-dinitrobenzoate, m. p. 106–107°, undepressed by admixture with methyl 3,5-dinitrobenzoate prepared directly from methyl alcohol.

[13] Lellmann and Benz, *Ber.*, **24**, 2115 (1891)

[14] Sommelet, *Compt. rend.*, **157**, 1443 (1913).

[15] Späth, *Monatsh.*, **34**, 1965 (1913).

[16] Sabalitschka and Tietz, *Arch. Pharm.*, **269**, 545 (1931).

[17] Decker and Pschorr, *Ber.*, **37**, 3396 (1904).

[18] Auwers and Daiche, *ibid.*, **32**, 3374 (1899).

[Contribution from the Noyes Chemical Laboratory, University of Illinois]

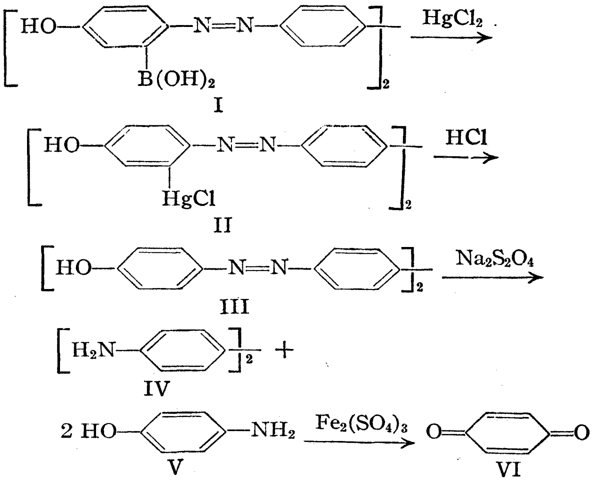
The Preparation of Some Azo Boronic Acids

By H. R. Snyder and Clay Weaver[1,2]

In an approach to the synthesis of boron-containing azo dyes desired for use in physiological studies the reactions of diazonium compounds with some aromatic boronic acids containing dialkylamino and hydroxyl groups have been examined. *m*-Hydroxybenzeneboronic acid and *m*-diethylaminobenzeneboronic acid were selected because of their ready availability. The diazonium compounds used in the coupling reactions were those obtained from benzidine, 4,4′-diaminodiphenic acid, *p*-aminobenzoic acid and *m*-aminobenzeneboronic acid.

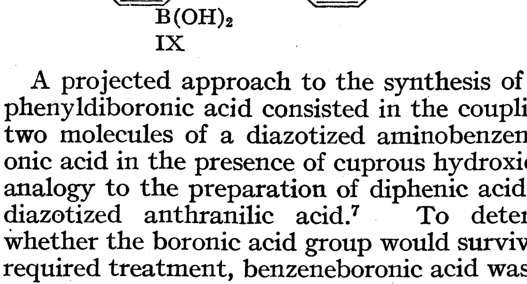
The most interesting question with regard to the proposed diazo coupling reactions concerned the stability of the aromatic boronic acids under the conditions required. *m*-Aminobenzeneboronic acid has been diazotized and the diazonium salt has been hydrolyzed to *m*-hydroxybenzeneboronic acid,[3] but the conditions employed differ greatly from those of coupling reactions. The boronic acid group is readily cleaved from the benzene ring by reagents such as copper[4] and silver[5] salts and aqueous solutions of the halogens,[4] and even by hot water,[4] so loss of the function during a diazo coupling would not be surprising.

The coupling of *m*-hydroxybenzeneboronic acid and *m*-diethylaminobenzeneboronic acid with the diazonium salts indicated was found to proceed without loss of the boronic acid function. Coupling would be expected to occur at the positions *para* to the hydroxyl and diethylamino groups. The dye from tetrazotized benzidine and *m*-hydroxybenzeneboronic acid was shown to have the expected structure (I). The structure proof was accomplished by removal of the boronic acid groups with mercuric chloride, hydrolysis of the mercury compound so formed, reduction of the resulting dye (III) to benzidine and *p*-aminophenol (V) which was identified by oxidation to *p*-benzoquinone.



m-Hydroxybenzeneboronic acid was coupled also with tetrazotized 4,4′-diaminodiphenic acid, with diazotized *p*-aminobenzoic acid and with diazotized *m*-aminobenzeneboronic acid. Evidently the boronic acid group can be present in either or both of the aromatic reagents subjected to the diazo coupling.

The *m*-diethylaminobenzeneboronic acid (VII) used was not isolated in the pure state. It was prepared from *m*-nitrobenzeneboronic acid by reduction in the presence of acetaldehyde.[6] No satisfactory solvent or solvent mixture for its recrystallization was found. Removal of the boronic acid group by treatment with ammoniacal silver nitrate converted it to diethylaniline (VIII), identified as the chloroplatinate, and the dye (IX) formed by coupling the crude *m*-diethylaminobenzeneboronic acid with diazotized *p*-aminobenzoic acid had the expected composition.



A projected approach to the synthesis of a biphenyldiboronic acid consisted in the coupling of two molecules of a diazotized aminobenzeneboronic acid in the presence of cuprous hydroxide, in analogy to the preparation of diphenic acid from diazotized anthranilic acid.[7] To determine whether the boronic acid group would survive the required treatment, benzeneboronic acid was subjected to the conditions of the diphenic acid preparation. The odor of benzene was evident immediately. The hydrocarbon was recovered by steam distillation and identified as the dinitro derivative. It appears unlikely that the so-called symmetrical coupling can be applied to diazotized aminoboronic acids.

---

(1) du Pont Post-Doctorate Research Assistant, 1941–1942.

(2) Present address: Experimental Station, E. I. du Pont de Nemours and Company, Incorporated, Wilmington, Delaware.

(3) Bean and Johnson, This Journal, **54**, 4415 (1932).

(4) Ainley and Challenger, *J. Chem. Soc.*, 2171 (1930).

(5) Seaman and Johnson, This Journal, **53**, 711 (1931).

(6) Emerson and Uraneck, *ibid.*, **63**, 749 (1941), describe the general method used.

(7) Atkinson and Lawler, "Org. Syn.," 2nd ed., Coll. Vol. I, 222 (1941).

One of the earliest methods of preparing aromatic boronic acids made use of the reaction between a diaryl mercury and boron chloride.[8] Apparently the use of more readily available mercurials, such as $ArHgOCOCH_3$ and $ArHgCl$, in similar reactions with esters of boric acid has not been attempted. Accordingly *o*-chloromercuriphenol and acetoxymercuribenzene were heated with *n*-butyl borate, but there was no evidence of the desired reactions when the reagents were heated in benzene or in the absence of solvents at temperatures as high as 150°.

Experimental

A. **Azo Dyes from *m*-Hydroxybenzeneboronic Acid.** (1) **2-(*p*-Carboxybenzeneazo)-5-hydroxybenzene-1-boronic Acid.**—A suspension of 0.9 g. of *p*-aminobenzoic acid in 10 ml. of 3 *N* hydrochloric acid was diazotized with 0.48 g. of sodium nitrite in 5 ml. of water. The cold diazonium salt solution was added dropwise to a cold solution of 0.9 g. of *m*-hydroxybenzeneboronic[3] acid in 10 ml. of 20% aqueous sodium hydroxide. The deep red mixture was allowed to stand for one hour, with occasional stirring, and then was added slowly to 10 ml. of cold 6 *N* hydrochloric acid. The gelatinous precipitate was coagulated by the addition of 50 ml. of ethanol and heating; after cooling the mixture was filtered through hardened filter paper. The orange solid was dissolved in 50 ml. of warm ethanol and caused to crystallize by dilution with an equal volume of warm water and cooling. After a second recrystallization it weighed 1.6 g. (88%) and melted at 254–256°. The boron content was determined by ignition of the residue from the combustion and weighing of the boric oxide so formed. Because of occlusion of carbonaceous material in the residue before final ignition, the carbon analyses of organoboron compounds often are low.

Anal. Calcd. for $C_{13}H_{11}BN_2O_5$: C, 54.6; H, 3.9; N, 9.8; B, 3.8. Found: C, 52.8; H, 4.3; N, 9.7; B, 4.2.

(2) a. **Preparation of 4,4′-bis-(2-Borono-4-hydroxybenzeneazo)-biphenyl.**[9]—The tetrazonium salt solution prepared from 6.7 g. of benzidine in 40 ml. of 7 *N* hydrochloric acid and 5 g. of sodium nitrite in 20 ml. of water was added to a cold (10°) solution of 10 g. of *m*-hydroxybenzeneboronic acid in a mixture of 20 g. of sodium carbonate in 80 ml. of water and 40 ml. of 10% aqueous sodium hydroxide. Stirring at 10° was continued for one hour. The deep purple mixture was poured into 50 ml. of cold concentrated hydrochloric acid and the solid was collected on a filter and washed free of chlorides with distilled water. The dry product weighed 12 g. It was recrystallized by dissolving it in the minimum quantity of hot ethanol, diluting with hot water and cooling. The deep red solid decomposed slowly at temperatures above 300°, but no definite melting or decomposition point could be discerned.

Anal. Calcd. for $C_{24}H_{20}B_2O_6N_4$: C, 59.8; H, 4.2; N, 11.6. Found: C, 61.6; H, 4.3; N, 11.4.

b. **Structure Proof.**—A solution of 12 g. of the dye in 200 ml. of hot ethanol was treated with an excess of mercuric chloride dissolved in 50% ethanol. The mixture was boiled under reflux for three hours, and the insoluble red mercury compound was collected and dried. A mixture of the red-brown powder (wt. 21 g.) and 100 ml. of 6 *N* hydrochloric acid was heated under reflux for two hours. The nearly black solid was collected by filtration and washed with water. After drying it weighed 11 g. It was mixed with 200 ml. of 10% sodium hydroxide at 60° and 25 g. of sodium hydrosulfite was added. After fifteen minutes, during which the temperature rose to 65°, a second 25-g. portion of sodium hydrosulfite was added. The mixture was heated on the steam-bath until no further fading of the color occurred. The solution was allowed to stand overnight and then neutralized to a *p*H of about 8 (Alk-Acid paper) with carbon dioxide. The tan precipitate was collected and digested twice with 50-ml. portions of warm 10% aqueous sodium hydroxide to separate the aminophenol from the benzidine. The combined extracts were acidified with 25% sulfuric acid and mixed with 100 g. of ferric sulfate and steam-distilled until 50 ml. of distillate had collected. On cooling, this distillate deposited 1.6 g. of *p*-benzoquinone, m. p. 113–115° (not depressed by admixture of authentic *p*-benzoquinone). The crude benzidine remaining from the alkaline extraction was heated with 100 ml. of water and the solution was decolorized. Cooling caused the separation of about 1 g. of pure benzidine, identified by melting point and mixed melting point.

(3) **4,4′-bis-(2-Borono-4-hydroxybenzeneazo)-diphenic Acid.**—A filtered solution of 2 g. of 4,4′-diaminodiphenic acid in 10 ml. of water and 5 ml. of concentrated hydrochloric acid was tetrazotized at 0° with 1 g. of sodium nitrite in 10 ml. of water. The resulting solution was added slowly to a cold solution of 2 g. of *m*-hydroxybenzeneboronic acid in 40 ml. of 5% aqueous sodium hydroxide containing 5 g. of sodium carbonate. The deep purple mixture was stirred for two hours, then heated to 75° and treated with a little charcoal. The filtered solution was added slowly with stirring to 20 cc. of cold concentrated hydrochloric acid. The resulting red colloidal suspension was heated to promote coagulation and filtered through a hardened filter paper. The solid was washed with water and dried (wt., 3.8 g.). It was redissolved in aqueous sodium hydroxide, treated with charcoal, filtered and acidified as before to yield a brick-red powder. This was dissolved in 50 ml. of ethanol, and the hot solution was filtered and diluted to incipient precipitation with hot water and cooled. The fine, red powder weighed 1.2 g.; an additional quantity of 1.9 g. was obtained by further dilution of the mother liquor. The solid had no definite melting point, but slowly decomposed at temperatures above 300°.

Anal. Calcd. for $C_{26}H_{20}B_2N_4O_{10}$: C, 54.8; H, 3.5; N, 9.8; B, 3.8. Found: C, 55.8; H, 3.9; N, 10.2; B, 3.2.

(4) **2-(3-Boronobenzeneazo)-5-hydroxybenzeneboronic Acid.**—*m*-Nitrobenzeneboronic acid was reduced catalytically in aqueous methanol and after displacement of the methanol by water the aminoboronic acid was diazotized without isolation. The diazonium solution prepared from 5.6 g. of the nitro compound was added slowly to a cold solution of 4.2 g. of *m*-hydroxybenzeneboronic acid in 100 ml. of 10% aqueous sodium hydroxide. The deep red solution was allowed to stand overnight and then poured into an excess of 25% sulfuric acid. The red colloidal suspension was decanted from a brown gum and the gum was extracted with hot water. The extract was combined with the suspension and the mixture was cooled and filtered. The brick-red solid (wt. 2 g.) was recrystallized from a mixture of 100 ml. of water and 10 ml. of ethanol. The product decomposed at temperatures above 350°. A solution of about 0.1 g. of the dye in 40 ml. of 50% ethanol containing 5 g. of mannitol was titrated against 0.05 *N* sodium hydroxide by means of a Hellige *p*H meter.

Anal. Calcd. for $C_{12}H_{12}B_2N_2O_5$: C, 50.4; H, 4.2; N, 9.8; B, 7.6; neut. equiv., 143. Found: C, 50.4; H, 4.4; N, 9.8; B, 7.7; neut. equiv., 142.

B. **2-(*p*-Carboxybenzeneazo)-5-diethylaminobenzeneboronic Acid.** (1) **Preparation of *m*-Diethylaminobenzeneboronic Acid.**—A solution of 3.4 g. of *m*-nitrobenzeneboronic acid and 3 ml. of glacial acetic acid in 30 ml. of ethanol was shaken with about 1 ml. of Raney nickel catalyst and filtered into a reduction bottle. After the addition of 3.4 ml. of freshly distilled acetaldehyde and about 0.05 g. of platinum oxide catalyst the mixture was shaken under hydrogen at 2–3 atmospheres pressure for thirty-six hours. The solution was filtered into a Claisen

---

[8] Michaelis and Becker, *Ber.*, **13**, 58 (1880); **15**, 180 (1882).

[9] The prefix "borono" is used to designate the boronic acid [—$B(OH)_2$] group.

flask and concentrated under diminished pressure at room temperature. The residual oil was dissolved in 30 ml. of 10% sulfuric acid, treated with Darco and added slowly to 100 ml. of 15% aqueous sodium bicarbonate. The pink precipitate was dissolved in 5% aqueous sodium hydroxide and treated with Norite. The solution was acidified with 10% sulfuric acid and added to a bicarbonate solution. The nearly white product, after drying *in vacuo* over phosphorus pentoxide, melted at 142–144°. No satisfactory solvent for recrystallization was found. About 0.5 g. of the solid was treated with ammoniacal silver nitrate,[5] and the diethylaniline formed was recovered by steam distillation and identified as the picrate and the chloroplatinate by melting points and mixed melting points.

(2) **Coupling Reaction.**—The diazonium salt solution prepared from 1.8 g. of *p*-aminobenzoic acid in 20 ml. of 3 *N* hydrochloric acid and 0.9 g. of sodium nitrite in 5 ml. of water was added slowly at 0° to 2.5 g. of the diethylaminobenzeneboronic acid in 10 ml. of 3 *N* hydrochloric acid. The resulting mixture was poured with stirring into 15 ml. of 6 *N* sodium hydroxide solution. The precipitate which formed in the deep violet solution was collected and dissolved in 50 ml. of glacial acetic acid. The filtered solution was diluted with 100 ml. of water and the red-brown solid which precipitated was recrystallized from 50% ethanol, yielding 2.9 g. (65%) of the pure substance, m. p. 248–250°.

Anal. Calcd. for $C_{17}H_{20}BN_3O_4$: C, 59.8; H, 5.9; B, 3.2. Found: C, 59.7; H, 5.7; B, 3.3.

C. Conversion of Benzeneboronic Acid to Benzene by the Action of Cuprous Hydroxide.—The reducing solution prepared from ammoniacal cupric sulfate[7] and hydroxylamine was mixed with benzeneboronic acid under the conditions of the diphenic acid preparation.[7] The odor of benzene was evident immediately. The hydrocarbon produced from 1 g. of the boronic acid was recovered by steam distillation and treated with nitric and sulfuric acids. The *m*-dinitrobenzene so formed, m. p. 87–89°, was identified by melting point and mixed melting point.

D. Attempts to Use Mercuriphenyl Derivatives in the Boronic Acid Synthesis.—No evidence of reaction was observed when a mixture of 8.5 g. of acetoxymercuribenzene and 23 g. of *n*-butyl borate was heated on the steam-bath for one hour. The mixture was heated at 140–150° for three hours and poured into excess 3 *N* hydrochloric acid. Evaporation of ether extracts of the aqueous solution yielded no benzeneboronic acid. Similar results were obtained in experiments in which benzene was used as solvent for the reagents.

A mixture of 8.2 g. of *o*-chloromercuriphenol, 16 g. of *n*-butyl borate and 50 ml. of benzene was heated under reflux for fourteen hours and then poured into excess 6 *N* hydrochloric acid. The organic liquid was removed by distillation and the hot aqueous solution was filtered and cooled. The recovery of *o*-chloromercuribenzene, m. p. 150°, was almost quantitative.

Summary

Several azo dyes containing the boronic acid group have been prepared by the action of diazonium salts on *m*-hydroxybenzeneboronic and *m*-diethylaminobenzeneboronic acids. One such dye has been prepared by coupling diazotized *m*-aminobenzeneboronic acid with *m*-hydroxybenzeneboronic acid. There is no indication of the loss of the boronic acid function during these couplings.

The cuprous hydroxide solution prepared from ammoniacal cupric sulfate and hydroxylamine is an effective reagent for the removal of the boronic acid group from the benzene nucleus.

Attempts to effect reaction between *n*-butyl borate and *o*-chloromercuriphenol or acetoxymercuribenzene have been unsuccessful.

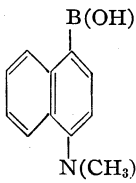
URBANA, ILLINOIS RECEIVED JULY 24, 1947

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

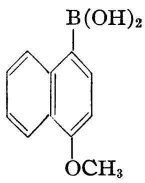
Synthesis and Reactions of Some Substituted Naphthaleneboronic Acids

BY H. R. SNYDER AND F. W. WYMAN[1]

It has been shown[2] that azoboronic acids can be obtained by coupling of diazonium compounds with *m*-hydroxybenzeneboronic acid and with *m*-diethylaminobenzeneboronic acid. There is no indication of displacement of the boronic acid function in such coupling reactions. In connection with a projected synthesis of boron-containing azo dyes of possible use in physiological studies, it became desirable to determine whether the boronic acid group attached to an aminonaphthyl or alkoxynaphthyl radical might be expected to withstand the conditions of the coupling reaction and other substitutions. It would appear that the most drastic tests of the stability of the boronic acid group in such substances could be made on compounds having the 1,4-orientation. Accordingly, 4-dimethylamino-1-naphthaleneboronic acid (I) and 4-methoxy-1-naphthaleneboronic acid (II) have been prepared for study.



I



II

The boronic acids (I and II) were prepared by the usual method from the Grignard reagents and butyl borate. Each substance melted with decomposition over a range which varied with the rate of heating and with the previous history of the sample. This behavior is characteristic of boronic acids and is to be ascribed to the dehydration of the substances (and their hydrates) to the boron oxides. Satisfactory combustion analyses of the compounds I and II were not attained, because of the varying degree of hydration of the analytical samples and the entrapment of particles of carbon in the glass-like residue of boric oxide

---

(1) Present address, Interchemical Corporation, New York, N. Y.

(2) Snyder and Weaver, THIS JOURNAL, **69**, 232 (1947).

formed in the combustion. However, both substances were alkali-soluble, showing the presence of the boronic acid group, and satisfactory neutralization equivalents were obtained on samples of both. The aminoboronic acid (I) was titrated with standard acid, with the aid of a *p*H meter, and the methoxyboronic acid was titrated with standard alkali in the presence of mannitol with phenolphthalein as the indicator.

The single recorded attempt to prepare *o*-dimethylaminobenzeneboronic acid apparently failed because of the extraordinary ease of hydrolysis of the substance, the only product isolated having been dimethylaniline.[3] This observation, together with that of detectable hydrolysis of 1-naphthaleneboronic acid during recrystallization from water,[4] leads to the prediction that 4-dimethylamino-1-naphthaleneboronic acid should be extremely labile. The properties of the substance are in accord with this prediction. Treatment of the aminoboronic acid, dissolved in cold glacial acetic acid, with dilute (1:1) nitric acid caused the displacement of the boronic acid group and the formation of 2,4-dinitro-1-dimethylaminonaphthalene. It is likely that the first step was the replacement of the boronic acid group, for under the identical conditions 1-dimethylaminonaphthalene was not nitrated. Enhancement of the reactivity of the boronic acid group by the amine group is indicated by the fact that α-naphthaleneboronic acid was only slightly attacked under the conditions mentioned, although it was converted to 1,3-dinitronaphthalene when the test was made with concentrated nitric acid and with a much longer time of reaction. A similar ejection of the boronic acid group from the benzene nucleus has been observed[3] in the nitration of benzeneboronic and *p*-methoxybenzeneboronic acids, but under unspecified conditions which may have been relatively more drastic than those employed here.

Both the boronic acid group and the dimethylamino group were replaced when the aminoboronic acid was treated with nitrous acid in strong acetic acid solution. Evidently 4-nitroso-1-dimethylaminonaphthalene first formed, but was hydrolyzed in the reaction mixture to the nitrosonaphthol. When the aminoboronic acid was heated with aqueous sodium bisulfite or with alcoholic picric acid the boronic acid group was replaced by hydrogen. The cleavage with picric acid, discovered in an attempt to prepare the picrate of the aminoboronic acid, occurred with surprising facility. In contrast, the boronic acid group was quite stable to hydrolysis by alkali in the absence of air; cleavage to 1-dimethylaminonaphthalene did occur, but part of the unchanged aminoboronic acid was recovered after four hours of boiling with 10% sodium hydroxide. More complicated reactions with aqueous alkali occurred in the presence of air; dimethylamine was evolved and a high-melting insoluble organic product containing neither boron nor nitrogen was formed.

When the aminoboronic acid was treated with diazotized *p*-aminobenzoic acid, the boronic acid group was replaced by the azobenzoic acid residue. The dye obtained was identical with that produced by the coupling with 1-dimethylaminonaphthalene and its conversion to 1,4-naphthoquinone established with certainty the 1,4-orientation of the amino and azo groups. 1-Naphthaleneboronic acid was stable to the diazonium salt under the conditions employed with I. Dyes obtained by coupling I with diazotized *m*-aminobenzoic acid, diazotized anthranilic acid and tetrazotized benzidine did not give qualitative tests for boron and were not further investigated.

4-Methoxy-1-naphthaleneboronic acid (II) was more stable to the various reagents. It was recovered from the treatment with dilute nitric acid in glacial acetic acid at temperatures near 0°, but was converted to 2,4-dinitro-1-naphthol when the reaction was carried out at room temperature. Similarly, it was unattacked by nitrous acid in strong acetic acid at about 0°, but at room temperature it was hydrolyzed to 1-methoxynaphthalene. Boiling 50% acetic acid converted it to the same product. When a solution of the boronic acid (II) in aqueous sodium hydroxide was boiled in an open beaker hydrolysis occurred slowly and 1-methoxynaphthalene was formed. The methoxyboronic acid (II) coupled with diazotized *p*-aminobenzoic acid, but the dye formed did not contain boron and it was not further investigated.

Experimental

4-(N,N-Dimethylamino)-1-bromonaphthalene.—N-Acetyl-1-naphthylamine was brominated according to the method of Meldola,[5] but with chloroform rather than acetic acid as the solvent. The bromoamide was hydrolyzed with ethanolic hydrochloric acid,[6] and the bromoamine was methylated by use of the procedure described by Gilman and Banner[7] for N,N-dimethyl-*o*-toluidine, except that a greatly increased quantity of water (2 liters for a run with 0.5 mole of amine) was employed in making up the reaction mixture. In most preparations the crude material was converted to the picrate by addition to a boiling 8% solution of picric acid (87.5% of the theoretical amount based on the amine methylated) in 95% ethanol. The crude picrate (m. p. 150–154°) which separated when the solution was cold was washed twice with cold ethanol, suspended in water, and treated with aqueous ammonia. The regenerated amine was collected in ether, dried over potassium carbonate and distilled; b. p. 137–139° (2 mm.); yield 55%. It was found possible to distil the crude amine, without the preliminary purification through the picrate, provided the pressure did not exceed 1 mm. nor the bath temperature 160°.

The amine was prepared also by direct bromination of dimethyl-1-naphthylamine, a procedure employed previously by Friedländer and Welmans,[8] who did not purify the product. In the present work an insufficient quantity

---

(3) Konig and Scharrnbeck, *J. prakt. Chem.*, [2] **128**, 153 (1930).

(4) Branch, Yabroff and Bettmann, THIS JOURNAL, **56**, 1850 (1934).

(5) Meldola, *Ber.*, **11**, 1906 (1878).

(6) Johnson and Sandborn, "Org. Syn.," 2nd ed., Coll. Vol. I, 111 (1941).

(7) Gilman and Banner, THIS JOURNAL, **62**, 344 (1940).

(8) Friendländer and Welmans, *Ber.*, **21**, 3127 (1888).

(95%) of bromine, as a 40% solution in carbon tetrachloride, was added during one and one-half hours to a cooled and stirred 1 *M* solution of the tertiary amine in the same solvent. The precipitated hydrobromide was collected, washed with the solvent and suspended in water. The free amine, regenerated by the addition of 10% sodium hydroxide solution, was collected in ether, dried and distilled at 1 mm.; b. p. 115–130° (1 mm.). Although this product contained some dimethyl-1-naphthylamine it could be used for the preparation of the Grignard reagent. It could be purified through the picrate, as described above, and the picrate was identical with that of the material made by methylation of the bromoamine; the melting point of either sample of picrate, after two recrystallizations from 95% ethanol, was 154–156°. The trinitrobenzene derivatives, m. p. 94–95°, also were identical; the trinitrobenzene derivative of a sample from the direct bromination was analyzed.

Anal. Calcd. for $C_{18}H_{15}O_6N_4Br$: C, 46.66; H, 3.24. Found: C, 46.80; H, 3.34.

To establish the 1,4-orientation of the product from the bromination a sample was converted to 4-dimethylamino-1-naphthoic acid by treatment of the Grignard reagent with carbon dioxide; the amino acid melted at 162–163° (lit.,[8] 163–165°).

4-Dimethylamino-1-naphthaleneboronic Acid.—The Grignard reagent was prepared by refluxing for two hours a mixture of 25 g. of the bromo compound, 2.4 g. of magnesium, a crystal of iodine and 250 ml. of dry ether. The resulting solution, cooled to room temperature, was added over a period of about one-half hour to a vigorously stirred solution of 50 g. of *n*-butyl borate in 500 ml. of dry ether, the temperature of which was maintained at −15°. The mixture was allowed to stand overnight in the cooling bath before it was hydrolyzed by the addition of 100 ml. of water. The ether layer was washed several times with 50-ml. portions of cold water and then extracted with six 25-ml. portions of 5% hydrochloric acid. The combined acid extracts were evaporated at room temperature to give 12.2 g. (48%) of crude hydrochloride of the aminoboronic acid (I). The material was stored in this form, and the free aminoboronic acid was generated as needed by the dropwise addition of 10% sodium hydroxide solution to an aqueous solution of the hydrochloride until no further precipitation occurred. After two similar reprecipitations from dilute acid and drying *in vacuo* at room temperature the 4-dimethylamino-1-naphthaleneboronic acid (I) melted at 82–85°. Its neutralization equivalent, as determined by titration with 0.05 *N* hydrochloric acid with the aid of a Hellige *p*H meter, was within the limits of 212–215 (calcd. 214.9).

Reactions of 4-Dimethylamino-1-naphthaleneboronic Acid. (a) **With Nitric Acid.**—To a stirred solution of 1 g. of the aminoboronic acid in 10 ml. of glacial acetic acid, cooled in an ice-bath, was added dropwise 1 ml. of a cold solution of equal volumes of water and concentrated nitric acid. After ten minutes the mixture was diluted with 75 ml. of cold water, and the yellow solid which formed was collected. This solid melted at 81–85°; after three recrystallizations from 95% ethanol it melted at 88–89°, alone or mixed with authentic[9] 2,4-dinitro-1-dimethylaminonaphthalene.

1-Naphthaleneboronic acid was recovered from similar experiments in which it was substituted for the aminoboronic acid. Even when the reaction mixture was allowed to stand overnight before dilution, the 1-naphthaleneboronic acid recovered was only slightly contaminated (m. p. 180–188°) and was readily purified [to a m. p. of 198–200° (lit.[3] not above 202°)] by a single reprecipitation from alkaline solution and one recrystallization from ethanol. When concentrated nitric acid was substituted for the diluted nitric acid and the reaction mixture was allowed to stand overnight, the only product isolated was 1,3-dinitronaphthalene, m. p. 143–144°, identified by a mixed melting point with an authentic specimen.

(b) **With Nitrous Acid.**—To a solution of 1 g. of the aminoboronic acid in 10 ml. of glacial acetic acid, vigorously stirred in an ice-bath, was added dropwise 1.5 ml. of 20% aqueous sodium nitrite solution. After fifteen minutes the mixture was diluted with 50 ml. of cold water and filtered. The solid was dissolved in dilute sodium hydroxide solution and reprecipitated with dilute hydrochloric acid. After recrystallization from aqueous ethanol it decomposed at 193–195° (lit.[10] for 4-nitroso-1-naphthol, 194°). It contained no boron.

Anal. Calcd. for $C_{10}H_7NO_2$: C, 69.36; H, 4.08. Found: C, 69.48; H, 4.09.

(c) **With Aqueous Sodium Bisulfite.**—A mixture of 2 g. of the aminoboronic acid and about 20 ml. of 20% aqueous sodium bisulfite solution was refluxed for four hours. Careful neutralization and reacidification of a portion of the cooled solution did not cause the separation of any solid; the addition of alkali caused the separation of an oily base. The oil was collected in ether, dried, recovered from the solvent and added to alcoholic picric acid. The picrate melted at 145–146° (lit.,[11] 145°) alone or mixed with the picrate of 1-dimethylaminonaphthalene.

(d) **With Picric Acid.**—To a boiling solution of 1 g. of picric acid in 25 ml. of 95% ethanol was added a solution of 1.2 g. of the aminoboronic acid in 10 ml. of ethanol. The mixture was refluxed for about fifteen minutes, after which it was cooled and the solid which separated was recrystallized from 95% ethanol. The picrate melted at 142–144°, and a mixture with the picrate of 1-dimethylaminonaphthalene melted at 143–144°.

Anal. Calcd. for $C_{18}H_{16}O_7N_4$: C, 54.00; H, 4.00. Found: C, 53.79; H, 4.05.

(e) **With Aqueous Sodium Hydroxide.**—A solution of 2 g. of the aminoboronic acid in 40 ml. of deoxygenated 10% aqueous sodium hydroxide was refluxed for four hours under an atmosphere of illuminating gas. Extraction of the cooled solution with ether and removal of the solvent gave a drop of an oil; this oil gave a picrate which melted at 145–146°, alone or mixed with the picrate of 1-dimethylaminonaphthalene. Acidification of the alkaline aqueous solution caused the separation of a solid which redissolved in excess acid. After two reprecipitations from dilute acid by the dropwise addition of dilute alkali the solid melted at 80–83°, and the melting point was not lowered by admixture of the aminoboronic acid (I).

In a similar experiment in which the alkaline solution was boiled in an open beaker for eight hours (with occasional addition of water to maintain an approximately constant volume) none of the aminoboronic acid was recovered. The only product isolated was a dark, neutral solid, containing neither nitrogen nor boron, for which no recrystallization solvent was found.

(f) **With Diazonium Salts.**—1. Diazotized *p*-aminobenzoic acid: To the cold diazonium chloride solution prepared from 1.3 g. of *p*-aminobenzoic acid were added a solution of 2 g. of the aminoboronic acid in 20 ml. of cold 10% hydrochloric acid and a solution of 14 g. of sodium acetate in 25 ml. of cold water. The mixture was stirred for six hours at 0–5° and then allowed to stand overnight at the same temperature. The red solid was separated, dried and recrystallized from absolute ethanol. The substance did not contain boron; it melted at 204–206° (dec.), and the melting point was unaffected by admixture of the dye [m. p. 204–206° (dec.)] obtained by coupling 1-dimethylaminonaphthalene with the same diazonium salt.

Anal. Calcd. for $C_{19}H_{17}O_2N_3$: C, 71.48; H, 5.36. Found: C, 71.86; H, 5.53.

---

(9) Ullmann and Bruck, *Ber.*, **41**, 3935 (1908).

(10) Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley and Sons, New York, N. Y., 1940, p. 229.

(11) "Organic Reagents for Organic Analysis," by the staff of Hopkin and Williams, Ltd., Chemical Publishing Co., Brooklyn, 1946, p. 138.

Reduction[12] of the dye and oxidation[13] of the diamine so formed gave 1,4-naphthoquinone, identified by melting point and mixed melting point.

2. Other diazonium salts: Coupling under the same conditions with diazonium salts from m-aminobenzoic acid, anthranilic acid and benzidine gave dyes which were found not to contain boron and were not investigated further.

4-Methoxy-1-naphthaleneboronic Acid.—To the Grignard solution (concentration about 0.8 M) from 4-methoxy-1-bromonaphthalene[14] was added dropwise an equimolar amount of n-butyl borate as an ether solution of concentration about 1.1 M while the temperature was maintained at $-60°$. The reaction mixture was allowed to remain in the cooling bath overnight. It was treated with water, and the product was recovered by several extractions of the ether solution with 2% aqueous sodium hydroxide. The crude boronic acid was obtained in 53% yield by acidification of the alkaline extracts. It was purified by reprecipitation from dilute alkali by acidification, followed by precipitation from ethanol by dilution with water. Samples dried *in vacuo* at room temperature underwent visible decomposition at about 150–155°, in an ordinary melting point determination, but the decomposition product (presumably the anhydride) did not melt completely at temperatures up to 250°. A reproducible melting point of 195° could be determined by the instant immersion method.[15] The boronic acid was titrated in 20% ethanol solution containing mannitol with 0.05 N sodium hydroxide solution to a phenolphthalein end-point; the neutralization equivalent was found to be within the limits of 199–203 (calcd. 201.8).

Reactions of 4-Methoxy-1-naphthaleneboronic Acid. (a) **With Nitric Acid.**—To a well-stirred suspension of one gram of the boronic acid in 10 ml. of glacial acetic acid at room temperature was added 1 ml. of a solution of equal volumes of concentrated nitric acid and water. Thirty minutes later the mixture was diluted with 50 ml. of cold water, and the solid which separated was recrystallized from 95% ethanol. The yellow solid melted at 138–139°, and the melting point was not changed by the addition of authentic 2,4-dinitro-1-naphthol.

When the experiment was repeated with the temperature of the reaction mixture maintained at about 2° the 4-methoxy-1-naphthaleneboronic acid was recovered.

(b) **With Nitrous Acid.**—To a vigorously stirred suspension of 1 g. of the acid in 10 ml. of glacial acetic acid at room temperature was added 1.5 ml. of 20% aqueous sodium nitrite solution. Thirty minutes later the mixture was filtered and the filtrate was diluted with 75 ml. of water. The diluted solution was extracted with ether and the oil which remained after evaporation of the ether was dissolved in ethanol, decolorized and treated with 1,3,5-trinitrobenzene. The crystals which formed melted at 138–139° (lit.[16] 138°) alone or mixed with the trinitrobenzene derivative of 1-methoxynaphthalene.

No reaction occurred when the experiment was carried out at 0°.

(c) **With Dilute Acetic Acid.**—A mixture of 1 g. of the boronic acid and 15 ml. of glacial acetic acid was refluxed for thirty minutes. Examination of the cooled solution revealed no evidence of reaction, so 10 ml. of water was added and the refluxing was continued for an additional half-hour. The cooled solution was diluted with 50 ml. of water and the oil which separated was extracted with ether. The ether extracts were washed with dilute alkali, dried and evaporated to give an oil which was identified as 1-methoxynaphthalene by conversion to the trinitrobenzene derivative as described in the preceding section.

(d) **With Aqueous Sodium Hydroxide.**—A solution of 1 g. of the boronic acid in 25 ml. of 10% aqueous sodium hydroxide was boiled gently for half an hour with occasional additions of water to keep the volume approximately constant. The cooled mixture was extracted with ether and the dried extracts were evaporated to give a small amount of an oil which was identified as 1-methoxynaphthalene by the melting point and mixed melting point of the trinitrobenzene derivative. Acidification of the alkaline solution caused the separation of 0.6 g. of the unchanged boronic acid (II).

Summary

4-Dimethylamino-1-naphthaleneboronic acid and 4-methoxy-1-naphthaleneboronic acid have been prepared and subjected to the action of various reagents. The boronic acid group of either substance is removed readily by mild hydrolysis or by replacement under the influence of reagents such as dilute acids, dilute bases, nitric acid, nitrous acid and certain diazonium salts. The boronic acid group is more highly labilized by the 4-dimethylamino group than by the 4-methoxyl group.

URBANA, ILLINOIS RECEIVED JULY 24, 1947

---

[12] Conant, Lutz and Corson, "Org. Syn.," Coll. Vol. I, ed. 2, p. 49.

[13] Fieser, *ibid.*, p. 383.

[14] Tourneau and Trefouel, *Bull. soc. chim.*, **45**, 121 (1929).

[15] Branch, Yabroff and Bettmann, THIS JOURNAL, **56**, 937 (1934).

[16] See p. 141 of the work cited in ref. 11.

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

The Synthesis of β-Carbolines. IV. 3-Aminoharman and Some of its Derivatives[1]

BY H. R. SNYDER, STANLEY M. PARMERTER[2] AND HOWARD G. WALKER[3]

In the preceding paper the synthesis of 6-aminoharman by the reduction of the nitro compound was reported. It is to be expected that the isomeric 3-aminoharman may be prepared from harman-3-carboxylic acid by application of the Hofmann[4] or Curtius[5] reaction. This paper reports the synthesis of 3-aminoharman from the acid azide and its conversion to the sulfanilyl derivative (III) and the 3-diethylaminopropyl derivative (IV), isolated as the dipicrate.

Preliminary tests indicated that the ester (I) could be converted to the hydrazide much more

---

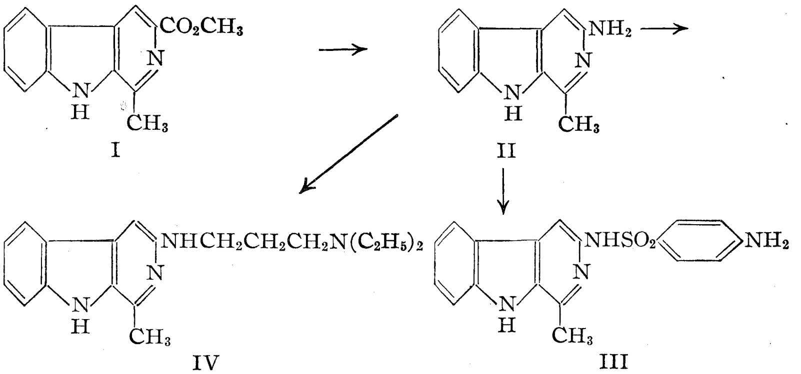
[1] For the preceding paper see Snyder, Parmerter and Katz, THIS JOURNAL, **69**, 222 (1947).

[2] Wm. S. Merrell Post-Doctorate Fellow, 1944–1945. Present address: Eastman Kodak Co., Rochester, N. Y.

[3] Wm. S. Merrell Post-Doctorate Fellow, 1946–1947. Present address: University of California at Los Angeles.

[4] See Wallis and Lane, *The Hofmann Reaction*, "Organic Reactions," Vol. III, John Wiley and Sons, New York, N. Y. 1946, p. 267.

[5] See Smith, *The Curtius Reaction*, "Organic Reactions," Vol. III, John Wiley and Sons, New York, N. Y., 1946, p. 337.



readily than to the amide, so that the Curtius reaction was chosen for the preparation of the amine (II). The azide, obtained by treatment of the hydrazide with cold aqueous nitrous acid, proved to be quite stable. It could be converted directly to the amine by refluxing with fifty per cent. acetic acid, but better yields of a more readily purified product resulted from the preparation and hydrolysis of the benzyl carbamate. The sulfanilyl derivative (III) was prepared by the reaction of the amine with acetylsulfanilyl chloride in the presence of pyridine[6] and hydrolysis of the acetyl group in the usual fashion. The 3-diethylaminopropyl derivative of the amine was prepared by refluxing an ethanol solution of the amine and 3-diethylaminopropyl chloride containing a trace of potassium iodide. The resulting triamine has been purified as the dipicrate; the free base and its salts with various mineral acids and carboxylic acids have resisted all attempts to induce crystallization.

Experimental

Harman-3-carbonyl Hydrazide.—A mixture of 10 g. of methyl 3-harmancarboxylate,[7] 50 ml. of 85% hydrazine hydrate, 100 ml. of *n*-amyl alcohol and 28 ml. of absolute ethanol was refluxed four hours. The solution was cooled overnight in the refrigerator (5°) before the tan needles were collected and washed with cold water and ether. The crude material melting at 295° (dec.) weighed 9.0 g. (yield, 90%). Concentration of the mother liquor gave 0.7 g. of less pure material. A sample recrystallized from ethanol (95%) melted at 288°.

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.04. Found: C, 65.04; H, 5.31.

Harman-3-carbonyl azide was prepared by dissolving 4.16 g. of the hydrazide in 200 ml. of water containing 2.5 ml. of concentrated hydrochloric acid. The solution was cooled to below 5°, and a solution of 1.38 g. of sodium nitrite in 5 ml. of water was added. The resulting mixture was allowed to stand in the cold with occasional stirring for fifteen minutes, and was then neutralized by the addition of excess saturated sodium bicarbonate solution. The pasty suspension thus formed was rather difficult to filter, but this method was found most satisfactory for the isolation of the solid azide. The crude azide was washed with cold water and then with ether before being dried to constant weight *in vacuo*. An approximately quantitative yield of azide was obtained. The crude product was used without purification. The compound appeared to be completely stable at room temperature.

Benzyl 3-Harmylcarbamate.—The preparation of the benzyl carbamate was carried out in a 100-ml. flask with a reflux condenser provided with a drying tube. A mixture of 4.27 g. of the azide, 40 ml. of dry xylene and 4.0 ml. of redistilled benzyl alcohol was placed in the flask and the temperature raised to 110–120° by means of an oil-bath. The evolution of nitrogen proceeded smoothly at this temperature. The heating was maintained for one-half hour and the reaction mixture was allowed to stand in the refrigerator overnight. The product was filtered, washed with cold xylene followed by low-boiling petroleum ether and dried; yield 4.48 g. (81%); m. p. 188–190°. No appreciable amount of material could be obtained by the addition of low-boiling petroleum ether to the mother liquor. A sample was recrystallized twice from *n*-butyl alcohol, m. p. 186–186.5°.

Anal. Calcd. for $C_{20}H_{17}O_2N_3$: C, 72.48; H, 5.19; N, 12.68. Found: C, 72.07; H, 5.50; N, 12.96.

3-Aminoharman from the Benzyl Carbamate.—A mixture of 9.75 g. of the carbamate, 50 ml. of diethylene glycol, 8.35 ml. of water and 8.35 g. of potassium hydroxide was stirred for one-half hour in a 200-ml. round-bottom flask equipped with an air condenser and immersed in an oil-bath at 150–160°. The cooled contents of the flask were poured into 325 ml. of ice and water and allowed to stand in an ice-bath for one and one-half hours before the solid product was filtered. The crude product (m. p., 223–226°) was recrystallized from dilute aqueous ethanol, yielding 4.80 g. (83%) of dried product, m. p. 226–227°. A sample of the 3-aminoharman which had been recrystallized several times from dilute ethanol melted at 228–229°.

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.09; H, 5.62. Found: C, 72.97; H, 5.58.

3-Sulfanilamidoharman.—In a 100-ml., two-necked flask equipped with a sealed stirrer and a reflux condenser protected by a drying tube was placed 3.72 g. of 3-aminoharman, 48 ml. of dry pyridine and 4.55 g. of acetylsulfanilyl chloride (commercial grade recrystallized once from chloroform). The mixture was heated on the steam-bath with stirring for three hours and then poured into 700 ml. of cold water. A crystalline product formed slowly and was allowed to stand in an ice-bath for one hour before it was filtered and washed well with cold water. A sample of this product was dried, m. p. 287–289° (dec.). The wet product (7.24 g.) was suspended in 207 ml. of 12% hydrochloric acid and heated on the steam-bath for thirty-five minutes with stirring. Since most of the solid had gone into solution at the end of this time, the solution was filtered. The residue remaining on the filter was heated for fifteen minutes with an additional 30-ml. portion of the dilute acid, and after filtration of this mixture the acid filtrates were combined, cooled and made alkaline with concentrated ammonium hydroxide. The mixture was allowed to stand in an ice-bath for one hour, and the slightly yellow crystals were filtered and recrystallized from a pyridine–water mixture. There was obtained 3.70 g. of recrystallized 3-sulfanilamidoharman (57%), m. p. 301–302° (dec.).

Anal. Calcd. for $C_{18}H_{16}O_2N_4S$: C, 61.35; H, 4.58. Found: C, 61.46; H, 4.41.

3-(3′-Diethylaminopropylamino)-harman.—A mixture of 0.85 g. of 3-aminoharman, 0.79 g. of γ-diethylaminopropyl chloride and 8.5 ml. of ethanol (95%) containing a crystal of potassium iodide was refluxed on the steam-bath for about thirty hours.[8] At the end of this time, the alcohol was removed by distillation, water was added

---

(6) Winterbottom, This Journal, **62**, 160 (1940).

(7) Snyder, Hansch, Katz, Parmerter and Spaeth, *ibid.*, **70**, 219 (1948).

(8) Method of Easton and Snyder, *ibid.*, **68**, 1550 (1946.)

to the reaction product and the resulting solution made basic with excess ammonium hydroxide. The organic material was taken up in chloroform, washed with water and dried over sodium sulfate. The product was converted to a picrate by removing the chloroform at reduced pressure, dissolving the residue in a minimum of absolute ethanol and adding an excess of a chilled, saturated solution of picric acid in absolute ethanol. After standing overnight in the refrigerator the crude picrate was filtered and placed in a Soxhlet extraction cup. The material was extracted with methanol until no further crystallization from the hot solvent occurred. There was obtained 1.35 g. of orange solid, m. p. 210–212° (dec.), which evidently was the dipicrate of 3-(3′-diethylaminopropylamino)-harman. After two more recrystallizations from methanol it melted at 213.5–215° (dec.).

Anal. Calcd. for $C_{31}H_{32}N_{10}O_{14}$: C, 48.44; H, 4.20. Found: C, 48.33; H, 4.20.

Summary

3-Aminoharman is prepared from methyl harman-3-carboxylate by means of the Curtius reaction. 3-Sulfanilamidoharman and 3-(3′-diethylaminopropylamino)-harman (as the dipicrate) are prepared from 3-aminoharman.

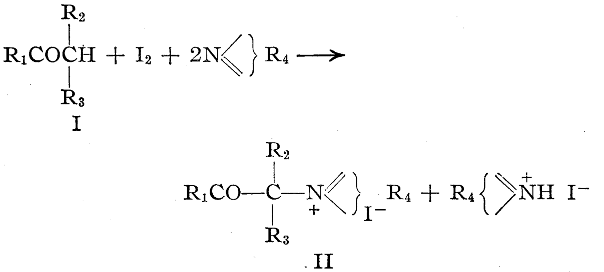
URBANA, ILLINOIS RECEIVED AUGUST 7, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Reaction of Ketones with Iodine and Pyridine

BY L. CARROLL KING, MARGARET MCWHIRTER AND R. L. ROWLAND

Previous papers from this Laboratory,[1] and from the National Cancer Institute,[2] have reported the preparation of quaternary salts of type (II) by means of the following reaction.



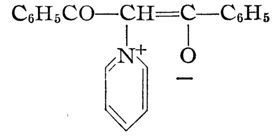
where $R_3 = R_2 = H$

Salts have been reported where R_1 was aryl[1a,1b,2] or a cyclopentanophenanthrene derivative[1a] and where N⟨⟩R₄ was any of a number of heterocyclic nitrogeneous bases.[1c,2] In the present paper this reaction has been extended to include variation in R_2 and R_3 and additional variation in R_1.

The quaternary salts obtained when R_1 was 2- or 3-phenanthryl, thienyl or any of a variety of substituted phenyl groups are listed in Table I. When R_2 was an alkyl or aryl side chain the reaction gave the expected quaternary salt in each case but with increasing length of the alkyl side chain the salts became more difficult to purify and crystallize. A pure quaternary salt was not obtained from isobutyrophenone ($R_2 = R_3 = CH_3$). Data for these materials are also reported in Table I.

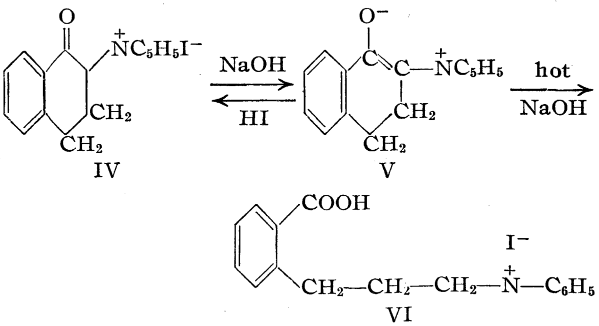
In addition to the substances reported in the tables, quaternary salts were prepared from dibenzoylmethane (R_2 = benzoyl), and from α-tetralone.

From the reaction of dibenzoylmethane with iodine and pyridine, 1-phenacylpyridinium iodide was isolated. The betaine (III) reported to be produced in 40% yield from the reaction of bromodibenzoylmethane with pyridine[3] was not observed.



III

From the reaction of α-tetralone with pyridine and iodine, 1-keto-2-tetrahydronaphthylpyridinium iodide (IV) was obtained. When (IV) was treated with cold alkali an orange betaine (V) separated. This substance could be reconverted to the salt (IV) and on prolonged alkaline hydrolysis in the presence of potassium iodide (IV) was converted to (VI). This behavior is analogous to that reported by Krollpfeiffer and Müller[4] for the corresponding pyridinium bromide.



Each of the quaternary salts reported was subjected to alkaline hydrolysis. The acids produced in these experiments are listed in Table II. No isodurylic acid was obtained from 1-(2,4,6-tri-

---

(1a) King, THIS JOURNAL, **66**, 894, 1612 (1944).

(1b) King, McWhirter and Barton, *ibid.*, **67**, 2089 (1945).

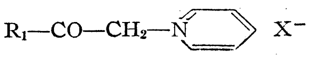
(1c) King and McWhirter, *ibid.*, **68**, 717 (1946).

(2) Hartwell and Kornberg, *ibid.*, **68**, 868, 1131 (1946).

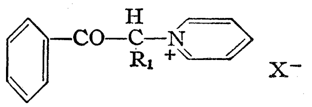
(3) Kröhnke, *Ber.*, **68**, 1177 (1935). However, this betaine was obtained when Kröhnke's procedure was used.

(4) Krollpfeiffer and Müller, *ibid.*, **68**, 1169 (1935)

Table I



R_1	X^-	Yield, %	Recrystn. solvent[k]	M. p.,[a] °C.	Formula	Percentage composition[b] Calcd.	Found	Calcd.	Found
p-F—C_6H_4—	I	20	W	179–180	$C_{13}H_{11}ONIF$	N, 4.08	3.80	I, 37.0	37.2
p-F—C_6H_4—	ClO_4		W	125–126	$C_{13}H_{11}O_5NClF$	C, 49.46	49.49	H, 3.51	3.94
p-Cl—C_6H_4—	I	72	W, A	217–218	$C_{13}H_{11}ONICl$	I, 35.3	35.0		
p-Cl—C_6H_4—	ClO_4		W, E	211–212	$C_{13}H_{11}O_5NCl_2$	C, 47.00	47.18	H, 3.34	3.39
p-Br—C_6H_4—	I	73	W, A	233–235	$C_{13}H_{11}ONIBr$	I, 31.4	31.1		
p-Br—C_6H_4—[c]	ClO_4		W, E	238–240	$C_{13}H_{11}O_5NClBr$	C, 41.46	41.85	H, 2.94	3.10
p-I—C_6H_4—	I	82	E	237–238	$C_{13}H_{11}ONI_2$	I, 28.1	28.2		
p-I—C_6H_4—	ClO_4		E	269–270	$C_{13}H_{11}O_5NICl$	C, 36.86	37.20	H, 2.62	2.79
p-CH_3—C_6H_4—	I	89	A	200–203	$C_{14}H_{14}ONI$	I, 37.4	37.1		
p-CH_3—C_6H_4—	ClO_4		A	152–153	$C_{14}H_{14}O_5NCl$	C, 53.94	54.27	H, 4.53	4.59
p-CH_3—OC_6H_4—[d]	I	71	W, A	218–219	$C_{14}H_{14}O_2NI$	I, 35.7	35.9		
p-CH_3—S—C_6H_4—	I	75	A	185–186	$C_{14}H_{14}ONIS$	I, 34.2	34.0	N, 3.78	3.96
p-CH_3S—C_6H_4—	ClO_4		W	181–182	$C_{14}H_{14}O_5NClS$	C, 48.91	49.07	H, 4.10	4.36
p-NO_2—C_6H_4—	I	78	W	211–212	$C_{13}H_{11}O_3N_2I$	I, 34.7	34.6	N, 7.57	7.35
p-NO_2—C_6H_4—[e]	ClO_4		W	183–185	$C_{13}H_{11}O_7N_2Cl$	N, 8.18	8.25		
p-C_6H_5—C_6H_4—	I	80	W, A	204–205	$C_{19}H_{16}ONI$	I, 31.6	31.7	N, 3.49	3.43
p-C_6H_5—C_6H_4—	ClO_4		W, A	241–242	$C_{19}H_{16}O_5NCl$	C, 61.05	61.48	H, 4.31	4.27
Mesityl	I	87	A, E	267–268	$C_{16}H_{18}ONI$	I, 34.6	34.4		
Mesityl[f]	ClO_4		A, E	276–277	$C_{16}H_{18}O_5NCl$	C, 56.56	56.68	H, 5.34	5.51
3-Phenanthryl	I	20	W	219–220	$C_{21}H_{16}ONI$	N, 3.29	3.56		
3-Phenanthryl	ClO_4		A, E	257–258	$C_{21}H_{16}O_5NCl$	N, 3.52	3.97		
2-Phenanthryl	I	30	M	223–224	$C_{21}H_{16}ONI$	N, 3.29	3.24		
2-Phenanthryl	ClO_4		W, E	240–242	$C_{21}H_{16}O_5NCl$	N, 3.52	3.66		
Thienyl	I	76	W, A	210–212	$C_{11}H_{10}ONIS$	I, 38.3	38.6		
Thienyl	ClO_4		W, A	215–217	$C_{11}H_{10}O_5NClS$	C, 43.51	43.52	H, 3.32	3.38



CH_3—[i]	I	40–60	....	....	....	......	...	.....	...
C_2H_5—	I	70	W	152–153	$C_{15}H_{16}ONI$[m]	C, 51.00	50.64	H, 4.56	4.73
C_2H_5—	ClO_4		W	133–134	$C_{15}H_{16}O_5NCl$	C, 55.30	55.57	H, 4.95	5.02
n-C_3H_7—[h]	I	80		Glass[g]	$C_{16}H_{18}ONI$[n]	C, 52.33	52.38	H, 4.93	4.84
n-C_4H_9—[h]	I	30	Ac, Et	123–125	$C_{17}H_{20}ONI$	I, 33.3	33.3	N, 3.67	3.49
C_6H_5—	I	80	W, A	158–162	$C_{19}H_{16}ONI$	I, 31.6	31.5		
C_6H_5—	ClO_4		W, A	175–176	$C_{19}H_{16}O_5NCl$	C, 61.05	61.47	H, 4.31	4.60
CH_3—, CH_3—[l]	I	60		Viscous glass[j]	$C_{15}H_{16}ONI$	I, 36.0	38.9		

[a] All melting points were observed on a Fisher–Jones melting point block. [b] Analyses by M. Ledyard and P. Craig. [c] Kröhnke, *Ber.*, 68, 1187 (1934); m. p. 241–242°, no analysis reported. [d] Hartwell and Kornberg, This Journal, **68,** 868 (1946). [e] Kröhnke and Heffe, *Ber.*, **70B,** 875 (1937); m. p. 185–186°, no analysis reported. [f] Kröhnke and Heffe, *ibid.*, **70B,** 874 (1937); m. p. 275°, no analysis reported. [g] Obtained as crystals from acetone-ether by cooling in a Dry Ice–acetone bath. These crystals became glass-like on warming to room temperature. [h] Perchlorate derivatives could not be obtained. [i] Reported in ref. 1a. [j] This compound was not obtained pure. [k] Symbols denote solvents as follows: W = water, E = ethylene glycol, A = alcohol, M = ethylene glycol monomethyl ether, Ac = acetone, Et = ethyl ether. Combinations of these symbols denote crystallization from the mixed solvents. [l] In this compound both of the hydrogens α- to the carbonyl group were replaced by methyl groups. [m] Calcd.: I, 35.9. Found: 36.0. [n] Calcd.: I, 34.6. Found: 34.2.

methylphenacyl)-pyridinium iodide by alkaline hydrolysis. This is consistent with the observation of Fuson[5] and co-workers for the corresponding pyridinium chloride.

This investigation was partially supported by a grant from the Abbott fund of Northwestern University and by a Grant-in-aid from the National Cancer Institute.

Experimental

Preparation of Ketones.—The ketones, with the exception of p-methylmercaptoacetophenone, are known. 2- and 3-acetophenanthrene were prepared by the procedure of Mosettig and van de Kamp,[6] and p-nitroacetophenone by the method of Walker and Hauser.[7] α-Tetralone, methyl thienyl ketone and dibenzoylmethane were prepared by methods described in "Organic Syntheses." The other ketones were prepared by Friedel–Craft reactions

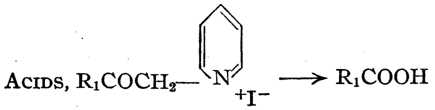
---

(5) Babcock, Nakamura and Fuson, This Journal, **54,** 4407 (1932).

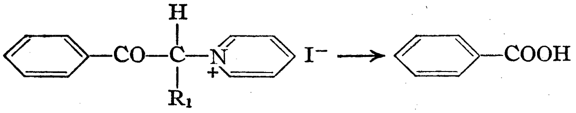
(6) Mosettig and van de Kamp, *ibid.*, **52,** 3704 (1930).

(7) Walker and Hauser, *ibid.*, **68,** 1386 (1946).

TABLE II



R1	Yield, %	M. p., °C.	Melting point reported, °C.
p-FC_6H_4-	70	181–182	186[a]
p-ClC_6H_4-	99	242–243	243[b]
p-BrC_6H_4-	87	249–250	250–251[c]
p-IC_6H_4-	83	268–269	266–267[d]
p-$CH_3C_6H_4$-	94	176–179	179[e]
p-$CH_3OC_6H_4$-	80	183–184	183–185[f]
p-$CH_3S—C_6H_4$	80	190–191	192[g]
p-$NO_2—C_6H_4$-	30	239–240	241[k]
p-$C_6H_5—C_6H_4$-	55	221–222	224[h]
3-Phenanthryl-	85	269–270	270[i]
2-Phenanthryl-	80	258–259	258.5–260[i]
Thienyl-	99	127–128	126–127[j]



Ethyl-	71	122
Propyl-	73	122
Butyl-	60	121
Phenyl-	70	121
CH_3- CH_3-[l]	25	121

[a] Schiemann and Wirkelmuller, "Organic Synthesis," Coll. Vol. II, 299. [b] Davies and Wood, *J. Chem. Soc.*, 1126 (1928). [c] Van Arendonk and Cupery, THIS JOURNAL, **53**, 3184 (1931). [d] Whitmore and Woodward, "Organic Syntheses," Coll. Vol. I, 325. [e] Gattermann, *Ann.*, **244**, 51 (1888). [f] Oppenheim and Pfaff, *Ber.*, **8**, 890 (1875). [g] Zincke and Jorg, *ibid.*, **43**, 3448 (1910). [h] Ciamician and Silber, *ibid.*, **28**, 1555 (1895). [i] Mosettig and van de Kamp, THIS JOURNAL, **52**, 3704 (1930). [j] Schorigin, *Ber.*, **43**, 1942 (1910). [k] Fischer, *Ann.*, **127**, 140 (1863). [l] In this compound, both R1 and the hydrogen alpha to the carbonyl group, were replaced by methyl groups.

using benzene or a substituted benzene and the appropriate acid chloride. In general the boiling point or melting point data for each of the ketones was in good agreement with that recorded in the literature.

***p*-Methylmercaptoacetophenone.**—To a mixture of 0.5 mole of phenyl methyl sulfide[8] and 1.0 mole of anhydrous aluminum chloride in carbon disulfide, 0.5 mole of acetyl chloride was added. After one hour the reaction mixture was decomposed by addition to a mixture of ice and hydrochloric acid and the water-insoluble product was crystallized from Skellysolve C; yield 70%, m. p. 79–80°.

Anal. Calcd. for $C_9H_{10}OS$: C, 65.03; H, 6.06. Found: C, 65.20; H, 6.26.

2,4-Dinitrophenylhydrazone m. p. 231–232°; crystallized from chloroform.

Anal. Calcd. for $C_{15}H_{14}O_4N_4S$: N, 16.18. Found: N, 16.14.

The para position for the methylmercapto group is indicated by conversion to the quaternary salt and subsequent alkaline cleavage to the known *p*-methylmercaptobenzoic acid.

Preparation of Quaternary Iodides.—The experimental procedure was identical with that previously reported.[1] The product from the reaction of 0.1 mole of ketone with 0.1 mole of iodine and excess pyridine was washed with ether and then with water. The residue was then crystallized from a suitable solvent. The solvents used for crystallization, the melting points, analyses, and percentage yields are listed in Table I.

Slight variations in the procedure were required for reactions of *n*-butyl phenyl ketone and *n*-amyl-phenyl ketone with iodine and pyridine. The following procedure facilitated the isolation of analytically pure products from these substances. The reaction mixtures were washed with ether and then extracted with acetone. Addition of water or ether to the acetone extracts resulted in the separation of an oil. This oil was crystallized twice from an acetone–ether mixture by cooling in a Dry Ice–acetone-bath. The crystals, which were collected by filtration, melted upon warming to room temperature. By drying this product *in vacuo*, an amber-colored glass with the proper carbon, hydrogen and iodine analyses was obtained from the reaction using *n*-butyl phenyl ketone. The liquid obtained by this method from the reaction of *n*-amyl phenyl ketone crystallized after two days.

Preparation of Quaternary Perchlorates.—The perchlorates were prepared in a manner similar to that reported in other papers.[1]

It is not possible by this method to prepare crystalline perchlorate salts from 1-(1-benzoylbutyl)-pyridinium iodide or from 1-(1-benzoylamyl)-pyridinium iodide. Attempts to prepare picrates from these two iodides also failed.

Alkaline Hydrolysis of Quaternary Iodides.—This was effected in a manner similar to that previously reported.[1] The data on yield and identity of the acids are reported in Table II.

Reaction of Dibenzoylmethane with Iodine and Pyridine.—This reaction was carried out in a manner similar to the general procedure described above with the exception that, during the reaction and in the process of purification, care was taken to exclude water. Nevertheless, no product possessing the characteristics of dibenzoylmethyl pyridinium betaine or the characteristics expected of 1-(dibenzoylmethyl)-pyridinium iodide was isolated. Instead, the only crystalline product was a solid, obtained in 20–25% yield, which was presumed to be 1-phenacylpyridinium iodide on the basis of the following properties; m. p. 213°.

Anal. Calcd. for $C_{13}H_{12}ONI$: N, 4.31; I, 39.0. Found: N, 4.05; I, 39.2.

1-Keto-2-tetrahydronaphthylpyridinium Iodide (IV).—One-tenth mole of α-tetralone was allowed to react with 0.1 mole of iodine and 0.2 mole of pyridine. The product was isolated as indicated in a previous paper,[1] and crystallized from water–alcohol; yield 55%, m. p. 218–220°.

Anal. Calcd. for $C_{15}H_{14}ONI$: C, 51.32; H, 4.02; I, 36.14. Found: C, 51.59; H, 4.25; I, 36.16.

The perchlorate m. p. 180–181°.

Anal. Calcd. for $C_{15}H_{14}O_5NCl$: C, 55.65; H, 4.36. Found: C, 55.46; H, 4.57.

The above iodide, by chromic acid oxidation, was converted to phthalic acid (identified as the anhydride).

1-Keto-2-tetrahydronaphthylpyridinium Betaine (V).—An excess of cold sodium hydroxide solution was added to a suspension of (IV) in water. A golden-red solid precipitated at once. The material which was collected by filtration was unstable on standing and was found to darken at about 65°. A sample of (V) when suspended in water and treated with perchloric acid was converted to the perchlorate of (IV); m. p. 179–180°. The filtrate from which (V) was isolated contained 93% of the iodine originally associated with the salt.

3-(2-Carboxyphenyl)-propylpyridinium Iodide (VI).—A suspension of 11.0 g. of (V) was warmed for one hour with dilute sodium hydroxide containing potassium iodide. The solution was then acidified with hydrogen iodide and the insoluble material separated by filtration. The filtrate was evaporated to a volume of 50–100 cc. and cooled. The light colored precipitate was taken up in absolute alcohol and precipitated with ether. The product weighed 4.0 g.; m. p. 180–182°.

---

(8) Knapp, *Monatsh.*, **56**, 66 (1930).

Anal. Calcd. for $C_{15}H_{16}O_2NI$: N, 3.80. Found: N, 3.68.

Summary

1. A series of quaternary salts, of interest in chemotherapy studies of cancer, has been prepared by treating iodine and pyridine with substituted methyl aryl ketones, with α-substituted acetophenones, and with α-tetralone.

2. The products obtained from the α-substituted acetophenones became increasingly difficult to purify as the length of the side chain increased, and no pure quaternary salt was obtained from isobutyrophenone.

3. Each of the quaternary salts, except that prepared from acetomesitylene, was converted into a characteristic carboxylic acid by the action of aqueous alkali.

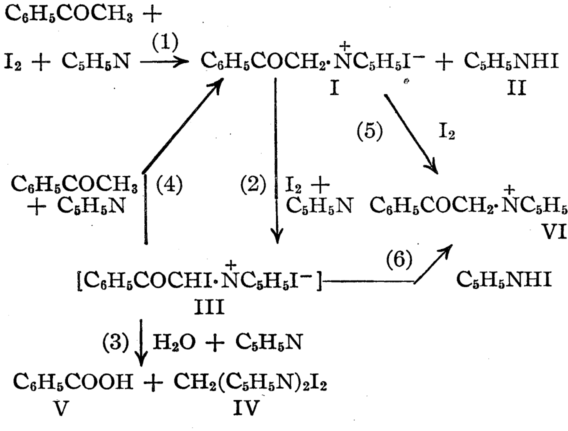
EVANSTON, ILLINOIS RECEIVED JULY 21, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Reaction of Ketones with Iodine, Pyridine and Water[1]

BY L. CARROLL KING

Acetophenone, on reaction with iodine, pyridine and water, gives a mixture consisting of phenacylpyridinium iodide (I), pyridine hydriodide (II), methylenedipyridinium diiodide (IV), phenacylpyridinium triiodide (VI) and benzoic acid (V). These products result from a number of reactions proceeding at the same time and may be explained by assuming the formation of α-iodophenacylpyridinium iodide (III) as an intermediate, thus



The salt (I) is first formed (reaction 1) and this may then react with iodine and pyridine to form III (reaction 2). Compound III may then react irreversibly with water and pyridine to form IV and V (reaction 3), or it may react with unchanged ketone and pyridine to regenerate I (reaction 4). Reaction 3 is the favored one in very dilute or homogeneous solution even if the ketone is present in excess (see example 4 of the experimental). Reaction 4 is favored in heterogeneous reaction mixtures or when the ketone concentration is high (see example 2 of the experimental). Reactions which produce phenacylpyridinium triiodide (VI) (reactions 5 and 6) are favored in heterogeneous reaction mixtures by an excess of iodine, whereas, in dilute or homogeneous solution, Reaction 3 is favored by excess iodine (see example 1 of the experimental).

Phenacylpyridinium iodide (I), when it reacted with iodine, pyridine and water, gave IV and V in somewhat better yields than those obtained when starting with the corresponding ketone. With a limited amount of water compound VI also was observed.

In experiments where both yields were measured, the mole yield of benzoic acid (V) was always in excess of the mole yield of methylenedipyridinium diiodide (IV) (see example 1 of the experimental). This discrepancy may be due to isolation difficulties, or it may be due to a reaction where iodine in water solution causes oxidation of I to benzoic acid and carbon dioxide.[2]

An attempt to isolate α-iodophenacylpyridinium iodide (III) from the reaction mixture failed. An attempt to prepare III by a method found satisfactory for preparation of the corresponding α-bromophenacylpyridinium bromide[3] (VII) gave none of the expected III but gave phenacylpyridinium triiodide (VI) in almost quantitative yield.

$$C_6H_5COCHBr\cdot\overset{+}{N}C_5H_5\ Br^- \qquad \text{VII}$$

Some reactions of the analogous α-bromophenacylpyridinium bromide (VII) would indicate that the intermediate (III) can enter into the reactions suggested but that III should not be isolable from these reactions. Thus, VII reacted with acetophenone and then with pyridine to give phenacylpyridinium bromide (analogous to reaction 4), with pyridine hydroiodide to give VI (analogous to reaction 6), and with water and pyridine to give methylenedipyridinium dibromide[3] (analogous to reaction 3).

The methylenedipyridinium diiodide (IV) isolated in the reaction studies was in each case compared in detail with an authentic specimen prepared by action of pyridine on methylene iodide.

---

[1] Paper no. 6 on the Reaction of Ketones with Halogens and Nitrogeneous Bases. For other papers in this series see King and co-workers, THIS JOURNAL, **66**, 894, 1612 (1944); **67**, 2089 (1945); **68**, 717 (1946); **70**, 239 (1948).

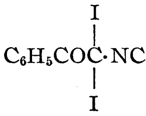
[2] Such a reaction was observed[3] when bromine water reacted with phenacylpyridinium bromide.

[3] Kröhnke, *Ber.*, **66**, 1386 (1933).

The compound described as phenacylpyridinium triiodide is new. The structure is based on two lines of evidence: (a) it is produced in nearly quantitative yield by reaction of iodine and phenacylpyridinium iodide (I) in glacial acetic acid, and (b) it was found to react with pyridine and acetophenone to give pyridine hydroiodide (II) and phenacylpyridinium iodide (I). This latter compound was present at the end of the reaction in mole quantity about twice that of the starting triiodide. The appearance of pyridine hydroiodide and this extra phenacylpyridinium iodide is evidence that iodine reacted with acetophenone and pyridine.[1] This may be represented as

$$C_6H_5COCH_2\overset{+}{N}C_5H_5I_3^- + C_5H_5COCH_3 \quad 2C_5H_5N \longrightarrow$$
$$2C_6H_5COCH_2\cdot\overset{+}{N}C_5H_5I^- + C_5H_5NHI$$

Had the compound VI been an iodinated substance such as VIII no pyridine hydroiodide



$$C_6H_5CO\overset{I}{\underset{I}{C}}\cdot NC_5H_5I$$

VIII

would have been produced in this reaction. Furthermore, since α-halogenated salts of this type (for example, VII) were shown to react readily with acetophenone and pyridine, three moles of I would have been produced for each mole of the starting substance had the starting substance been VIII.

Experimental

Reaction of Acetophenone with Iodine, Pyridine and Water.—These reactions were studied by determination of the amount of some of the isolable reaction products under a variety of conditions. A summary of the general procedure and typical results is illustrated by the following examples.

Example 1.—A mixture consisting of 0.025 mole of acetophenone, 0.05 mole of iodine, 20 cc. of pyridine and 2.5 moles of water[4] in an open flask was heated to dryness on the steam-bath. The residue was leached with ether (1.6 g., 55%[5] of benzoic acid was isolated from the ether extract). The solid remaining was leached with acetone (25 mg. of phenacylpyridinium triiodide[6] (VI) was isolated from the acetone extract). The solid remaining after the acetone extraction was then leached with hot absolute alcohol. (From the alcohol extract 1.2 g., 14%,[5] of phenacylpyridinium iodide (I) and a quantity of pyridine hydroiodide[7] was obtained.) The residue left after alcohol extraction was methylenedipyridinium diiodide[6] (IV); yield 2.5 g. or 24%.[5]

A duplicate experiment gave 1.7 g. of I and 1.7 g. of IV.

Example 2.—A mixture consisting of 0.1 mole of acetophenone, 0.1 mole of iodine, 20 cc. of pyridine and 45 g. (2.5 moles) of water[8] in an open flask was heated for fifteen hours on the steam-bath. From the residue 18.5 g., 57%,[5] of I, pyridine hydroiodide in quantity and a trace of IV were obtained.

Example 3.—A mixture consisting of 0.025 mole of acetophenone, 0.025 mole of iodine, 20 cc. of pyridine and 45 g. (2.5 moles) of water,[4] when heated as in Example 1, gave 0.7 g., 14%,[9] of IV, a quantity of pyridine hydroiodide, a trace of phenacylpyridinium iodide (I) and benzoic acid.

Example 4.—A solution consisting of 5.0 g. (0.041 mole) of acetophenone, 100 cc. of pyridine, 300 cc. of water and 1.0 g. (0.004 mole) of iodine[4] was evaporated to dryness on the steam-bath. The residue consisted of pyridine hydroiodide, benzoic acid and 0.30 g. of IV, 36%.[9] No phenacylpyridinium iodide could be detected.

Reaction of Phenacylpyridinium Iodide with Iodine, Pyridine and Water.—A solution of 0.025 mole of I in 50 cc. of water was treated with 10 cc. of pyridine and 0.025 mole of iodine. The solution was placed in an open flask and heated to dryness on the steam-bath. Benzoic acid was present as a sublimate. The residue was successively leached with ether, acetone and absolute alcohol, and finally crystallized from alcohol containing a small amount of water; yield 4.4 g. (42%) of methylenedipyridinium iodide.[6] When a similar experiment was carried out using a limited amount of water, a mixture similar to that described in example 1 was obtained.

α-Bromophenacylpyridinium Bromide (VII).—This substance was prepared according to the directions of Kröhnke.[3] It was crystallized twice from glacial acetic acid; m. p. 219°.[10]

Anal. Calcd. for $C_{13}H_{11}ONBr_2$: Br, 44.8. Found: Br, 45.5.

Reaction of VII with Pyridine and Acetophenone.—A mixture of 5.0 g. of VII, 7 cc. of acetophenone and 10 cc. of pyridine was heated for three hours on the steam-bath. The mixture was diluted with ether and filtered. The product was phenacylpyridinium bromide; yield 7.8 g.; m. p. 219°.

Anal. Calcd. for $C_{13}H_{12}ONBr\cdot H_2O$: Br, 27.0. Found: Br, 26.2. The perchlorate had m. p. 189.°

Reaction of VII with Pyridine Hydroiodide.—A mixture of 0.01 mole of VII and 10 g. of pyridine hydroiodide was dissolved in boiling glacial acetic acid. An intense iodine color developed. The solution was cooled, filtered, and the solid leached with acetone. Phenacylpyridinium triiodide (VI) was recovered from the acetone extract; yield 1 g.; m. p. 111–112°.

Methylenedipyridinium Diiodide (IV).—A mixture consisting of 3 cc. of methylene iodide and 10 cc. of pyridine was heated for one hour on the steam-bath. The crystalline product which separated was washed with ether and crystallized four times from alcohol containing a little water; m. p. 223–224°. This substance is insoluble in absolute alcohol, and very soluble in water.

Anal. Calcd. for $C_{11}H_{12}N_2I_2$: I, 59.7; N, 6.42. Found: I, 59.0; N, 6.72.

The diperchlorate showed m. p. 232–235°.

Anal. Calcd. for $C_{11}H_{12}N_2Cl_2O_8$: N, 7.57. Found: N, 7.63.

The picrate gave m. p. 245–249°.[11]

Phenacylpyridinium Triiodide (VI): Method I.—A solution of 5 g. of phenacylpyridinium iodide (I) in 40 cc. of hot water–alcohol was added to a solution of 10 g. of potassium iodide and 5 g. of iodine in 40 cc. of water. A red oil precipitated; it was separated by decantation, dissolved in hot absolute alcohol, and the solution cooled. The red-brown flaky crystals obtained were crystallized four times from absolute alcohol; yield 5 g.; m. p. 114–115°.

---

[4] This mixture was homogeneous after heating for a few minutes on the steam-bath.

[5] Based on the ketone.

[6] Characterized by detailed comparison with the authentic material as described elsewhere in this paper.

[7] The amount of this substance was not determined. It was present in considerable quantity in all reaction mixtures.

[8] This mixture was not homogeneous.

[9] Based on iodine assuming all iodine was used according to reactions 1, 2 and 3.

[10] Kröhnke[3] reported the melting point of this compound as 219° after crystallizing from water or alcohol. The substance prepared in this Laboratory shows marked decomposition in the range 120–150°, but most of it persists until 219–220°.

[11] The melting point of this substance was reported as 230° by Schmidt, *Arch. Pharm.*, **251**, 186 (1913). In several preparations we have never observed this value.

Anal. Calcd. for $C_{13}H_{12}NOI_3$: I, 65.8; N, 2.42. Found: I, 63.0; N, 2.48.

This substance is very slightly soluble in water, benzene and ether, moderately soluble in absolute alcohol, and very soluble in acetone. A suspension of it in water slowly turns starch to a blue color.

Method II.—A solution of 0.05 mole of phenacylpyridinium iodide in 75 cc. of boiling glacial acetic acid was treated with 0.05 mole of iodine. On cooling, the triiodide (VI) separated; yield, 95%; m. p. 111–113°.

Reaction of Phenacylpyridinium Triiodide (VI) with Acetophenone and Pyridine.—A solution consisting of 2.57 g. (0.0044 mole) of VI in 5 g. of acetophenone and 5 g. of pyridine was heated for two hours on the steam-bath. At the end of this time most of the color had disappeared and a light brown crystalline solid was present in the reaction flask. This solid was separated and thoroughly washed with ether; yield 3.6 g. of crude solids. The material was then digested with 10 cc. of warm water, the suspension cooled in an ice-bath and filtered. The solid, weight 2.54 g. (0.0078 mole), was phenacylpyridinium iodide (I). The water-soluble portion was concentrated and treated with perchloric acid. Pyridine perchlorate, 0.9 g. (0.0044 mole), m. p. 285°, separated. This was considered proof that pyridine hydroiodide was present in the reaction mixture as an ether insoluble salt and hence had been formed in the original reaction.

Summary

1. The reaction of acetophenone with iodine, pyridine and water was studied and five products separated and identified. A reaction scheme to explain these products is given and independent experiments were carried out to establish each of the postulated reactions.

2. Phenacylpyridinium triiodide was prepared and it was demonstrated that it contains the triiodide ion.

EVANSTON, ILLINOIS RECEIVED AUGUST 11, 1947

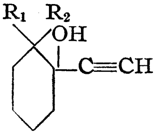
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, LABORATORIES OF THE MOUNT SINAI HOSPITAL]

The Action of Formic Acid on Ethynylcarbinols[1]

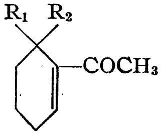
BY J. D. CHANLEY

Ethynylcarbinols on treatment with formic acid yield isomeric unsaturated carbonyl compounds. Rupe,[2] in the years 1926–1929, studied this isomerization in a number of instances and originally concluded that the reaction products were unsaturated aldehydes. Fischer and Löwenberg,[3] however, showed that the interaction of 1-ethynyl-1-cyclohexanol (IA) and formic acid yielded the isomeric ketone, 1-acetyl-1-cyclohexene (IIA) and not cyclohexylideneacetaldehyde (IIIA), as postulated by Rupe; they suggested that ketones always were the main products of this type of reaction and that aldehydes, if formed, were present in small quantities. Rupe,[4] accepted their evidence and suggestion, but insisted that some aldehyde was present in each reaction product he had previously described.[5] Hurd and Christ[6a] also repeated Rupe's work on 1-ethynyl-1-cyclohexanol and phenylmethylethynylcarbinol and chose for further study the action of formic acid on ethynylbornyl alcohol. They reported that only the corresponding ketones 1-acetyl-1-cyclohexene, acetophenone and 2-acetyl-6-hydroxycamphane were formed and went beyond Rupe's modified concept by doubting the presence of any aldehydes in Rupe's reaction products. However, their products must have contained some aldehydes, since their ketones, like Rupe's, gave a positive test for aldehydes with Schiff reagent. However, they discounted the significance of this test.[6b]

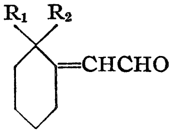
In the present paper evidence will be offered to show that 1-ethynyl-1-cyclohexanol (IA) on treatment with formic acid and after careful fractionation gives, in addition to the main product, 1-acetyl-1-cyclohexene (IIA) (50% yield), a small but significant quantity of cyclohexylideneacetaldehyde (0.8% yield). As a second example we prepared the new 1-ethynyl-2,2-dimethyl-1-cyclohexanol (IB) which on similar treatment gave the new ketone 2,2-dimethyl-1-acetyl-1-cyclohexene (IIB) (56% yield) and the new aldehyde 2,2-dimethylcyclohexylideneacetaldehyde (IIIB) (6% yield). Neither of the above mentioned pure ketones gave a positive test for aldehydes with Schiff reagent.



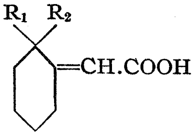
I



II



III



IV

For formulas IA-IVA, $R_1 = R_2 = H$; for IB-IVB, $R_1 = R_2 = CH_3$

---

[1] This investigation was supported in part by a grant in aid from the United Hospital Fund, New York City, to Dr. Harry Sobotka. It grew out of a project, conducted by Dr. Harry Sobotka and coworkers, dealing with syntheses in the carotenoid group.

(2) Rupe and co workers, *Helv. Chim. Acta*, **9**, 672 (1926); **11**, 449, 656, 965 (1928).

(3) Fischer and Löwenberg, *Ann.*, **475**, 203 (1929).

(4) Rupe and Hirschmann, *Helv. Chim. Acta*, **14**, 688 footnote (1931).

(5) Subsequently Rupe claimed that 1-ethynyl-2-isopropyl-5-methyl-1-cyclohexanol, 1-ethynyl-3-isopropyl-6-methyl-1-cyclohexanol and ethynylfenchyl alcohol were rearranged exclusively to unsaturated aldehydes of type III (see Rupe and Kuenzy, *Helv. Chim. Acta*, **14**, 708 (1931); **17**, 283 (1934)).

(6a) Hurd and Christ, THIS JOURNAL, **59**, 118 (1937).

(6b) *Cf.* also Price and Meisel, *ibid.*, **69**, 1497 (1947).

It is further shown that the unsaturated ketones IIA and IIB may be oxidized to the corresponding unsaturated glyoxals which are rearranged under the influence of hydroxyl-ion to the glycolic acids.

The empirical formulas of both aldehydes (IIIA and IIIB) were established by analysis of the liquids or their semicarbazones. Their structures were ascertained by air oxidation to their respective acids, cyclohexylideneacetic acid (IVA) and 2,2-dimethylcyclohexylideneacetic acid (IVB), which showed no depression in melting point on admixture with the corresponding authentic samples.[7a,b] The semicarbazone of cyclohexylideneacetaldehyde melted at 188–192°. Although this is not in agreement with the values reported in the literature,[8a] its ultraviolet spectrum, $\lambda_{\max} = 269$ mμ, $\epsilon_{\max} = 33{,}800$, is in fair agreement and the spectrum of the liquid aldehyde, $\lambda_{\max} = 237$ mμ, $\epsilon_{\max} = 14{,}400$, confirms the findings of Aldersley and Burckhardt[8b]. This corroborative evidence shows that our sample of cyclohexylideneacetaldehyde was reasonably pure. The ultraviolet spectrum of the new aldehyde (IIIB) and that of its semicarbazone was very similar to that of aldehyde (IIIA) and its semicarbazone (Fig. 1); both aldehydes gave positive tests with Schiff reagent.

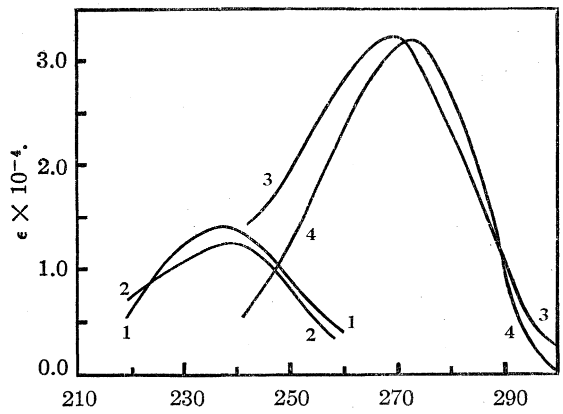


Fig. 1.—Molecular extinction curves of: (1) cyclohexylideneacetaldehyde; (2) 2,2-dimethylcyclohexylideneacetaldehyde; (3) semicarbazone of cyclohexylideneacetaldehyde; (4) semicarbazone of 2,2-dimethylcyclohexylideneacetaldehyde.

The assignment of structure IIB to the new ketone, prepared from the corresponding ethynylcarbinol (IB), is based on its synthesis, analysis and ultraviolet absorption spectrum. Its spectrum and that of its semicarbazone closely resemble those of compound IIA and its semicarbazone[9] (Fig. 2). The possibility that a methyl group may have migrated or that a five-membered ring might have been formed and thus lead to an isomeric unsaturated ketone may be discounted, since no plausible rearrangement could give an α,β-unsaturated ketone.

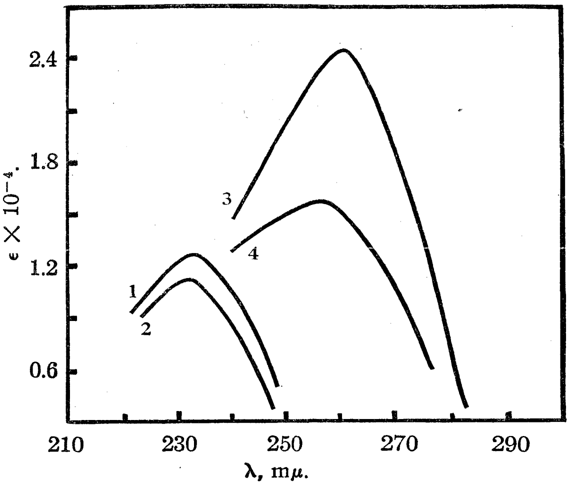
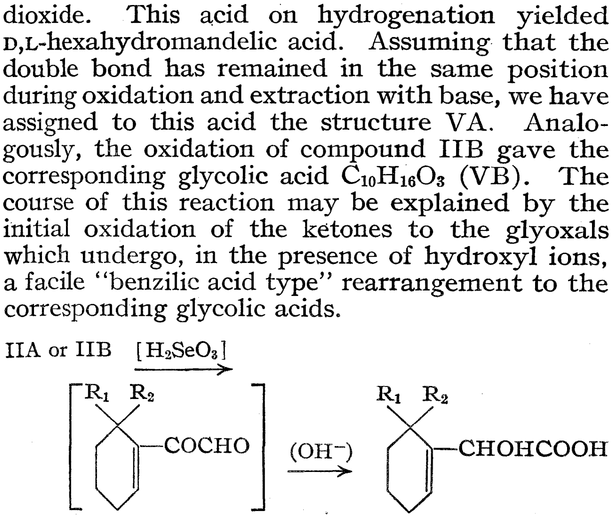


Fig. 2.—Molecular extinction curves of: (1) 1-acetyl-1-cyclohexene; (2) 2,2-dimethyl-1-acetyl-1-cyclohexene; (3) semicarbazone of 1-acetyl-1-cyclohexene; (4) semicarbazone of 2,2-dimethyl-1-acetyl-1-cyclohexene.

1-Acetyl-1-cyclohexene (IIA), on oxidation with selenous acid, yielded a red oil which was extracted with sodium carbonate solution and then with sodium hydroxide solution. Acidification of the sodium hydroxide extract gave a solid acid, $C_8H_{12}O_3$, which was now soluble in sodium bicarbonate solution with evolution of carbon dioxide. This acid on hydrogenation yielded D,L-hexahydromandelic acid. Assuming that the double bond has remained in the same position during oxidation and extraction with base, we have assigned to this acid the structure VA. Analogously, the oxidation of compound IIB gave the corresponding glycolic acid $C_{10}H_{16}O_3$ (VB). The course of this reaction may be explained by the initial oxidation of the ketones to the glyoxals which undergo, in the presence of hydroxyl ions, a facile "benzilic acid type" rearrangement to the corresponding glycolic acids.



VA, $R_1, R_2 = H$
VB, $R_1, R_2, = CH_3$

---

(7) (a) Wallach, *Ann.*, **365**, 261 (1909); (b) Elliot and Linstead, *J. Chem. Soc.*, **776** (1938).

(8) (a) Dimroth, Ber., **71**, 1333 (1938), gives a m. p. of 210°; Aldersley and Burckhardt, *J. Chem. Soc.*, 545 (1938), report m. p. of 205°.

(8) (b) Aldersley, Burckhardt, Gillam and Hindley, *J. Chem. Soc.*, 10 (1940), report $\lambda_{\max} = 240$ mμ, $\epsilon_{\max} = 15{,}900$ for the aldehyde and $\lambda_{\max} = 272$ mμ, $\epsilon_{\max} = 28{,}000$ for the semicarbazone, whereas Dimroth (ref. 8a) gives $\lambda_{\max} = 232$ mμ, $\epsilon_{\max} = 17{,}400$ and $\lambda_{\max} = 274$ mμ, $\epsilon_{\max} = 32{,}300$ for the two compounds, respectively.

(9) The low value, $\lambda_{\max} = 255$ mμ, for the semicarbazone of compound IIB is not unique. A more extreme case is β-ionone, $\lambda_{\max} = 293.5$ mμ, the semicarbazone of which has a maximum at $\lambda = 276.5$ mμ. See Burawoy, *J. Chem. Soc.*, 20 (1941).

Experimental[10,11]

2,2-Dimethyl-1-cyclohexanone.—Crude dimethylcyclohexanone was prepared in 2-mole batches from 2-methyl-1-cyclohexanone[12] essentially according to Haller and Cornubert.[13] Sodamide was freshly prepared,[14] and methyl iodide was used rather than methyl sulfate. The crude reaction product was fractionated through a packed column of 13–15 theoretical plates and the impure ketone fraction boiling at 168–173° was collected and purified by regeneration from its pure semicarbazone.[15] Pure ketone, boiling at 170–170.5° (cor.) (761 mm.), $n^{20}\text{D}$ 1.4482 was obtained in an over-all yield of 30%; reported[15] b. p. 169–170°, (cor.) (768 mm.), $n^{25}\text{D}$ 1.4460. The semicarbazone melted at 199–201°; reported m. p. 197–198°,[15] 201–202°[7b]; oxime m. p. 93–94°; reported 93–93.5°.[16]

Anal. Calcd. for $C_8H_{14}O$: C, 76.13; H, 11.18. Found: C, 75.56; H, 11.14. Calcd. for $C_9H_{17}N_3O$: C, 58.98; H, 9.35; N, 22.92. Found: C, 59.00; H, 9.12; N, 23.30.

1-Ethynyl-1-cyclohexanol (IA), b. p. 72.5–73° (11 mm.), $n^{25}\text{D}$ 1.4810, m. p. 28–30°, was prepared in 1-mole batches in 50% yield according to the directions of Campbell and co-workers.[17]

1-Ethynyl-2,2-dimethyl-1-cyclohexanol (IB), b. p. 113–113.5° (49 mm.), $n^{25}\text{D}$ 1.4790 was prepared analogously[17] in 0.5-mole batches in 68% yield from the pure ketone (IIB) and sodium acetylide. It gave a white precipitate with alcoholic silver nitrate solution.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.82; H, 10.63.

1-Acetyl-1-cyclohexene (IIA) and Cyclohexylideneacetaldehyde (IIIA).—The conditions of the reaction described below are those of Rupe with minor modifications. A mixture of 65 g. (0.5 mole) of 1-ethynyl-1-cyclohexanol and 400 ml. of formic acid (90%) was gently heated under reflux until a vigorous reaction ensued. After heating under reflux for forty–fifty minutes the mixture was poured into 2 liters of ice water. The petroleum ether extract was washed with sodium hydroxide solution (10%) and the residue from the petroleum ether was steam-distilled. The organic layer in the steam distillate was separated, dried and gave a positive test with Schiff reagent. It was carefully fractionated under reduced pressure through a column of 8–10 theoretical plates which was fitted with a total condensation still head and an electrically heated outer jacket. This column had an internal diameter of 12.5 mm. and was packed for 30 cm. with 1.5 mm. diameter single helices made from 25 gauge stainless steel. Table I gives the properties of the five fractions collected.

The **semicarbazone** prepared from fraction B, 1-acetyl-1-cyclohexene melted at 220–221°, $\lambda_{\max.}$ = 260.5 mμ, $\epsilon_{\max.}$ = 24,200. Reported m. p. 220–221°[6a] and $\lambda_{\max.}$ = 260.5 mμ, $\epsilon_{\max.}$ = 20,150.[18]

The **semicarbazone** prepared from fraction E, cyclohexylideneacetaldehyde, melted at 188–192° and further recrystallizations from ethanol and methanol did not alter the melting point.

TABLE I

Fraction	Yield, g.	B. p., °C., 49 mm.	$n^{20}\text{D}$	$\lambda_{\max.}$, mμ	$\epsilon_{\max.}$	Schiff reaction[b]
A	3.5	76–111	1.4435– 1.4893	...	....	Neg.
B	32.0	111	1.4900	232[18]	12,500	Neg.
C	3.0	111–115[a]	1.4920	...	....	Slightly pos. in one min.
D	0.5	115–117	1.4958	...	....	Pos. in 30 sec.
E[c]	0.5	.....	1.5020	237	14,400	Pos. instantly

[a] At this point, temperature of the outer heating jacket was raised to 150°. [b] Freshly prepared reagent, according to Shriner and Fuson, "The Systematic Identification of Organic Compounds," New York, N. Y., 1940, p. 62, was used without solvent. [c] This fraction was obtained from the "holdup" of the column by reducing the pressure to 5 mm.

Anal. Calcd. for $C_9H_{15}N_3O$: C, 59.68; H, 8.35; N, 23.20. Found: C, 59.63; H, 8.55; N, 23.31.

2,2-Dimethyl-1-acetyl-1-cyclohexene (IIB), 2,2-Dimethylcyclohexylideneacetaldehyde (IIIB) and Compound $C_{10}H_{14}$.—The reaction mixture of 65 g. (0.42 mole) of 1-ethynyl-2,2-dimethyl-1-cyclohexanol (IB) and 350 ml. formic acid (90%) was worked up in the same manner as described above. Table II gives the properties of the five fractions obtained by distillation.

TABLE II

Fraction	Yield, g.	B. p., °C. 49 mm.	$n^{25}\text{D}$	$\lambda_{\max.}$ mμ	$\epsilon_{\max.}$	Schiff reaction
A	3.0	80–85	1.4682	...	....	Neg.
B	3.0	114–118	1.4772– 1.4800	...	....	Neg.
C	36.5	118–118.5	1.4810	232	10,100	Neg.
D	0.5	118.5–141	1.4840	...	....	Pos.[a]
E	4.0	141–143	1.5010	239	12,000	Pos.[a]

[a] The color development was not instantaneous because of the insolubility of the aldehyde in the reagent. A purple color developed after a minute of shaking and was concentrated in the insoluble aldehyde layer.

The **semicarbazone** prepared from fraction C (Table II), 2,2-dimethyl-1-acetyl-1-cyclohexene, and recrystallized from ethanol melted at 200–201.5°, $\lambda_{\max.}$ = 255 mμ, $\epsilon_{\max.}$ = 15,600. Ten recrystallizations from ethanol and methanol did not alter its physical properties.

Anal. Calcd. for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.24; H, 9.21; N, 20.37.

2,2-Dimethyl-1-acetyl-1-cyclohexene obtained by steam distilling an equimolecular mixture of the pure semicarbazone and phthalic anhydride, boiled at 115.8–116° (47 mm.), $n^{25}\text{D}$ 1.4815, $\lambda_{\max.}$ = 232 mμ, $\epsilon_{\max.}$ = 12,000. It gave no coloration with Schiff reagent.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.02; H, 10.48.

Fraction E, 2,2-dimethylcyclohexylideneacetaldehyde, on redistillation, boiled at 130–130.5° (32 mm.), $n^{25}\text{D}$ 1.5022, $\lambda_{\max.}$ = 239 mμ, $\epsilon_{\max.}$ = 12,300 and gave a purple color with Schiff reagent.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.05; H, 10.56.

The **semicarbazone** prepared from fraction E, Table II, and recrystallized from methanol, melted at 220°; $\lambda_{\max.}$ = 273 mμ, $\epsilon_{\max.}$ = 32,300.

Anal. Calcd. for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.28; H, 9.31; N, 19.93.

Fraction A (Table II) on redistillation boiled at 81.8° (54 mm.), $n^{25}\text{D}$ 1.4700, showed no absorption in the range

---

(10) The ultraviolet absorption spectra measurements were made on a Beckman Quartz Spectrophotometer Model D. U. and absolute alcohol was used as solvent. All melting points are corrected.

(11) Microanalyses by Dr. Gertrude Oppenheimer, Microchemical Laboratory, The California Institute of Technology, Pasadena, California.

(12) We are indebted to Drs. Luthy and Fiori of Givaudan-Delawanna, Inc., Delawanna, New Jersey, for supplying this compound.

(13) Haller and Cornubert, *Bull. soc. chim.*, [4] **41**, 367 (1927).

(14) Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

(15) Adamson, Marlow and Simonsen, *J. Chem. Soc.*, 774 (1938).

(16) Johnson and Posvic, THIS JOURNAL, **67**, 505 (1945).

(17) K. Campbell, B. Campbell and Eby, *ibid.*, **60**, 2282 (1938).

(18) Evans and Gillam, *J. Chem. Soc.*, 815 (1941); 565 (1943), also report $\lambda_{\max.}$ = 233.5 mμ, $\epsilon_{\max.}$ = 9,660 for this ketone.

from 216 to 300 mμ and gave a white precipitate with alcoholic silver nitrate solution.

Anal. Calcd. for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.47; H, 10.30.

Oxidation of Cyclohexylideneacetaldehyde (IIIA) to Cyclohexylideneacetic Acid (IVA).—One-tenth of a ml. of Fraction E (Table I) was allowed to stand exposed to the air for three days. The resulting semisolid crystalline mass was dissolved in ether and extracted several times with 10% sodium carbonate solution. The combined alkaline extracts, on acidification, yielded 40 mg. of the acid, m. p. 89–90°, which after recrystallization from petroleum ether (b. p. 40–60°), melted at 90–92° and showed no depression of melting point on admixture with authentic cyclohexylideneacetic acid, m. p. 90–92°, prepared by the dehydration of (1-hydroxycyclohexyl)-acetic acid[19] according to the direction of Wallach[7a] who reports m. p. 91°.

Oxidation of 2,2-Dimethylcyclohexylideneacetaldehyde (IIIB) to 2,2-Dimethylcyclohexylideneacetic acid (IVB).—In a similar manner 1 ml. of 2,2-dimethylcyclohexylideneacetaldehyde, after standing two weeks, exposed to the air, gave 300 mg. of 2,2-dimethylcyclohexylideneacetic acid, m. p. 89–90°. The acid after recrystallization from acetic acid, melted at 90–91° and showed no depression of melting point on admixture with an authentic sample[20]; m. p. 90–91°; reported[7b] m. p. 91–92°.

(1-Cyclohexenyl)-glycolic Acid (VA).—A solution of 6.2 g. (0.05 mole) of 1-acetyl-1-cyclohexene and 6.5 g. (0.05 mole) of selenous acid in 40 ml. of dioxane was heated under reflux for three and one-half hours, decanted from the precipitated selenium and evaporated to dryness *in vacuo* under nitrogen. The ethereal solution of the residue was thoroughly extracted with sodium carbonate solution (10%). (At this point, much red selenium precipitates and is allowed to sink into the carbonate solution.) The carbonate extract gave only intractable tars upon acidification. The ether layer was then extracted six times with dilute sodium hydroxide solution (10%). The combined sodium hydroxide extracts were filtered, warmed on the steam-bath, acidified with a slight excess of warm dilute hydrochloric acid and filtered from precipitated tarry material. The filtrate was saturated with salt and precipitation induced by scratching the sides of the container; 1.5 g. of a yellow colored solid, m. p. 122–124° was collected. After recrystallization from Skellysolve L (b. p. 97–129°), with Norite, a colorless solid acid, m. p. 126–126.5° was obtained. It was now soluble in sodium bicarbonate solution with evolution of carbon dioxide; yield 1.4 g.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75; neut. equiv., 156.2. Found: C, 61.61; H, 8.04; neut. equiv., 159.0.

Hydrogenation of Compound VA to D,L-Hexahydromandelic Acid.—Two hundred and forty-seven mg. (0.00157 mole) of compound VA, in glacial acetic acid, was hydrogenated at atmospheric pressure with platinum oxide; 98% of the theoretical amount of hydrogen was absorbed. The resulting acid recrystallized from chloroform melted at 134–135° and showed no depression of m. p. in admixture with D,L-hexahydromandelic acid of m. p. 135–136°, prepared from D,L-mandelic acid by hydrogenation. Reported m. p. 134–135°.[21]

(2,2-Dimethyl-1-cyclohexenyl)-glycolic Acid (VB).—Similarly, 4.2 g. ($^1/_{30}$ mole) of 2,2-dimethyl-1-acetyl-1-cyclohexene (IIB) was treated with 3.6 g. ($^1/_{30}$ mole) of selenous acid in 20 ml. of dioxane with the following modifications. The sodium hydroxide extract after acidification was not filtered, since the acid separates in a semi-solid state at this point. The precipitated orange-colored crude acid was purified by dissolving in a small amount of hot sodium carbonate solution (10%) treated with norite, filtered and reprecipitated by the addition of dilute hydrochloric acid solution. Yield was 0.9 g., m. p. 118–120°. Two recrystallizations from ethanol–water mixture gave the pure colorless acid, m. p. 121°.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76; neut. equiv., 184.2. Found: C, 65.08; H, 8.71; neut. equiv., 186.5.

Acknowledgment.—The author wishes to thank Dr. Harry Sobotka for his interest and suggestions, and Mrs. Edith Rosen Kaplan and Miss Bernice Hamerman for their very able assistance.

Summary

1. 1-Ethynyl-1-cyclohexanol is isomerized under the influence of formic acid to 1-acetyl-1-cyclohexene (50% yield) and cyclohexylideneacetaldehyde (0.8% yield). Similarly 2,2-dimethyl-1-ethynyl-1-cyclohexanol gave 2,2-dimethyl-1-acetyl-1-cyclohexene (56% yield) and 2,2-dimethylcyclohexylideneacetaldehyde (6% yield).

2. The selenous acid oxidation product of 1-acetyl-1-cyclohexene on treatment with a dilute solution of sodium hydroxide yielded (1-cyclohexenyl)-glycolic acid. Similarly 2,2-dimethyl-1-acetyl-1-cyclohexene yielded (2,2-dimethyl-1-cyclohexenyl)-glycolic acid. An interpretation of the course of this reaction is given.

New York, N. Y. Received April 23, 1947

---

(19) We are indebted to Dr. Erwin Schwenk of Schering Corp., Bloomfield, New Jersey, for a sample of this acid.

(20) The authentic sample was prepared in the following manner: ethyl (2,2-dimethyl-1-hydroxycyclohexyl)-acetate (prepared according to Simonsen, *et al.*[15]) was hydrolyzed with alcoholic potassium hydroxide and dehydrated with acetic anhydride according to the directions of Elliott and Linstead.[7b]

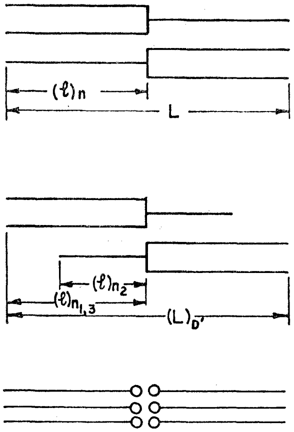
(21) Freudenberg, Brauns and Siegel, *Ber.* **56**, 197 (1923).

[CONTRIBUTION FROM THE PROCTER AND GAMBLE CO.]

Triple Chain-Length Structures of Saturated Triglycerides[1]

BY E. S. LUTTON

The nature of the polymorphism of the glyceride series, tristearin, tripalmitin, etc., has been made clear by the work of Clarkson and Malkin[2] and others.[3,4,5] The "triple-melting" phenomena of these glycerides are due to three crystalline forms—α, β' and β. These forms are of double-chain-length (DCL) structure, with their molecules presumably in Malkin's "tuning fork" type of configuration. The arrangement is indicated schematically in Fig. 1 along with other DCL structures, one for a fatty acid and another for a mixed triglyceride.



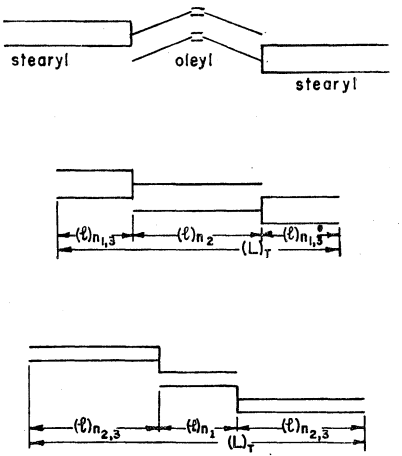
(a) Simple triglyceride

(b) Mixed triglyceride

(c) Fatty acid

Fig. 1.—Double-chain-length structures.

According to Malkin, *et al.*,[6] and others[7,8] many mixed saturated triglycerides are analogous to tristearin in their polymorphic forms. But these authors have shown that there may be serious departures from the tristearin plan, notably with regard to long spacings and DCL structure. No comprehensive scheme has been advanced which treats in any clear-cut way these departures from DCL structure. The presentation of such a scheme is attempted in this paper. It is shown that most, but not all, departures from normal long spacing values can be explained by crystallization of the mixed glycerides in triple-chain-length (TCL) structures similar to those proposed for the mixed saturated-unsaturated triglyceride 2-oleyl distearin.[5,9] In the saturated case, as in the unsaturated case, the TCL structures are presumed to arise from the sorting of chains, short chains from long chains instead of unsaturated from saturated chains. This process of sorting apparently gives rise to both tuning fork structures and a newly proposed "chair" type of molecular arrangement (see Fig. 2).



(a) 2-Oleyldistearin

(b) Symmetrical or "tuning fork" arrangement

(c) Unsymmetrical or "chair" arrangement

Fig. 2.—Triple-chain-length structures.

The quadruple-chain-length (QCL) structures which are discussed later are regarded as doubled DCL structures.

A simple geometric basis is proposed for classifying the various reported triglyceride forms as DCL, TCL or QCL structures. In developing this basis the following assumptions are made:

1. With regard to cross-sectional structures, as characterized by short spacings, there are three structure types which may be identified according to Table I.

TABLE I

CROSS-SECTIONAL STRUCTURE TYPES

Type	Identification
α	A single strong line corresponding to approx. 4.15 Å.
β'	Usually two (but occasionally more) strong lines corresponding to approx. 4.2 and 3.8 Å.
β	A strong (usually strongest) line corresponding to approx. 4.6 Å.

2. With regard to longitudinal structure, as revealed by long spacings, there are three structure types which are distinguished as indicated in Table II. Each of these conceivably may be, and one of them actually is, associated with all three cross-sectional types.

---

[1] Presented in part to the American Society for X-Ray and Electron Diffraction, December 5, 1946.

[2] Clarkson and Malkin, *J. Chem. Soc.*, 666 (1934).

[3] Bailey, *et al.*, *Oil & Soap*, **22**, 10 (1945).

[4] Lutton, THIS JOURNAL, **67**, 524 (1945).

[5] Filer, *et al.*, *ibid.*, **68**, 168 (1946).

[6] (a) Malkin and Meara, *J. Chem. Soc.*, 103 (1939); (b) Carter and Malkin, *ibid.*, 577 (1939); (c) Malkin and Meara, *ibid.*, 1141 (1939); (d) Carter and Malkin, *ibid.*, 1518 (1939).

[7] Filer, *et al.*, THIS JOURNAL, **67**, 2085 (1945).

[8] Sidhu and Daubert, *ibid.*, **69**, 1451 (1947).

[9] Lutton, *ibid.*, **68**, 676 (1946).

TABLE II

LONGITUDINAL STRUCTURE TYPES

Type	Identification
DCL	Long spacings of approx. normal length
TCL	Long spacings approx. 50% longer than normal
QCL	Long spacings approx. twice normal

There is, in theory, no exclusion of the possibility of other cross-sectional and longitudinal structure types.

Calculation of Long Spacings

If it be assumed that for any specified cross-sectional type the angle of tilt and consequently the contribution to long spacing per chain is approximately the same as in single fatty acid triglycerides, a simple calculation for long spacings can be postulated. Contributions per chain are indicated by (l) values shown in Table III.

TABLE III

CONTRIBUTIONS OF SINGLE CHAINS

Triglyceride	n	Long spacings of simple triglycerides $L\alpha^b$	$L\beta'^c$	$L\beta^b$	Long spacing per chain $(l\alpha)_n$	$(l\beta')_n$	$(l\beta)_n$
Tricaprin	10	(30.6)[a]	(28.2)[a]	26.8	15.3	14.1	13.4
Trilaurin	12	35.6	32.85	31.2	17.8	16.4	15.6
Trimyristin	14	41.2	37.65	35.8	20.6	18.8	17.9
Tripalmitin	16	45.6	42.3	40.6	22.8	21.15	20.3
Tristearin	18	50.6	46.8	45	25.3	23.4	22.5

[a] Extrapolated. [b] Malkin, *et al.*, ref. 2. [c] Lutton, ref. 4.

Obviously $(l_\alpha) = {}^1/_2L_\alpha$, etc.

Now it follows from the linear variation of (l) values with number of carbons that the following simple expressions can be given

$$(l_\beta)_n = 2.0 + 1.138\ n \qquad (1)$$

$$(l_{\beta'})_n = 2.5 + 1.163\ n \qquad (2)$$

$$(l_\alpha)_n = 2.8 + 1.250\ n \qquad (3)$$

Arithmetically the long spacing calculation for mixed glycerides is simply a matter of obtaining the average chain length contribution, C, and multiplying by the right "multiplicity factor," *i. e.*, 2 for DCL, as indicated in Table IV.

TABLE IV

CALCULATED LONG SPACING VALUES IN TERMS OF (l) VALUES

β Cross-sectional type

Long spacing type	Calculated value	
DCL	$(L\beta)_\mathrm{D} = 2 \times \dfrac{(l\beta)_{n_1} + (l\beta)_{n_2} + l\beta)_{n_3}}{3} = 2\ C\beta$	(4)
TCL	$(L\beta)_\mathrm{T} = 3 \times \dfrac{(l\beta)_{n_1} + (l\beta)_{n_2} + (l\beta)_{n_3}}{3} =$ $(l\beta)_{n_1} + (l\beta)_{n_2} + (l\beta)_{n_3} = 3\ C\beta$	(5)
QCL	$(L\beta)_\mathrm{Q} = 4 \times \dfrac{(l\beta)_{n_1} + (l\beta)_{n_2} + (l\beta)_{n_3}}{3} = 4C\beta$	(6)

Similar values are postulated for beta prime and alpha cross-sectional types.

Now, from relations (1), (2) and (3), (L) values may be simply derived from the total number of acyl carbons, *e.g.:* letting $(n_1 + n_2 + n_3) = N$

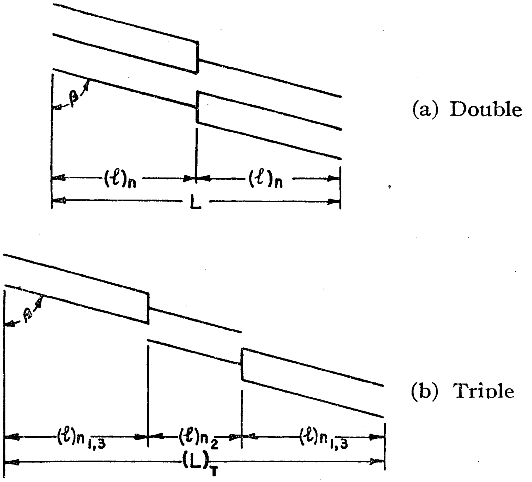
$$(L_\beta)_\mathrm{T} = 3\ C_\beta = 6.0 + 1.138\ N \qquad (7)$$

$$(L_{\beta'})_\mathrm{T} = 3\ C_{\beta'} = 7.5 + 1.163\ N \qquad (8)$$

$$(L_\alpha)_\mathrm{T} = 3\ C_\alpha = 8.4 + 1.250\ N \qquad (9)$$

with corresponding relations for DCL and QCL structures. By these equations, all calculated long spacing values were derived.

Geometrically, TCL structures may be represented as in Fig. 2 (in projection) or Fig. 3 (with the tilt indicated). It is not possible to represent DCL structures neatly for mixed glycerides. In Fig. 1 such a structure is represented with long spacing value designated as $(L)_{\mathrm{D}'}$ to distinguish it from the shorter $(L)_\mathrm{D}$ value defined as in equation (4). QCL structures are regarded as essentially doubled DCL structures, the manner and basis for doubling not being understood except that they are in some way associated with chain length difference in the glycerides.



(a) Double

(b) Triple

Fig. 3.—Assumed constancy of tilt angle for given "form."

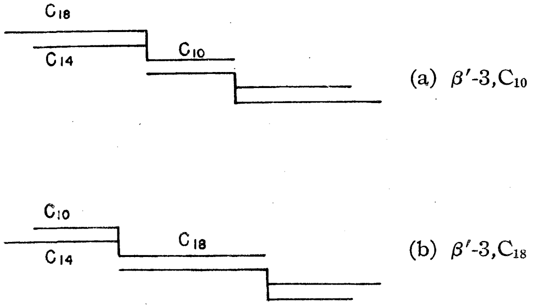
Additional quantities are defined to express the departure of experimental from calculated values

$$(\Delta_\beta)_\mathrm{D} = L_\beta - (L_\beta)_\mathrm{D} \qquad (10)$$

$$(\Delta_\beta)_\mathrm{T} = L_\beta - (L_\beta)_\mathrm{T} \qquad (11)$$

$$(\Delta_\beta)_\mathrm{Q} = L_\beta - (L_\beta)_\mathrm{Q} \qquad (12)$$

where L_β is the experimental value, (L_β) values are calculated as previously described and (Δ_β) values represent the differences.



(a) β'-3,C_{10}

(b) β'-3,C_{18}

Fig. 4.—Alternative triple structures for C_{18}, C_{14}, C_{10}.

Similar (Δ) values are defined for alpha and beta prime forms.

In Tables V and VI, the experimental L and derived (Δ) values are recorded for all mixed saturated glycerides for which data have been published.

Fortunately only one (Δ) value needs to be calculated for a given form. It is generally evident by inspection if, for instance, $(\Delta)_T$ is preferable to $(\Delta)_D$ or $(\Delta)_Q$.

The L values of Tables V and VI are plotted in Figs. 5 and 6 along with lines which express the calculated (L) values. It is these plots which most strikingly reveal that all the available long spacing data with one exception correspond with the concept of either DCL, TCL or QCL structure.

TABLE V

DIFFERENCES BETWEEN EXPERIMENTAL[6a,b,c,d,e] AND CALCULATED LONG SPACINGS

Recording of $(\Delta)_D$, $(\Delta)_T$ or $(\Delta)_Q$ value signifies, respectively, double, triple, or quadruple (doubled double) chain length structure.

					Diacid triglycerides					
		Alpha		Beta prime				Beta		
Triglyceride	N	$L\alpha$	$(\Delta)_D$	$L\beta'$	$(\Delta)_D$	$(\Delta)_T$	$(\Delta)_Q$	$L\beta$	$(\Delta)_D$	$(\Delta)_T$
$C_{10}C_{12}C_{12}$	34	[c]		30.4	−1.0			31.8	+1.9	
$C_{12}C_{14}C_{14}$	40			35.3	−0.8			36.5	+2.1	
$C_{14}C_{16}C_{16}$	46	43.9	−0.2	40.3	− .4			41.5	+2.6	
$C_{16}H_{18}C_{18}$	52	48.8	− .1	44.7	+ .7			46.5	+3.0	
$C_{12}C_{10}C_{12}$	34							30.0	+0.1	
$C_{14}C_{12}C_{14}$	40	39.6	+ .7	36.7	+ .6			34.7	+0.3	
$C_{16}C_{14}C_{16}$	46	44.4	+ .3	42.4	+1.7			39.0	+0.1	
$C_{18}C_{16}C_{18}$	52	50.5	+1.6	47.5	+2.1			44.2	+0.7	
$C_{12}C_{10}C_{10}$	32							28.4	+0.1	
$C_{14}C_{12}C_{12}$	38			34.5	−0.1			33.0	+0.1	
$C_{16}C_{14}C_{14}$	44	42.8	+0.5	39.5	+ .3			37.7	+0.2	
$C_{18}C_{16}C_{16}$	50	47.8	+ .5	43.9	+ .1			42.5	+0.5	
$C_{10}C_{12}C_{10}$	32			29[a]	− .9			[d]		
$C_{12}C_{14}C_{12}$	38			33.6[a]	−1.0			[d]		
$C_{14}C_{16}C_{14}$	44	45.0	+2.7	38.1[a]	−1.1			[d]		
$C_{16}C_{18}C_{16}$	50	50.2	+2.9	43.2[a]	−0.6			[d]		
$C_{10}C_{14}C_{14}$	38			33.8	− .8			35.2	+2.3	
$C_{14}C_{16}C_{16}$	44	43.4	+1.1	38.5	− .7			39.8	+2.5	
$C_{14}C_{18}C_{18}$	50	48.5	+1.2	43.4	− .4			45.0	+3.1	
$C_{14}C_{10}C_{14}$	38			33.7	− .9			52.5		3.2
$C_{16}C_{12}C_{16}$	44	44.6	+2.3	77.0			−0.7 × 2	59.0		2.9
$C_{18}C_{14}C_{18}$	50	49.5	+2.2	44.7	− .9			65.8		2.9
$C_{14}C_{10}C_{10}$	34			31.3	− .1			47.5		2.8
$C_{16}C_{12}C_{12}$	40			36.2	+ .1			54.6		3.0
$C_{18}C_{14}C_{14}$	46	46.4	+2.3	41.7	+1.0			61.4		3.1
$C_{10}C_{14}C_{10}$	34			30.3	−1.1			46.5		1.8
$C_{12}C_{16}C_{12}$	40			35.5[a]	−0.6			[d]		
$C_{14}C_{18}C_{14}$	46	44.0	−0.1	40.0[a]	− .7			[d]		
$C_{10}C_{16}C_{16}$	42			74.1			− .55 × 2			
$C_{12}C_{18}C_{18}$	48	47.4	+1.8	42.8	+ .5					
$C_{16}C_{10}C_{16}$	42	39.0	−1.6	74.0			− .6 × 2	56.5		2.7
$C_{18}C_{12}C_{18}$	48	47.1	+1.5	42.4	+ .1			63.7		3.7
$C_{16}C_{10}C_{10}$	36							49.7		2.7
$C_{18}C_{12}C_{12}$	42	(41.7)[e]	(+1.1)[e]	38.7,	+1.1			57.0		3.2
				(38.0, 55.0)[e]	(0.4)[e],	(−1.4)[e]		(57.2)[e]		(3.4)[e]
$C_{10}C_{16}C_{10}$	36							49.5		2.5
$C_{12}C_{18}C_{12}$	42	40.8	+0.2	37.5	− .1			56.8		3.0
$C_{10}C_{18}C_{18}$	46	73.7[b]		60.0[e]		−1.1				
$C_{18}C_{10}C_{18}$	46			76.3			−2.55 × 2	61.2		2.9
$C_{18}C_{10}C_{10}$	38			51.0		−0.8		52.6		3.3
$C_{10}C_{18}C_{10}$	38							51.6		2.3

[a] Malkin's listing changed from beta to beta prime on the basis of short spacing data. [b] $(\Delta\alpha)_T = 7.8$, $(\Delta\alpha)_Q = -7.3 \times 2$. [c] Blank, no data. [d] Probably no form exists. [e] Data of E. S. L.

TABLE VI

DIFFERENCES BETWEEN EXPERIMENTAL[7,8] AND CALCULATED LONG SPACINGS TRIACID TRIGLYCERIDES

Triglyceride	N	Beta prime				Beta		
		$L\beta'$	$(\Delta)_D$	$(\Delta)_T$ I	$(\Delta)_T$ II	$L\beta$	$(\Delta)_D$	$(\Delta)_T$
$C_{18}C_{10}C_{16}$	44					60.0		3.9
$C_{18}C_{12}C_{16}$	46					61.2		2.9
$C_{18}C_{14}C_{16}$	48	41.5	−0.8			63.4		2.7
$C_{18}C_{10}C_{14}$	42					57.3		3.5
$C_{18}C_{12}C_{14}$	44					59.8		3.7
$C_{18}C_{16}C_{14}$	48					40.5	0.0	
$C_{18}C_{10}C_{12}$	40					54.9		3.3
$C_{18}C_{14}C_{12}$	44	40.1	−2.2			59.6		3.5
$C_{18}C_{16}C_{12}$	46	43.3	−0.8			62.4		4.0
$C_{18}C_{12}C_{10}$	40	35.6[a,b]	− .5					
		53.0		−1.1 (β'-3, C_{18})				
$C_{18}C_{14}C_{10}$	42	54.3,		−2.1 (β'-3, C_{18})				
		56.1[a,b]			−0.3 (β'-3, C_{10})			
$C_{18}C_{16}C_{10}$	44	38.5[a,b]	− .7					
		59.0			−0.3 (β'-3, C_{10})			
$C_{16}C_{14}C_{12}$	42					35.7	− .2	
$C_{14}C_{12}C_{10}$	36	33.4	.4					

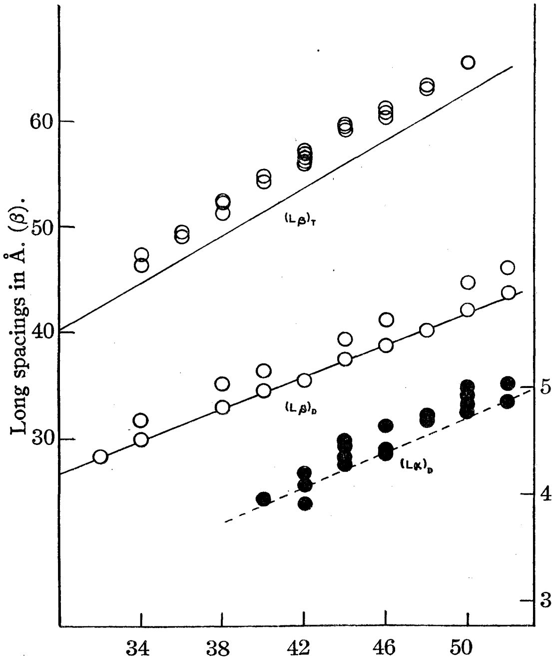
[a] Higher melting form. [b] Filer's listing changed from β to β' on the basis of short spacing data.

Agreement of Calculation and Experiment

Alpha Form (None reported for triacid triglycerides)

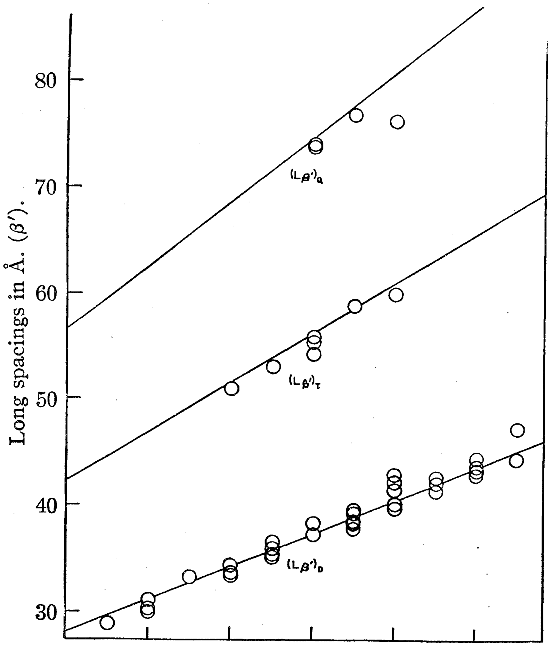
Among the cases for which data are reported for alpha forms, there are fourteen examples of agreement within 1.6 Å. between experiment and calculated DCL structure. Experimental error is usually of the order 0.5 Å. (but in individual cases it may be greater). In the untilted hydrocarbon chain each carbon corresponds to 1.27 Å. of length, wherefore it might be said that the correspondence between calculation and experiment is, in these cases, within about 1 carbon atom.

The six cases of rather poor agreement (1.6 < (Δ), absolute value <2.9) involve glycerides having a large difference (4, 6 or 8 carbons) between



N = total no. acyl carbons per triglyceride.

Fig. 5.—O—experimental long spacings (β), ●—experimental long spacings (α); solid lines—calculated long spacings for β-2 and β-3, dashed line—calculated long spacings for α-2.



N = total no. acyl carbons per triglyceride.

Fig. 6.—Circles, experimental long spacings (β'); solid lines, calculated long spacings for β'-2, -3, and -4.

longer and shorter chains. It might be expected that the fit in these cases would be irregular at the chain ends. In the case of $C_{10}C_{18}C_{18}$ agreement is so poor for any basis of calculation that (Δ) values are given only in a footnote.

Beta Prime Form

Diacid Triglycerides.—Agreement between experiment and calculation is better for the beta prime form. There are twenty-seven examples of DCL structure showing agreement within 1.1 Å. and two with (Δ) values of 1.7 and 2.1 Å. For three glycerides, the evidence points to TCL structure with agreement within 1.4 Å. (For $C_{18}C_{12}C_{12}$, the author's data indicate both double and triple structures, of which Malkin reported only the double structure.) Only for the beta prime form are QCL (or doubled DCL) structures obtained. There are three cases whose agreement is within 2 × 0.7 Å. and a single case of poor agreement, 2 × 2.5 Å.

It should be pointed out that the stable forms of the $C_{n-2}C_nC_{n-2}$ glycerides are tabulated as beta prime. Both the data of Malkin[5a] and data of this Laboratory[10] are best interpreted as indicating that these compounds are dimorphous exhibiting alpha and beta prime forms but not beta. Likewise Malkin's so-called beta forms of $C_{12}C_{16}C_{12}$, $C_{14}C_{18}C_{14}$, and $C_{10}C_{18}C_{18}$ seem to be best classified as beta prime.

Triacid Triglycerides.—The designation of forms for the $C_{18}C_{n2}C_{n3}$ glycerides by Filer, *et al.*,[7] was stated by them to be tentative. They simply labelled the lower melting of two forms beta prime and the higher melting beta. Several changes are here made to bring the designations more nearly in line with the recognized short spacing basis for labelling glyceride forms. These designations should perhaps be as tentative as those of Filer, *et al.*,[7] and they lead into as yet untested speculations.

There are five forms recorded as DCL beta prime. Experiment and calculation agree within 0.8 Å. except in the case of $C_{18}C_{16}C_{12}$ which shows a (Δ) value of -2.2 Å.

There are four forms designated as TCL beta prime, two for one compound, $C_{18}C_{14}C_{10}$. Agreement with experiment is within 1.1 Å. except in one case where $(\Delta) = 2.1$ Å. The form of $C_{18}C_{12}C_{10}$ is interpreted to be analogous with the beta prime form of $C_{18}C_{10}C_{10}$. That of $C_{18}C_{16}C_{10}$ is probably analogous with the beta prime form of $C_{10}C_{18}C_{18}$ (listed by Malkin as beta, but here as beta prime). All four of these structures are presumably of the chair type as opposed to the tuning fork type of structure.

The forms of $C_{18}C_{14}C_{10}$, because of alternative possibilities are of special if somewhat speculative interest. They can be interpreted to be of the chair type, but as differing according to whether C_{14} goes with C_{10} or C_{18}, *i.e.*, whether C_{10} or C_{18} is the lone chain (see Fig. 4). An alternative "tuning fork" type structure seems to be ruled out because it is unlikely that C_{10} and C_{18} would line up side by side.

It is assumed simply on the basis of $(\Delta)_T$ values that the lower melting form of $C_{18}C_{14}C_{10}$ is more nearly analogous to the TCL beta prime form of $C_{18}C_{12}C_{10}$, and is therefore β'-3,C_{18} (C_{18} being the lone chain) and the higher melting form corresponds to that of $C_{18}C_{16}C_{10}$, and is therefore β'-3,-C_{16}. Examination of the detailed short spacing data of Filer, *et al.*,[7] gives little support to this association of forms, but does not preclude it in any way.

Beta Form

Diacid Triglycerides.—There are 15 DCL beta structures indicated. Of these eight show (Δ) values of 0.7 or smaller. Seven show values near 2.5 Å. It will be noted that where (Δ) values are large, the glycerides are of the general types $C_{n-2}C_nC_n$ and $C_{n-4}C_nC_n$.

It is of special interest that more than half of the reported beta forms or 18 out of 33 correspond to TCL structure. In these cases $(\Delta_\beta)_T$ has an average value of $+2.9$ Å. Deviations from this value in no case exceed 1.1 Å. It might be that the greater number of glyceryl groups per chain (2 for 3 instead of 1 for 2) accounts for the increased length, or, of course, a real difference in angle of tilt between DCL and TCL structures may be involved.

TCL structures do not appear for beta forms of these diacid glycerides unless one chain is 4 carbons longer than the other and not then for $C_{n-4}C_nC_n$ glycerides.

Of further interest is the absence of any beta form for $C_{12}C_{16}C_{12}$ and $C_{14}C_{18}C_{14}$ which are near relatives of $C_{n-2}C_nC_{n-2}$ glycerides whose stable forms appear to be beta prime. The glyceride $C_{10}C_{14}C_{10}$ does show a beta form but of TCL structure.

Triacid Triglycerides.—Of the forms that are unequivocally beta, all are of TCl structure except those of $C_{18}C_{16}C_{14}$ and $C_{16}C_{14}C_{12}$ which are DCL in analogy to the beta forms of $C_{18}C_{16}C_{16}$ and $C_{16}C_{14}C_{14}$ or $C_{16}C_{16}C_{14}$ and $C_{14}C_{14}C_{12}$ but unlike those of $C_{18}C_{14}C_{14}$ and $C_{18}C_{12}C_{12}$. The glycerides $C_{18}C_{14}C_{16}$ and $C_{16}C_{12}C_{14}$ which are more nearly symmetrical show TCL structure.

The $(\Delta)_T$ values for the TCL structures show an average of $+3.4$ in good agreement with the $+2.9$ value for diacid triglycerides. Perhaps a better relation than (7) for calculating TCL values for beta forms would be

$$(L_\beta)_{T'} = 3C_\beta + 3.0 = 9.0 + 1.138\,N \quad (13)$$

Evidence from Intensities.—The postulated triple (or sextuple) structure for 2-oleyldistearin was supported by approximate agreement of observed relative intensities with those calculated from a very simple model.[9] No adequate intensity data on long spacings for the saturated

---

(10) Quimby and Lutton, unpublished.

glycerides here considered have been reported. To observe such intensities the compound 1-stearyldilaurin was prepared after the manner of Malkin, *et al.*[6d] It was obtained in four polymorphic forms characterized in Table VII.

TABLE VII

FORMS OF 1-STEARYLDILAURIN

	Preparation	Main short spacings	M. p., °C.[a]
α	Melted, chilled 0°	4.13 VS	21.0
β'-2	Melted, crystallized 30 min. 22.0°	4.23 VS, 4.06 S−, 3.77 S+	31.0
β'-3	β'-2, held 10 min. 32°	4.30 M, 4.17 M, 3.94 S	38.0
β	Solvent crystallized 16°, or β'-3 held 1 day 38°	4.60 VS, 3.84 S	44.6

[a] Malkin, ref. 6d, gave m. p's. as 20, 31, 41.5 and 45°.

Two of the 1-stearyldilaurin forms are called "beta prime" in an effort to follow as closely as possible the basis for nomenclature outlined at the beginning of this paper. Long spacing observations distinguish sharply between the so-called "beta prime" forms. A partial record appears in Table VIII.

TABLE VIII

LONG SPACING DATA FOR 1-STEARYLDILAURIN

Form	Magnitude of L. S.	Relative intensity 2nd and 3rd orders	Probable structure type	(Δ) Å.
α	41.7	$3 >> 2$	Double	$(\Delta\alpha)_D = 1.1$
β'-2	38.0 (38.7[a])	$3 \geqq 2$ $(2 << 1)$	Double	$(\Delta\beta')_D = 0.5$
β'-3	55.0	$2 >> 3$	Triple	$(\Delta\beta')_T = -1.25$
β	57.2 (57.0[a])	$2 > 3$	Triple	$(\Delta\beta)_T = 3.8$

[a] Malkin, ref. 6d.

Support for the TCL concept is given in Table VIII. The intensity results, so far as shown, correlate with postulated structure type. It is according to expectations that *a double structure for 1-stearyldilaurin should have a weak second order* and that *a triple structure should have a weak third order*. Attempts to find a more detailed agreement between observed and calculated intensities, according to previous procedure,[9] were unsuccessful. Failure was due, it is thought, to the degree of imperfection of the highly simplified model that was employed.

It is presumed that QCL structure would show intensity distributions similar to those of DCL structures, *i. e.*, weak fourth (instead of second as for DCL) and probably strong sixth (instead of third) order.

Conclusions

The following generalizations apply to the data now available. These can be best understood by reference to Tables VI, for triacid glycerides, and IX, a summary table for diacid triglycerides.

Alpha Forms.—DCL structures prevail among alpha forms. Long spacing values, all indicating DCL, have been reported for compounds having a difference of as much as 6 carbons in chain length, but no values have been reported for a difference of 8 carbons. It is possible that triple structures might occur for the larger difference.

TABLE IX

DESIGNATION OF STRUCTURE LENGTH FOR DIACID TRIGLYCERIDES. A SUMMARY FOR C_{10} TO C_{18}

Triglyceride type	No. compds.	α	β'	β
$C_{n-2}C_nC_n$	4	D[a]	D	D
$C_nC_{n-2}C_n$	4	D	D	D
$C_nC_{n-2}C_{n-2}$	4	D	D	D
$C_{n-2}C_nC_{n-2}$	4	D	D	[d]
$C_{n-4}C_nC_n$	3	D	D	D
$C_nC_{n-4}C_n$	3	D	D, (Q)[c]	T
$C_nC_{n-4}C_{n-4}$	3	(D)[c]	D	T
$C_{n-4}C_nC_{n-4}$	3	(D)[c]	D	[d] (T)[c]
$C_{n-6}C_nC_n$	2	(D)[c]	D), (Q)[c]	(T)[c]
$C_nC_{n-6}C_n$	2	D	(D), (Q)[c]	T
$C_nC_{n-6}C_{n-6}$	2	[D][c]	(D), [T][c]	T
$C_{n-6}C_nC_{n-6}$	2	[b]	(D)[c]	T
Mixed C_{10}-C_{18}	4	(?)[c,e]	T, (Q)[c]	T

[a] D = DCL; Q = QCL; T = TCL. [b] No data. [c] ( ) = one example; [ ] = one example, data of ESL. [d] Probably no form exists. [e] Uncertain from data, (Δ) > 7 Å.

Beta Prime Forms.—DCL structure is the usual one for beta prime forms. However, according to the data of Malkin, *et al.*, and Filer, *et al.*, if there is a chain length difference of as much as eight carbons, TCL structures predominate among beta prime forms of unsymmetrical triglycerides. (The author has found TCL structure with the six carbon difference in 1-stearyldilaurin.) In the case of beta prime only, QCL structures appear to be possible for chain length differences of four or more carbons.

Beta Forms.—Triple structure is much more likely for beta forms but seems not to occur unless there is a chain difference of at least four carbons. For difference of six carbons or greater there are no reported cases of other than TCL beta. The reported behavior of samples of *four carbon difference* can be described by the following four statements:

1. $C_{n_1}C_{n_2}C_{n_3}$, $n_1 > n_3 < n_2$ (or $n_3 > n_1 < n_2$)—Structures are double.
2. $C_{n_1}C_{n_2}C_{n_3}$, $n_1 > n_2 < n_3$—Structures are triple.
3. $C_nC_{n-4}C_{n-4}$—Structures are triple.
4. $C_{n-4}C_nC_{n-4}$—No beta form (beta prime may be stable as for $C_{n-2}C_nC_{n-2}$) except for $C_{10}C_{14}C_{10}$ which shows beta of triple structure.

It is a reasonable hope that, as further experimental evidence rounds out the record on triglyceride polymorphism, an increasing degree of order will become apparent.

Acknowledgment.—The author is indebted to Dr. R. H. Ferguson and others of this laboratory for many helpful discussions of this subject.

Summary

Polymorphic forms of many mixed saturated triglycerides show long spacing values which are abnormally large, that is, they are too large to per-

mit their associated crystal structures to be classified as typical double-chain-length structures. It is shown in this paper that most of these abnormal values can be interpreted as due to triple-chain-length structures analogous to that of the mixed unsaturated C_{18} triglyceride, 2-oleyldistearin. This triple structure presumably arises from a sorting of chains—sorting of short from long chains in the case of mixed saturated triglycerides, in manner similar to the sorting of unsaturated from saturated chains for 2-oleyldistearin.

These considerations lead to the proposal of a new type of molecular configuration in triglyceride crystals, a "chair" type of arrangement for certain unsymmetrical compounds in contrast to the generally accepted "tuning fork" arrangement.

Long spacings corresponding to quadruple-chain length structure have also been noted.

IVORYDALE, OHIO RECEIVED[11] AUGUST 13, 1947

[11] Original manuscript received March 6, 1947.

[CONTRIBUTION FROM THE DIVISION OF MEDICINAL CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

The Skraup Reaction with Acrolein and its Derivatives[1]

BY HARRY L. YALE AND JACK BERNSTEIN

A recent report[2] from these laboratories has described the synthesis of 6-methoxy-8-nitroquinoline in 42.3% yield, by a modified Skraup reaction. Some additional studies on the utilization of this reaction in the preparation of quinoline derivatives have now been completed. The results are summarized in Table I. Method A refers to the reaction conditions previously reported[2] while Method B is a new modification of the Skraup reaction employing acrolein and 85% phosphoric acid with arsenic acid as the oxidizing agent at 100°.

TABLE I

SKRAUP REACTION WITH ACROLEIN AND ITS DERIVATIVES

Amine	Quinoline derivative Yield, % Method A	Method B	M. p., °C. Found
Aniline[a]	Trace	3[b]	199–200
o-Nitroaniline	32	26	87–88
p-Nitroaniline	28	32	147–148
p-Anisidine	13	...	27
p-Bromoaniline	5[b]	5[b]	209
2-Amino-4-nitroanisole	5	59	148–149
2-Amino-5-nitroanisole[c]	30	67	147–148[g]
4-Amino-5-nitroveratrole	36	51	125–126
3-Nitro-4-aminoanisole[d,e,f]	42	60	157–158

[a] Ardashev, *J. Gen. Chem.* (*U. S. S. R.*), **16**, 47 (1946), recently has reported the synthesis of quinoline in poor yield from aniline and acrolein in the presence of sulfuric and hydrochloric acids. [b] Isolated as the picrate. [c] β-Ethoxypropionaldehyde by Method B gave 60% yield. [d] The acetylated amine with acrolein by Method A gave 43% yield. [e] The amine with various acrolein derivatives by Method A gave: with β-ethoxypropionaldehyde, 39%; with β-ethoxypropionaldehyde diethyl acetal, 34%; with acrolein diethyl acetal, 21%. [f] The amine with α-methylacrolein gave the corresponding methyl quinoline in 19% yield by Method A; in 59% yield by Method B, m. p. 173–174°. *Anal.* Calcd. for $C_{11}H_{10}O_3N_2$: C, 60.55; H, 4.59; N, 12.84. Found: C, 60.87; H, 4.64; N, 12.96, 12.76. [g] *Anal.* Calcd. for $C_{10}H_8O_3N_2$: N, 13.72. Found: N, 13.52.

In the preparation of 6-methoxy-8-nitroquinoline by Method B a 60% yield is obtained at 100°, however, at 25°, the yield is 25% and at 65°, 54%; The use of 100% phosphoric acid has only a very slight advantage over 85% acid (65% yield as compared to 60%) but a marked decrease in yields occur with 75% acid (35%) and 50% acid (24%).

Acrolein diethyl acetal, β-ethoxypropionaldehyde and β-ethoxypropionaldehyde diethyl acetal, each of which is capable of yielding acrolein under the modified Skraup conditions, were substituted for acrolein in the reaction with 3-nitro-4-aminoanisole and 2-amino-5-nitroanisole; each gave slightly lower yields of the substituted quinoline.

Acknowledgment.—The authors are indebted to Mr. W. A. Lott for his interest and encouragement. The microanalyses were carried out by Mr. J. F. Alicino.

Experimental

All temperatures are uncorrected.

Method B.—Skraup Reactions with Phosphoric Acid.—A mixture of 33.6 g. (0.2 mole) of 3-nitro-4-aminoanisole and 56.8 g. (0.4 mole) of arsenic acid in 200 ml. of 85% phosphoric acid was placed in a 1-liter, 3-necked flask fitted with a thermometer, dropping funnel, reflux condenser and mercury-sealed stirrer. The reaction mixture was warmed to 100° and 19 ml. (0.3 mole) of acrolein added dropwise with vigorous stirring. The rate of addition was regulated so as to maintain the temperature at 100 ± 2°. After all the acrolein had been added (twenty-five minutes), the reaction mixture was stirred for an additional thirty minutes during which time the temperature was maintained at 100° by warming with an oil-bath. The solution was poured into 800 ml. of water, treated with Hyflo and decolorizing carbon and filtered. The filtrate was made alkaline with aqueous ammonia and the precipitated product filtered. The dried solid was refluxed with 600 ml. of ethyl acetate and decolorizing carbon, filtered, and concentrated until crystallization started. The product weighed 25 g. (60% yield), m. p. 157–158°.

Summary

A modified Skraup reaction with acrolein and α-methylacrolein has been carried out with substituted anilines. The reaction has been extended to include compounds capable of yielding acrolein, *in situ*.

NEW BRUNSWICK, N. J. RECEIVED APRIL 28, 1947

---

[1] Presented before the Division of Organic Chemistry of the American Chemical Society, Atlantic City, N. J., April 15, 1947.

[2] Yale, THIS JOURNAL, **69**, 1230 (1947).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF RICHMOND]

Local Anesthetics. III. Aroyl Derivatives of β-Methyl-β-monoalkylamino Propanols

BY J. STANTON PIERCE, ROBERT D. GANO AND J. M. LUKEMAN

In previous papers[2,3] from this Laboratory, the preparation of alkoxybenzoates of β-monoalkylaminoethanols, β-methyl-β-monoalkylaminopropanols and β-monoalkylaminobutanols was described. Some of the products were found to be effective as local anesthetics. It thus seemed advisable to prepare esters of the above β-secondary aminoalkanols with other aromatic acids. Therefore, we have prepared cinnamates,[4] alkoxycinnamates, hydrocinnamates and alkoxyhydrocinnamates of β-monoalkylaminoethanols, β-methyl-β-monoalkylaminopropanols and β-monoalkylaminobutanols. Usually, the derivatives of β-methyl-β-monoalkylaminopropanols proved to be more readily purified than the derivatives of the other amino alcohols, so the esters of this series were studied more thoroughly than the others and are reported in this paper. Also, phenylurethans of β-methyl-β-monoalkylaminopropanols are being prepared and will be reported in a subsequent publication.

TABLE I

AROYL INTERMEDIATES

Alkyl substituent	Alkoxybenzaldehyde B. p., °C.	Mm.	Yield, %	Alkoxycinnamic acid M. p., °C. (cor.)	Yield, %	Alkoxyhydrocinnamic acid M. p., °C. (cor.)	Yield, %	Alkoxyhydrocinnamoyl chloride B. p. °C.	Mm.	Yield, %
p-Methyl	[y]			169–170[a]	63	101–102[b]	54	165–180[c]	17	81
p-Ethyl	136–139[d]	13	39	191–192[e]	55					
p-*n*-Propyl	154–157[e]	31	60	165–166[e]	61	95–96[f]	88	174–177[g]	31	65
p-*n*-Butyl	183–186[d]	41	66	153–154[e]	51	85–86[h]	92	195–197[i]	26	66
o-Ethyl	[y]			130–131[j]	70	74–75[j]	80	165–170[k,l]	30	49
o-*n*-Butvl	172–175	26	36	87–89[m]	3					
None				[y]		48–49[n]	81	135–140[o]	40	92

[a] Pandya and Vahida, ref. 6. [b] Matsuo, *J. Biol. Chem.*, **35**, 291–296 (1918). [c] Barger and Walpole, *J. Chem. Soc.*, 1724 (1909). [d] Sommelet and Marszak, *Compt. rend.*, **198**, 2256–2258 (1934). [e] Stoermer and Wodarz, *Ber.*, **61B**, 2323–2330 (1928). [f] Calcd.: neut. equiv., 208.1. Found: neut. equiv., 210.2, 211.4. [g] Calcd.: neut. equiv., 113.3. Found: neut. equiv., 111.7, 110.6, 111.5. [h] Calcd.: neut. equiv., 222.1. Found: neut. equiv., 221.8, 220.0, 221.9. [i] Calcd.: neut. equiv., 120.3. Found: neut. equiv., 117.6, 117.4. [j] Paal and Schiedewitz, *Ber.*, **63B**, 766–778 (1930). [k] Neutral equivalent; theory, 106.3. Found: 108.0, 108.9. [l] Most of the samples for the determinations of neutral equivalents were prepared by Doris Colley and analyses were made by Audrey Grubin. [m] Stoermer and Ladewig, *Ber.*, **47**, 1795–1803 (1914). [n] Vavon, *Compt. rend.*, **149**, 999; "Beilstein," **9**, 509. [o] Rupe, *Ann.*, **369**, 319 (1909); "Beilstein," **9**, 511. [y] Purchased.

Experimental

p-**Butoxybenzaldehyde.**—The alkoxybenzaldehydes were made by converting phenolic aldehydes into alkoxybenzaldehydes by the method Cohen and Dudley[5] used for the preparation of alkoxybenzoic acid esters. In a typical synthesis, one half mole each of *p*-hydroxybenzaldehyde and *n*-butyl bromide were added to 200 ml. of absolute alcohol in which 11.5 g. of sodium had been dissolved. After refluxing for six hours, the alcohol was distilled off and the residue was added to 500 ml. of water. Twenty-five grams of salt then was added and the mixture was extracted thrice with ether and the solution was washed with sodium hydroxide solution. The ether then was distilled off and the residue was vacuum distilled.

p-**Methoxycinnamic Acid.**—The alkoxycinnamic acids, when not obtainable from Eastman Kodak Co., were made by condensing alkoxybenzaldehyes with malonic acid, with pyridine as catalyst, as described by Pandya and Vahida.[6] *p*-Methoxycinnamic acid was prepared by heating 0.50 mole each of *p*-methoxybenzaldehyde and malonic acid and 0.20 mole of pyridine in an open tube at 130° for twelve hours. The acid was isolated by dissolving the mixture in dilute sodium hydroxide, filtering, acidifying and filtering with suction. It was purified by recrystallization from aqueous alcohol.

p-**Propoxyhydrocinnamic Acid.**—The alkoxyhydrocinnamic acids were prepared by reduction of the corresponding alkoxycinnamic acids with hydrogen, with Raney nickel as catalyst. *p*-Propoxycinnamic acid (52 g.) was hydrogenated in 200 ml. of alcohol with 3 g. of Raney nickel under 25 lb. pressure in two hours. The alcoholic solution was concentrated to half its volume and hot water was added. On cooling the *p*-propoxyhydrocinnamic acid was precipitated almost quantitatively.

p-**Amyloxycinnamoyl Chloride.**—In a typical preparation of an alkoxycinnamoyl chloride, *p*-amyloxycinnamic acid was refluxed for one hour with four equivalents of thionyl chloride. The excess reagent was removed by evaporation in vacuum with the addition of benzene. The crude *p*-amyloxycinnamoyl chloride was used for condensation with amino alcohol hydrochlorides without further purification.

o-**Ethoxyhydrocinnamoyl Chloride.**—The alkoxyhydrocinnamoyl chlorides were prepared by the action of phosphorus pentachloride on the acids. *o*-Ethoxyhydrocinnamoyl chloride was prepared by refluxing equimolar

---

(1) Acknowledgment for advice is made to Dr. E. Emmet Reid, Research Adviser to the Department of Chemistry of the University of Richmond.

(2) J. Stanton Pierce, J. M. Salsbury and J. M. Fredericksen. THIS JOURNAL, **64**, 1691–1694 (1942).

(3) J. Stanton Pierce, J. M. Salsbury, Walter W. Haden and L. H. Willis, *ibid.*, **64**, 2884–2885 (1942).

(4) David H. Miller, in this Laboratory, prepared β-monobutylaminoethyl cinnamate hydrochloride, m. p. 132–133° (cor.). Calcd. for $C_{15}H_{22}O_2NCl$: Cl, 12.53. Found: 12.77. A. F. Beale, Jr., also carried out some work on this series of esters.

(5) J. B. Cohen and H. W. Dudley, *J. Chem. Soc.*, 1732–1751 (1910).

(6) Pandya and Vahida, *Proc. Indian Acad. Soc.*, **4A**, 134–139 (1936).

TABLE II[a]

β-METHYL-β-MONOALKYLAMINOPROPYL CINNAMATE, HYDROCINNAMATE, ALKOXYCINNAMATE AND ALKOXYHYDROCINNAMATE HYDROCHLORIDES, $ArCOOCH_2C(CH_3)_2NHR \cdot HCl$

Acid (Ar)	R	M. p., °C. (cor.)	Molecular formula	Chlorine, %		Free base			
						B. p.,		Nitrogen, %	
				Calcd.	Found[b]	°C.	Mm.	Calcd.	Found[c]
Cinnamic	*n*-Propyl	164–165	$C_{16}H_{24}O_2NCl$	11.91	12.07				
Cinnamic	*n*-Butyl	162–163	$C_{17}H_{26}O_2NCl$	11.37	11.19				
Cinnamic	*n*-Amyl	112–113	$C_{18}H_{28}O_2NCl$	10.88	11.20				
Hydrocinnamic	*n*-Propyl	178–179	$C_{16}H_{26}O_2NCl$	11.82	12.12	177–178	3.5	5.32	5.50
Hydrocinnamic	*n*-Butyl	116–117	$C_{17}H_{28}O_2NCl$	11.29	11.59				
Hydrocinnamic	*n*-Amyl	85–86	$C_{18}H_{30}O_2NCl$	10.81	10.60	181–188	2.8	4.80	4.42
Hydrocinnamic	*n*-Hexyl	90–91	$C_{19}H_{32}O_2NCl$	10.37	10.05				
p-Methoxycinnamic	Ethyl	189–190	$C_{16}H_{24}O_3NCl$	11.30	11.38				
p-*n*-Butoxycinnamic	*n*-Propyl	144–145	$C_{20}H_{32}O_3NCl$	9.59	10.14				
	n-Butyl	154–155	$C_{21}H_{34}O_3NCl$	9.24	9.18				
o-Ethoxyhydrocinnamic	*n*-Propyl	Oil				193–196	3.0	4.56	4.32
p-*n*-Propoxyhydrocinnamic	*n*-Butyl	95–96	$C_{20}H_{34}O_3NCl$	9.53	9.83				
p-*n*-Butoxyhydrocinnamic	*n*-Butyl	109–111	$C_{21}H_{36}O_3NCl$	9.19	9.57				

[a] In this table are listed only the amino alcohol esters which were satisfactorily purified by recrystallization of the hydrochloride or distillation of the free base. These products are being tested pharmacologically by Dr. H. B. Haag, of the Medical College of Virginia, and will be reported elsewhere. [b] Chloride was determined by the Volhard method as modified by J. R. Caldwell and H. V. Moyer, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38, 39 (1935). [c] Nitrogen was determined by titration of the free base with standard hydrochloric acid, with modified methyl red as indicator.

quantities (0.15 mole) of *o*-ethoxyhydrocinnamic acid and phosphorus pentachloride on a boiling water-bath for one hour. The phosphorus oxychloride was removed by vacuum distillation and the acid chloride was purified by vacuum distillation.

Hydrochlorides of β-Methyl-β-monoalkylaminopropyl Cinnamates, Alkoxycinnamates, Hydrocinnamates and Alkoxyhydrocinnamates.—The β-monoalkylamino-β-methylpropanols were prepared and condensed with aroyl halides by methods described in previous publications[2,3] from this Laboratory. Equimolar quantities of amino alcohol hydrochlorides and aroyl halides were heated on a water-bath from one to six hours, depending on the rate of reaction. In a few cases an oil-bath, heated gradually to 150°, was used. As in previous reports, the reaction mixture was dissolved in water, filtered and extracted with isopropyl ether to remove impurities, and treated with sodium hydroxide to set free the amino alcohol esters. These esters were taken up in isopropyl ether and the hydrochlorides precipitated by addition of dry hydrogen chloride. Various solvents were used for recrystallization but a mixture of anhydrous acetone and anhydrous ether proved satisfactory in most cases. In a few cases in which recrystallization of the hydrochloride of the amino alcohol ester did not take place readily, the free base was purified by vacuum distillation.

Summary

The hydrochlorides of a series of β-methyl-β-monoalkylaminopropyl cinnamates, hydrocinnamates, alkoxycinnamates and alkoxyhydrocinnamates have been prepared and described.

RICHMOND, VA. RECEIVED AUGUST 25, 1947

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

The Occurrence of Rutin in a Wild Cherry, *Prunus melanocarpa* (A. Nels.) Rydb.

BY JAMES F. COUCH

In connection with the researches being conducted at this Laboratory[2] on the production of rutin for medicinal use a species of wild cherry was examined with the result that significant quantities of rutin were found in the leaves. This is the first species of the genus *Prunus* from which this glucoside has been isolated, although the presence of other flavonol glucosides in different species of the genus has been reported.

Rochleder[3] found a trace of a quercetin glucoside in *P. cerasus* L., and Finnemore[4] isolated quercimeritrin from a commercial bark probably of *P. emarginata* Walp. Power and Moore[5] obtained less than 0.1% of a quercetin glucoside which they named serotrin from the leaves of *P. serotina* Ehrh. This substance melted at the same temperature as quercimeritrin but on comparison with an authentic sample the authors concluded that it was a different substance.

Rutin has now been found in the leaves of "black chokecherry" (*P. melanocarpa* (A. Nels.) Rydb.) in substantial quantities. This species ranges from Alberta and British Columbia southward to California and New Mexico[6] in accessible

---

(1) One of the Laboratories of the Bureau of Agricultural & Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) J. F. Couch, C. F. Krewson, J. Naghski and M. J. Copley, *Bur. Agri. Ind. Chem.*, AIC-115, April, 1946. [Processed.]

(3) F. Rochleder, *S-Ber. Wien. Acad.*, Abt. II, **59**, 219–247 (1869).

(4) H. Finnemore, *Pharm. J.*, **85**, 604–607 (1910).

(5) F. B. Power and C. W. Moore, *J. Chem. Soc.*, **97**, 1099–1112 (1910).

(6) I. Tidestrom, *Flora of Utah and Nevada*, "U. S. Natl. Herbarium," Vol. 25, Gov't. Printing Office, Washington, D. C., 1925, p. 285.

localities and may prove to be a commercial source of the drug. Several samples of leaves collected at different stages of growth and at two different altitudes were examined. The leaves were collected in 1936 and 1937 near the Salina Experiment Station, Salina, Utah, in connection with studies on poisoning of livestock by cyanogenetic plants. They were air dried and had been stored in the laboratory for ten years. Crude rutin was obtained from a composite lot of these samples in 1937 but was not investigated further at that time. Analyses of the samples are in Table I.

TABLE I

Lot no.	Date collected, 1936	Approximate altitude, ft.	Moisture,[7] %	Rutin,[7] % mfb
47-7	June 15	8000	6.00	1.57
47-6	Aug. 17	8000	7.20	1.44
47-9	Aug. 20	8500	6.15	3.13
47-10	Composite	8000	7.60	1.63
	1937			
47-8	June 17	8500	6.40	3.88

The figures indicate a considerably greater content of rutin in leaves collected at the higher altitude but do not show much difference between young (June collections) and older (August) leaves.

Experimental

A quantity of the air-dried leaves (6,646 g.) was coarsely powdered, moistened with alcohol and extracted in a glass percolator with alcohol. The solvent was distilled from the percolate and the greenish residue was thoroughly extracted with boiling distilled water. The water solution was filtered from the fatty materials and allowed to cool. After standing several days a considerable quantity of brown flocculent material separated. This was filtered and redissolved in boiling water. The filtered solution deposited the substance on cooling. The crude rutin (24.0 g.) was greenish in color and contained 88% of the pure glucoside. This was bottled and preserved for several years. The rutin (2 g.) was purified by dissolving in alcohol (50 ml.), filtering from some amorphous matter, and diluting to 500 ml. with water containing 2 ml. of concentrated hydrochloric acid. The rutin which slowly precipitated during the ensuing twenty-four hours was of bright yellow color and crystallized in the characteristic microscopic fan-shaped bundles of needles. It was filtered, washed with water and dried at 110°. The plastic range ("melting point") was 172–174° raised by recrystallization from alcohol and from water to 190–192°. A spectrophotometric examination by W. L. Porter identified the substance as rutin by the following constants: The ultraviolet absorption spectrum of the anhydrous sample was characterized by absorption maxima near 3627 and 2577 Å., specific extinction coefficient, 32.6 liter g.$^{-1}$ cm.$^{-1}$ at 3627 Å., extinction ratio of 0.875 for wave lengths 3752 and 3627 Å. The corresponding figures for authentic rutin are: 3627 and 2577 Å., 32.5 at 3627 Å. and 0.875.

Anal.[8] Calcd. for $C_{27}H_{30}O_{16}$: C, 53.11; H, 4.95. Found: C, 52.92; H, 4.99.

Summary

Rutin has been isolated in significant quantities from black chokecherry, a species native to the mountain region of the western United States.

PHILADELPHIA 18, PA. RECEIVED JULY 23, 1947

---

(7) Analyses made by C. S. Fenske, Jr., of this Laboratory.

(8) Analysis by C. L. Ogg.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Isolation of Rutin from a Citrus Hybrid

BY C. F. KREWSON AND J. F. COUCH

The discovery of Szent-Györgyi and co-workers[2] that citrus fruits contain a substance not identical with hesperidin or any other identified constituent of these fruits has led to much chemical and physiological research in an endeavor to isolate and characterize the active compound, which has been termed vitamin P.[3] Investigations begun in 1943 have established the fact that rutin, a flavonol glucoside present in some forty species of plants, has the physiological activity attributed to vitamin P.[4] The question whether the activity reported from citrus fruits which may be due to the presence of rutin has been investigated in this Laboratory. Valencia oranges, grapefruit and both green and ripe lemons, reported to be most active of the citrus fruits with respect to vitamin P activity, have been examined without revealing the presence of rutin. These have been subjected to three extraction procedures: the usual alcoholic technique,[5] a special process involving enzymatic hydrolysis of pectin, and an alkali extraction. In no case was rutin found by the alcoholic extraction. In the instance of a hybrid fruit, rutin was found by the other two processes, the alkali extraction described below being more effective.

Two years ago we obtained from the orchard of A. C. Krewson, Plymouth, Florida, specimens of a citrus fruit of the size and form of grapefruit but with a distinct odor and flavor of the lemon. The

---

(1) One of the Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) P. L. Armentano, *et al.*, *Deut. Med. Woch.*, **62**, 1326–1328 (1936).

(3) V. Bruckner and A. Szent-Györgyi, *Nature*, **138**, 1057 (1936).

(4) J. Q. Griffith, Jr., J. F. Couch and M. A. Lindauer, *Proc. Soc. Exptl. Biol. Med.*, **55**, 228–229 (1944); J. F. Couch, C. F. Krewson, J. Naghski and M. J. Copley, U. S. Department of Agriculture, Mimeograph Circular AIC-115, April, 1946.

(5) J. F. Couch and C. F. Krewson, U. S. Department of Agriculture Mimeograph Circular AIC-52, July, 1944.

juice of these fruits served to make excellent "lemonade." The hybrid has been tentatively identified by F. E. Gardner of the Bureau of Plant Industry, Soils, and Agricultural Engineering, United States Department of Agriculture, as a cross between grapefruit and Satsuma orange, produced during experiments on cross-breeding citrus fruits and named Satsumelo.

Examination of the peel of these fruits finally resulted in the isolation of significant quantities of rutin after the usual alcoholic extraction had been unsuccessful. Exhaustive maceration with alkalies extracted the constituent slowly. Rind of green fruits picked January 3, 1946, gave 3.2% of rutin (moisture-free basis), whereas the rind of ripe fruit picked the previous year, February 10, 1945, gave approximately 0.9%, and that of overripe fruit picked April 28, 1945, yielded about 0.1% of rutin.

These data are consistent with the facts obtained with other rutiniferous plants[6] that immature tissues, plants or fruits contain more rutin than more mature tissues. Rutin appears to be associated with the most actively metabolizing portions of the plant, a fact in harmony with Szent-Györgyi's view that the flavonols form part of the oxidation–reduction chain in the plant cell.[7]

No trace of rutin was found, in repeated attempts both by alcoholic and alkali extraction techniques, in the peeled fruit, the pressed juice of the peeled fruit, the pulp of the peeled fruit, the fermented whole fruit, or in the air-dried leaves of the tree from which the fruits were obtained.

Experimental

The minced peel of the hybrid (258.5 g.) was mixed with 757 ml. of distilled water and sufficient 3 *N* sodium hydroxide solution to bring the mixture to a *p*H of 11, and stirred for one hour. The residue after filtration was again macerated with sodium hydroxide solution for one hour and filtered. This treatment was repeated twice more. The filtrates were separately adjusted to *p*H 4.5 with hydrochloric acid and allowed to stand in a refrigerator. The first two extracts yielded 1.50 and 0.36 g. of rutin, respectively, a total of 1.86 g. or 3.23% of the moisture-free material. The substance recrystallized from boiling water gave a plastic range ("melting point") of 185.5 to 187.5° (cor.). Spectrophotometric examination of the material after recrystallization from absolute ethanol revealed absorption maxima at wave lengths 2575 and 3625 Å. with a specific extinction coefficient of 32.74 at 3625 Å. Purified rutin from buckwheat, after recrystallization from absolute ethanol, shows maxima at the same wave lengths, with a coefficient of 32.55 at 3625 Å.[8]

A portion of the rutin was further purified by solution in alcohol and recrystallization from water.

Anal.[9] Calcd. for $C_{27}H_{30}O_{16}$: C, 53.11; H, 4.95. Found: C, 53.07; H, 5.11.

Hydrolysis of Rutin.—The purified glucoside (0.200 g.) was heated one hour with 8 ml. of 5% sulfuric acid and cooled overnight. The precipitated quercetin was filtered, washed and recrystallized from ethanol. When it was dried at 110° it melted at 313–313.5°.

Anal.[9] Calcd. for $C_{15}H_{10}O_6$: C, 59.61; H, 3.34. Found: C, 59.57; H, 3.45.

The pentaacetate melted at 194–196° and showed no depression when mixed with authentic quercetin pentaacetate. The carbohydrates produced by hydrolysis of the rutin were identified as rhamnose and glucose by the usual methods.

Summary

Rutin has been isolated from the rind of Satsumelo, a hybrid citrus fruit resulting from a cross between grapefruit and Satsuma orange.

PHILADELPHIA 18, PA. RECEIVED AUGUST 9, 1947

---

[6] J. F. Couch, J. Naghski and C. F. Krewson, *Science*, **103**, 197–198 (1946).

[7] S. Szent-Györgyi, "Studies on Biological Oxidation and Some of Its Catalysts," Barth, Leipzig, 1937, pp. 67–98.

[8] The specific extinction coefficient of purified rutin from buckwheat previously reported (THIS JOURNAL, **69**, 572–573 (1947)), 31.9 liter g.$^{-1}$ cm.$^{-1}$, is raised to 33.22 by addition of a small quantity of acetic acid to the rutin solution prepared for spectrophotometric examination. The addition of this acid increases the coefficient but renders it insensitive to accidental traces of alkali present on the glassware or in the solvent. See W. L. Porter, B. A. Brice, M. J. Copley and J. F. Couch, U. S. Department of Agriculture Mimeograph Circular AIC-159, July, 1946, "Tentative Spectrophotometric Method for the Determination of Rutin in Various Preparations." Recrystallization of the purified buckwheat rutin from absolute ethanol, followed by application of the modified procedure, results in a specific extinction coefficient of 32.55 at 3625 Å., with an unchanged extinction ratio of 0.875 ± 0.004 for wave lengths 3750 and 3625 Å. We are indebted to W. L. Porter for the spectrophotometric work.

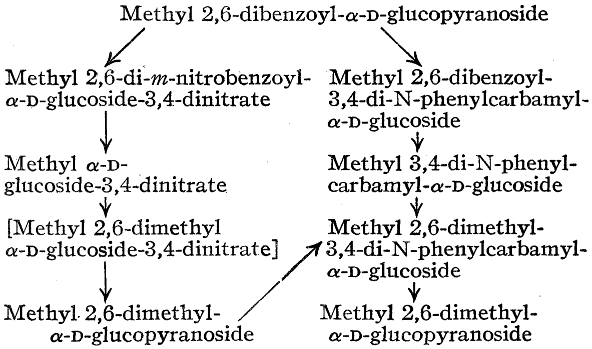
[9] Analyses by C. L. Ogg of this Laboratory.

[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

Methyl 2,6-Dimethyl-α-D-glucopyranoside

BY RICHARD E. REEVES

In connection with current work an alkali-stable glucopyranoside substituted in positions 2 and 6 was desired; accordingly, the preparation of methyl 2,6-dimethyl-α-D-glucoside was undertaken. The β-form of this glucoside has been prepared by Bell and Synge.[1a] The α-glucoside was obtained by two different routes, as shown in the diagram below. All substances except the starting material are previously unreported; the compound enclosed in brackets was not characterized.



The glucoside has not yet been obtained in the crystalline state, but the preparations from the two series exhibited almost identical rotatory values and gave satisfactory analyses. The nature of the reactions employed allows the belief that the α-pyranoside structure persisted throughout both series. This view is supported by the high positive rotation of the final glucoside, and by its quantitative reconversion to the crystalline methyl 2,6-dimethyl-3,4-di-N-phenylcarbamyl-α-D-glucoside.

The nitrate series of reactions is of significance with regard to the assignment of structure to the final product because, as Bell and Synge[2] have pointed out, nitrate groups do not migrate.

Nitration of methyl 2,6-dibenzoyl-α-D-glucopyranoside at positions 3 and 4 proceeded smoothly with simultaneous nitration of the benzoyl radicals. The di-m-nitrobenzoyl derivative, obtained in fair yield, was a satisfactory intermediate.

N-Phenylcarbamyl derivatives (phenylurethans, carbanilates) are extensively used to characterize alcohols, and they have been so employed in the sugar series.[3] They have also been used by Hearon, Hiatt and Fordyce[4] to block certain positions, taking advantage of their relatively great resistance against acid catalyzed alcoholysis to allow the selective removal of acyl radicals at other positions.

Methyl 2,6-dimethyl-α-D-glucopyranoside in cuprammonium hydroxide solution was found to be strongly dextrorotatory as expected from the study of other cuprammonium-glucoside complexes. The rotatory shift (sp. rot. cupra − sp. rot, water) was approximately +950°. The corresponding value previously found[5] for methyl 2-methyl-β-D-glucopyranoside (+1054°) was attributed to complex formation at the 3-4 position although in that instance there was some uncertainty due to the presence of a free hydroxyl group at position 6. The present glucoside, having the 6 position blocked by a methyl group, allows no doubt as to its site of complex formation being the 3-4 position. It is intended to discuss in a later communication the significance of the properties of various cuprammonium–glycoside complexes with regard to conformation of the pyranoside ring.

Experimental

All melting points were observed between crossed polaroids by means of a Fisher–Johns melting point apparatus, drilled to allow the passage of a 1 mm. beam of light.

Except where the mercury blue line is specifically mentioned, the optical rotations were measured with the sodium D line. The mercury blue line (436 mμ) was isolated for aqueous solutions by Corning filters 511 and 038; for cuprammonium solutions, by filter 038 only. All rotations were measured at 25°.

The cuprammonium contained 15 g. copper, 240 g. ammonia and 1 g. glycerol per liter.

Methyl 2,6-dibenzoyl-α-D-glucopyranoside, m. p. 141.5–142°, was prepared in small lots by the method of Lieser and Schweizer.[6]

The Nitrate Series

Methyl **2,6-*Di-m*-nitrobenzoyl-α-D-glucoside 3,4-Dinitrate.**—Methyl 2,6-dibenzoyl-α-D-glucopyranoside, 1.4 g., was dissolved in a mixture of 49 ml. of chloroform and 21 ml. of 100% nitric acid, previously cooled to 0°. The solution was kept for fifteen minutes in an ice-bath after which ice water was added and the chloroform layer extracted, washed with ice water, cold potassium bicarbonate solution, water and dried over calcium chloride. Removal of solvent *in vacuo* left a sirup which yielded 1.6 g. of crystals from alcohol. After two recrystallizations from alcohol the product melted at 148–149°, sp. rot. +167° ± 3° ($CHCl_3$, *c*, 1.1).

Anal. Calcd. for $C_{21}H_{18}O_{16}N_4$ (582.38): C, 43.31; H, 3.11; N, 9.62. Found: C, 43.18, 43.25; H, 3.11, 3.20; N, 9.52, 9.55 (micro Dumas).

Methyl α-D-Glucoside 3,4-Dinitrate.—Two grams of the substance described above was dissolved in 6 ml. of absolute methanol containing 2.5 mg. of sodium. The solution turned slightly yellow and deposited crystals within a very short time. When crystallization appeared

---

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

[1a] D. J. Bell and R. L. M. Synge, *J. Chem. Soc.*, 833–836 (1938).

[2] D. J. Bell and R. L. M. Synge, *ibid.*, 836–838 (1938).

[3] M. L. Wolfrom and D. E. Pletcher, THIS JOURNAL, **62**, 1151–1153 (1940).

[4] W. M. Hearon, G. D. Hiatt and C. R. Fordyce, *ibid.*, **66**, 995–997 (1944).

[5] R. E. Reeves, *J. Biol. Chem.*, **154**, 49–55 (1944).

[6] Th. Lieser and R. Schweizer, *Ann.*, **519**, 271–278 (1935).

to be complete the solution was filtered and the crystals rinsed with cold methanol. After drying in a vacuum desiccator the crystals weighed 935 mg. and melted at 77–78°, alone or mixed with an authentic sample of methyl *m*-nitrobenzoate (m. 77–78°). The yield amounts to 74% of the theoretical amount of methyl *m*-nitrobenzoate.

The combined filtrate and washings were acidified with a trace of glacial acetic acid. Removal of solvent in a current of air left 1.3 g. of crystals. Two recrystallizations from benzene gave 0.86 g. of product, m. p. 132–134°, sp. rot. +183° ± 4° (methanol, *c*, 0.85).

Anal. Calcd. for $C_7H_{12}O_{10}N_2$ (284.18): C, 29.58; H, 4.27; N, 9.86. Found: C, 30.08, 29.85; H, 4.42, 4.33; N, 9.46, 9.52 (micro Dumas).

Methyl 2,6-Dimethyl-α-D-glucopyranoside.—The dinitrate described above, 1.075 g., was dissolved in 25 ml. of methyl iodide and refluxed with 5 g. of silver oxide and 2 g. of anhydrous calcium sulfate for eight hours. The solution was then filtered, the salts washed with boiling chloroform, and the combined filtrate and washings evaporated to dryness *in vacuo*. The sirupy product, weighing 1.09 g., consisted largely of methyl 2,6-dimethyl-α-D-glucoside 3,4-dinitrate.

Anal. Calculated for $C_9H_{16}O_{10}N_2$ (312.24): OCH_3, 29.82. Found: OCH_3, 31.1.

Since the above sirup did not seem amenable to further purification the entire sample was dissolved in 10 ml. of glacial acetic acid and warmed with iron dust and a few magnesium turnings. A violent reaction occurred and nitrogen oxide gases were evolved. In a few moments the diphenylamine test for nitrate became negative and the solution was then filtered. The salts were extracted with acetone and acetic acid. The filtrate and extracts were concentrated to dryness *in vacuo* and the residue was once taken to dryness with water, and once with absolute alcohol. The residue was extracted with warm acetone, filtered, and the filtrate transferred to a micro-distillation outfit. The solvent was removed in a current of air and the residue was distilled at 130–140° and approximately 0.01 mm. pressure. The distillate amounted to 333 mg. It was a viscous, almost colorless, sirup. Its specific rotation was as follows: D line +156° ± 2° (water, *c*, 1.44); Hg blue line +285° ± 3° (water, *c*, 1.44); Hg blue line +1230° ± 12° (cupra., *c*, 0.45). The substance was very hygroscopic; it was dried at 55° in vacuum over phosphorus pentoxide for analysis. The analytical values are in agreement with those required for a methyl dimethylglucoside.

Anal. Calcd. for $C_9H_{18}O_6$ (222.23): C, 48.64; H, 8.16; OCH_3, 41.89. Found: C, 48.12, 48.19; H, 8.22, 8.21; OCH_3, 41.7.

The N-Phenylcarbamate Series

Methyl 2,6-Dibenzoyl-3,4-di-N-phenylcarbamyl-α-D-glucoside.—Methyl 2,6-dibenzoyl-α-D-glucopyranoside, 4.02 g. was dissolved in 20 ml. of anhydrous pyridine and 40 ml. of anhydrous benzene. Five ml. (100% excess) of freshly distilled phenyl isocyanate was added and the solution was refluxed one and one-half hours, being protected from atmospheric moisture with a calcium chloride tube. The solvent and excess reagent were removed *in vacuo*. The residue was dissolved in alcohol and yielded crystals on cooling. After two recrystallizations from alcohol, 3 g. of product, m. p. was 202–203°, sp. rot. +103° ± 1° ($CHCl_3$, *c*, 2.8), was obtained.

Anal. Calcd. for $C_{35}H_{32}O_{10}N_2$ (640.63); C, 65.62; H, 5.04; N, 4.37. Found: C, 65.71, 65.61; H, 5.15, 5.05; N, 4.14, 4.33 (micro Kjeldahl).

Methyl 3,4-Di-N-phenylcarbamyl-α-D-glucoside.—Preliminary experiments indicated that the benzoyl groups could not be selectively saponified from the preceding compound using alcoholic alkali solutions. However, the following procedure was successfully employed: Two and five-tenths grams of the above substance was placed in a glass-stoppered flask with 20 ml. of absolute methanol containing 1% anhydrous hydrogen chloride. The flask was kept in an incubator at 40° with occasional shaking. After five days the substance had passed into solution, and after two more days the hydrogen chloride was removed with a cold solution of ethereal diazomethane, and the solvents removed *in vacuo*. The residue recrystallized from alcohol, melted at 213–218°, sp. rot. +128° ± 4° (acetone, *c*, 0.52), weighed 0.9 g.

Anal. Calculated for $C_{21}H_{24}O_8N_2$ (432.42): C, 58.33; H, 5.59; N, 6.48. Found: C, 58.42, 58.13; H, 5.54, 5.59; N, 6.38, 6.48 (micro Dumas).

Methyl 2,6-Dimethyl-3,4-di-N-phenylcarbamyl-α-D-glucoside.—Five and three-tenths grams of the preceding substance was dissolved in 50 ml. of alcohol-free acetone and 50 ml. of methyl iodide. The solution was stirred under reflux at 40–45° with 5 g. of silver oxide and 2 g. of anhydrous calcium sulfate. Fifteen grams more silver oxide was added during the reaction, which was allowed to continue for twenty-two hours. The mixture was filtered and the salts washed with boiling chloroform. The solvents were removed and the residue, dissolved in alcohol, slowly deposited 1.2 g. of crystals, m. p. 225–227. After recrystallization to constant m. p. from dilute alcohol the substance melted at 235–236°, and showed a sp. rot. of +87° ± 2° ($CHCl_3$, *c*, 0.72).

Anal. Calcd. for $C_{23}H_{28}O_8N_2$ (460.47): C, 59.99; H, 6.13; N, 6.09; OCH_3, 20.22. Found: C, 59.80, 59.88; H, 6.10, 6.09; N, 6.35, 6.08 (micro Dumas); OCH_3, 20.15.

Methyl 2,6-Dimethyl-α-D-glucopyranoside.—Two hundred and thirty mg. of the preceding product dissolved in alcohol was warmed under reflux. On adding 10 ml. of 0.39 *N* barium hydroxide solution through the condenser a white precipitate gradually formed. Refluxing was continued for four hours; then carbon dioxide was passed through the solution to remove the excess barium. The precipitate was removed by filtration and the solution evaporated to dryness *in vacuo*. The residue, amounting to 106 mg., was transferred to a micro distillation outfit and distilled at 120–140° at approximately 0.01 mm. The product, a colorless, viscous, sirup, showed approximately the same properties as the sample prepared from the nitrate series: sp. rot. D line, +152° ± 2° (water, *c*, 1.57); Hg blue line, +1240° ± 12° (cupra., *c*, 0.52).

Anal. Calcd. for $C_9H_{18}O_6$ (222.23): OCH_3, 41.89. Found: OCH_3, 41.22.

Di-N-phenylcarbamate of Methyl 2,6-Dimethyl-α-D-glucoside from the Nitrate Series.—Sixty-three mg. of glucoside was dissolved in 1.5 ml. of dry pyridine and 1 ml. of dry benzene containing 220 mg. of phenyl isocyanate. The solution was sealed in a small glass tube and kept at 100° for twenty hours. The tube was then cooled, opened and the volatile material removed under vacuum. The crystalline residue was treated with chloroform, filtered and the filtrate made up to 4-ml. volume. This solution showed an optical rotation of +1.45° (0.5 dm.) corresponding to 133 mg. of product of sp. rot. +87°. (The theoretical yield would be 131 mg.) The chloroform was removed in a current of air; and after two recrystallizations from dilute alcohol, 37 mg. of crystals m. p. 233–235°, sp. rot. +95° ± 3° ($CHCl_3$, *c*, 0.80), was obtained. The melting point of this preparation was not depressed when mixed with the corresponding substance from the N-phenylcarbamate series.

Acknowledgments.—The micro carbon–hydrogen and Dumas nitrogen analyses were performed by Lawrence E. Brown, and the Zeisel methoxyl analyses by L. W. Mazzeno, Jr.

Summary

Methyl 2,6-dimethyl-α-D-glucopyranoside has been synthesized by two different methods. Its optical rotations in water and cuprammonium hydroxide solution are given.

NEW ORLEANS, LOUISIANA RECEIVED AUGUST 9, 1947

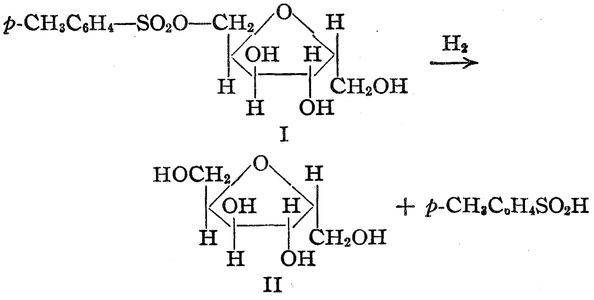
[CONTRIBUTION FROM THE ORGANIC CHEMICAL INSTITUTE OF THE HUNGARIAN UNIVERSITY "BOLYAI" AT CLUJ-KOLOZSVÁR, RUMANIA]

Alcohols of the Sugar Group. IV. 2,5-Anhydro-L-iditol

BY L. VARGHA, T. PUSKÁS AND E. NAGY

Experiments reported in Part III[1] of this series have resulted in the elucidation of the structure and configuration of a monotoluenesulfonyl anhydrohexitol[2] which has been shown to represent the 1-*p*-toluenesulfonyl 2,5-anhydro-L-iditol (I). However, we have been unable to prepare the 2,5-anhydro-L-iditol from this derivative by hydrolysis, or from the 1,6-diiodo derivative in the usual manner. In the meantime Professor Freudenberg has kindly called our attention to one of his earlier experiments in which he succeeded in producing diacetone-glucose from its 3-*p*-toluenesulfonyl derivative by reductive scission with sodium amalgam.[3] Since we have been interested in the elimination of the *p*-toluenesulfonyl group from its esters, we applied this method not only to (I) but also to the *p*-toluenesulfonyl esters of other polyhydric alcohols.

By treatment of (I) in dilute alcohol with sodium amalgam we obtained, beside the sodium salt of *p*-toluenesulfinic acid, a sirupy product, the acetate of which was separated into two fractions by distillation under diminished pressure. On saponification of the higher boiling fraction, a uniform, crystalline substance was obtained which proved to be the expected 2,5-anhydro-L-iditol (II). The lower boiling fraction, probably a dianhydrohexitol according to the analytical data, could not be brought to crystallization even after removal of its acetyl residues.



I

II

We also carried out, in a similar way, the reduction of the 6-*p*-toluenesulfonyl[4] and 5,6-di-*p*-toluenesulfonyl 1,2-monoacetone-glucofuranose,[5] respectively. From the former compound, beside a sirupy substance of unknown structure, crystalline 1,2-monoacetone-glucofuranose was obtained in about 40% yield, whereas the 5,6-di-*p*-toluenesulfonyl compound gave rise to 5-*p*-toluenesulfonyl 3,6-anhydro-1,2-monoacetone-glucofuranose[6] and a small quantity of an unidentified product.

From these results it can be concluded that although the reductive cleavage of the *p*-toluenesulfonyl esters into alcohols and *p*-toluenesulfinic acid often can be carried out without difficulty, yet, simultaneously, as undesirable by-products, anhydro compounds may also form by splitting out of *p*-toluenesulfonic acid from the esters. The occurrence of the latter process cannot be avoided by carrying out the reduction in approximately neutral medium as by passing carbon dioxide gas through the solution. Under such experimental conditions 6-*p*-toluenesulfonyl 1,2-monoacetone-glucofuranose gave 5,6-anhydro-1,2-monoacetone-glucofuranose[7] in surprisingly good yield (70%), while the 5,6-di-*p*-toluenesulfonyl 1,2-monoacetone-glucofuranose remained unchanged.

Experimental

Reduction of 1-*p*-Toluenesulfonyl 2,5-Anhydro-L-iditol by Sodium Amalgam. 2,5-Anhydro-L-iditol Tetraacetate and Dianhydro-hexitol Diacetate.—Ten grams of 1-*p*-toluenesulfonyl 2,5-anhydro-L-iditol (I) in 160 cc. of 80% alcohol was stirred three days at 15° with 200 g. of 2% sodium amalgam. The solution was then neutralized with carbon dioxide, filtered from the precipitated sodium bicarbonate and evaporated to a residue which was extracted with 30 cc. of pyridine. From the aqueous solution of the insoluble part crystalline *p*-toluenesulfinic acid (m. p. 88°) was isolated by treatment with strong sulfuric acid. Concentration of the pyridine solution *in vacuo* yielded a thick sirup (4.6 g.) which was acetylated by treatment overnight with 20 cc. of acetic anhydride and 30 cc. of pyridine at room temperature. After removal of the pyridine *in vacuo* the residue was dissolved in chloroform, the solution treated with water, dried, then the solvent evaporated. The sirupy substance was submitted to fractionate distillation under 0.003 mm. pressure. The first fraction distilled at 108–124° bath temperature, the second one at 124–140°; yields, 1.8 and 3.3 g., respectively.

According to analytical data, the first fraction represents a dianhydro-hexitol diacetate. It is a clear sirup, easily soluble in organic solvents, but almost insoluble in water or petroleum ether; $[\alpha]^{20}_D$ +5.15° in chloroform solution (*c*, 2.329).

Anal. Calcd. for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.14; H, 6.25.

The second fraction shows similar solubility behavior and, according to the analytical data, consists of 2,5-anhydro-L-iditol tetraacetate; $[\alpha]^{20}_D$ −13.2° in chloroform solution (*c*, 1.9556).

Anal. Calcd. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.06. Found: C, 50.97; H, 6.52.

2,5-Anhydro-L-iditol (II).—After addition of 11 g. of barium hydroxide dissolved in 130 cc. of water to the solution of 3.3 g. of 2,5-anhydro-L-iditol tetraacetate in 20 cc. of alcohol, the mixture was shaken on the machine for twenty-four hours. Then the excess alkali was neutralized with carbon dioxide, the barium carbonate filtered off, and the soluted barium precipitated by the equiv-

---

[1] Vargha and Puskás, *Ber.*, **76**, 859 (1943).

[2] Vargha, *ibid.*, **68**, 1377 (1935).

[3] Freudenberg and Brauns, *ibid.*, **55**, 3238 (1922). We wish to thank Prof. Freudenberg for this information.

[4] Ohle and Spencker, *ibid.*, **59**, 1836 (1926).

[5] Ohle and Dickhauser, *ibid.*, **58**, 2593 (1925).

[6] Ohle, Vargha and Erlbach, *ibid.*, **61**, 1211 (1928).

[7] Ohle and Vargha, *ibid.*, **62**, 2345 (1929).

alent amount of sulfuric acid. After filtration the solution was concentrated *in vacuo*, the remaining sirup dissolved in a little absolute alcohol and the solution mixed with absolute ether to incipient turbidity. The substance crystallized at 0° in colorless prisms which were easily soluble in water; yield, 1.1 g., m. p. 111–113°; $[\alpha]^{20}_D$ +12.6° in aqueous solution (*c*, 2.525).

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.94; H, 7.55.

Dianhydro-hexitol.—The solution of 1.8 g. of dianhydrohexitol diacetate in 12 cc. of alcohol was shaken for twenty-four hours with 7 g. of barium hydroxide in 80 cc. of water. After removal of the barium as described above and concentration of the solution *in vacuo*, there was obtained a sirup which was easily soluble in water and in alcohol; $[\alpha]^{20}_D$ +12.3° in aqueous solution (*c*, 3.079).

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.80. Found: C, 49.63; H, 7.02.

Reduction of the 6-*p*-Toluenesulfonyl 1,2-Acetone-glucofuranose by Sodium Amalgam.—Two grams of the substance was stirred at 15° for twenty-four hours in 30 cc. of 80% alcohol with 25 g. of 2% sodium amalgam. After neutralization and removal of the barium as described above, the solution was concentrated *in vacuo* and the residue extracted with ethyl acetate. The insoluble portion proved to be the sodium salt of *p*-toluenesulfinic acid. From its aqueous solution the crystalline acid with m. p. 88° was isolated. From the concentrated ethyl acetate solution the 1,2-acetone-glucofuranose with m. p. 158° crystallized; yield, 0.5 g. After evaporation of the mother liquid an oily residue (0.6 g.) remained.

The reduction was also carried out by simultaneous introduction of carbon dioxide gas. In this case a colorless substance was isolated which showed, after recrystallization from benzene, all the properties of the 5,6-anhydro-1,2-acetone-glucofuranose; yield, 70%, m. p. 132°. The crystals had $[\alpha]^{20}_D$ −26.4° in aqueous solution (*c*, 3.025).

Reduction of the 5,6-Di-*p*-toluenesulfonyl 1,2-Acetone-glucofuranose by Sodium Amalgam.—The reduction was carried out as described above. From the concentrated ethyl acetate extract a colorless substance was isolated which proved to be identical with 5-*p*-toluenesulfonyl 3,6-anhydro-1,2-acetone-glucofuranose; m. p. alone and also in admixture with an authentic sample 133°. The ethyl acetate mother liquor contained a small quantity of an oily product. When the reduction was carried out in the presence of carbon dioxide gas the starting material was recovered almost quantitatively.

Summary

The reductive cleavage of several *p*-toluenesulfonyl polyhydric alcohols by sodium amalgam has been investigated under various experimental conditions.

It has been found that the reaction, in consequence of reduction, often yields the corresponding polyhydric alcohols and *p*-toluenesulfinic acid, but simultaneously, as products of a competitive reaction, anhydro compounds may also form by splitting out of *p*-toluenesulfonic acid.

By treatment of 1-*p*-toluenesulfonyl 2,5-anhydro-L-iditol with sodium amalgam 2,5-anhydro-L-iditol in crystalline state has been prepared.

Cluj-Kolozsvár, Rumania Received January 31, 1947

[Contribution from the Chemical Laboratory of the University of Kansas]

Addition Compounds of Sulfur Dioxide with Three Isomeric Lutidines[1]

By Henry A. Hoffman and Calvin A. VanderWerf

The interesting results obtained in a recent study[2] of the sulfur dioxide–pyridine and the three sulfur dioxide–picoline systems suggested the present investigation, which comprises temperature–composition equilibria studies of the three systems consisting of sulfur dioxide with each of the bases, 2,6-lutidine, 2,3-lutidine and 2,4-lutidine.

Experimental[3]

Purification of Materials.—Dry sulfur dioxide was obtained by passing commercial grade[4] gas through a train consisting of one tower containing saturated barium chloride solution, a tower containing calcium chloride granules, and finally two towers containing phosphoric anhydride. The rate of flow was controlled carefully and a slow stream of sulfur dioxide was allowed to pass through the train for an hour before the required amount was collected in a special freezing point cell[5] which was cooled in a Dry Ice-bath and attached to a drying tube containing phosphoric anhydride. The freezing point of sulfur dioxide collected in this manner was −74.0°.[6]

Purification of 2,6-lutidine[7] was accomplished through the crystalline urea–2,6-lutidine complex reported by Reithof.[8] The crystals of the complex were washed first with cold water, then with alcohol, and finally steam distilled. The portion of distillate boiling constantly at 95.6° under a pressure of 739 mm. was made alkaline with sodium hydroxide pellets and the lutidine layer separated and dried over three separate portions of sodium hydroxide pellets. Distillation of the dried product through a Todd column into a receiver protected from the atmosphere by means of a drying tube containing potassium hydroxide yielded 2,6-lutidine which boiled at 143.7°[9] at 741 mm. and gave a freezing point (from cooling curve) of −5.9°.[10]

The 2,3-lutidine was purified through a previously unreported urea–2,3-lutidine complex which melted at 119.8–121.7°. The crystalline complex was washed with cold water, then with alcohol, and dried. Fusion of the

---

[1] Abstracted from a thesis presented by Henry A. Hoffman to the Graduate Faculty of the University of Kansas in partial fulfilment of the requirements for the degree of Master of Arts.

[2] K. R. Hoffman and VanderWerf, This Journal, **68**, 997 (1946).

[3] All boiling points are corrected.

[4] Furnished by the Ohio Chemical and Mfg. Co., Cleveland, Ohio.

[5] Davidson, Sisler and Stoenner, This Journal, **66**, 779 (1944).

[6] Dry sulfur dioxide prepared according to the method of Hoffman and VanderWerf (ref. 2) gave essentially the same results as the tank product described above despite the slight difference noted in the freezing point.

[7] All three lutidines used were obtained from the Reilly Tar and Chemical Company.

[8] U. S. Patent 2,295,606, September 15, 1942.

[9] Lidstone, *J. Chem. Soc.*, 241 (1940), reported the value 144.4° at 760 mm.

[10] In exact agreement with the value reported by Coulson and Jones, *J. Soc. Chem. Ind.* (*London*), **65**, 169 (1946).

dry material brought about decomposition with the formation of two layers. The top layer, consisting of 2,3-lutidine, was separated, dried for two weeks over sodium hydroxide pellets, refluxed over solid sodium hydroxide, and finally fractionated through a Todd column to yield the pure amine, b. p. 161.0° at 736 mm.,[11] f. p. (from cooling curve), −9.8°.

The 2,4-lutidine was first distilled through a three-foot Vigreux column, a middle fraction boiling between 142 and 150° at 743 mm. being collected in a receiver protected from the atmosphere by means of a drying tube containing sodium hydroxide pellets. The distillate was stored over sodium hydroxide pellets for two weeks, then refluxed over solid sodium hydroxide for twenty-four hours, and finally fractionated through a Todd column. The pure material boiled at 158.5° at 742 mm.; repeated attempts to obtain a freezing point resulted only in the formation, at low temperatures, of an extremely viscous glass.

Apparatus and Procedure.—A freezing point cell similar to that described in a previous publication from this Laboratory[5] was employed in the determination of the temperature–composition diagrams. A Leeds and Northrup Micromax recorder, calibrated at the melting point of ice, the boiling point of ammonia, the freezing point of pyridine, and the sublimation point of carbon dioxide, was used for the direct recording of the cooling curves. Appreciable reduction of the abnormal supercooling often encountered when an excess of any of the lutidines was present could be realized if the sample was first cooled rapidly until crystallization occurred, then warmed until the last crystal just disappeared, and finally cooled again, this time very slowly. The level to which the temperature rose immediately after the first break in the cooling curve for the second cooling, was taken as the equilibrium temperature. All freezing points were determined at least twice. Data obtained in this way are believed to be correct, even for the steeper portions of the freezing point curves, to 1.5°.

Results

The experimental data are shown below in graphical form. Compositions, as indicated, are given in mole per cent.

A. As shown in Fig. 1, sulfur dioxide and 2,6-lutidine form a single stable compound, $SO_2\cdot(CH_3)_2C_5H_3N$, which melts congruently at 4.0°. The eutectics are: (1) 3.7 mole per cent. 2,6-lutidine, f. p. −75.5°, and (2) 78.1 mole per cent. 2,6-lutidine, f. p. −18.0°.

B. As indicated in Fig. 2, sulfur dioxide and 2,3-lutidine form a single stable compound, $SO_2\cdot(CH_3)_2C_5H_3N$, which melts congruently at 18.5°. The eutectics are: (1) 8.7 mole per cent. 2,3-lutidine, f. p. −78.8°, and (2) 76.5 mole per cent. 2,3-lutidine, f. p. −17.5°.

C. As indicated in Fig. 3, sulfur dioxide and 2,4-lutidine form two compounds, (1) probably either $2SO_2\cdot(CH_3)_2C_5H_3N$ or $3SO_2\cdot2(CH_3)_2C_5H_3N$, which undergoes decomposition into sulfur dioxide and solution at a temperature somewhat below its melting point and (2) $SO_2\cdot(CH_3)_2C_5H_3N$, which melts congruently at −8.3°. The eutectics are: (1) 4.9 mole per cent. 2,4-lutidine, f. p. −78.0°, and (2) 75.1 mole per cent. 2,4-lutidine, f. p. −23.1°. All attempts to establish points in the region beyond 80.0% 2,4-lutidine were unsuccessful because of the extremely high viscosities of the glassy mixtures formed in these concentration ranges.

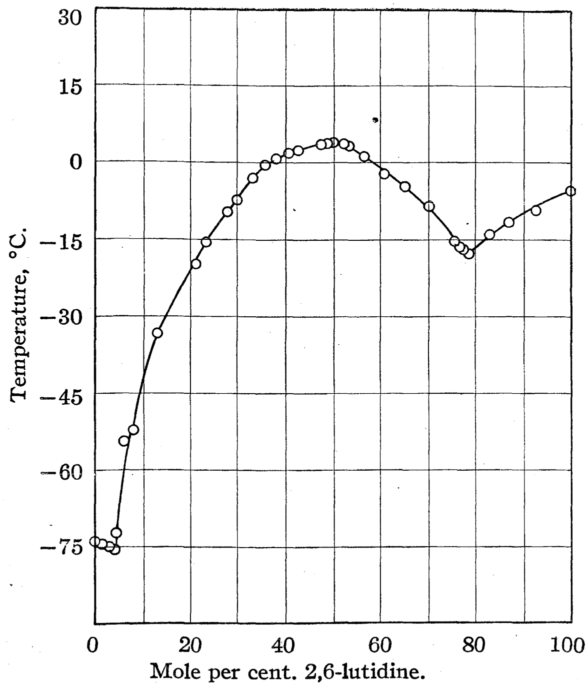


Fig. 1.—System sulfur dioxide–2,6-lutidine.

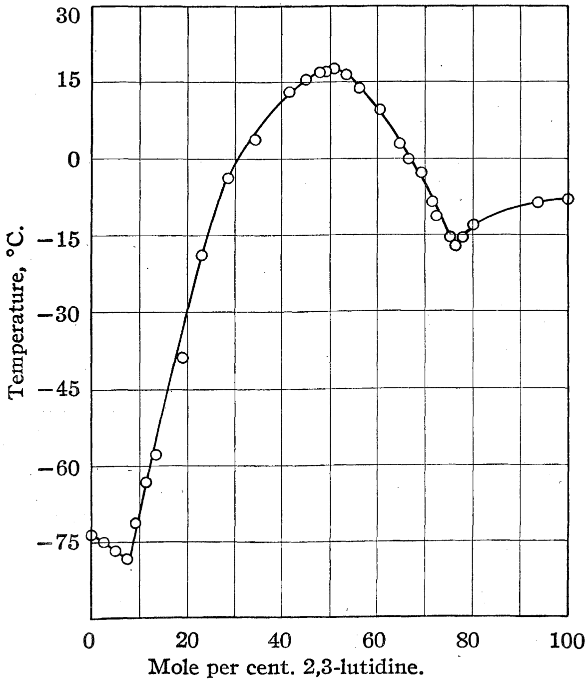


Fig. 2.—System sulfur dioxide–2,3-lutidine.

Discussion

A comparison of the behavior of the picolines and of the lutidines with respect to the formation of stable solid compounds with sulfur dioxide reveals that, in general, the presence of an additional methyl group, located at the α-position in the various picoline molecules, has little effect on the

---

[11] Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 365 (1939), reported a boiling point of 162–164° at 760 mm.

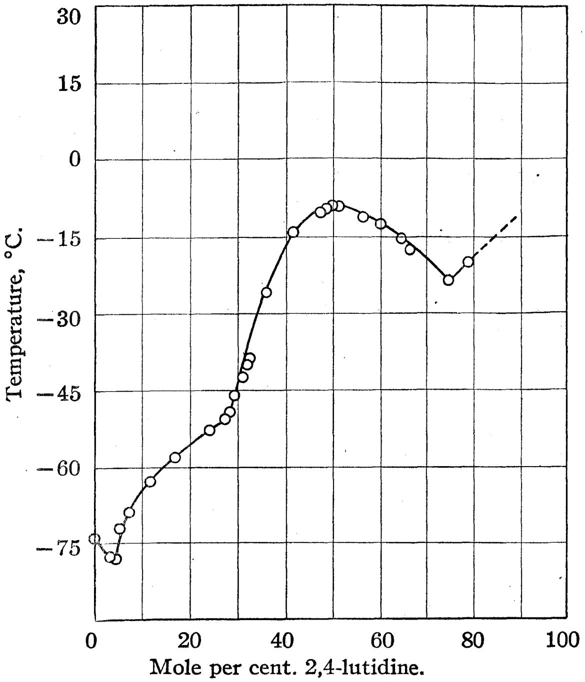


Fig. 3.—System sulfur dioxide–2,4-lutidine.

number or nature of solid compounds formed. Thus, the curve for the sulfur dioxide–2,3-lutidine system is strikingly similar to that for the sulfur dioxide–β-picoline system, a stable 1:1 solid compound being formed in each case. Likewise, the curve for the sulfur dioxide–2,4-lutidine system resembles closely that for the sulfur dioxide–γ-picoline system. Stable 1:1 solid compounds are formed in both cases; the unstable addition compound observed in the case of sulfur dioxide–2,4-lutidine appears to be either a 2:1 compound, corresponding exactly to that in the sulfur dioxide–γ-picoline system, or a 3:2 compound, which would correspond to the higher melting of the two compounds formed in the system sulfur dioxide–α-picoline.

In general, the slope of the sulfur dioxide–2,6-lutidine curve is markedly like that for sulfur dioxide–α-picoline. Stable 1:1 solid compounds are formed in both systems, but no stable solid analog of the 3:2 compound observed in the sulfur dioxide–α-picoline system was formed when 2,6-lutidine was used in place of α-picoline.

Summary

1. Temperature–composition data are presented for the three systems consisting of sulfur dioxide with 2,6-lutidine, 2,3-lutidine and 2,4-lutidine.

2. It has been shown that sulfur dioxide forms stable 1:1 solid addition compounds with each of the three lutidines studied. In addition, with 2,4-lutidine, either a 2:1 or a 3:2 compound, which undergoes transition near its melting point, is formed.

3. The behavior of sulfur dioxide in the formation of solid addition compounds with these three lutidines is compared with its behavior toward the picolines.

LAWRENCE, KANSAS RECEIVED AUGUST 25, 1947

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

Phase Equilibrium Studies on Pyridine–Amide Systems[1]

BY STEPHEN STEPHANOU,[2] CALVIN A. VANDERWERF AND HARRY H. SISLER[3]

In studies of the systems acetamide–ammonia and formamide–ammonia, previously reported from this Laboratory,[4] evidence for the existence of the addition compounds $CH_3CONH_2{\cdot}NH_3$ and $HCONH_2{\cdot}NH_3$ was presented. By analogy with the ammonium salts of acetic and formic acids and with the sodium salts of acetamide and formamide, these addition compounds were considered to be ammonium aquo-ammono salts, in which a single N-hydrogen atom of the amide is, in each case, involved in the bonding between the amide and ammonia molecules. Similarly, it was suggested that the formation of a second addition compound of probable formula $HCONH_2{\cdot}2NH_3$, formed in the formamide–ammonia system, may perhaps take place through the interaction of the second hydrogen atom on the amide group with an ammonia molecule. It was pointed out, however, that the possibility that a second molecule of ammonia might be joined by the sharing of its electron pair with the electron deficient carbon atom of formamide is not precluded.

In the present investigation, a series of systems consisting of pyridine with each of several different amides has been studied in an attempt to explore the possibility of the formation of addition compounds of amines with amides which have no hydrogen atom available for bonding. Choice of pyridine as the base was dictated by the following advantages: it has a convenient melting point, it exhibits little tendency to undercool, and, as a tertiary amine, it cannot undergo exchange reactions with amides. The N,N-disubstituted amides

---

[1] Abstracted from a thesis presented by Stephen Stephanou to the Graduate Faculty of the University of Kansas in partial fulfilment of the requirements for the Degree of Master of Science.

[2] Kansas University Fellow, 1945.

[3] Present address: Department of Chemistry, The Ohio State University, Columbus, Ohio.

[4] Sisler, Davidson, Stoenner and Lyon, THIS JOURNAL, **66**, 1888 (1944); Sisler, VanderWerf and Stephanou, *ibid.*, **68**, 2538 (1946).

used were studied in the order of increasing positive charge on the carbonyl carbon atom, as predicted on theoretical grounds.

Experimental[5]

Materials.—The pyridine was dried over sodium hydroxide pellets for at least two weeks and then distilled through a 5-foot packed column; b. p. 114.6° at 740 mm., f. p. (from cooling curve) −41.5°.

The formamide was purified as described previously.[4]

N-Phenylformamide was obtained by four hours of refluxing of aniline with formic acid. Recrystallized three times from diethyl ether, the product was isolated as colorless prisms, f. p. (from cooling curve) 45.3°.

N,N-Diethylacetamide, prepared by refluxing diethylamine with excess acetic anhydride for four hours, was purified by distillation through a 5-foot packed column; b. p. 90.1–91.0° at 30 mm.

N,N-Diphenylacetamide was prepared by acetylation of diphenylamine with acetic anhydride and was obtained as colorless needles, m. p. 100.1°, by repeated recrystallization from alcohol–water.

N,N-Diphenylformamide was isolated as colorless prisms, m. p. 71.5°, by the recrystallization from alcohol–water of the crude product obtained by refluxing diphenylamine with formic acid.

N-Methyldiacetamide, prepared from N-methylacetamide[6] by treatment with acetic anhydride, was purified by distillation through a 5-foot packed column; b. p. 114.0–114.5° at 61 mm., f. p. (from cooling curve) −25.0°.[7]

Anal. Calcd. for $C_5H_9O_2N$: N, 12.2. Found: N, 12.5, 12.4.

N-Methylphthalimide, obtained by the reaction of phthalic anhydride with methylamine, was purified by distillation; b. p. 285.0–286.1° at 736 mm., m. p. 133.1–133.5°.

Method.—The systems were studied by means of the freezing point method; all cooling curves were recorded directly by means of a Brown Electronik Strip Chart Potentiometer. The cell used was similar to the one described in a previous paper from this Laboratory.[8] All points were determined at least twice. Data obtained by this method are believed to be correct, even for the steeper portions of the freezing point curves, to 1.0°. In order to increase the accuracy, all equilibrium temperatures above 65° in the system pyridine–N-methylphthalimide were determined in sealed tubes as previously described.[9] Each f. p. determined by this method is believed to be correct within 0.7°.

Results

The experimental data are shown below in graphical form. Compositions, as indicated, are given in mole per cent.

As represented graphically in Figs. 1, 2, 3, 4, 5

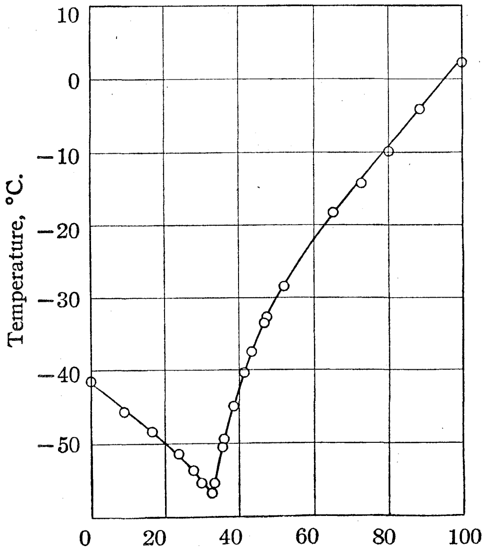


Fig. 1.—System pyridine–formamide.

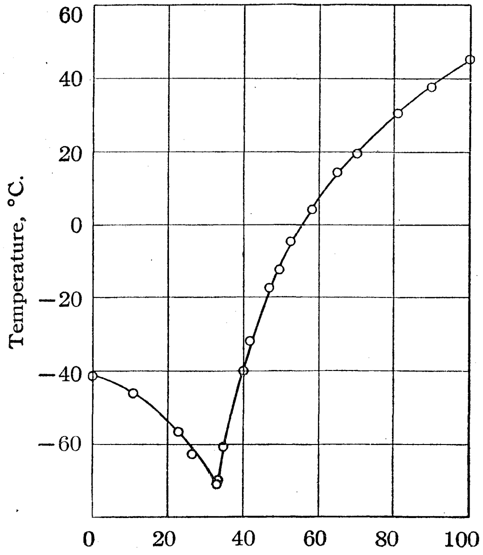


Fig. 2.—System pyridine–N-phenylformamide.

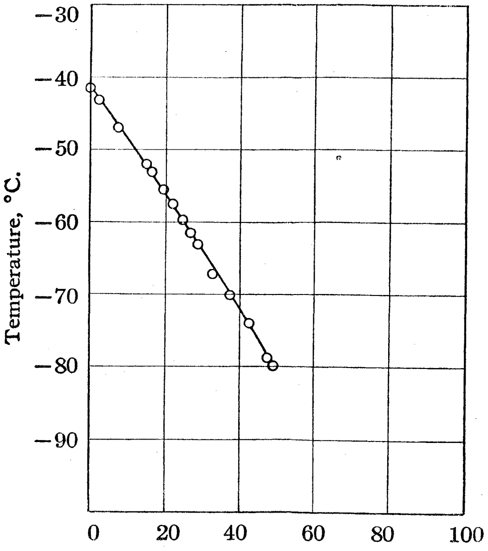


Fig. 3.—System pyridine–N,N-diethylacetamide.

---

[5] All melting and boiling points are corrected.

[6] Best obtained by method of Galat and Elion, THIS JOURNAL, **65**, 1566 (1943).

[7] D'Alelio and Reid, *ibid.*, **59**, 109 (1937), reported a melting point of −46°. Our product boiled at 194.5° at 741 mm., in agreement with their value 194.2°.

[8] Davidson, Sisler and Stoenner, *ibid.*, **66**, 779 (1944).

[9] Davidson and McAllister, *ibid.*, **52**, 507 (1930).

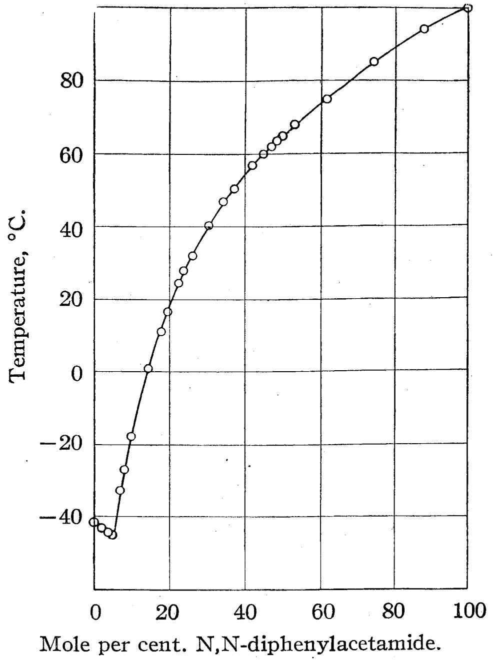


Fig. 4.—System pyridine–N,N-diphenylacetamide.

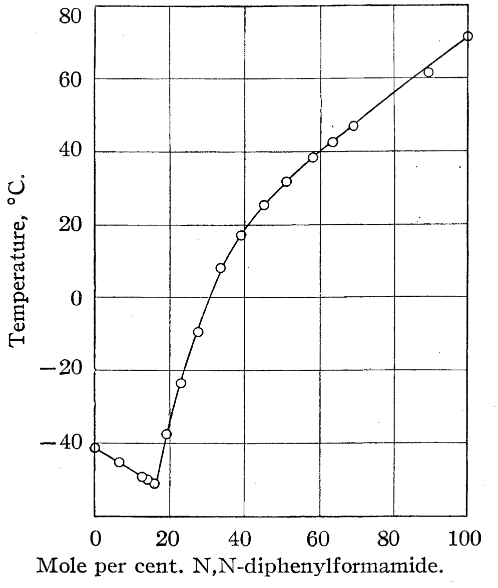


Fig. 5.—System pyridine–N,N-diphenylformamide.

and 6, respectively, the six systems consisting of pyridine with formamide, N-phenylformamide, N,N-diethylacetamide, N,N-diphenylacetamide, N,N-diphenylformamide and with N-methyldiacetamide showed no evidence of compound formation. The respective eutectics for the various systems are: 32.3 mole per cent. formamide, f. p. −56.7°; 33.0 mole per cent. N-phenylformamide, f. p. −71.0°; 4.9 mole per cent. N,N-diphenylacetamide, f. p. −44.9°; 16.2 mole per cent. N,N-diphenylformamide, f. p. −51.0°; 36.3 mole per cent. N-methyldiacetamide, f. p. −64.7°.

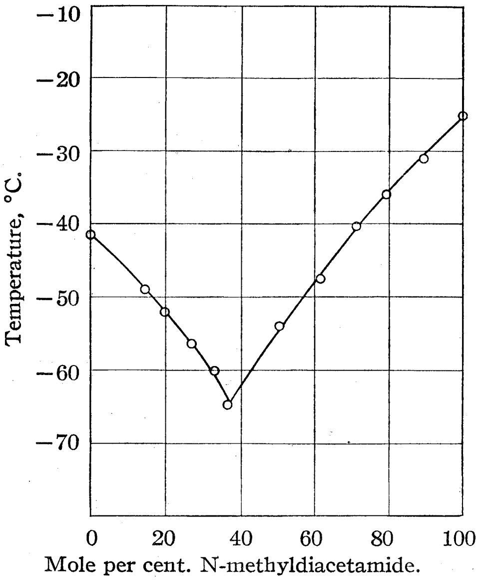


Fig. 6.—System pyridine–N-methyldiacetamide.

All attempts to establish points in the pyridine–N,N-diethylacetamide curve in the region from 49–100% amide were unsuccessful because of the extremely high viscosities of the glassy mixtures formed in this concentration range. The usual expedients, such as the sudden cooling, with liquid air, of a short platinum wire fused into the bottom

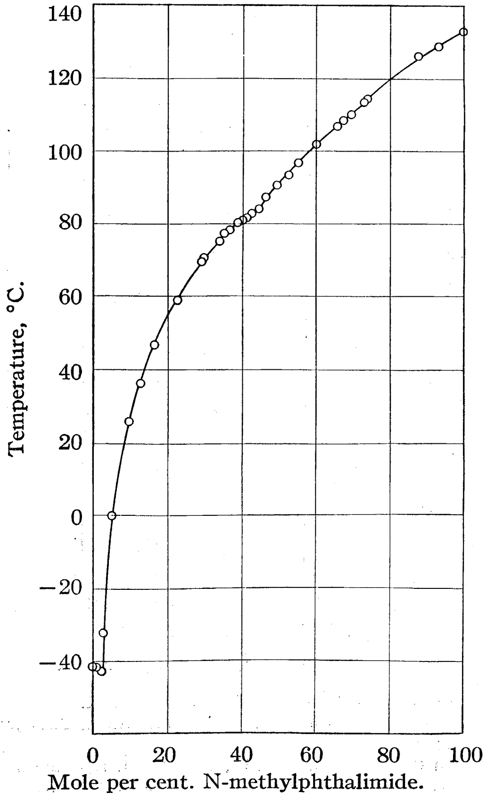


Fig. 7.—System pyridine–N-methylphthalimide.

of the freezing point cell, or prolonged storing of the mixture in a liquid air-bath, failed to induce crystallization.

As shown graphically in Fig. 7, pyridine and N-methylphthalimide form a single compound, $C_6H_4(CO)_2NCH_3 \cdot C_5H_5N$, which undergoes dissociation to N-methylphthalimide and solution at a temperature just below its melting point, which, as indicated by a short extrapolation, is approximately 82°. The eutectic is 2.2 mole per cent. N-methylphthalimide, f. p. $-42.7°$.

Discussion of Results

The fact that pyridine forms no solid addition compound with formamide in the temperature range indicated is not surprising, inasmuch as pyridine has a much lower tendency to donate its unshared electron pair than ammonia. Even with N-phenylformamide, which would be expected to be a stronger acid than formamide itself, no solid compound is observed. Of the remaining five amides, N,N-diethylacetamide, N,N diphenylacetamide, N,N-diphenylformamide, N-methyldiacetamide and N-methylphthalimide, the last-named would be expected, on the basis of the electron theory, to possess the most positive carbonyl carbon atom, *i. e.*, the carbonyl carbon atom of lowest electron density. It may possibly be significant, therefore, that, although no solid compound is formed between N,N-diethylacetamide, N,N-diphenylacetamide, N,N-diphenylformamide, or N-methyldiacetamide and pyridine, even down to eutectic temperatures as low as -51.0 and $-64.7°$, nevertheless N-methylphthalimide and pyridine form a solid 1:1 compound stable at temperatures up to 80°. At present, however, the structure of the compound $C_6H_4(CO)_2NCH_3 \cdot C_5H_5N$ is entirely problematical. Evidence for the type of bonding in such a solid binary compound can be obtained only by studies of the chemical reactions and crystal and molecular structures of the compound, and of the deviations from ideality in dilute solutions included in the system. Investigations of this type are in progress in this Laboratory.

Summary

1. Temperature–composition data are presented for the seven systems consisting of pyridine with each of the following amides: formamide, N-phenylformamide, N,N-diethylacetamide, N,N-diphenylacetamide N,N-diphenylformamide, N-methyldiacetamide and N-methylphthalimide.

2. It has been shown that N-methylphthalimide and pyridine form a 1:1 addition compound, the existence of which cannot be accounted for logically in terms of hydrogen-bonding.

LAWRENCE, KANSAS RECEIVED APRIL 4, 1947

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

The Absorption of Oxygen by Sodium in Liquid Ammonia: Evidence for the Existence of Sodium Superoxide

BY WILLIAM H. SCHECHTER, HARRY H. SISLER[1] AND JACOB KLEINBERG

It is well known that potassium, rubidium and cesium combine directly with oxygen[2] to form superoxides[3] of the formula MO_2, in which the oxygen exists as an ion of the structure $-:\ddot{\mathrm{O}}\overset{\cdot\cdot\cdot}{-}\ddot{\mathrm{O}}:$.[4] Similar compounds of alkaline earth metals have not yet been isolated in the pure form, although calcium superoxide (as an admixture to the extent of 8.7% in calcium peroxide) and barium superoxide (about 8% in barium peroxide) have been obtained by the action of 30% hydrogen peroxide on the corresponding hydroxides.[5] Magnetic studies on the impure calcium superoxide prepared in this manner demonstrate the presence of the O_2^- ion in this substance.[6]

Up to the present the existence of sodium superoxide has not been reported. Joannis[2a] described the preparation in liquid ammonia at $-50°$ of an oxide of the formula Na_2O_3, whereas Kraus and Whyte[2d] found no evidence for any oxide higher than the peroxide in the same solvent at $-33°$. Preliminary experiments in this Laboratory at approximately $-77°$ in liquid ammonia indicated the formation, by the direct combination of the elements, of a higher oxide than sodium peroxide. The results, however, were not consistent, indicating that the oxide formed was unstable; hence the oxygen uptake of sodium in liquid ammonia at $-77°$ was studied quantitatively. In the present report an apparatus is described for the study of low temperature reactions in liquid ammonia involving gas absorption, and evidence for the existence of sodium superoxide is presented.

Experimental

The apparatus employed (Fig. 1) is suitable for use only at temperatures at which the vapor pressure of the solvent has a known, moderately low value. The volume of gas absorbed by a solution can be calculated from the observed change in volume in the gas buret C; if the reaction is not too rapid, it is possible to determine its rate.

---

[1] Present address: Department of Chemistry, The Ohio State University, Columbus, Ohio.

[2] (a) Joannis, *Compt. rend.*, **116**, 1370 (1893); (b) Holt and Sims, *J. Chem. Soc.*, **65**, 432 (1894); (c) Rengade, *Ann. chim. phys.*, [8] **11**, 348 (1907); (d) Kraus and Whyte, THIS JOURNAL, **48**, 1781 (1926).

[3] The investigators cited above believed that they had obtained tetroxides of the formula M_2O_4; however, later work (ref. 4) showed the correct formula to be MO_2.

[4] Neuman, *J. Chem. Phys.*, **2**, 31 (1934).

[5] Traube and Schulze, *Ber.*, **54**, 1626 (1921).

[6] Ehrlich, *Z. anorg. Chem.*, **252**, 370 (1944).

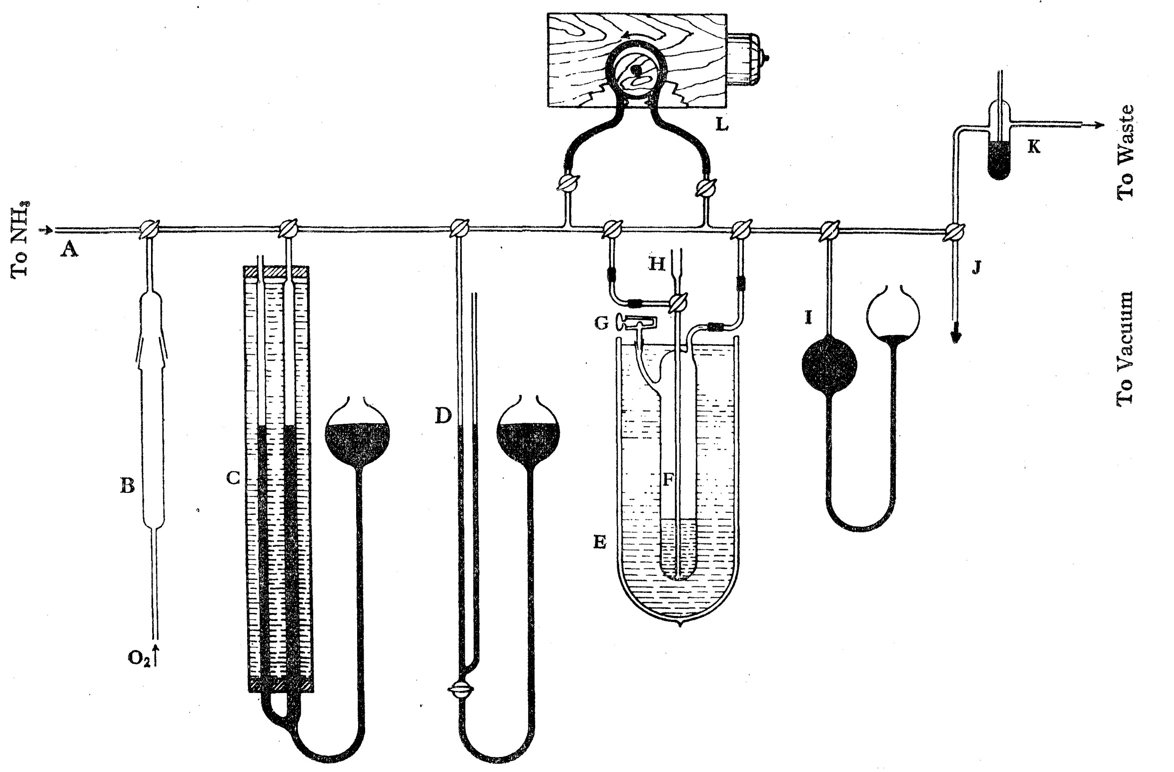


Fig. 1.

A sample of sodium of the desired size is cut in a dry-box containing phosphorus pentoxide. The metal is placed in the tared sampling stopcock G and the plug is rotated. After the ground glass cap has been replaced over the male joint, the stopcock is removed from the dry-box and weighed. The sampling stopcock is then placed at the point shown (Fig. 1) in the system, which has been previously dried by flushing for a considerable time with anhydrous (dried over sodium) ammonia.

The system is again flushed with ammonia, the stopcock J is closed, and the required volume of ammonia is condensed in the reaction cell F by means of the cold bath E, which consists of a mixture of equal volumes of carbon tetrachloride and chloroform to which Dry Ice has been added. The temperature of this mixture, by which the reaction cell is surrounded also during the process of oxidation, is between −77 and −79°.

When the ammonia has been condensed, oxygen is permitted to enter through the drying tube B, containing anhydrous magnesium perchlorate, until the buret C is almost filled. The system is then isolated by closing the stopcock above the drying tube. At this point, with the eccentric pump L turned on, oxygen from the buret is forced through the reaction cell and is collected in the reservoir I. With the manipulation of the appropriate stopcocks the gas is returned to the buret, and the cycling process is then repeated until the oxygen and the liquid ammonia are mutually saturated. During the cycling process and throughout subsequent operations, the level of the cooling liquid on the reaction cell is kept as nearly constant as possible, in order to avoid changes in oxygen volume. This is necessary because the sampling stopcock cannot be covered by the cooling bath.

Once the initial static volume in buret C has become constant, the pump L is turned on and, with the proper adjustment of stopcocks, oxygen at a rate of 850–900 cc. per minute is cycled through the reaction cell. (By regulated clamping of the rubber tubing leading to the pump, the rate of oxygen flow may be adjusted to any desired lower value.) By turning stopcock G the sodium sample is dropped into the liquid ammonia. The system is kept at approximately atmospheric pressure during the oxidation by raising the mercury leveling bulb of buret C to continually higher levels as the oxygen is consumed. When the oxygen has proceeded to the point where there is no longer any noticeable change in the mercury level in the buret, the pump is turned off, the system permitted to come to apparent equilibrium and the final static volume obtained. The change in volume is then corrected for temperature, pressure and the vapor pressure of liquid ammonia to give the standard volume of oxygen absorbed by the known weight of sodium.

After the absorption data have been obtained, the cold bath is removed and the ammonia allowed to boil off through the trap K to the waste jars. A slow flow of oxygen through the reaction cell is maintained during the removal of ammonia; this sweeps the last traces of ammonia from the system, thus preparing it for the analysis.

For the analysis the cell, now cooled by an ice–water-bath is connected with the measuring buret only, and both the cell and the buret contain oxygen at atmospheric pressure. A 10-ml. portion of catalyst solution (to be described presently) is added from H and the cell, which is connected to the rest of the system by means of Tygon tubing, is shaken to hasten the decomposition of oxide (or oxides); the quantity of oxygen liberated is calculated from the volume change in the buret. The decomposition of the cold, dilute, acidic solutions of hydrogen peroxide, formed upon the addition of acid to peroxides and superoxides of the alkali metals, is catalyzed by a solution which is 0.6 molar with respect to hydrochloric acid and 2 molar with respect to ferric chloride. To correct for the volume change due to the addition of the catalyst, a blank run is made with no oxide present.

Discussion of Results

The results of oxygen absorption studies are given in Table I. It is evident from these data that in liquid ammonia at −77°, sodium absorbs,

TABLE I

THE OXYGEN UPTAKE OF SODIUM IN LIQUID AMMONIA AT −77°

			Uptake, cc. (S. T. P.)			Analyses cc. O_2 (S. T. P.) liberated		
Na, g.	Dilution, cc. NH_3/g. Na	O_2 flow, cc./min.	Calcd. for NaO_2	Obs.	% of theoretical uptake	Calcd. for NaO_2	Obs.	% of theoretical liberation
0.0266	380	850–900	25.9	23.3	90	19.4	10.8	56
.0235	380	850–900	22.9	21.0	92	17.1	9.3	53
.0428	430	850–900	41.7	35.8	86	31.2	15.9	51
.0616	680	700–750	59.9	51.3	86	45.0	22.3	50
.0317	760	*ca.* 150	30.8	26.2	85	23.1	12.1	52
.0343	770	*ca.* 150	33.4	30.9	93	25.0	12.0	48
.0279	810	850–900	27.1	24.3	90	20.3	10.1	50
.0183	1200	850–900	17.8	16.0	90	13.4	7.3	54
.0213	1240		20.7	18.7	90	15.5	8.9	57
.0163	1780	850–900	15.8	14.4	91	11.9	5.6	47
.0293	1830	850–900	28.5	24.9	87	21.4	11.9	56
.0191	2490	850–900	18.6	16.8	90	13.9	6.9	50

from oxygen which is being cycled rapidly through the solution, a volume approaching that required for sodium superoxide. It is apparent that in liquid ammonia a temperature below −33° is essential for the formation of an oxide higher than sodium peroxide, since Kraus and Whyte[2d] have demonstrated that the peroxide is the highest oxide formed by the rapid oxidation of sodium at the boiling point of ammonia.

As mentioned previously, the amount of oxygen absorbed by the sodium is calculated from the volume change in the buret during the oxidation. This calculation is made on the assumptions that oxygen behaves as an ideal gas under the conditions of the experiment, and that the absolute pressure of the ammonia in the buret is the same before and after the oxidation, *i. e.*, that it is equal to the vapor pressure of the liquid ammonia solution. The first assumption is valid within the experimental error, but the second is true only if sufficient time is allowed for the system to reach equilibrium. The calculated oxygen uptake data, as given in Table I, are based on the assumption that such equilibrium had been attained.

In no case was the theoretical absorption for sodium superoxide quite realized. It is possible that this may be accounted for in part by insufficient time having been allowed for the system to come to equilibrium after oxidation, and in part by contamination of the sodium during the sampling process. Nevertheless, there is no plausible explanation other than the formation of sodium superoxide that will account for the absorption of such large quantities of oxygen.

The unstable nature of the superoxide is indicated by the results of the analyses, which were made after the ammonia had been permitted to evaporate and the product allowed to reach room temperature. Roughly half the volume of oxygen required for sodium superoxide is liberated upon analysis. At present we have no explanation for the approximately constant values obtained on analysis. The quantity of oxygen liberated is too large to be accounted for solely on the basis of decomposition of sodium peroxide. In each case the volume liberated is approximately 50% greater than that calculated for the peroxide. The reaction product before analysis is visibly heterogeneous, appearing to be a mixture of a yellow[7] and a white substance.

Acknowledgment.—The authors are indebted to the Office of Naval Research for a grant which made this and continuing investigations possible.

Summary

1. An apparatus for studying low temperature reactions in liquid ammonia involving gas absorption is described.

2. Evidence for the existence of sodium superoxide, based upon oxygen absorption in liquid ammonia at −77°, is presented.

LAWRENCE, KANSAS RECEIVED JULY 1, 1947

---

[7] Although pure sodium superoxide has not been prepared, it is of interest to note that potassium superoxide is yellow in color.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF ETHYL CORPORATION]

A Thermal Investigation of the Ternary System Mg–Na–Pb. II. The Compound MgNaPb and Several Cross Sections

BY GEORGE CALINGAERT, HYMIN SHAPIRO AND IVAR T. KROHN

In a recent note,[1] it was disclosed that the compound $Mg_4Na_4Pb_3$ had been discovered in the course of a thermal investigation of the ternary system Mg–Na–Pb. The investigation has now resulted in the discovery of a second compound and the partial elucidation of several important cross sections. The new compound, MgNaPb, was shown to be of the peritectic type rather than of the open maximum type, as the first compound, $Mg_4Na_4Pb_3$.

Method of Investigation

In this thermal study, two principal methods of attack were used: the investigation of cross sections of the ternary diagram, and the investigation of alloys having atomic ratios of small whole numbers. The first method was used mostly for determining the locations of ternary eutectic points and binary eutectic curves, and in the regions close to the binary compounds—in other words, for clarifying the general structure of the equilibrium diagram. The choice of cross sections was limited to those between binary compounds, between a compound and an element, and at a fixed concentration of one of the elements. The second method was used in spot attempts to discover ternary compounds, since compounds are usually characterized by atomic ratios of small whole numbers. Of course, the usefulness of this method is limited to compounds having open maxima. For peritectic compounds it is necessary to correlate several types of data, as will be discussed later.

The thermal analysis data for each alloy were plotted with millivolts and time as the coördinates. The cooling curves were interpreted after the manner of Tammann.[2] The differences in millivolts between successive readings were sometimes plotted against time in order to evaluate the precision of the results.

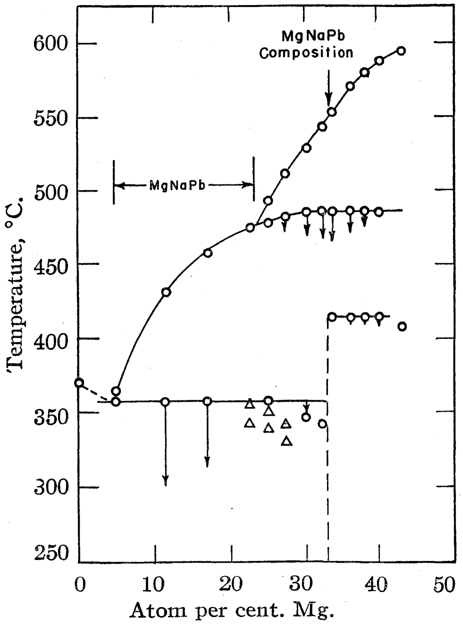


Fig. 1.—NaPb–Mg cross section (passing through 50% Na–50% Pb): time scale for temperature breaks, 50° = twenty minutes.

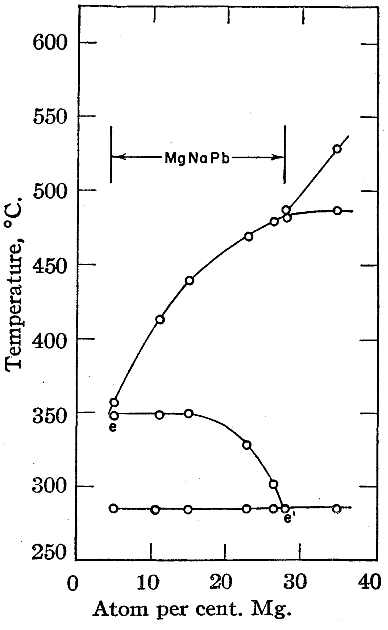


Fig. 2.—Cross section parallel to NaPb–Mg cross section and passing through 47.5% Na–52.5% Pb.

Experimental

Chemicals, Apparatus and Procedure.—All alloy melts were prepared from mixtures of magnesium, lead and NaPb or Na_4Pb alloy. The magnesium was Dow extruded bar of purity over 99.9%, and the lead was Asarco brand, over 99.95% pure. The NaPb was alloy from the stock used for the manufacture of tetraethyllead. The Na_4Pb was prepared from sodium and the Asarco lead, and analyzed 30.96% sodium as compared with the theoretical of 30.74%. The analytical figures were used in computing the quantities of alloy ingredients required.

The alloy melts were made in 200- to 300-g. batches under an atmosphere of nitrogen or helium purified over hot copper filings; the gases seemed to be equally effective up to about 550°, but above this temperature helium was

---

[1] Calingaert, Shapiro and Krohn, THIS JOURNAL, **68**, 520 (1946).

[2] Tammann, "A Textbook of Metallography," The Chemical Catalog Co., Inc., New York, N. Y., 1925, p. 181.

TABLE I

THERMAL ANALYSIS OF CROSS SECTIONS PARALLEL TO NaPb–Mg CROSS SECTION

Cooling method	Atom per cent. Mg	Atom per cent. Na	Temperature breaks I T, °C.	I Min.	II T, °C.	II Min.	III T, °C.	III Min.
			NaPb–Mg Cross Section					
S. C.	5.00	47.50	365.6	9	...	..	357.2	30
S. C.	11.50	44.24	432.2	5	...	..	358.9	38
S. C.	17.00	41.50	455.9	6	...	..	355.7	33
R. T.	22.50	38.75	476.1	4	...	..	343.0–356.1	[a]
R. T.	25.00	37.50	493.0	[b]	479.2	4.5	339.8–351.1	[a]
R. T.	27.27	36.36	512.3	[b]	482.5	5	331.1–341.8	[a]
R. T.	30.00	35.00	528	[b]	485	6.5	348	3
R. T.	32.00	34.00	544	[b]	486	7	342.5	1.5
S. C.	33.33	33.33	555.0	[b]	486.1	14[c]	415.1	2
R. T.	36.00	32.00	571.8	[b]	486.2	5.5	416.4	>2
R. T.	38.00	31.00	580.8	[b]	486.0	5	415.6	1.8
R. T.	40.00	30.00	588.2	[b]	485.2	2	416.4	2.5
S. C.	42.85	28.57	594.2	>8	407.2	3	404.2–439.5	[a]
R. T.	50.00	25.00	587.9	7	521.0	4	411.2–424.9	[a]
			Cross Section Passing through 47.5% Na–52.5% Pb					
S. C.	23.00	36.00	470.8	5	329.6	7	284.6	11
R. T.	26.50	34.25	480.6	2.5	303.6	[b]	284.6	5
R. T.	28.00	33.50	485.2	[b]	482.8	3	283.8	4.2
R. T.	35.00	30.00	529.2	[b]	486.6	7	284.2	3
			Cross Section Passing through 52.5% Na–47.5% Pb					
S. C.	12.00	46.50	436.8	3	345.6	19	329.2	10
R. T.	15.00	45.00	454.9	2.5	339.4–349.1	[a]	331.4	3
R. T.	18.00	43.50	473.8	[b]	460.9	3.5	331.9	[d]
R. T.	20.00	42.50	483.8	[b]	465.4	3.5	329.2–336.9	[a]
R. T.	25.00	40.00	521.4	[b]	472.8	4	328.6	5.5
S. C.	35.00	35.00	583.0	<1	476.8	3	407.9	<1

[a] Supercooled break. Initial and maximum temperatures are given. [b] The break was indicated by a sudden change in the slope of the curve. [c] The time value of 14 minutes is equivalent to 7.8 minutes at the R.T. cooling rate. [d] Time of break difficult to estimate because of supercooled nature. There was some levelling off at 331.9°.

TABLE II

THERMAL ANALYSIS OF $NaPb–Mg_2Pb$ CROSS SECTION

Cooling method	Atom per cent. Mg	Atom per cent. Na	Temperature breaks I T, °C.	I Min.	II T, °C.	II Min.	III T, °C.	III Min.
R. T.	66.66	...	552.5	22	...	..	...	..
R. T.	57.48	6.90	552.3	10	...	..	...	..
R. T.	45.25	16.06	524.7	7	...	..	...	..
S. C.	44.00	17.00	531.9	5	405.5	1	287.1	11
S. C.	40.00	20.00	519.0	6	426.7	1	287.5	12
S. C.	37.33	22.00	509.0	4	438.0	2	287.1	11
R. T.	31.58	26.32	477.0	3	...	..	282.7	12
R. T.	29.83	27.63	474.4	3	453.1	1	284.0	16
R. T.	28.06	28.96	464.9	2	452.1	1	284.9	17
R. T.	26.98	29.76	460.2	1	455.4	1	286.1	16
R. T.	26.26	30.31	462	1	...	..	286.0	17
R. T.	22.57	33.07	453.3	6	352	1	281.9	19
S. C.	21.60	33.80	453.0	4	312	1	284.3	16
R. T.	20.67	34.49	452	[a]	...	..	284.5	13
R. T.	19.94	35.05	450.4	5	299.2	1	280	15
R. T.	18.77	35.92	447.1	6	309.1	6	285.4	15
R. T.	16.82	37.39	443.5	3	330.7	7	281.0	15
R. T.	14.84	38.87	428.6	3	336.1	9	281.5	11
R. T.	12.82	40.38	426.7	2	345.7	10	283.9	10
R. T.	8.69	43.48	397.9	2	353.0	17	285.5	8
R. T.	6.58	45.07	381.5	3	353.5	19	281.9	6
R. T.	4.42	46.68	355.7	28	...	..	282.7	6
R. T.	2.24	48.32	359	19	356	12	283.6	3
R. T.	0.91	49.32	364.3	27	...	..	...	..
R. T.	...	50.00	370.0	31	...	..	...	..

[a] The break was indicated by a sudden change in the slope of the curve.

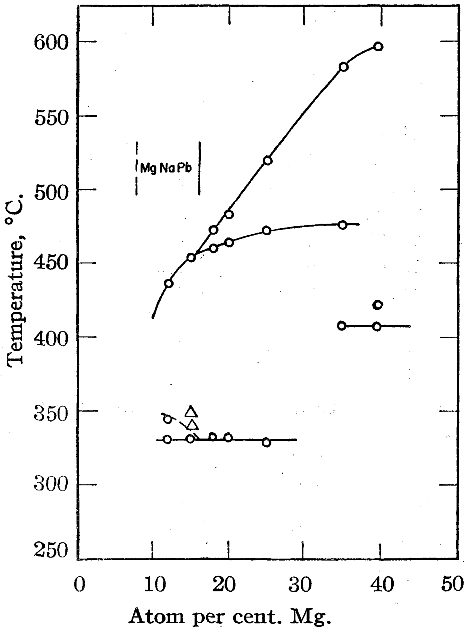


Fig. 3.—Cross section parallel to NaPb–Mg cross section and passing through 52.5% Na–47.5% Pb.

TABLE III

THERMAL ANALYSIS OF 15 ATOM PER CENT. MAGNESIUM CROSS SECTION

Cooling method	Atom per cent. Mg	Na	Temperature breaks I T, °C.	Min.	II T, °C.	Min.	III T, °C.	Min.	IV T, °C.	Min.
S. C.	15.00	15.00	303.1	2	286.0	18	256.0	8	...	..
S. C.	15.00	22.14	331.4	[a]			295.6	34	...	..
R. T.	15.00	27.00	359.9	2	288.0	<1	287.1	29	...	..
S. C.	15.00	29.00	372.1	2	311.7	<1	287.5	39	...	..
S. C.	15.00	32.00	384.9	4	291.5	<1	286.0	31.5	...	..
S. C.	15.00	35.00	411.8	3	292	<1	285.9	28.5	...	..
S. C.	15.00	37.00	423.5	4	315.5	7	284.7	27	...	..
S. C.	15.00	38.00	428.1	3	327.5	7	283.2	27	...	..
S. C.	15.00	40.00	443	<1	351	20	287	12	...	..
S. C.	15.00	41.50	444.3	4	355.5	21	284.9	7.5	...	..
S. C.	15.00	45.00	451.5	7	348.5	17	328.9	8	321.9	2

[a] The break was indicated by a sudden change in the slope of the curve.

TABLE IV

THERMAL ANALYSIS OF Na_4Pb–Mg_2Pb CROSS SECTION

Cooling method	Atom per cent. Mg	Na	Temperature breaks I T, °C.	Min.	II T, °C.	Min.	III T, °C.	Min.	IV T, °C.	Min.
S. C.	65.00	2.00	550.7	20	531.0	4	466.3	1	....	..
S. C.	63.64	3.64	552.4	16	514.0	2	502.2	1	467.5	3
S. C.	60.83	7.00	553.5	20	500.4	2.5	465.9	3	....	..
S. C.	59.58	8.50	554.1	21	547	<1	501.0	1	466.1	5
S. C.	58.33	10.00	553.5	18	547	<1	478.0	4	....	..
S. C.	57.14	11.43	551.9	16	542.4	3	478.8	6	396.7–397.7[a]	..
S. C.	55.00	14.00	551.0	<1	546.5	18	475.9	2	395.7–400.0[a]	..
S. C.	53.30	16.00	553.7	<1	547.0	16	477.9	3	397.5–409.7[a]	..
S. C.	50.83	19.00	566.0	<1	546.7	10	476.7	2	398.3–412.7[a]	..
S. C.	50.00	20.00	567.2	<1	542.0	5	474.4	1	396.4–411.5[a]	..
S. C.	49.17	21.00	572.1	3	546.6	8	471.9	<1	397.1–412.6[a]	..
S. C.	48.33	22.00	574.3	3	547.2	12	...		414.0–434.9[a]	..
S. C.	46.67	24.00	580.6	8	...	..	...	..	404.7–427.8[a]	..
S. C.	42.85	28.57	594.2	>8	407.2	<1	...	..	404.2–439.5[a]	..
S. C.	41.72	29.94	592.5	19	405.2	7	...	..	395.1–400.2[a]	..
S. C.	40.50	31.40	596.3	14	455.9	<1	407.1	10	....	..
S. C.	39.46	32.65	596.7	22	419.6	<1	408.0	5	....	..
S. C.	38.32	34.00	596.9	22	...	..	398.9	3	....	..
S. C.	36.36	36.36	600.7	23	...	..	383.8	1	....	..
S. C.	34.16	39.00	596.5	15	...	..	...	..	....	..
S. C.	30.83	43.00	594.0	16	...	..	...	..	....	..
S. C.	27.49	47.00	587.4	11	...	..	...	..	....	..
S. C.	25.00	50.00	582.0	5	...	..	...	..	....	..
S. C.	21.66	54.00	571.4	4.5	...	..	...	..	....	..
S. C.	16.67	60.00	551.2	4.5	...	..	...	..	....	..
S. C.	11.11	66.66	516.8	<1	430.7	4.5	341.5–342.5[a]	..	....	..
S. C.	7.50	71.00	475.2	<1	434.0	6	343.9–346.8[a]	..	....	..
S. C.	5.00	74.00	439.2	<1	356.9	<1	352.2–361.6[a]	..	....	..
S. C.	2.50	77.00	400.1	<1	363.7	6	356.9–375.6[a]	..	....	..

[a] Supercooled break. Initial and maximum temperatures are given.

used exclusively. Both open iron crucibles and closed iron bombs were employed. Iron was used because the binary equilibrium diagrams show that iron does not interact with any of the three metals in the system within the temperature range of this study; examination of the vessels after many experiments substantiated this fact. Above 600° the closed bombs were used exclusively on account of the substantial vapor pressure of the alloy at the higher temperatures. These bombs, 2 in. i.d. and 2.125 in. inside height, were threaded on the upper outside edge for 0.75 in., and fitted with 0.5-in. thermocouple wells extending in through the bottom. For easy removal, the screw covers were hexagonal in shape.

The open crucibles, of $^1/_{32}$-in. wall thickness, were covered with a slotted iron disc which centered a stirrer and thermocouple in the melt. The thermocouple was encased in 4-mm. Pyrex tubing, which was not attacked at the temperatures employed. The stirrer consisted of a $^1/_{16}$-in. iron rod welded perpendicularly to a 1-in. iron disc. The crucible was centered in an iron pot by means of a triangular tripod. The pot, cylindrical in shape and of 0.125-in. thickness, was fitted with a special cover

TABLE V

THERMAL ANALYSIS OF 50 ATOM PER CENT. LEAD CROSS SECTION

Cooling method	Atom per cent.		Temperature breaks					
			I		II		III	
	Mg	Na	T, °C.	Min.	T, °C.	Min.	T, °C.	Min.
S. C.	4.54	45.45	352.3	<1	348.0	<1	285.1	12
R. T.	12.50	37.50	384.9	2	320.0	7	286.0	23
S. C.	15.00	35.00	411.8	3	292	<1	285.9	28.5
S. C.	16.66	33.33	414.0	3	331	<1	284.6	36
S. C.	18.50	31.50	413.1	2	398	<1	286.5	33
S. C.	20.00	30.00	422.9	<1	398.2	2	288.0	30
R. T.	25.00	25.00	432.1	2	[a]	...	285.0	29
S. C.	27.50	22.50	451.9	2	302	<1	288.1	42
S. C.	33.00	17.00	463.7	<1	...	...	248.8	11
S. C.	35.00	15.00	474.1	3	...	...	295.5	20
S. C.	37.50	12.50	455.4	3	289.4	15	252	<1
R. T.	42.50	7.50	465.7	2	254.1	<1	253.3	<1
R. T.	45.00	5.00	467.3	<1	253.3	<1	252.8	<1

[a] Break of doubtful validity.

which was fastened to the pot by screws and contained two holes corresponding to those in the crucible cover. The cover was also fitted with a steel gas inlet tube. The entire pot assembly could be lifted by means of two bolts screwed into the cover. The pot fitted closely into a Hoskins electric furnace, whereas the bomb assembly was centered in the furnace by means of a magnesia block.

The alloy was cooled either against room temperature, with the heat turned off, or at a constant cooling rate of 1°/minute. For the latter, a calibrated electrical system was used consisting of a Variac and a variable resistor connected in parallel to the furnace. During heating, the resistor was by-passed.

The crucible or bomb was charged with the proper mixture of magnesium, lead, and NaPb or Na_4Pb, in a box flushed for a minimum of one hour with inert gas. The assembly of the apparatus was completed under inert gas, after which it was placed in the furnace chamber and fitted with an iron–constantan thermocouple. When the crucible was used, nitrogen or helium was passed through the iron pot at the rate of 1 or 2 liters/min. With the bomb, an inert atmosphere was not required in the furnace chamber.

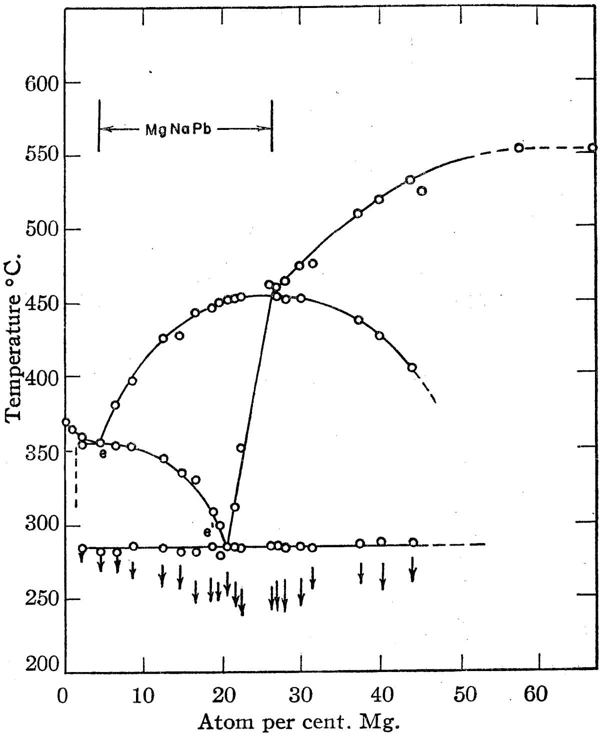


Fig. 4.—NaPb–Mg_2Pb cross section: time scale for temperature breaks, 50° = twenty minutes.

The constituents of the alloy were heated to a temperature 75 to 100° above the predicted temperature of the primary break in the cooling curve of the alloy, if above 450°. For alloys with lower primary breaks, it

TABLE VI

THERMAL ANALYSIS OF MISCELLANEOUS ALLOYS

Cooling method	Atom per cent.		Temperature breaks							
			I		II		III		IV	
	Mg	Na	T, °C.	Min.	T, °C.	Min	T, °C.	Min.	T, °C.	Min.
S. C.	3.00	27.28	312.4	25	...	...	291.6	6	...	..
S. C.	9.00	24.71	...	...	...	...	295.4	37	...	..
S. C.	12.00	23.43	317.2	2	...	...	295.6	34	...	..
S. C.	15.00	22.14	331.4	3	...	...	295.6	34	...	..
S. C.	30.00	15.71	434	5	...	...	294.9	23	...	..
S. C.	14.73	4.78	...	...	...	...	252.9	36	...	..
S. C.	14.28	28.57	370.8	<1	294.0	<1	288.6	30	....	..
S. C.	5.00	55.00	331.6	1	...	...	326.2	36	...	..
S. C.	10.00	55.00	339.1	<1	...	...	326.4	29	...	..
S. C.	37.50	37.50	589.8	11	...	...	559.9	11	...	..
S. C.	44.44	33.33	596	<1	570.9	7	561.2	25	...	..
R. T.	19.25	21.14	372.0	<1	294.9	4	284.6	12	...	..
S. C.	15.58	51.08	408.4	2	...	...	329.2	22	...	..
S. C.	45.27	14.72	461.3	<1	290.5	<1	287.1	<1	...	..
S. C.	9.00	50.00	420.9	5	337.7[a]	...	332.9	11	326.9	5
R. T.	12.50	50.00	457.9	<1	421.2	<1	330.9	23[a]	...	..
R. T.	20.51	39.11	471.0	5	354	13	285.5	4	...	..
R. T.	27.50	32.50	478.1	2	...	...	285.8	5	...	..
R. T.	30.00	30.00	477.8	3	...	...	286.9	7	...	..
R. T.	32.50	35.00	564.4	...	484.9	7	329	<1	...	..
R. T.	35.00	27.50	502.0	2	486.0	2	286.8	5	...	..

[a] Supercooling.

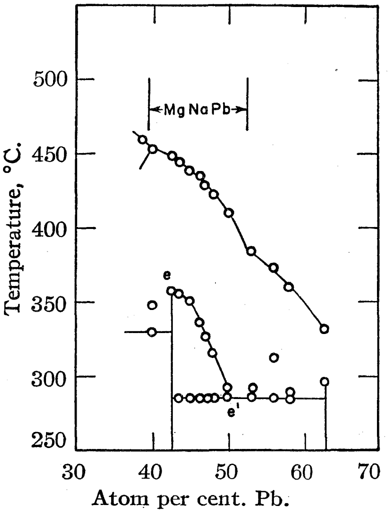


Fig. 5.—Cross section at 15 atom per cent. magnesium.

was necessary to raise the temperature to approximately 500° to dissolve the magnesium. Alloys made in crucibles were stirred for a minimum of forty-five minutes to ensure complete solution of the ingredients at the maximum heating temperature. Similarly, alloys made in bombs were vigorously shaken by means of tongs for at least five minutes over a forty-five minute heating period. No trouble was encountered in dissolving the alloy metals in the bombs since the temperatures were usually above 650°, the melting point of magnesium, the highest melting ingredient.

After the alloy was thoroughly mixed, shredded magnesia insulation was placed over the furnace to a depth of about 3 in. If the crucible was being used, the stirrer was lifted out of the molten alloy and fixed in this position by a small clamp. The temperature of the furnace was held constant for about thirty minutes to bring the insulation to temperature equilibrium.

Most of the alloys were cooled at the constant rate of 1°/minute to give a more easily interpreted cooling curve and to favor the establishment of equilibrium conditions in the alloy. Cooling against room temperature was used as a check on roughly half of the alloys cooled at the constant cooling rate, and sometimes when the necessary time for constant rate cooling (about five hours) was lacking.

The cooling rates for cooling against room temperature varied from approximately 4°/minute at 500° to approximately 1°/minute at 250°. For a few alloys, heating curves were taken, in order to detect temperature breaks below 200° and to confirm temperature breaks obtained on cooling. The heating rates varied from 1°/minute to 4°/minute, the former rate being used on alloys of special interest.

After the cooling curve was obtained, the alloy apparatus was cooled to room temperature and opened in an inert atmosphere. The alloy was coarsely crushed and was inspected for undissolved constituents, if any, crystallinity, color, and brittleness. It was then stored in paraffin-sealed bottles for microscopic examination. Thirty alloy specimens were polished and photomicrographed.

Results and Discussion

The results of thermal analysis are given in Tables I–VI. Two abbreviations are used: R. T., denoting cooling against room temperature; and S. C., cooling at a constant rate of 1° per min. The alloys are classified as belonging either to a specific cross section, such as Na_4Pb–Mg_2Pb, NaPb–Mg_2Pb, NaPb–Mg, Na_2Pb_5–Mg_2Pb, 15% atom magnesium, or 50% atom lead, or to a region, such as the lead corner. An alloy located at the intersection of two cross sections is found in the tables for both cross sections.

For alloys in the various cross sections of Tables I–IV, the temperature breaks are plotted in Fig. 1–6. The length of the solid vertical line immediately below an isothermal break is proportional to the time of the break. In several cross sections, notably the Na_4Pb–Mg_2Pb cross section, the final temperature breaks were characterized by a sharp rise and fall in temperature, which indicates a high degree of supercooling. This type of break is designated in the plots by triangles, which show both the beginning and the end of the temperature rise.

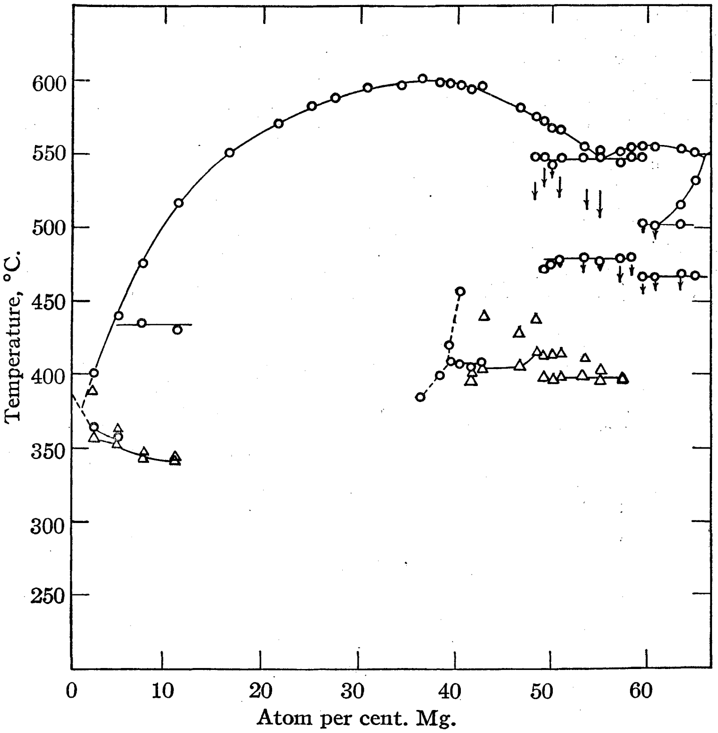


Fig. 6.—Na_4Pb–Mg_2Pb cross section. Time scale for temperature breaks, 50° = twenty minutes.

MgNaPb Surface of Primary Crystallization.—The surface of primary crystallization of the compound MgNaPb is bounded in part by the two incomplete binary eutectic curves and the one peritectic curve (GG') shown in Fig. 7. The temperatures along the curves are given at various points. The loci of the curves were determined from Fig. 1–5 and also from several other cross-sectional plots not shown in this paper.[3] The lim-

---

(3) The complete experimental data are given in Ethyl Corporation reports LTD 46-22 and LTD 47-32, which are available on request.

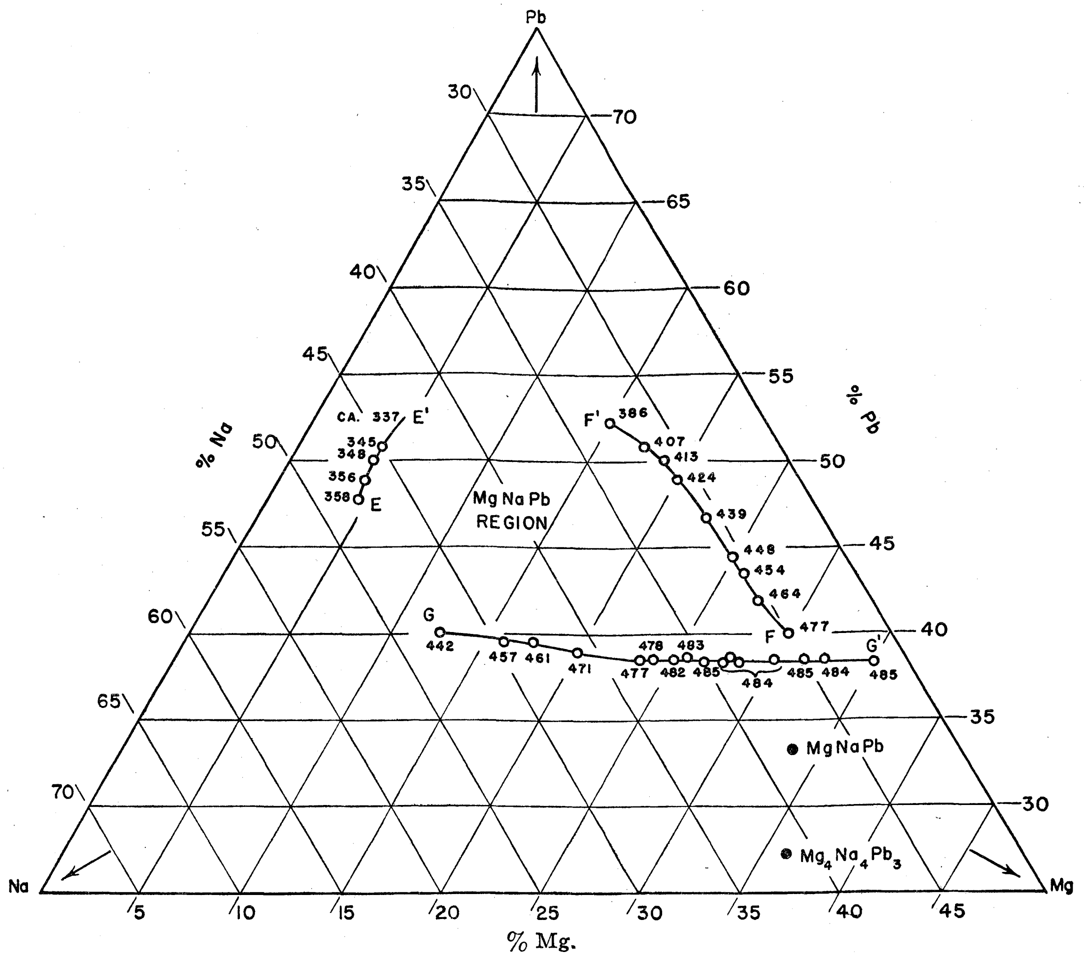


Fig. 7.—Binary eutectic curves of the region of primary crystallization of MgNaPb.

its of the surface of primary crystallization of MgNaPb are also indicated in Fig. 1–5.

From the cross-sectional shapes of the surface of primary crystallization of the compound (Fig. 1–5) and the isothermal plots of the primary temperature breaks (Fig. 8), it is evident that the surface of primary crystallization possesses no open-maximum point. It should be noted that the alloys in this region exhibited two or three temperature breaks; in general, the primary break was represented by a sharp change in the slope of the cooling curve and not by an isothermal flat.

MgNaPb Composition.—The method used to locate the compound MgNaPb is based on the fact that within the region of primary crystallization of a compound all alloys along a straight line passing through the compound composition will give the same secondary break, representing the intersection of the line with a binary eutectic curve bounding the region. Several such lines, each representing a simple secondary temperature break on the same binary eutectic curve, must themselves intersect at the location of the ternary compound.

Of the available data on the two eutectic curves (EE′, FF′) shown in Fig. 7, only that portion of the curve EE′ descending in temperature from the NaPb–Mg cross section in the direction of the Pb corner was used to locate the MgNaPb compound. The curve GG′ cannot be used for this purpose, since it cannot be reached *via* the primary precipitation of this compound.

In Fig. 2, 4 and 5, the curves for the secondary temperature breaks corresponding to the curve EE′ are indicated by ee′. By and large, the curves ee′ are well established. They show a gradual but sufficient change in temperature to define the lines of interest (the alloy compositions having the same secondary temperature break). Figure 9 shows four such lines, for the secondary breaks of 358, 340, 320 and 285°. (The 285° line gives, in reality, those compositions which show a second and final temperature break corresponding to a 285° eutectic.) On extrapolation, these lines intersect at the alloy composition $33^1/_3$ atom per cent. Mg, $33^1/_3$ atom per cent. Na and $33^1/_3$ atom per cent. Pb, or MgNaPb.

From the aforementioned analysis curves EE′ and FF′ in Fig. 7 are binary eutectic curves char-

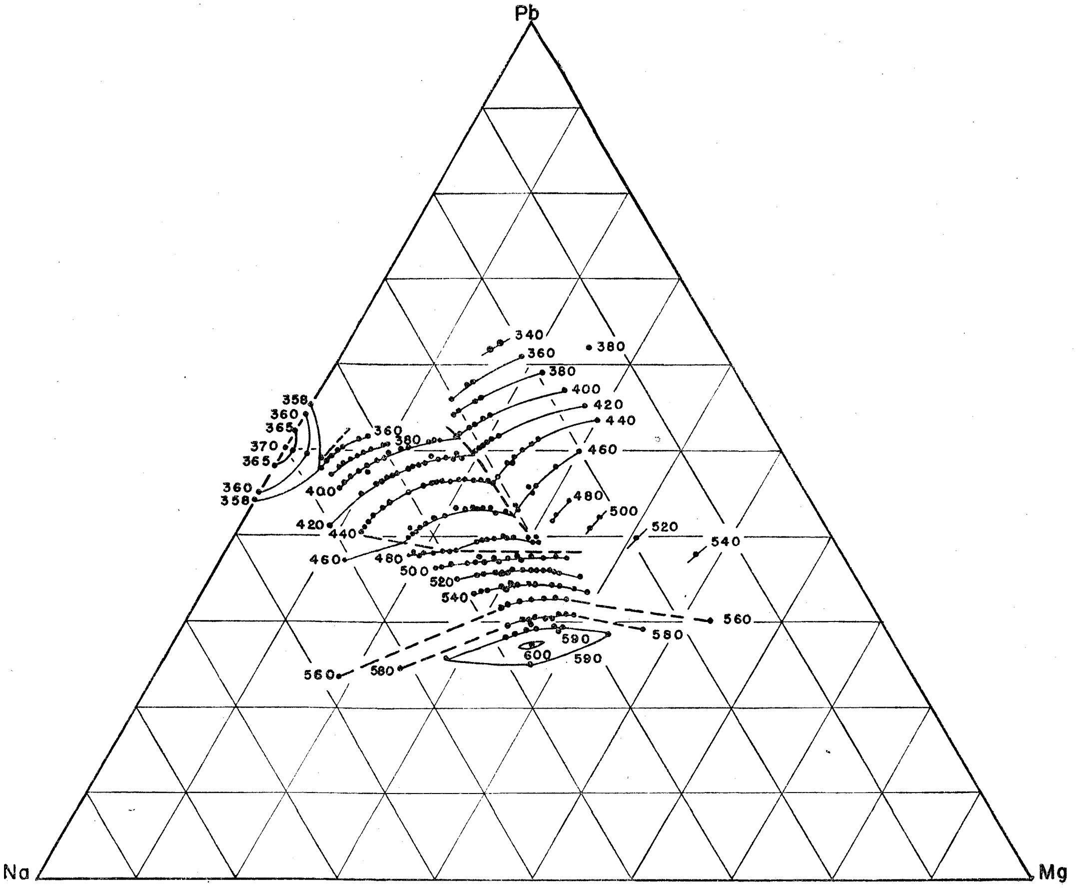


Fig. 8.—Isothermal curves of primary crystallization of the MgNaPb region and surrounding area.

acterized by the simultaneous crystallization of two different species. On the other hand, curve GG′ is apparently a binary peritectic curve at which solid and liquid react to give a second solid phase. The reaction must be

$$Mg_4Na_4Pb_3 + \text{liq.} \longrightarrow MgNaPb$$

Microscopic examination of the polished surface of the alloy MgNaPb revealed two regions. The main phase was dark-colored and constituted more than 90% of the surface area. The minor region was silver in color. Other alloys examined in the neighborhood of the alloy MgNaPb disclosed two or three regions, with the main phase being present in amounts below 90%.

Na_4Pb–Mg_2Pb Cross Section.—The Na_4Pb–Mg_2Pb cross section is shown in Fig. 6. The range of primary crystallization of the ternary compound $Mg_4Na_4Pb_3$ (at 36.36 atom per cent. magnesium in the Na_4Pb–Mg_2Pb cross section) appears to be quite large. The absence of lower breaks within part of the range is suggestive of solid solution in the compound. On the other hand, the ranges of primary crystallization of the binary compounds within the ternary system are very limited. Na_4Pb extends into the ternary diagram for less than 2.5 atom per cent. magnesium and Mg_2Pb for less than 2.0 atom per cent. sodium (approximately equivalent to 65 atom per cent. magnesium). The approximate equality of the initial temperature breaks between 55 and 65 atom per cent. magnesium might suggest a very flat surface of primary crystallization for Mg_2Pb. However, the existence in this region of non-isothermal breaks and of several lower temperature breaks precludes this possibility, which ordinarily would require a single secondary temperature break. The long duration of the initial temperature breaks for these alloys (Table IV) suggests that a ternary compound of high magnesium-to-sodium ratio may exist close to the cross section.

Temperature breaks characterized by a sharp rise were observed principally in the Na_4Pb–Mg_2Pb cross section.

Solid Solubility in the NaPb–Mg_2Pb Cross Section.—The NaPb–Mg_2Pb cross section, shown in Fig. 4, is well defined up to 45 atom per cent. magnesium. The limit of solid solubility in NaPb lies somewhere between 0.91 and 2.24 atom per cent. magnesium as measured along the cross section. With the former alloy, only a single temperature break was obtained and the presence of a single phase was confirmed by micro-

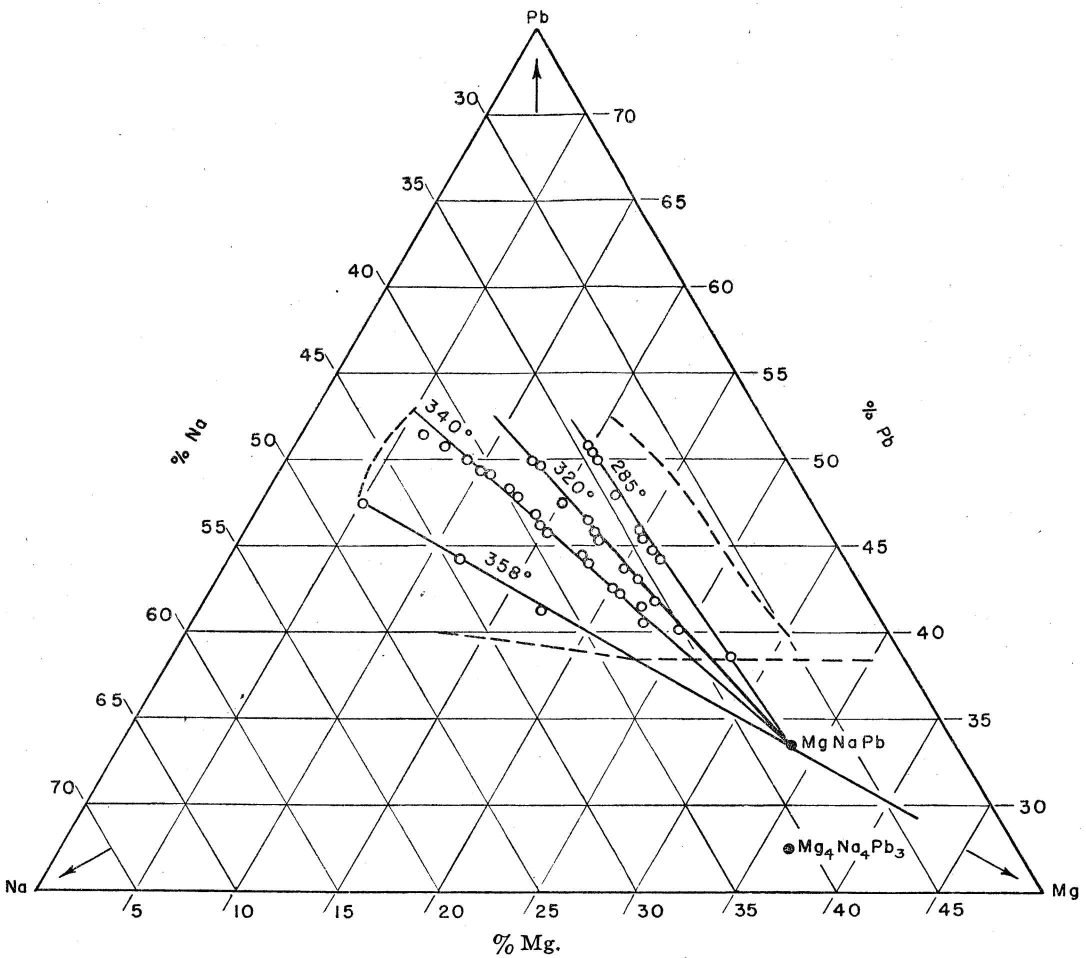


Fig. 9.—Method of locating the compound MgNaPb.

scopic investigation. With the latter alloy, three temperature breaks were obtained. No further attempt was made to establish more exactly the limits of solubility.

Summary

Approximately 120 individual alloy compositions within the ternary system Mg–Na–Pb were investigated by thermal analysis. The system was shown to be complex. A second compound, MgNaPb, was discovered, but unlike the first compound, $Mg_4Na_4Pb_3$ (which is of the open maximum type), it is of the peritectic type.

Several important cross sections of the system were partly elucidated. The lead corner was indicated to be the simplest region, while solid solutions were discovered in two regions and supercooling in others. Thirty alloys were photomicrographed, including the compound MgNaPb.

DETROIT, MICHIGAN RECEIVED AUGUST 18, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Magnetic Measurements on 2,2'-Benzothiazyl Disulfide and bis-(9-Ethoxy-10-phenanthryl) Peroxide

BY HOWARD G. CUTFORTH[1] AND P. W. SELWOOD

The purpose of this investigation was to test the possible formation of free radicals in appreciable concentrations from diaryl disulfides and diaryl peroxides.

The existence of reversible dissociation to free radicals has been amply demonstrated for the C–C, N–N and Cl–Cl bonds.[2] It has also been shown that the following apparently do not dissociate: Si–Si, Ge–Ge, Sn–Sn, Pb–Pb and As–As.

There appears to be no direct evidence that diaryldisulfides dissociate. But some of these compounds show deviations from Beer's law, an ability to react with triarylmethyl radicals, and certain chemical properties which suggest free radical reaction mechanism.[3]

Most of the evidence for free radical formation from peroxides lies in the kinetic evidence from polymerization reactions.[4–6] Other evidences include deviations from Beer's law and subnormal molecular weights at the freezing point of benzene.[7,8] The photochemical dissociation of peroxides into free radicals has often been proposed.[9–11] But the existence of univalent oxygen can scarcely be considered as established.

The possible formation of free radicals by disulfides and peroxides is of interest because it would add to the very small list of elements (C, N, Cl) which definitely show reversible dissociation. There are also practical reasons for wanting to know whether free radical concentration can be appreciable in polymerization and vulcanization, and in cystine and related compounds and derivatives of biochemical interest.

Our choice of the two compounds: 2,2'-benzothiazyl disulfide and bis-(9-ethoxy-1-phenanthryl) peroxide was based on the following considerations: The disulfide is of importance in the processing of rubber, although the mechanism by which it operates is little understood. There is a possibility that this mechanism involves free radicals. Furthermore, the compound is reversibly thermochromatic; the color begins to appear in toluene solution at about 80°.

The peroxide was chosen for study because the phenanthryl groups appear to offer a good opportunity for resonance stabilization of an aroxy radical, and because molecular weight studies by Goldschmidt[8] indicate that dissociation occurs.

Experimental

Preparation of Materials.—The 2,2'-dibenzothiazyl disulfide was obtained from the United States Rubber Company through the courtesy of Dr. R. H. Ewart.

The bis-(9-ethoxy-10-phenanthryl) peroxide was prepared from crude phenanthrene in three steps. First, phenanthrenequinone was prepared as described by Adkins.[12] From the quinone, 9-ethoxy-10-phenanthrol was prepared by the method of Fourneau and Matti.[13] The phenanthrol with ethyl alcohol of crystallization had a melting range of 77–79° which agrees with 77° as reported by Japp.[14] bis-(9-Ethoxy-10-phenanthryl) peroxide was obtained by mild alkaline oxidation of the phenanthrol.[2] The peroxide was crystallized from a very small amount of benzene. The resulting sample decomposed at 138–139°, which agrees with 138° reported by Goldschmidt. *Anal.* C, found 83.88, calcd. 83.78; H, found 6.14, calcd. 6.07; O, found 9.98, calcd. 10.15. This is for the peroxide crystallized with two moles of benzene.

Benzene and toluene used as solvents in these studies were prepared by repeated extraction with concentrated sulfuric acid until the acid layer had no color. After the solvent was washed with distilled water, sodium bicarbonate solution, and again with distilled water, it was dried overnight over sodium. Finally it was distilled from sodium, and the middle third collected for use.

Density and Magnetic Susceptibility Measurements.—Density measurements and magnetic measurements on the Gouy balance have been described,[15,16] as has the treatment of data.[17]

The effect of light on the magnetic susceptibility of the diaryl peroxide was investigated on a very sensitive type of magnetic balance, using a horizontal suspension and a permanent magnet. This balance will be described in a forthcoming publication.

Preparations of Solutions.—The disulfide and peroxide solutions investigated on the Gouy balance were prepared in an apparatus shown in Fig. 1, as follows:

The apparatus was evacuated through E, with metallic sodium in A. This was allowed to stand overnight. The solute was introduced to chamber D, and the solvent was poured into bulb A. After the apparatus had been evacuated and sealed at E, the solvent was distilled from A to F by cooling F. Subsequently, the solvent was filtered through a sintered glass disc, the solute in D was dissolved, the solution was filtered through a second sintered glass disc, and the remainder of the apparatus was sealed off at I.

The peroxide dissolved quite readily, but the toluene had to be heated to get appreciable disulfide into solution. By tilting the apparatus the magnetic sample tube J and the expansion pycnometer K were filled to the correct height and were sealed off at their respective constrictions.

Photochemical Dissociation.—No further description is needed for the Gouy type of magnetic measurements, which were performed over a range of temperature. But the method

---

[1] Present address: Rohm and Haas Company, Philadelphia, Pa.

[2] Waters, "The Chemistry of Free Radicals," Oxford University Press, Oxford, 1946.

[3] Schonberg, *Naturwissenschaften*, **21**, 561 (1933).

[4] Farmer and Michael, *J. Chem. Soc.*, 513 (1942).

[5] Kharasch, Chio and Brown, THIS JOURNAL, **62**, 2393 (1940).

[6] Wieland, Ploetz and Indest, *Ann.*, **532**, 166 (1937) *et seq.*

[7] Pummerer and Cherbuliez, *Ber.*, **47**, 2957 (1914).

[8] Goldschmidt and Schmidt, *ibid.*, **55**, 3194 (1922).

[9] Norrish and Banford, *Nature*, **138**, 1016 (1936).

[10] Glazebrook and Pearson, *J. Chem. Soc.*, 567 (1937).

[11] Walker and Wild, *ibid.*, 1132 (1937).

[12] Oyster and Adkins, THIS JOURNAL, **43**, 208 (1921).

[13] Fourneau and Matti, *Bull. soc. chim.*, **9**, 633 (1942).

[14] Japp, *Ber.*, **13**, 1306 (1879).

[15] Preckel and Selwood, THIS JOURNAL, **63**, 3397 (1941).

[16] Haller and Selwood, *ibid.*, **61**, 85 (1939).

[17] Selwood, "Magnetochemistry," Interscience Publishers, Inc. New York, N. Y., 1943, p. 124.

used for determining the effect of light on the magnetic susceptibility of peroxide solutions requires some further description.

A sample of peroxide was dissolved in benzene by mixing the two at room temperature. The magnetic sample tube and a 10-ml. weighing bottle were filled from a pipet. No special precautions were taken to exclude air because oxygen is reported to have little effect on peroxides of this type.[8] The solution so obtained was roughly analyzed for weight per cent. of peroxide.

The temperature of the suspended system during these observation was 25°. Changes of susceptibility were observed as linear displacements of the sample tube. These displacements were observed with a microscope and micrometer eyepiece. First, the sample was irradiated until a constant displacement was obtained. Then the system was left in the dark until a rest point was obtained.

Irradiation of the sample was furnished by two 200-watt tungsten lamps and by one mercury vapor lamp. However, as the sample tube was Pyrex glass, very little ultraviolet light reached the sample.

The time required for equilibrium in displacement was approximately thirty-five minutes. Observations were continued for thirty minutes after equilibrium had been reached.

Control experiments were made on pure benzene.

The quantity measured in the horizontal balance is the displacement, D. This displacement is perpendicular to the lines of flux in the magnetic field, and is caused by a change in magnetic susceptibility of the solution. Displacements could easily be read to 1×10^{-4} centimeter. This displacement was equivalent to a change of 4.68×10^{-10} unit of susceptibility.

Both in the light and in the dark we have the familiar relationship that $\chi_m = \chi_1 p_1 + \chi_2 p_2$, where χ_m is the susceptibility of the solution, χ_1 and χ_2, susceptibilities of the solute and solvent, and p_1 and p_2, weight fractions of solute and solvent. The temperature, fraction of solvent and susceptibility of solvent remain constant in light and dark; hence, the change in susceptibility on illumination of the sample

$$\Delta\chi = p_1(\chi_1^{\text{light}} - \chi_1^{\text{dark}})$$

but χ_1^{light} is equal to the algebraic sum of χ_1^{dark} and the susceptibility of any free radical which may be formed. Therefore,

$$\Delta\chi = p_1\chi_r$$

where χ_r is the susceptibility of the free radical. The molar paramagnetism for one unpaired electron spin at 25° is 1280×10^{-6}, so that the paramagnetic susceptibility for complete dissociation would be

$$2 \times 1280 \times 10^{-6}/M$$

where M is the molecular weight of the peroxide.

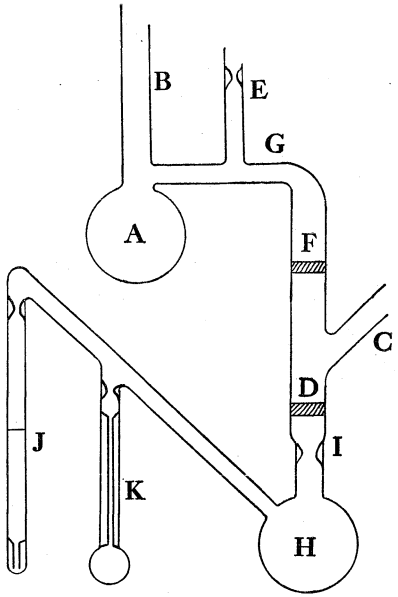


Fig. 1.—Apparatus for preparing peroxide and sulfide solutions and for filling pycnometer and magnetic sample tube.

The fraction of peroxide converted to free radicals is then

$$\alpha = \chi_r M/2 \times 1280 \times 10^{-6}$$

or, in terms of displacement in the horizontal magnetic balance

$$\begin{aligned}\alpha &= \Delta\chi M/2 \times 1280 \times 10^{-6} p \\ &= 1.8 \times 10^{-3}\, DM/p_1\end{aligned}$$

At a concentration of 3% peroxide, as little as 0.15% dissociation could be detected.

Results

Calibration of the Gouy magnetic balance was done with pure benzene and toluene, for which the susceptibilities at 25° were taken as -0.7065×10^{-6} and -0.7060×10^{-6}, respectively. The densities and susceptibilities at other temperatures as determined for this investigation are given in Table I. Table II shows the densities and susceptibilities of the diaryl peroxide dis-

TABLE I

DENSITIES AND MAGNETIC SUSCEPTIBILITIES OF BENZENE AND TOLUENE

Temp., °C.	Benzene		Toluene	
	d	$-\chi \times 10^6$	d	$-\chi \times 10^6$
10	0.8894 ± 0.0005	0.7072		
20	.8788	.7068		
25	.8734	.7065	0.8615	0.7060
30	.8680	.7064		
40	.8573	.7074		
50	.8465	.7084	.8283	.7068
60	.8356	.7094		
75			.8150	.7070
100			.7895	.7095
125			.7622	.7137
150			.7346	.7180

TABLE II

DENSITIES AND SUSCEPTIBILITIES OF BIS-(9-ETHOXY-10-PHENANTHRYL) PEROXIDE

Temp., °C.	Density of soln.	$\chi \times 10^6$ soln.	$\chi \times 10^6$ solute
Solvent, benzene; molality of peroxide, 0.0759			
20	0.8878	−0.7058	−0.677
30	.8773	− .7055	− .680
40	.8668	− .7059	− .663
Solvent, toluene; molality of peroxide, 0.00788			
20	.8675	− .7038	− .156
30	.8580	− .7044	− .215
40	.8487	− .7043	− .126
50	.8395	− .7051	− .239

solved in benzene and in toluene. The susceptibilities of the solutions are shown, in addition to the susceptibilities of the solute.

It will be noted that the solute is diamagnetic in all cases, and that it shows no temperature coefficient of susceptibility. The susceptibilities in toluene are numerically smaller than expected, but the low concentration of the solution renders the results in this solvent less accurate. We conclude that, under the conditions of these experiments, the diaryl peroxide is not dissociated to free radicals to an extent greater than 2%. This compares with a dissociation of 62% at room temperature reported by Goldschmidt.

However, the effect of light on the peroxide gave a positive change of susceptibility. The results are shown in Table III. The deflection was in the direction of increasing algebraic susceptibility. If this change is due to dissociation, then the degree of dissociation under these conditions is 6%. The measurements on the Gouy balance are done with the sample in the dark. Presumably Goldschmidt's molecular weight determination was done with the sample not specially protected from the light. He reports that the dissociation proceeds slowly. There is, therefore, not necessarily any contradiction between the earlier results and those reported here.

TABLE III

EFFECT OF LIGHT ON THE SUSCEPTIBILITY OF BIS-(9-ETHOXY-10-PHENANTHRYL) PEROXIDE

Temperature 25°; molality of peroxide, 0.0556

Condition	Scale reading cm. $\times 10^4$ Pure benzene	Peroxide soln.
Illuminated	26.0	11.0
Dark	25.0	29.0
Illuminated	25.0	12.0

We turn now to the results on the disulfide. These are given in Table IV.

TABLE IV

DENSITIES AND SUSCEPTIBILITIES AND DEGREE OF DISSOCIATION (α) OF 2,2'-BENZOTHIAZYL DISULFIDE

Solvent, toluene; molality of disulfide, 0.0148

Temp., °C.	Density soln.	$\chi \times 10^6$ soln.	$\chi \times 10^6$ solute	$\chi \times 10^6$ radical	α
25	0.8652	−0.7055	−0.6012	....	...
100	.7917	− .7077	− .3415	0.1996	0.032
125	.7672	− .7086	.3292	.8703	.151
150	.7427	− .7090	1.114	1.656	.305

Some comment is called for on the correction to be applied for the diamagnetism of the free radical. There are three ways of obtaining this correction. The first is to assume that no dissociation occurs at room temperature, hence the diamagnetism per gram of free radical is -0.6012×10^{-6}. Possibly this should be modified slightly because of the rupture of an S–S bond. The second method is by the use of Pascal's constants. These give a diamagnetism for the free radicals of -0.5400×10^{-6}. The third method is to measure the susceptibility of mercaptobenzothiazole and to correct for the additional hydrogen. The susceptibility of mercaptobenzothiazole at 25° was measured in toluene solution and found to be -0.5554×10^{-6}. Correction for the hydrogen atom gives a diamagnetism of the free radical of -0.5411×10^{-6}. This value was used in calculating the results shown in Table IV. Use of the larger diamagnetism derived from the disulfide at 25° would raise the degrees of dissociation somewhat.

However, the important conclusion is that the disulfide definitely forms free radicals. It is assumed that this occurs through dissociation across the sulfur–sulfur bond, but pending completion of ebullioscopic and other measurements now in progress it can scarcely be accepted as proved that dissociation produces the free radicals. Excitation to a triplet state would yield comparable magnetic results.

If dissociation actually occurs with the formation of thiol radicals then it is clear that the sulfur–sulfur bond breaks with considerably more difficulty than the carbon–carbon bond in hexaarylethanes. This result is, of course, not unexpected. The results reported here are scarcely accurate enough to make worthwhile a calculation of a heat of dissociation for the disulfide. But the heat is obviously greater than the 11 or 12 kilocalories per mole found for the hexaarylethanes.

The most interesting phase of these observations is the fact that free radicals must be formed in large amounts at temperatures used in the vulcanization of rubber with the disulfide. There is also raised the possibility that free radical concentration may be calculated for disulfides of biochemical interest at the temperature of the animal body.

It is a pleasure to acknowledge the support of the United States Rubber Company in connection with this work.

Summary

Magnetic measurements show that bis-(9-ethoxy-10-phenanthryl) peroxide does not dissociate appreciably in the dark in benzene or toluene solutions up to 50°. But exposure of the solu-

tion to light results in a magnetic change which could be interpreted as being due to appreciable dissociation.

A considerable degree of free radical formation is observed with 2,2′-dibenzothiazyl disulfide. The concentration of the thiol radicals in toluene has been measured up to 150°.

EVANSTON, ILLINOIS RECEIVED JUNE 20, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, SCHOOL OF MEDICINE, THE JOHNS HOPKINS UNIVERSITY]

Reaction Kinetics of Aliphatic Tertiary β-Chloroethylamines in Dilute Aqueous Solution. I. The Cyclization Process[1]

BY BARNETT COHEN, ERVIN R. VAN ARTSDALEN[2a] AND JOSEPH HARRIS[2b]

In contrast to ordinary alkyl halides, alkylamines possessing a halogen atom in the beta to omega position undergo a distinctive intramolecular transformation as the initial detectable reaction in polar solvents. The transformation yields halide ion and a more or less stable heterocyclic compound. In the case of the primary and secondary amines, the heterocycle may be either an imine or an imonium ion, depending on the *p*H of the solution. The tertiary amines can yield only the corresponding imonium ions.

The kinetics of the initial cyclization of a number of *primary* halogenated alkylamines has been reported.[3] The forward process of ring-formation was established as a unimolecular reaction, the rate of which was shown to be influenced by the length of the side-chain, by the substituents thereon, by the nature of the halogen and, especially, by the nature of the solvent.[4] The process is known to be reversible, but the kinetics of the reverse reaction seems not to have been studied, except for unsuccessful attempts[5] to determine an equilibrium constant in the β-bromoethylamine system. The failure was due to interference by side-reactions. It is known that in certain cases, at least, cyclic dimerization and linear polymerizations of the haloalkylamines can take place and become quantitatively important,[6] especially in concentrated solutions and at elevated temperatures.[7]

This report on a series of nine tertiary β-chloroethylamines supplements the older observations on the analogous primary amines. The compounds were of the general type $RR'NCH_2CH_2Cl$, where R and R′ represent an alkyl group or a β-substituted ethyl group. Analytic evidence adduced here and elsewhere[6,8] shows that these compounds undergo the following initial reversible reaction

$$RR'NCH_2CH_2Cl \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} RR'\overline{\overset{+}{N}CH_2C}H_2 + Cl^- \quad (1)$$

The first-order kinetics of the forward reaction can be established with relative ease because the reverse reaction is very much slower. The cyclic imonium ion is a reactive compound, but it possesses in many cases a fair degree of stability in water and can accumulate as reaction (1) proceeds.[6] The properties in solution and the reaction kinetics of the ethylenimonium ion will be considered in a subsequent report. In connection with the present discussion, it may be stated that the reaction kinetics indicates unequivocally that this ion is a singly charged cation.

Cyclization cannot occur when a proton is coordinated with the nitrogen atom of the amine. Consequently, in the case of these compounds, which are more or less weak bases, the rate of cyclization becomes a function of *p*H in solutions of moderate and low *p*H. In such cases, the observed rate constant, k'_1, is defined by the relation

$$k'_1 = \alpha k_1 = \frac{K'_a k_1}{K'_a + [H^+]}$$

where k_1 is the rate constant at *p*H conditions under which the ammonium ion is fully dissociated ($\alpha = 1$), and K'_a is the apparent dissociation constant of the ammonium ion as an acid.

It is obvious that the subsequent cyclization of a second and a third β-chloroethyl group, if present in these tertiary amines, is possible only after the antecedent heterocycle has been broken down,[9] *e. g.*, by hydrolysis. The rates of such subsequent cyclizations can best be determined by kinetic study of the corresponding chlorohydrins, as has been done in the case of N-methyl-bis-(β-chloroethyl)-amine and its chlorohydrin (see

---

(1) The work described in this report was performed in major part under a contract recommended by the National Defense Research Committee, between the Office of Scientific Research and the Johns Hopkins University.

(2) (a) Present address: Department of Chemistry, Cornell University, Ithaca, N. Y. (b) The volunteer assistance of Marie E. Perkins is gratefully acknowledged.

(3) Freundlich, *et al.*, *Z. physik. Chem.*, **76**, 99 (1911); **79**, 681 (1912); **101**, 177 (1922); **122**, 39 (1926); **166A**, 161 (1933).

(4) Salomon, *Helv. Chim. Acta*, **16**, 1361 (1933); *Trans. Faraday Soc.*, **32**, 153 (1936).

(5) Freundlich and Neumann, *Z. physik. Chem.*, **87**, 69 (1914).

(6) Golumbic, Fruton and Bergmann, *J. Org. Chem.*, **11**, 518 (1946). This and the seven succeeding papers describe the chemical properties of the tertiary β-chloroethylamines.

(7) *Cf.* Lehmann, Thompson and Marvel, THIS JOURNAL, **55**, 1977 (1933).

(8) Hartley, Powell and Rydon, 1942, 1943. Unpublished data obtained in Great Britain; also *J. Chem. Soc.*, 513, 519, 527 (1947).

(9) This restriction need not apply to analogous secondary bis-β-halogenated amines which should permit double cyclization at a *p*H favorable to the ionization of the coördinated proton created by the initial cyclization.

TABLE I

TERTIARY ALKYL β-CHLOROETHYLAMINES: $\begin{matrix}\mathrm{R}\\ \mathrm{R'}\end{matrix}\!\!>\!\mathrm{NCH_2CH_2Cl}$. ANALYSES OF THE HYDROCHLORIDES, APPARENT ACID DISSOCIATION EXPONENTS, AND KINETIC CONSTANTS FOR THE INITIAL CYCLIZATION OF THE AMINES IN WATER

R	R′	M. p., °C. cor.	Analyses, % Calcd. N	Calcd. Total Cl	Found N	Found Total Cl	pK'_a ($\Gamma/2$ = 0.0025) 0°		25°		10^2k_1 (min.$^{-1}$) 0°	15°	E kcal.[h] per mole	$\Delta F^‡$ kcal.[i] per mole	$\Delta S^‡$ E. U[i]
$—CH(CH_3)_2$	$—CH_2CH_2Cl$	211–212	6.35	48.22	6.3	48.3	7.3	±0.05	7.0	±0.05	5.51	49.0	23.0	19.7	10.0
$—(CH_2)_2CH_3$	$—CH_2CH_2Cl$	118–119[a]	6.35	48.22	6.4	48.2	7.02	± .02	6.7	± .05	2.02	21.7	24.8	20.3	14.6
$—(CH_2)_3CH_3$	$—CH_2CH_2Cl$	95–96	5.97	45.34	6.1	45.3	6.97[f]	± .02	6.63[f]	± .02	1.54	15.4	24.0	20.4	11.1
$—CH_2CH_3$	$—CH_2CH_3$	210–211[b]	8.14	41.21	8.0	41.3	9.18	± .02	8.82	± .02	1.58	14.5	23.1	20.4	7.8
$—CH_2CH_3$	$—CH_2CH_2Cl$	141–142	6.78	51.50	6.8	51.6	6.8	± .05	6.57	± .05	1.17	12.8	25.0	20.6	14.2
$—CH_2CH_2Cl$	$—CH_2CH_2Cl$	130–131[c]	5.81	58.85	5.7	59.2	4.66[g]	± .02	4.39[g]	± .02	0.69	7.3	24.7	20.9	12.1
$—CH_2CH_2OCH_3$	$—CH_2CH_2Cl$	132–133	5.92	44.96	5.9	45.0	5.73[f]	± .02	5.47[f]	± .02	.49	5.2	24.6	21.1	11.0
$—CH_3$	$—CH_2CH_2Cl$	109–110[d]	7.28	55.25	7.2	55.1	6.78	± .02	6.45	± .02	.23	2.4	24.1	21.5	7.7
$-CH_3$	$-CH_2CH_2OH$	[e]	8.05	40.74	7.9	40.6	7.83	± .02	7.5	± .05	.27	2.3	21.9[i]	21.5	0.0

[a] Reported 118–119.5° by G. H. Coleman, personal communication. [b] Reported 211° by R. L. Shriner, personal communication; 210–211° by Gough and King, *J. Chem. Soc.*, 2426 (1928). [c] Reported 130–131° by Ward, THIS JOURNAL, **57**, 916 (1935). [d] Reported 110° by Jensen and Lundquist, *Dansk. Tid. Farm.*, 15, 201 (1941). [e] Hygroscopic; chief impurity water, m. p. 50°, R. L. Shriner, personal communication; 54° (ref. 8). [f] $\Gamma/2$ = 0.0015. [g] $\Gamma/2$ = 0.001. [h] ±1 kcal. Reported for primary β-bromoethylamine and β-chloroethylamine, 24.9 and 27.5 kcal., respectively (ref. 4). [i] ±2 kcal. [i] ±4 E. U. Calcd. for 0° assuming transmission coef. = 1 (ref. 18).

Table I, last two compounds). Unless otherwise specified, this report deals with the first cyclization process.

Experimental

Temperatures (except at 0°) were maintained to ±0.05° in an electrically controlled, light-oil bath. Crushed melting ice surrounded the vessel of well-stirred solution in the measurements at 0°.

Materials.—The stable crystalline hydrochlorides of nine tertiary β-chloroethylamines[10] were employed. The free amines were sufficiently soluble in water for the purposes of these studies; however, the low solubilities of N-benzyl- and N-cyclohexyl-bis-(β-chloroethyl)-amines did not permit comparable evaluation of their properties. The purity and identity of the hydrochlorides is indicated by our analytical data shown in Table I. Total chlorine was determined after digestion of the samples in strong NaOH. Ionic chlorine (not recorded in Table I) was also determined and found to check the analyses reported. The melting points were accompanied by more or less sintering and decomposition.

Determination of pK'_a.—The apparent acid dissociation constant of each amine was determined by electrometric titration. The measuring system consisted of a glass electrode and a Type 7660 Leeds and Northrup potentiometer–electrometer. The electrode was standardized with 0.05 M potassium acid phthalate (primary standard, reagent grade) on the basis of the following values: pH 4.005[11] at 0° and pH 4.00[11,12] at 10° and 25°. Linearity in response of the electrode to pH-change was checked in standardized (Clark and Lubs) phosphate buffers at pH 6 and 8. In more alkaline regions, the electrode was standardized in borate buffers of known pH.

The titrations were made with standardized 2 N sodium hydroxide delivered from a calibrated microburet graduated in 0.001 ml. into 100 ml. of an aqueous 0.0025 M solution of each amine hydrochloride. The volume change was negligible, and the added Na^+ ion was too low in concentration to influence the glass electrode significantly in the alkaline region. Instability of some of the compounds made it necessary to complete their titrations within 5 to 8 min. The degree of contamination from carbon dioxide of the air during a titration was found to be 1 × 10^{-4} milliequiv./minute per 100 ml. of water at pH 9.0, and 15°. Titrations of the amines were so conducted as to hold the maximum carbon dioxide-contamination to less than 0.001 milliequiv. for the total of 0.250 milliequiv. of compound titrated. The apparent dissociation constant, in terms of pK'_a, was calculated from the titration data in the usual manner,[13] using for pK_w the values: 14.940 at 0°, and 14.340 at 15° (ionic strength 0.0025).[14] The pK'_a values thus determined are shown in Table I. The temperature coefficient, $-\Delta pK'_a/\Delta 10°$, was found to be 0.2 (range, 0.17 to 0.23 ± 0.02). Increase in ionic strength from 0.0025 to 0.15, with sodium chloride, produced the same increase (0.05) in pK'_a as that reported for the NH_4^+ ion.[14]

Rate Measurements.—In order to hold side reactions, such as polymerizations, within negligible limits, the compounds were studied at sufficiently low concentrations. The criterion for this was established by the uniformity of the first order rate constants found for the cyclization in 0.0005 to 0.1 M solutions of the type compound, N-methyl-bis-(β-chloroethyl)-amine. In general, the concentration used was 0.0025 M. The kinetics of the cyclization was determined most conveniently and accurately by the rate of production of Cl^-, and confirmed on occasion by measurement of the rate of decrease of the parent amine or of production of the cyclic imonium ion.

The stock solution of each amine hydrochloride, 0.1 to 0.5 M, was prepared by dissolving the appropriate, accurately weighed amount of carefully dried hydrochloride in iced 0.001 to 0.05 N HCl. In sufficiently acid stock solutions, cyclization with Cl^- evolution did not occur at a measurable rate. The solutions of compounds with $pK'_a > 6$ could be preserved for one to three days at 0 to 5° without detectable decomposition. The usual procedure in making a rate measurement was as follows. The aqueous medium, 99 ml., containing the calculated amount of sodium hydroxide for the predetermined pH, plus 0.0002 to 0.0004% sulfonphthalein indicator and other reagents as required, was brought to constant temperature; and then, under vigorous stirring, there was added rapidly from a chilled, calibrated, all-glass syringe, 1.00 ± 0.005 ml. of the stock solution. Zero time was taken at the half-time of delivery of the solution. The momentary, initial change in temperature was negligible. The reaction was quenched in successive samples by withdrawing usually 10 ml. and adding it with stirring to 0.01 to 0.02 N nitric or sulfuric acid. Time of quenching was taken

---

(10) We are indebted to Dr. George H. Coleman, Dr. Ralph L. Shriner and Dr. Calvin Golumbic for furnishing one or more samples of these compounds.

(11) M. Dole, "The Glass Electrode," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 156.

(12) MacInnes, Belcher and Shedlovsky, THIS JOURNAL, **60**, 1094 (1938).

(13) Van Slyke, *J. Biol. Chem.*, **52**, 525 (1922).

(14) Everett and Wynne-Jones, *Proc. Roy. Soc.* (*London*), **169A**, 190 (1938).

at the half-time of delivery of the sample. Cl^- evolved in the cyclization process was determined in the quenched samples by differential potentiometric titration with standardized silver nitrate.[15] Ethylenimonium ion was measured by its uptake of thiosulfate[6] and the residual $S_2O_3^=$ was determined iodimetrically. Residual amine was only roughly determined, after acidification of the mixture to quench the reaction, by rapid potentiometric acid–base titration at 0 to 5°.

The pH was held constant without buffers by adding micro-quantities of alkali or acid to the reaction mixture as required and using a glass electrode or the appropriate sulfonphthalein as pH indicator. The acid production was evaluated according to the experimental conditions and was assignable (a) to more or less slight hydrolysis of the initial cyclic product of the amine, (b) to H^+ from the ammonium ion of the amine when the cyclization was conducted at a pH at which $\alpha < 1$, or (c) to zero-order contamination by atmospheric carbon dioxide during prolonged runs. Under proper conditions, there was little or no pH-change during the major part of the cyclization process when the product was one of the more stable ethylenimonium ions.

A stopwatch, reading to 0.01 minute and standardized against an electric clock, was used to time the reactions.

Errors.—In the case of the more strongly basic amines, the reaction was necessarily conducted at a pH at which α was less than 1. This involved an error of ±0.02 to 0.05 in the pK'_a determination and the pH maintenance. In the case of those compounds having a pK'_a between 6.5 and 7.0, the corresponding maximum probable error in the rate constant was 2 to 3%. For the two compounds with a pK'_a higher than 7 (see Table I), the corresponding maximum probable errors were three to five times as great. The fact that duplicate determinations agreed to ±5% was probably due to a compensation of errors. Errors due to temperature variations and the preparation and analysis of the solutions were small. In most cases the over-all error was within 10%; it was somewhat greater, within 15%, for the last compound of Table I.

Results and Discussion

Rapid, successive acid–base titrations of one of these tertiary amines as the reaction progressed gave symmetrical titration curves, centered at $pH = pK'_a$, which finally merged with the titration curve of water of the same ionic strength. The disappearance of the amine during the reaction, and the absence of other titratable base in the pH range 3 to 11 are consistent with the interpretation that the transformation product is a quaternary ammonium ion.

TABLE IIa

INITIAL CYCLIZATION RATE OF $C_2H_5N(CH_2CH_2Cl)_2$

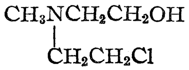
Temp. 0.0°. Initially, [amine·HCl] = [NaOH] = 0.0026 mole/liter; neutralized thymol blue, 0.0004%; pH 9.1; $\alpha \cong 1.00$.

Reaction time, min.	Cl^- produced, %[a]	$k_1 \times 10^2$ min.$^{-1}$
2.15	3.0	(1.4)
8.1	11.9	1.27
15.0	17.8	1.02
25.2	26.7	1.12
40.0	39.2	1.26
60.0	51.3	1.11
90.0	66.3	1.23
123.0	77.2	1.18
	Av.	1.17 ± 0.09
	Duplicate	1.17

[a] 100% = 1 equivalent of Cl^- per mole of amine.

TABLE IIb

CYCLIZATION RATE OF



$$CH_3\underset{\displaystyle CH_2CH_2Cl}{\overset{}{N}}CH_2CH_2OH$$

Temp. 15.0°. Initially, [amine·HCl] = 0.0025 mole/liter; NaOH to pH 7.9, α = 0.715; neutralized phenol red, 0.0002%.

Reaction time, min.	Cl^- produced, %	$\alpha k_1 \times 10^2$ min.$^{-1}$
5.0	9.7	(2.03)
10.0	15.8	1.41
20.0	28.1	1.58
30.0	40.5	1.88
40.0	48.5	1.48
60.0	63.0	1.65
90.0	77.4	1.64
		Av. 1.61 ± 0.16

$k_1 = 0.0161/0.715 = 0.023$ min.$^{-1}$

The initial cyclization of each of the compounds followed a uniform unimolecular course throughout the major portion of the process. By way of illustration, Tables IIa and IIb show the results of two typical determinations based on measurements of the production of chlorine ion.

Within the experimental error, the rate of Cl — evolution from the type compound, N-methyl-bis-(β-chloroethyl)-amine, was independent of the ionic strength of the solution (Table III).

TABLE III

EFFECT OF IONIC STRENGTH ON RATE OF CYCLIZATION

0.005 M $CH_3N(CH_2CH_2Cl)_2$, pH 8.0, 30.0°

$[Na_2SO_4]$ mole/liter	Total ionic strength	k_1 min.$^{-1}$
0	0.005	0.197
0.005	.020	.190
.050	.155	.187
.50	1.51	.199
.93	2.80	.202

Subsequent hydrolysis of the cyclic imonium ion was generally much slower, so that the second cyclization, if any, did not make a detectable appearance until the initial cyclization was well advanced. This is in accord with repeated observations that the early phase of the cyclization, when conducted under appropriate pH conditions, occurred without detectable acid production at 0° and 15°. A closer examination was made of the acid production during the initial cyclization of N-methyl-bis-(β-chloroethyl)-amine at 25°, with the aid of the glass electrode. The titration, compared with the per cent. cyclization (computed), during the first eight minutes gave the results shown in Table IV. The very small amount of acid produced and its progressive increase agree, within experimental error, with the values computed from the separately determined constants for a system of two consecutive first-order proc-

---

[15] MacInnes and Dole, THIS JOURNAL, **51**, 1119 (1929).

esses. There was no evidence during any of these cyclizations for the appearance of extra acid assignable to a concurrent reaction of water with the postulated intermediate carbonium ion.

TABLE IV

ACID PRODUCTION DURING CYCLIZATION OF $CH_3N(CH_2CH_2Cl)_2$

Temp. 25.0°. Initially, [amine·HCl] = [NaOH] = 3.513×10^{-3} mole/liter; pH 8.8; $\alpha = 1.00$.

Reaction time, min.	Cyclization, %	Acid produced, % Obs.	Acid produced, % Calcd.[a]
2.0	17.8	0.02	0.02
3.0	25.3	.03	.05
4.0	32.4	.07	.08
5.0	38.7	.10	.12
6.0	44.5	.15	.17
7.0	49.6	.20	.23
8.0	54.3	.28	.28

[a] % Acid = $100\,[1 - (k_2/(k_2 - k_1))e^{-k_1t} + (k_1/(k_2 - k_1))e^{-k_2t}]$; $k_1 = 0.098$ min.$^{-1}$; $k_2 = 1.16 \times 10^{-3}$ min.$^{-1}$ (unpublished data).

In the presence of $S_2O_3^{=}$, the rates of initial cyclization of the bis-(β-chloroethyl)-amines determine the rates of thiosulfate uptake by the corresponding cyclic transformation products. In such cases, the cyclization rates measured by the thiosulfate uptakes agreed well with those measured by the production of Cl^-. An example is shown in Table V which includes also the result obtained by direct titrimetric estimation of the decomposing amine.

The results of the kinetic measurements at 0 and 15° are summarized in Table I in which the compounds are listed in the order of decreasing k_1 at 15°. Inspection of this table shows that the rate constants for members of the homologous series of compounds, N-methyl- through N-*n*-butyl-bis-(β-chloroethyl)-amine, including the isopropyl homolog, fall in the order of the electron-donating abilities of these amines as measured by the respective pK_a' values.

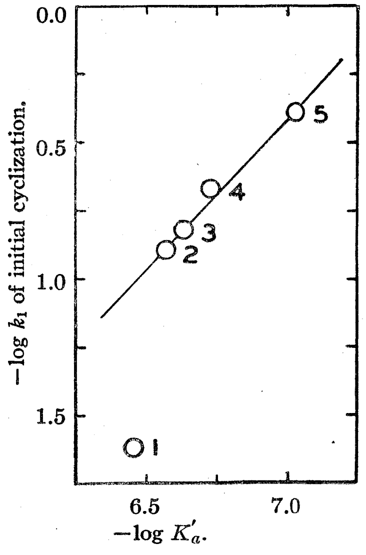


Fig. 1.—Relation of rate and dissociation constants at 15° of homologous tertiary bis-(β-chloroethyl)-amines, $RN(CH_2CH_2Cl)_2$: 1, R = methyl; 2, ethyl; 3, *n*-butyl; 4, *n*-propyl; 5, isopropyl.

TABLE V

INITIAL CYCLIZATION RATE OF $(CH_3)_2CHN(CH_2CH_2Cl)_2$

Temp. 0.0°. Initially, [amine·HCl] = 0.0025, and $[Na_2S_2O_3]$ = 0.025 mole/liter; 0.0002% phenol red; NaOH to pH 7.4; $\alpha = 0.557$.

Reaction time, min.	$S_2O_3^{=}$ uptake, %[a]	$\alpha k_1 \times 10^2$ min.$^{-1}$
2.0	5.0	(2.5)
5.0	15.6	3.41
9.0	22.8	2.87
20.1	49.8	3.44
28.1	62.0	3.45
		Av. 3.29 ± 0.28

$k_1 = 0.0329/0.557 = 0.059 \pm 0.005$ min.$^{-1}$

By Cl^- production = .055 ± 0.004 min.$^{-1}$

By amine decomp. = .057 ± 0.007 min.$^{-1}$

[a] 100% = 1 mole $S_2O_3^{=}$ per mole of amine.

Figure 1 shows that the relation between log k_1 and log K_a' is linear for these homologous bis-(β-chloroethyl)-amines, with appreciable deviation only in the case of the N-methyl homolog. Deviation is often observed in the case of the first member of a series of alkyl homologs in numerous properties. The similar, but not strictly homologous compound N-β-methoxyethyl-bis-(β-chloroethyl)-amine does not fit into this linear relation, its cyclization rate being about ten times greater than would be predicted from its pK_a' value. The significance of this behavior has not been established. The effect might be due to the basicity of the methoxyl group or to direct interaction of this group with the β-chlorine atom. The unlikely possibility of competitive cyclization involving displacement of the methoxyl group is excluded because such competition would be expected to *retard* the apparent rate of normal cyclization as measured by production of Cl^-.

Illustrative of the importance of the properties determining the pK_a' in controlling the rate of cyclization is the following comparison in which the amines *a* to *c* are arranged in decreasing order of pK_a' and k_1. On ordinary statistical grounds,

		pK_a'	k_1
(*a*)	$(C_2H_5)_2NCH_2CH_2Cl$	8.82	0.145
(*b*)	$C_2H_5N(CH_2CH_2Cl)_2$	6.57	.128
(*c*)	$N(CH_2CH_2Cl)_3$	4.39	.073

compound *a* might be regarded as having one, *b* two, and *c* three chances for the initial cyclization to occur; yet compound *a*, despite this least favorable chance, undergoes the most rapid cyclization. In the above series of three compounds, the progressive decrease in pK_a' is due to the cumulative decrease in basicity of the central nitrogen atom induced by successive β-substitutions of chlorine.

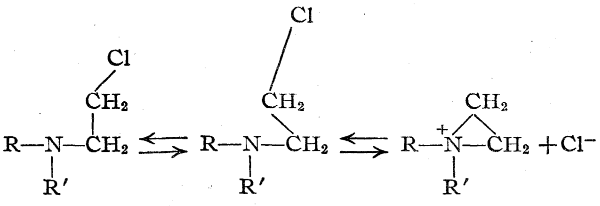
In terms of the transition state theory of chemical reaction, the linear relationship between log k_1 and log K'_a suggests that the free energy changes ($-RT$ ln k_1) associated with the equilibrium between the initial and transition states in the cyclization of the homologous bis-(β-chloroethyl)-amines is directly proportional to the free energy changes ($-RT$ ln K'_a) involved in the acid–base dissociations of the corresponding amines. Such a relation in a group of closely related reactions has been observed[16] frequently, for example in general acid–base catalysis,[17] and in the second order reactions of certain types of substituted benzene derivatives.[16] The present limited series of homologous aliphatic tertiary amines involving a unimolecular process provides a further instructive example of this correlation.

The parameters E and A of the empirical Arrhenius equation

$$k_1 = Ae^{-E/RT}$$

have been computed. The values for the activation energy, E, are given in Table I. The frequency factor, A, in the kinetics of this series of compounds is found to have values between $10^{14.9}$ to $10^{16.4}$ sec.$^{-1}$, and compares with the value of 10^{15} sec.$^{-1}$ recomputed from the data[4] for the cyclization of primary β-bromoethylamine. This level of A, associated with the displacement of the halogen for closure of the three-membered ring, is about 10^1 to 10^3 times greater than the values, 10^{13} to $10^{13.7}$ sec.$^{-1}$, reported for the closure of analogous primary amines to 4-, 5- and 6-membered rings,[4] or the values 10^{13} to 10^{14} sec.$^{-1}$ predictable from the theory of absolute reaction rates for unimolecular reactions with low entropy of activation and high transmission coefficient.[18] The higher frequency factor, which can be regarded as a measure of the greater occurrence of cyclization, is consistent with the concept of a coiled configuration of the side chain incident to formation of the incipient ring in the activated complex of the β-chloroethylamines in water.

The process of cyclization evidently consists of an intramolecular displacement of the alkyl halogen by the basic nitrogen atom of the tertiary β-chloroethylamine. In this process, the strongly polar molecule tends to coil up toward the ring position under the influence of the polar solvent, so that the general configuration of the activated complex (II) would be expected to resemble both the normal molecule (I) and the cyclic end-product (III).



(I) (II) (III)

The thermally activated complex, upon rupture of its stretched C–Cl bond, would yield a carbonium ion. The latter, however, should have but a momentary existence, because its need for sharing an electron pair is most easily satisfied by the unshared pair on the nitrogen, the positive charge moving from C to N in the newly formed ring compound. The ring closure must be much more rapid than either the possible reaction of the carbonium ion with water or the activation of the parent amine with ejection of Cl^-, because electron donor–acceptor reactions are much faster than those associated with thermally activated covalent bond dissociations, which in the present case involve the not inconsiderable strengths of the oxygen–hydrogen and carbon–chlorine bonds. Thus the carbonium ion concentration during the cyclization of these amines should be practically nil, and the experimental observations previously discussed, and illustrated in Table IV, are in harmony with this interpretation.

Summary

1. The apparent acid dissociation exponents (pK'_a) of nine tertiary β-chloroethylamines have been measured in dilute aqueous solution at 0 and 15°.

2. Studies of the initial, detectable reaction of these compounds, in dilute aqueous solution under controlled conditions of pH at temperatures between 0 and 30°, show that a chloride ion and a relatively stable cyclic imonium ion are formed by a strictly first order process. A mechanism for this reaction has been proposed. A linear correlation has been shown to exist between pK'_a and $-\log k_1$ for this process in the case of a series of homologous alkyl bis-(β-chloroethyl)-amines.

BALTIMORE 5, MD. RECEIVED JULY 16, 1947

---

[16] Hammett, *Chem. Rev.*, **17**, 125 (1935).

[17] Brönsted, *ibid.*, **5**, 231 (1928).

[18] Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., New York, N. Y., 1941.

[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES (A DIVISION OF SOCONY-VACUUM OIL CO., INC.) RESEARCH AND DEVELOPMENT DEPARTMENT]

Metalation Studies in the Thiophene Series. I. Preparation of 2-Thienylsodium and the 5-Halo-2-thienylsodiums

JOHN W. SCHICK AND HOWARD D. HARTOUGH

It has been found that 2-thienylsodium can be prepared in 84% yields from 2-chlorothiophene and metallic sodium in an inert solvent above 50°. Likewise, yields up to 89% have been obtained from thiophene, sodium amalgam, and an alkyl or aryl halide. The yields were determined from the isolated 2-thiophenecarboxylic acid after carbonation and acidulation.

Schorigin[1] metalated thiophene with diethylmercury and sodium. Gilman and Breuer[2] metalated thiophene in substantially the same fashion with 2,2′-difurylmercury and sodium to obtain a 16% yield of 2-thiophenecarboxylic acid after carbonation.

Investigations in these laboratories indicated that thiophene could not be metalated directly. Further, it was found that thiophene, an alkyl or aryl halide, and sodium gave no 2-thienylsodium. This would indicate that mercury is essential to the metalation.

When 2-chlorothiophene and sodium reacted in an inert solvent above 50°, the normal metathetical reaction occurred to yield 84% of 2-thienylsodium. Table I indicates the solvents and temperatures that were employed and the products that were isolated.

TABLE I

EFFECT OF SOLVENT AND TEMPERATURE ON THE METALATION OF 2-CHLOROTHIOPHENE

Solvent	Temp., °C.	% Yield of 2-thiophene-carboxylic acid
Anisole	40	..
Anisole	50–55	3
Diphenyl ether	40	..
Butyl ether	40–50	..
Butyl ether	50–55	3
Isopropyl ether	67–70	<1
Diethyl ether	−30	..
Diethyl ether	0	16[a]
Diethyl ether	35–39	92[a]
Benzene	80–84	84
Toluene	112	31

[a] The product isolated was 5-chloro-2-thiophenecarboxylic acid.

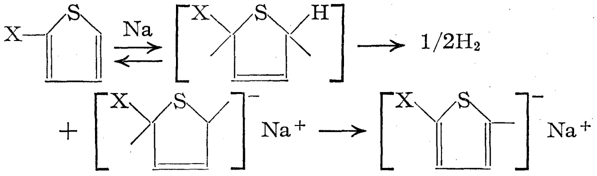
Solvent volume had a marked effect upon the yield of 2-thiophenecarboxylic acid from 2-chlorothiophene and sodium. The yields decreased from 84 to 20% when the benzene solvent volume was decreased from one liter to 100 ml. per mole of 2-chlorothiophene. A marked increase in reaction rate was noted with lower amount of solvent and cooling was necessary in order to control the reaction.

Further studies revealed that 5-halo-2-thienylsodium compounds, heretofore unknown, could be prepared by the direct metalation of the 2-halothiophenes with sodium below 50° if ethyl ether was employed as a solvent.

Direct metalation of a heterocyclic ring involving replacement of an acidic hydrogen by an alkali metal has been carried out in small yields by other investigators. Gilman and Breuer[2] metalated furan and 2-methylfuran with a liquid sodium–potassium alloy. Somewhat better yields of the organo-alkali compounds were obtained by indirect metalation, or "transmetalation," through the action of sodium on dialkyl- or diaryl-mercury in the presence of heterocyclic compounds. Wooster and Mitchell[3] and Conant and Wheland[4] arranged the very weak acids (hydrocarbons) in a series of acid strengths, based on their metathetical reaction with organo-alkali compounds.

Gilman and Wright[5] prepared 3-furylsodium by reacting 3-iodofuran with a sodium-potassium alloy. Subsequent carbonation yielded 3-furoic acid.

The 2-halo(chloro-, bromo- and iodo-)-thiophenes are unique in their reaction with sodium in that the same reaction does not occur as with 3-iodofuran. Instead, they metalate in the 5-position with the liberation of hydrogen and the formation of 2-halo-5-thienylsodium (preferable nomenclature is 5-halo-2-thienylsodium). A possible mechanism can be indicated as



Carbonation and acidulation of the 5-halo-2-thienylsodium yielded the corresponding 5-halo-2-thiophenecarboxylic acid.

Factors influencing the yield of 5-chloro-2-thienylsodium are the quantity of ether solvent, the particle size of the sodium, the presence of mercury, and the temperature.

Diethyl ether was the only solvent in which the reaction took place. No reaction was observed in butyl ether, diisopropyl ether, diphenyl ether, anisole, hexane, benzene, and toluene. Judging

---

(1) Schorigin, *Ber.*, **43**, 1938 (1910).

(2) Gilman and Breuer, THIS JOURNAL, **56**, 1123 (1934).

(3) Wooster and Mitchell, *ibid.*, **52**, 688 (1930).

(4) Conant and Wheland, *ibid.*, **54**, 1212 (1932).

(5) Gilman and Wright, *ibid.*, **55**, 2893 (1933).

from the work of Scott, Walker and Hansley[6] methyl ether, methyl ethyl ether and the dialkyl ethers of ethylene glycol would also be suitable solvents.

The yields are dependent on the amount of ether solvent used. Yields decreased from 92 to 50% on reducing the amount of solvent from one liter to 100 ml. per mole of 2-chlorothiophene. The reaction rate is increased greatly and cooling is necessary with less solvent.

Reduction of the particle size of the sodium from approximately 16 mesh to a fine dust increased the yields from 20 to 70%. In order to produce more finely divided or more active sodium, a 70% sodium amalgam was employed. In this manner the yields of 5-chloro-2-thiophenecarboxylic acid were increased from 70 to 92%. The mercury was recovered without appreciable loss.

The optimum temperature is the reflux temperature of ethyl ether, 35–39°. Below that temperature the yields decrease for comparable reaction times, and the reaction proceeds slowly below 0°.

The 5-chloro- and 5-bromo-2-thienylsodium are brown amorphous materials while 5-iodo-2-thienylsodium has a blue cast. They are only slightly soluble in ether. They are stable in an inert atmosphere, but when free of solvent and exposed to air they are oxidized rapidly with evolution of light and heat, similarly to Raney nickel.

Lithium did not appear to react in ethyl ether solvent and potassium yielded scission products.

Most of the work was carried out with 2-chlorothiophene. Since only single runs were made with 2-bromothiophene and 2-iodothiophene to study the versatility of the reaction, the yields of 35 and 33%, respectively, need not be considered the highest obtainable.

Experimental

Preparation of Sodium Shot.—The sodium shot was prepared from molten sodium in toluene by vigorous stirring while cooling until there was no chance of coagulation. The excess toluene was decanted through a glass-wool plug in the side arm of the flask and the sodium shot was blanketed with the solvent to be used in the next step. Sodium amalgam was prepared in a similar manner.

Transmetalation of Thiophene with Ethyl Chloride and Sodium Amalgam Sand.—A cold mixture of 16 g. (0.25 mole) of ethyl chloride in 200 ml. of anhydrous diethyl ether was added dropwise over a one hour period to a cooled (5–10°), vigorously stirred mixture of 49 g. (0.58 mole) of thiophene, 100 ml. of anhydrous diethyl ether and freshly prepared sodium amalgam sand containing 15 g. (0.65 gram atom) of sodium and 25 g. (0.125 gram atom) of mercury. The reaction was carried out in the usual Grignard type apparatus under a nitrogen atmosphere. After the addition was completed, the ice-bath was removed and the reaction mixture was refluxed for two and one-half hours. After cooling to 25°, it was carbonated with freshly crushed Dry Ice. The temperature rose momentarily, but it was kept below 30°. The unreacted sodium was destroyed with 50 ml. of ethanol after which 150 ml. of distilled water was added cautiously. Acidulation of the aqueous layer with 75 ml. of concentrated hydrochloric acid yielded 19 g. (60%) of crude 2-thiophenecarboxylic acid. White needles were obtained from hot water, m. p. 128–129°. The neutral equivalent was 124 (calculated, 128). A mixed melting point with an authentic sample of 2-thiophenecarboxylic acid[7] gave no depression.

Transmetalation of Thiophene with Bromobenzene and Sodium Amalgam Sand.—A cold mixture of 78 g. (0.5 mole) of bromobenzene in 300 ml. of anhydrous diethyl ether was added dropwise over a one-hour period to a cooled mixture (5–10°) of 200 ml. of anhydrous diethyl ether, 63 g. (0.75 mole) of thiophene and sodium amalgam sand containing 25 g. (1.09 gram atoms) of sodium and 10 g. (0.05 gram atom) of mercury. After the addition was completed, the mixture was stirred an additional half an hour before removing the ice-bath. When the mixture was warmed slightly, the temperature rose rapidly and an ice-bath was required to control the reaction. After subsiding, it was warmed to reflux for two hours after which it was cooled to 5° and carbonated with freshly crushed dry ice. The unreacted sodium was destroyed with 50 ml. of ethanol and 150 ml. of distilled water was added cautiously. The acidulation of the aqueous layer with 70 ml. of concentrated hydrochloric acid yielded 57 g. (89%) of crude 2-thiophenecarboxylic acid.

Metalation of 2-Chlorothiophene with Sodium.—A mixture of 118 g. (1 mole) of 2-chlorothiophene was added directly to 1000 ml. of benzene and sodium amalgam sand containing 50 g. (2.17 gram atoms) of sodium and 29 g. (0.145 gram atom) of mercury. The mixture was warmed at 80–82° for four hours. The reaction was cooled to 5–10° and carbonated with freshly crushed Dry Ice. The excess sodium was destroyed with 20 ml. of ethanol after which 400 ml. of distilled water was added cautiously. The aqueous solution was filtered and acidulated with 225 ml. of concentrated hydrochloric acid, yielding 108 g. (84%) of crude 2-thiophenecarboxylic acid.

The same procedure was followed when solvents other than benzene were used.

Preparation of 5-Chloro-2-thienylsodium and 5-Chloro-2-thiophenecarboxylic Acid. a. 2-Chlorothiophene and Sodium.—A solution of 118 g. (1.0 mole) of 2-chlorothiophene in 700 ml. of anhydrous diethyl ether was added dropwise with stirring (in an atmosphere of nitrogen) over a period of four hours to a suspension of 35 g. (1.5 gram atoms) of freshly prepared sodium shot in 300 ml. of refluxing anhydrous diethyl ether in the usual Grignard reaction apparatus. The surfaces of the sodium shot darkened immediately and in a short time the ether solution acquired a gray cast. After the addition was complete, the reaction mixture was refluxed for an additional two hours. It was then cooled in an ice-bath to 25° and carbonated by adding freshly crushed Dry Ice. The temperature rose momentarily, but was never permitted to rise above 30°. The temperature fell rapidly when the carbonation was complete. One hundred milliliters of ethanol was added dropwise to destroy the unreacted sodium after which 350 ml. of distilled water was added cautiously. The aqueous solution was separated and acidulated with 230 ml. of concentrated hydrochloric acid. The precipitated 5-chloro-2-thiophenecarboxylic acid weighed 115 g. (70%). White needles were obtained from hot water—m. p. 153–153.5°.[8,9] The observed neutral equivalent was 163 (calcd. 162.5). A mixed melting point with an authentic sample of 5-chloro-2-thiophenecarboxylic acid[7] gave no depression.

b. 2-Chlorothiophene and Sodium Amalgam Sand.—A solution of 118 g. (1.0 mole) of 2-chlorothiophene in 700

---

[6] Scott, Walker and Hansley, THIS JOURNAL, **58**, 2442 (1936).

[7] Prepared by the method of Hartough and Conley, THIS JOURNAL, **69**, 3096 (1947).

[8] Gattermann and Romer, *Ber.*, **19**, 690 (1886), lists the melting points of 5-chloro-, 5-bromo- and 5-iodo-2-thiophenecarboxylic acid as 140, 139.5 and 131°, respectively.

[9] Steinkopf, Jacob and Penz, *Ann.*, **512**, 161 (1934), gave m. p. of 146–147° for 5-chloro-2-thiophenecarboxylic acid and 141–142° for 5-bromo-2-thiophenecarboxylic acid.

ml. of anhydrous diethyl ether was added dropwise with stirring (in an atmosphere of nitrogen) over a period of two hours to a suspension of sodium amalgam sand containing 35 g. (1.5 gram atoms) of sodium and 25 g. (0.125 gram atom) of mercury dispersed in 300 ml. of refluxing anhydrous diethyl ether. The same procedure was followed as described in "a." Acidulation of the aqueous layer with 174 ml. of concentrated hydrochloric acid yielded 150 g. (92%) of 5-chloro-2-thiophenecarboxylic acid.

Preparation of 5-Bromo-2-thienylsodium and 5-Bromo-2-thiophenecarboxylic Acid from Sodium and 2-Bromothiophene.—Following the procedure described in "a" above, 41 g. (0.25 mole) of 2-bromothiophene was reacted with 13.5 g. (0.59 gram atom) of sodium and the mixture worked up as before: eighteen grams (35%, of a red oil separated which crystallized on cooling. White needles of 5-bromo-2-thiophenecarboxylic acid were obtained by sublimation, m. p. 140.5–141.5°.[8,9] The observed neutral equivalent was 202 (calcd. 207). A mixed melting point with an authentic sample (m. p. 141–141.5°) of 5-bromo-2-thiophenecarboxylic acid[7] gave no depression.

Preparation of 5-Iodo-2-thienylsodium and the Corresponding 5-Iodo-2-thiophenecarboxylic Acid from Sodium and 2-Iodothiophene.—Following the procedure described in "a" above, 55 g. (0.25 mole) of 2-iodothiophene was treated with 9 g. (0.38 gram atom) of sodium and worked up as before. Twenty-one grams (33%) of a red oil separated from solution which crystallized on cooling. White needles of 5-iodo-2-thiophenecarboxylic acid were obtained by sublimation, m. p. 132.5–133.5°.[8,10] The observed neutral equivalent was 250 (calcd. 253).

Acknowledgment.—The authors wish to thank Dr. D. E. Badertscher for his advice and interest and Mrs. Josephine S. Piel for her assistance in the experimental work.

Summary

2-Thienylsodium has been prepared in yields of 60–89% from an alkyl or aryl halide, sodium amalgam, and thiophene, and in yields of 84% from 2-chlorothiophene and sodium amalgam.

2-Chloro-, 2-bromo- and 2-iodothiophenes have been metalated with sodium without replacement of the halo- atom, and the 5-halo-2-thienyl sodium compounds so formed were carbonated to give 2-chloro-, 5-bromo- and 5-iodo-2-thiophenecarboxylic acids in yields of 70, 35 and 33%, respectively. With 70% sodium amalgam, instead of sodium, the yield of 5-chloro-2-thiophenecarboxylic acid was 92%. Diethyl ether was the only solvent which gave satisfactory results. A decrease in solvent volume resulted in lower yields, but increases in the rate of reaction were noted. The reaction proceeded satisfactorily at 30–40°, but above 50° normal replacement of the halogen atom by sodium occurred.

RECEIVED JUNE 12, 1947

---

[10] Rinkes, *Rec. trav. chim.*, **53** [4], 640 (1934), lists m. p. of 133–134° for 5-iodo-2-thiophenecarboxylic acid.

[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Aromatization Studies. VI. Aminobiphenyls and Naphthylamines

BY E. C. HORNING, M. G. HORNING AND E. JANE PLATT[1]

The preparation of alkyl anilines from alkylcyclohexenones, by aromatization of the corresponding azines, was described in a previous paper.[2] This method provides a way of obtaining amines with alkyl substituents whose character or position are such that the compound would be difficult or impossible to obtain by ordinary aromatic substitution routes. Further investigation of this method has now shown that it can be applied also to the preparation of aminobiphenyls and naphthylamines; it appears therefore to be generally applicable in the aromatic series.

The aminobiphenyls obtained were 3-amino-5-methyl-4′-methoxy-biphenyl, 3-amino-5-methyl-2′,3′-dimethoxybiphenyl and 3-amino-5-methyl-3′,4′-dimethoxybiphenyl. The azines were prepared from the corresponding arylcyclohexenones,[3] and the aromatization was carried out in triethylbenzene with a 5% palladium–carbon catalyst. The amines were isolated in the form of their acetyl derivatives. The yields were uniformly in the vicinity of 50%, as in the case of alkylanilines,[2] but we have as yet no information on the fate of the rest of the material or on the mechanism of the reaction.

The tetralones which were converted to the corresponding aminonaphthalenes were tetralone-1, 7-methyltetralone-1 and 7-ethyltetralone-1. 7-Substituted tetralones may be obtained readily by the usual succinoylation method from benzene derivatives, and this route offers a means of obtaining many 7-substituted 1-naphthylamines. The yields here were lower (about 20%), although this appeared to be due more to difficulties in isolation of pure acetyl derivatives than to the aromatization itself.

The aromatization of these azines in a boiling solvent at a moderate temperature (214°) with a reflux period of only thirty minutes indicates the high degree of effectiveness of Hartung's palladium–carbon catalyst[4] in aromatization reactions.

Acknowledgment.—We are indebted to the Research Corporation for a grant in support of this work.

Experimental

All melting points are corrected. Analyses are by Miss Sarah H. Miles.

---

[1] Rohm and Haas Research Assistant.

[2] Horning and Horning, THIS JOURNAL, **69**, 1907 (1947).

[3] Horning and Field, *ibid.*, **68**, 384 (1946).

[4] "Organic Syntheses," **26**, 77 (1946).

TABLE I

AZINES OF KETONES

Ketone	Formula	M. p., °C.	Yield, %	Analyses, %			
				C		H	
				Calcd.	Found	Calcd.	Found
Derivative of 2-cyclohexen-1-one							
3-Methyl-5-(*p*-methoxyphenyl)-	$C_{28}H_{32}O_2N_2$	190.5–191.5	58	78.47	78.43	7.53	7.50
3-Methyl-5-(3′,4′-dimethoxyphenyl)-	$C_{30}H_{36}O_4N_2$	168–170[a]	64[b]	73.74	73.79	7.43	7.21
3-Methyl-5-(2′,3′-dimethoxyphenyl)-	$C_{30}H_{36}O_4N_2$	175–176[c]	52[d]	73.74	73.89	7.43	7.17
Tetralone-1	$C_{20}H_{20}N_2$	142–143[e,f]	66[g]	...	...	..	..
7-Methyltetralone-1	$C_{22}H_{24}N_2$	146–147[h]	50	83.50	83.63	7.64	7.50
7-Ethyltetralone-1	$C_{24}H_{28}N_2$	102–103[h]	25[i]	83.67	83.68	8.19	8.07

[a] Recrystallized from aqueous acetic acid. [b] Reflux period 3.3 hours. [c] Recrystallized from cyclohexanebenzene. [d] Reflux period one hour. Water was added to the solution, and the supernatant liquor decanted after cooling. The residue was treated with 100 ml. of boiling methanol to yield a crystalline product. [e] Reported, 143–144°. Blout, Eager and Gofstein, THIS JOURNAL, **68**, 1983 (1946). [f] Recrystallized from cyclohexane. [g] Reflux period two hours. [h] Recrystallized from methanol. [i] Reflux period one hour; water was added to yield the product.

TABLE II

ACETYL DERIVATIVES OF AMINES

Amine	M. p., °C.	Yield, %	Formula	Analyses, %			
				Calcd.		Found	
				C	H	C	H
3-Amino-5-methyl-4′-methoxybiphenyl	158–159[a]	54	$C_{16}H_{17}O_2N$	75.26	6.71	75.29	6.67
3-Amino-5-methyl-2′,3′-dimethoxybiphenyl	118–118.5[a]	53	$C_{17}H_{19}O_3N$	71.56	6.71	71.57	6.76
3-Amino-5-methyl-3′,4′-dimethoxybiphenyl	108–109[b]	55	$C_{17}H_{18}O_3N$	71.56	6.71	71.72	6.71
1-Aminonaphthalene	158–159[a]	15	$C_{12}H_{11}ON$				
7-Methyl-1-aminonaphthalene	180–181[a]	16	$C_{13}H_{13}ON$	78.36	6.57	78.44	6.50
7-Ethyl-1-aminonaphthalene	149–150[a]	21	$C_{14}H_{15}ON$	78.84	7.09	78.84	7.06

[a] Recrystallized from cyclohexane–ethyl acetate. [b] Recrystallized from benzene–ethyl acetate.

Preparation of Azines. 3-Methyl-5-(*p*-methoxyphenyl)-2-cyclohexen-1-one Azine.—A mixture of 10.8 g. of 3-methyl-5-(*p*-methoxyphenyl)-2-cyclohexen-1-one, 1.9 g. of 85% hydrazine hydrate and 1 drop of concentrated hydrochloric acid, in 30 ml. of ethanol, was maintained under reflux for one hour. The product crystallized from solution during the reflux period; the yield was 6.3 g. (58%) of yellow azine, m. p. 186–189°. Recrystallization from methanol gave a sample melting at 190.5–191.5°, with shrinking.

The yields, properties, and analyses of the azines prepared are described in Table I. The general method of preparation was modified in each case as described in the footnotes.

Aromatization of Azines.—The aromatization reaction was carried out in the same fashion for all azines, but the method of isolation of the resulting aromatic amines varied. In cases where the hydrochlorides of the amines were water-insoluble, it was not possible to use the previously described method.[2] A typical aromatization is described.

A mixture of 5.0 g. of 3-methyl-5-(*p*-methoxyphenyl)-2-cyclohexen-1-one azine, 1.5 g. of 5% palladium–carbon catalyst,[4] and 15 ml. of triethylbenzene was heated under reflux for thirty minutes. After cooling, the catalyst was removed by filtration, and washed with 15 ml. of warm benzene.

In this case, the solution was added to 200 ml. of water containing 15 ml. of concentrated hydrochloric acid and steam-distilled. The aqueous solution was chilled and filtered to remove 3.5 g. of crystalline hydrochloride, m. p. 230–232° (dec.). The hydrochloride was treated with 50 ml. of 5% sodium hydroxide solution and 50 ml. of ether. The alkaline solution was extracted with ether, and the combined ether solutions washed and dried. After evaporation, the residue was acetylated by adding 15 ml. of pyridine and 10 ml. of acetic anhydride. This mixture, after standing overnight, was poured into 100 ml. of ice water and the crystalline material removed by filtration. The yield and properties of the product are in Table II.

In the case of the other two aminobiphenyls, the isolation procedure followed that described previously.[2]

The alkylnaphthylamines could not be extracted satisfactorily from ether with aqueous acid. In consequence, the benzene–triethylbenzene solution was treated immediately with 25 ml. of pyridine and 15 ml. of acetic anhydride. After standing overnight, the solution was poured into water and steam-distilled. On cooling, the product separated in part as a colorless, crystalline precipitate, and in part as a gummy, dark mass. The gum was removed mechanically, and the crystalline material collected separately. It was found in each case that the crystalline material was of a high state of purity, and that a smaller amount of additional considerably less pure material could be obtained by treatment of the gum with appropriate solvents. The yields given in Table II represent only the yield of pure material obtained directly.

Summary

The aromatization of several 3-methyl-5-aryl-2-cyclohexen-1-one and tetralone-1 azines to the corresponding 3-amino-5-methylbiphenyls and 1-aminonaphthalenes, using a palladium–carbon catalyst in boiling triethylbenzene, is described. This method has been applied previously to the synthesis of alkyl anilines; it is apparently general for the aromatic series.

PHILADELPHIA, PENNSYLVANIA RECEIVED JUNE 25, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Chromatography of Cuban Blackstrap Molasses on Clay; Some Constituents of an Odor and Pigment Fraction[1]

BY W. W. BINKLEY[2] AND M. L. WOLFROM

In continuation of our work[3-5] on the chromatographic isolation of constituents of cane juice and cane blackstrap molasses, we have isolated from the latter a fraction which is only weakly held by the adsorbents employed. Concentrated in this fraction are the odoriferous constituents to which the molasses, and the rums derived therefrom, owe in the main their characteristic taste and odor. The concentration of such a fraction had been noted previously.[5] Further amounts have now been prepared and subjected to some detailed study. The fraction least adsorbed on a fuller's earth type of clay was isolated from 1 kg. of a typical Cuban cane blackstrap molasses by ethanol–acetone elution in the presence of some water. The aqueous solution obtained after organic solvent removal was extracted with petroleum ether and the extract on solvent removal yielded a viscous, green liquid with a strong odor of cane molasses. The yield was 0.4% of the original molasses. The odor of this material was highly volatile and disappeared completely on standing in the laboratory for several weeks. It could be trapped by condensation at low temperatures. The condensate (Fraction A) reacted with 2,4-dinitrophenylhydrazine. It is under further investigation.

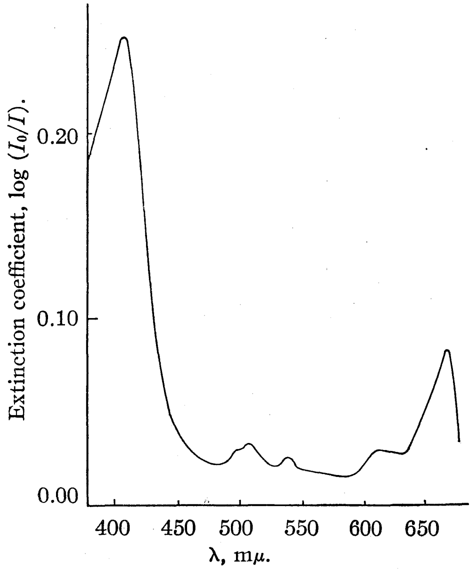


Fig. 1.—Absorption spectrum of green coloring matter (in ether) from Cuban Blackstrap molasses: Beckman spectrophotometer (Model DU); 1.00-cm. cell; measured by Mr. Bernard Wildi of this Laboratory.

The fraction (Fraction B) residual after Fraction A removal was further chromatographed on Silene-EF[6] and was divided into six fractions (Table I). The green color of this hydrocarbon-soluble mixture was identified as chlorophyll *a* by its absorption spectrum (Fig. 1). This spectrum shows that the substance is nearly pure chlorophyll *a* containing no more than a few per cent. of what is probably chlorophyll *b* as indicated by the slight absorption in the region 560–570 mμ. The presence of such unaltered chlorophyll *a* in blackstrap molasses seems remarkable.

TABLE I

EFFLUENT FRACTIONS FROM THE CHROMATOGRAM FROM 2.0 g. OF FRACTION B FROM CANE BLACKSTRAP MOLASSES[a]

Fraction	Eluate volume, ml.	Color	Yield, mg.	Substances present
1	250	Golden	511	Fats, "melissyl" alcohol, sterols
2	100	Colorless	39	"Melissyl" alcohol, trace of sterols
3	250	Green	146	Sterols, chlorophyll[a]
4	250	Green	149	Sterols, chlorophyll[a]
5	150	Light green	8	Chlorophyll[a]
6[b]			882	
		Total	1735 (86.7%)	

[a] See experimental portion for details. [b] By acetone extraction of column.

From the various Silene fractions there was isolated "melissyl" (synonym "myricyl") alcohol, a sterol fraction and a fat fraction. "Melissyl" alcohol was found free in the molasses, which had however been subjected to some alkaline treatment in its manufacture. Melissyl alcohol has been reported as a major component of the cane wax[7-9] isolable from the clarification muds formed in the manufacture of raw sugar. The melting point of natural "melissyl" alcohol will vary with the source. Its formula is generally considered to be $CH_3(CH_2)_{28}CH_2OH$ but actually it is very probably a mixture of close homologs, as has been

---

[1] Presented before the Division of Sugar Chemistry and Technology at the 112th Meeting of the American Chemical Society, New York, N. Y., September, 1947.

[2] Sugar Research Foundation Fellow of The Ohio State University Research Foundation (Project 190).

[3] W. W. Binkley, Mary G. Blair and M. L. Wolfrom, THIS JOURNAL, **67**, 1789 (1945).

[4] W. W. Binkley and M. L. Wolfrom, *ibid.*, **68**, 1720 (1946).

[5] W. W. Binkley and M. L. Wolfrom, *ibid.*, **69**, 664 (1947).

[6] L. W. Georges, R. S. Bower and M. L. Wolfrom, *ibid.*, **68**, 2169 (1946).

[7] J. E. Q. Bosz, *Arch. Suikerind. Nederland-Indië*, **28**, 969 (1920); *Chem. Centr.*, **91**, III, 637 (1920).

[8] N. L. Vidyarthi and N. Narasingarao, *J. Indian Chem. Soc.*, **16**, 135 (1939); *C. A.*, **33**, 9700 (1939).

[9] R. T. Balch, U. S. Patent 2,381,420 (1945); R. T. Balch, "Wax and Fatty Byproducts from Sugarcane," No. 3, Technological Report Series, Sugar Research Foundation, Inc., 1947.

demonstrated by Koonce and Brown[10] for the "melissyl" alcohol fraction of carnauba wax.

The sterol fraction ((m. p. 142–143°, cor.), $[\alpha]^{26}\mathrm{D}$ $-38°$ in chloroform) isolated was a typical phytosterol such as has been reported in studies on crude cane wax.[9] It is undoubtedly a mixture of the sitosterol type but was obtained in this work in too small amount to allow of further fractionation.

Saponification of the main fat fraction yielded further quantities of "melissyl" alcohol, glycerol (identification by a color test) and an unsaturated acid that on catalytic hydrogenation yielded stearic acid and on hydroxylation yielded a tetrahydroxystearic acid which was shown by its melting point (156°, cor.) and analysis to be essentially α-sativic acid.[11] The parent unsaturated acid is thus in all probability linoleic acid. It is of interest to note that this acid is the major acid present in cane wax.[9]

Finally, we wish to call attention to the demonstration that the chromatographic techniques established for separation of carbohydrate mixtures are also applicable to the separation of non-carbohydrate systems.

Experimental

Chromatographic Isolation of an Odor and Pigment Fraction.—The Cuban cane blackstrap molasses employed in this work was the same sample described previously.[3,5] One kilogram of this molasses was diluted with 250 ml. of water and made into a smooth paste by the addition of 400 g. of clay.[12] This paste was added with good agitation to a mixture of 3.6 liters of absolute ethanol and 2.4 liters of acetone; the agitation was continued for one hour after the addition of the paste. The supernatant liquor was removed with the aid of a siphon. The precipitate was transferred to a percolator and washed with 3 liters of acetone. The supernatant liquor and the percolator effluent were combined and concentrated to a volume of approximately 1 liter under reduced pressure at a bath temperature of 50°. This concentrate was poured into a 2-liter liquid-liquid extractor,[13] diluted with 1 liter of water and extracted for twenty-four hours with petroleum ether (b. p. 30–60°). A turbid, green extract was obtained. Removal of solvent under reduced pressure yielded a viscous, green liquid with a strong odor of cane blackstrap molasses; yield 4.1 g. (0.41% of the original molasses).

Separation of the Molasses Odor Fraction (Fraction A).—The concentrate (4.1 g.) was heated for two hours at 100–110° under a pressure of 0.03 mm. and the distillate (Fraction A) that formed was collected in traps surrounded with a mixture of solid carbon dioxide and acetone. The traps were washed with ethanol (95%). The collected washings had a strong odor of molasses and gave a precipitate with 2,4-dinitrophenylhydrazine reagent. The undistilled concentrate (Fraction B, 4.0 g.) had a fatty odor. The nature of Fraction A is under further investigation. It is highly volatile.

Chromatography of the Residual Fraction (Fraction B).—An amount of 2.0 g. of the residual concentrate dissolved in 40 ml. of benzene, was added at the top of a 150 × 80 mm. (diam.) column[14] of a mixture (150 g.) of 5 parts (by wt.) of "Silene-EF"[15] and 1 part of "Celite."[16] The chromatogram was developed with 1250 ml. of 500/1 benzene[17]/ethanol[18] (volume ratio). The effluent was collected in five fractions and pertinent data relative to these fractions are listed in Table I. The column was extruded and extracted for twenty-four hours with acetone in a Soxhlet extractor. The substances eluted from the adsorbent (Fraction B-6) were waxy solids with a strong fatty acid odor. They were completely soluble in 0.1 *N* sodium hydroxide.

Anal. Saponification equiv., 694 (1.44 ml. of 0.1 *N* sodium hydroxide per 100 mg.).

Isolation of "Melissyl" Alcohol, a Sterol Fraction and a C_{18} Unsaturated Fatty Acid Fraction from Fraction B-1.—Fraction B-1 (Table I) was a viscous, light amber liquid with a fatty odor.

Anal. Unsaponifiable matter, 65%; saponification equiv., 741 (1.35 ml. of 0.1 *N* sodium hydroxide per 100 mg.); free fatty acid, absent; iodine no., 96 (7.57 ml. of 0.1 *N* I_2 per 100 mg.).

An amount of 426 mg. of Fraction B-1, 5 ml. of ethanol (95%) and 0.5 ml. of aqueous 50% potassium hydroxide were heated under reflux for two hours on a steam-bath. The reaction mixture was cooled to room temperature and extracted with ether. The ether-soluble fraction (Fraction B-1-a) was washed with water until free of alkali; yield 267 mg.

An amount of 242 mg. of Fraction B-1-a, dissolved in 5 ml. of benzene was added at the top of a 175 × 35 mm. (diam.) column of a mixture (45 g.) of 5 parts (by wt.) of "Silene-EF" and 1 part of "Celite." The chromatogram was developed with 90 ml. of 500/1 benzene/ethanol. The column was extruded and two well-defined zones, a narrow upper zone 70 to 75 mm. from the top of the column and a wide zone at the bottom of the column, were detected with the aid of ultraviolet light. The zones were isolated and eluted with acetone. Zone yields for the upper and lower zones were 124 and 110 mg., respectively after solvent removal. The material from the upper zone crystallized from ethanol (95%) as needles; yield 40 mg., m. p. 139–141° (cor.); Liebermann–Burchard sterol test[19] positive. Plates were obtained from a benzene solution of the lower zone; yield 30 mg., m. p. 83–84° (cor.). These crystalline substances were identical with those of a similar nature (phytosterol fraction and "melissyl" alcohol, respectively) described and further characterized below.

The potassium hydroxide solution (Fraction B-1-b), containing fatty acids and glycerol, from the saponification of Fraction B-1 was acidified with hydrochloric acid and extracted with three 25-ml. portions of chloroform. The water layer was set aside for glycerol recovery (see below). The residue, 137 mg., from the chloroform extracts was a soft paste with a fatty odor. This paste reacted with alkaline permanganate and bromine in carbon tetrachloride; its ethanolic solution was acid to litmus; its lead salt was soluble in ether.

Anal. Neutral equiv., 302 or 3.31 ml. of 0.1 *N* sodium hydroxide per 100 mg., iodine no., 118 or 9.28 ml. of 0.1 *N* I_2 per 100 mg.

Following the general procedure of Brown and coworkers[20] for the separation of unsaturated from saturated fatty acids by low temperature crystallization, an amount of 150 mg. of the above fatty acid fraction was dissolved

---

(10) S. D. Koonce and J. B. Brown, *Oil & Soap*, **21**, 167, 231 (1944).

(11) B. H. Nicolet and H. L. Cox, THIS JOURNAL, **44**, 144 (1922).

(12) Florex XXX, a Florida fuller's earth, supplied by the Floridin Co. of Warren, Pa.

(13) S. E. Q. Ashley and W. M. Murray, Jr., *Ind. Eng. Chem., Anal. Ed.*, **10**, 367 (1938).

(14) Column dimensions refer to the adsorbent.

(15) A hydrated calcium acid silicate produced by the Columbia Chemical Co., Barberton, Ohio.

(16) No. 535, a siliceous filter-aid manufactured by Johns–Manville Co., New York, N. Y.

(17) All benzene employed was free of thiophene.

(18) Absolute ethanol was employed in all chromatographic operations.

(19) C. Liebermann, *Ber.*, **18**, 1803 (1885); H. Burchard, Diss. Rostock (1890), *Chem. Centr.*, **61**, II, 25 (1890).

(20) J. B. Brown, *Chem. Revs.*, **29**, 333 (1941).

in 1 ml. of acetone and cooled to −50 to −60° by a bath of solid carbon dioxide and trichloroethylene. The frozen mass was allowed to thaw slowly until an amorphous solid separated. This solid was collected rapidly on a filter and washed with 0.5 ml. of cold acetone; yield 30 mg. An ethanolic solution of this solid yielded a noncrystalline, highly solvated, amorphous solid. A viscous liquid (Fraction F) was obtained from the filtrate of the above precipitation after removal of the acetone; yield 120 mg. This liquid (120 mg.) was dissolved in 10 ml. of absolute ethanol and hydrogenated in the presence of 50 mg. of platinic oxide. After six alternate evacuations and additions of hydrogen (to 1 atm. pressure), the reaction mixture was warmed to 50° and shaken for several hours. The catalyst was removed by filtration. The filtrate was allowed to reflux for two hours with 150 mg. of potassium hydroxide to saponify any ethyl esters formed during the hydrogenation. This solution was diluted with 50 ml. of water and acidified with hydrochloric acid. The precipitated fatty acid was collected on a filter; yield 116 mg. An ethanolic (95%) solution of the precipitate gave crystals; m. p. 68–68.5°. Recrystallization from absolute ethanol gave plates, m. p. 69–69.5° (cor.) undepressed on admixture with an authentic specimen of stearic acid (m. p. 70–71°, cor.).

In another experiment, an amount of 100 mg. of the above unsaturated fatty acid fraction (Fraction F) was dissolved in 30 ml. of 0.03 *N* potassium hydroxide and to the cooled (5°) solution was added dropwise under good agitation a solution of 20 mg. of potassium permanganate in 5 ml. of water. Five minutes after the completion of the addition, the reaction mixture was decolorized with sulfur dioxide. A white, flocculent precipitate formed which was crystallized from ethanol; yield 30 mg. (0.008% original molasses), m. p. 156° (cor.).

Anal. Calcd. for $C_{17}H_{31}(OH)_4CO_2H$: C, 62.04; H, 10.42. Found: C, 61.96; H, 10.28.

The aqueous layer from the fatty acid isolation was adjusted to *p*H 7–8, evaporated to dryness on a steam-bath and extracted with ethyl acetate. A few droplets of a viscous liquid was obtained after solvent removal and this residue gave a positive pyrogallol–sulfuric acid test for glycerol.[21]

Isolation of "Melissyl" Alcohol from Fraction B-2.—This fraction was crystalline. Plates were obtained on recrystallization from benzene; yield 20 mg. (total yield of "melissyl" alcohol, 0.01% original molasses), m. p. 83–84° (cor.) undepressed on admixture with a specimen of "melissyl" alcohol (m. p. 87–87.5°, cor.) separated from carnauba wax by fractional crystallization. The mother liquor showed a positive Liebermann–Burchard[19] sterol test.

Anal. Calcd. for $C_{30}H_{62}O$: C, 82.11; H, 14.24. Found: C, 81.74; H, 14.18.

Conversion to the acetate with sodium acetate and acetic anhydride gave crystals; m. p. 66–67° (cor.).

Characterization and Further Isolation of the Phytosterol Fraction and Identification of Chlorophyll *a*.—Fractions B-3 and B-4 were crystalline. When an ethanolic solution of these fractions was allowed to evaporate at room temperature, nearly colorless, elongated plates formed near and on the bottom of the container. The green color and some crystals collected higher up on the walls of the container. Careful washing with cold ether removed nearly all of the green color. The washings were used for the determination of absorption spectra (see below). A total of 250 mg. of crystals was obtained from Fractions B-3 and B-4. These were combined and yielded colorless crystals from ethanol (95%); m. p. 142–143° (cor.), $[\alpha]^{26}\mathrm{D}$ −38° (*c* 4.9, 2-dm. tube, chloroform), Liebermann–Burchard sterol test[19] positive. A benzene solution of these crystals fluoresced in ultraviolet light.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.88; H, 11.99. Found: C, 83.64; H, 11.90.

The material of Fraction B-5 was amorphous. The green colored substance from Fractions B-3, B-4 and B-5 was combined and its absorption spectrum in ether solution is shown in Fig. 1. The spectrum is that of chlorophyll *a* with a probable slight admixture of chlorophyll *b* or pheophytin *a*; yield 0.00004% original molasses (calcd. from absorption spectrum).

Acknowledgment.—The laboratory assistance of Mr. John Kolbas is acknowledged. We are pleased to acknowledge also the assistance of Professor Paul Rothemund of this department and the Kettering Foundation, Yellow Springs, Ohio, in interpreting the absorption spectrum data.

Summary

By chromatographic methods the following trace constituents were isolated from a sample of Cuban cane blackstrap molasses: "melissyl" alcohol, chlorophyll *a* (identification by absorption spectrum), a phytosterol fraction (m. p. 142–143°, $[\alpha]^{26}\mathrm{D}$ −38° in chloroform) and a fat fraction in which the presence of glycerol and linoleic acid was indicated. The highly volatile odor fraction was concentrated and shown probably to consist in part of carbonyl compounds.

COLUMBUS, OHIO RECEIVED AUGUST 13, 1947

---

(21) S. P. Mulliken, "Identification of Pure Organic Compounds," Vol. I, John Wiley and Sons, New York, N. Y., 1904, p. 169.

[CONTRIBUTION FROM WESTERN REGIONAL RESEARCH LABORATORY[1]]

Esters of Lima Bean Pod and Corn Cob Hemicelluloses

BY J. F. CARSON AND W. DAYTON MACLAY

This paper describes the preparation of the acetate, propionate and butyrate of lima bean pod hemicellulose and the acetate, propionate, butyrate, caprate, laurate, myristate, palmitate and benzoate of corn cob hemicellulose. It also reports studies on the fractionation of some of these esters by extraction with organic solvents.

Husemann[2] obtained molecular weights of xylans from wheat straw and beechwood by osmotic and viscometric measurements of the corresponding methyl ethers, mixed methyl ether acetates, and benzyl ether acetates. His results indicated that undegraded xylans from wheat straw and beechwood were homogeneous, with chain lengths of approximately 150 repeating anhydroxylose units. Both Husemann[2] and Heuser and Schlosser[3] reported that xylan diacetates were poorly soluble in organic solvents, hence the application of the more soluble mixed ether acetates. Recently Millatt and Stamm[4] have prepared acetates of aspen hemicellulose from which molecular weights were determined.

Numerous investigators[5] have studied the xylan–glucuronide type of hemicellulose by fractional precipitation from alkaline solutions and by copper precipitation. In most cases, convincing evidence of the homogeneity of the various fractions was lacking. Many of the fractions contained varying amounts of hexosan either chemically combined in the xylan chain or simply as mixtures. O'Dwyer[6] and Anderson and co-workers[7] have presented evidence that some hemicellulose fractions, particularly from the sapwood of English oak, lemon wood, and black locust sapwood contain anhydroglucose units chemically united to anhydroxylose units. These fractions were observed to give violet to blue colors with iodine. Digestion with taka-diastase or saliva produced polysaccharides free of hexose no longer giving the color with iodine, but the enzymatic hydrolysis required a considerably longer time than expected for a physical mixture of xylan and starch.

The hemicelluloses used for esterification were obtained by alkaline extraction of corn cob and lima bean pod holocellulose. The holocellulose was extracted successively with boiling water, 2% sodium carbonate, and 5 and 24% potassium hydroxide solutions. The yields and composition of the two fractions of corn cob and lima bean pod hemicelluloses obtained by extraction with potassium hydroxide are recorded in Table I.

TABLE I

HEMICELLULOSE FRACTIONS

Holocellulose	Concn. of potassium hydroxide	Yield[a]	$[\alpha]^{25}D$ (2% KOH)	Xylan,[b] %	Uronic anhydride[c]	Methoxyl[d]
Corncob	5	22	−98.2	89.3	6.2	0.7
Corncob	24	8	−91.1	83.4	4.5	.7
Lima bean pod	5	17	−44.7	74.8	7.9	1.4
	24	8	−58.9	71.8	4.7	0.7

[a] Yields are based on dry weight of the hollocellulose. [b] Xylan was determined by furfural distillation and precipitation as the phloroglucide and was corrected for the furfural equivalent of the uronic anhydride. [c] Uronic anhydride analyses were performed by the procedures of Lefevre and Tollens, as modified by McCready, Swenson and Maclay (*Ind. Eng. Chem., Anal. Ed.*, **18**, 290 (1946)). [d] Methoxyl was determined by Clark's modification of the Vieböch–Schwappach method (*J. Assoc. Off. Agr. Chem.*, **22**, 100, 622 (1939)). The samples contained no adsorbed alcohol, as was demonstrated by humidification in a desiccator over water.

The esters, except the benzoate, were prepared by reaction with pyridine and acid anhydride or acid chloride under relatively mild conditions. Benzoylation was performed by reaction with benzoyl

TABLE II

HEMICELLULOSE ESTERS

Source of xylan	Ester	Acyl, % Calcd.[a]	Acyl, % Found[b]
Lima bean pod	Acetate	38.8	39.3
Lime bean pod	Propionate	45.1	45.8
Lima bean pod	Butyrate	50.9	51.0
Corncob	Acetate	39.0	39.5
Corncob	Propionate	45.2	45.5
Corncob	Butyrate	51.3	50.8
Corncob	Caprate	70.0	69.9
Corncob	Laurate	73.0	70.0
Corncob	Myristate	75.7	72.2
Corncob	Palmitate	77.9	76.4
Corncob	Benzoate	60.9	57.5

[a] The theoretical per cent. acyl was calculated from the composition of the original hemicellulose. The original hemicelluloses were analyzed for xylan, methoxyl and uronic anhydride, and the residual unaccounted-for material was assumed to be hexosan. The calculated values include the contribution of each of these, assuming no loss on esterification. [b] % acyl was measured by alkaline saponification of the esters by the procedure of Genung and Mallatt (*Ind. Eng. Chem., Anal. Ed.*, **13**, 369 (1941)). The caprate, laurate, myristate, palmitate and benzoate were also analyzed by saponification, followed by acidification, extraction of the free organic acid and titration.

---

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Husemann, *J. prakt. Chem.*, **263**, 13 (1940).

(3) Heuser and Schlosser, *Ber.*, **56**, 392 (1923).

(4) Millatt and Stamm, *J. Phys. Chem.*, **51**, 134 (1947).

(5) (a) Norris and Preece, *Biochem. J.*, **24**, 59, 973 (1930); (b) Preece, *ibid.*, **25**, 1304 (1931); (c) Angell and Norris, *ibid.*, **30**, 2159 (1936); (d) Buston, *ibid.*, **29**, 196 (1935); Anderson and Kaznarich, *J. Biol. Chem.*, **111**, 549 (1935).

(6) O'Dwyer, *Biochem. J.*, **28**, 2116 (1934); **31**, 254 (1937); **33**, 712 (1939).

(7) Anderson, Seeley, Stewart, Redd and Westerbike, *J. Biol. Chem.*, **135**, 189 (1940).

TABLE III

FRACTIONATION OF LIMA BEAN POD HEMICELLULOSE ESTERS

Ester	Fractionation Solvent	Insoluble %	Composition of hemicellulose regenerated from insoluble fraction, % Xylan	Uronic anhydride	Methoxyl	$[\alpha]^{25}D$ (2% KOH)
Acetate	Chloroform-acetone (1:1) 100 parts	92	76	8.1	1.3	....
Propionate	Chloroform-acetone (1:1) 100 parts	90	77	8.0	1.2	....
Butyrate	Chloroform-acetone (1:1) 100 parts	85	75	9.1		....
Butyrate[a]	Dioxane, 100 parts	88	77	6.4		−45.1
Acetate	Pyridine, 50 parts	86	77	8.0	1.2	−44.9
Propionate	Pyridine, 50 parts	82	75	5.4	1.4	−44.4
			Composition[b] of original hemicellulose (5% KOH extraction)			
			75	7.9	1.4	−44.7

[a] A second fractionation of the dioxane-insoluble butyrate under the same conditions yielded an insoluble portion amounting to 90%. Analysis of the regenerated polysaccharide indicated no change in composition. [b] Determination of L-arabinose by the diphenylhydrazine method of Wise and Peterson (*Ind. Eng. Chem.*, **22**, 362 (1930)) showed arabinose to be absent. Tests for mannose (phenylhydrazine) and for galactose (mucic acid) were negative.

chloride and aqueous sodium hydroxide. The esters and their analyses are recorded in Table II.

All of the esters had very low solubilities in organic solvents such as chloroform, dioxane, acetone, nitrobenzene and *m*-cresol. For example, only 25% of the dipropionate and 30% of the dibutyrate of corn cob hemicellulose were soluble in two hundred parts of dioxane, and only 8, 10 and 15% of lima bean pod hemicellulose diacetate, dipropionate and dibutyrate, respectively, were soluble in one hundred parts of chloroform–acetone (1:1). Since hexosan triesters, if not of too high molecular weight, are usually more soluble in organic solvents than are the xylan esters, it was thought that extraction of the esters with organic solvents and regeneration of the polysaccharide from the insoluble ester fraction would enrich the xylan content, if the non-pentosan components were merely present in a mixture. Lima bean pod diacetate, dipropionate, and dibutyrate were fractionated with a 1:1 chloroform–acetone mixture; the dibutyrate was also fractionated with dioxane, and the diacetate and dipropionate were fractionated with pyridine. In each case, the insoluble fraction was saponified and the regenerated polysaccharide analyzed for xylan and uronic anhydride. These results are compiled in Table III for comparison with the original hemicellulose.

The analyses in Table III show that, although in two cases the uronic anhydride content was decreased by treatment with organic solvents, the xylan content was increased only slightly and remained practically constant. The material unaccounted-for as xylan, uronic anhydride, and methoxyl in the original hemicellulose fraction was approximately 16.5% and for the saponified insoluble fractions the smallest figure obtained for this value was approximately 14.5%. Apparently very little extraction of hexosan was accomplished. Moreover, the specific rotation of the regenerated fractions were close to that of the original. Further, when the saponified pyridine-insoluble fractions of the lima bean pod hemicellulose diacetate and dipropionate were re-dissolved in alkali and precipitated by the copper method,[8] the polysaccharides were recovered in practically quantitative yields with the same specific rotations and xylan and uronic anhydride contents as the original. The lima bean pod hemicelluloses isolated by 5 and by 24% potassium hydroxide extraction, and all of the fractions isolated as described gave a violet to blue color with iodine. That the blue color was not due to starch carried through the fractionations was shown by the fact that digestion with saliva for five days did not change this property, and extraction with boiling calcium chloride solution[9] (density 1.3) left a residue still colored blue or violet when treated with iodine. The corn cob hemicelluloses did not give the colors. The failure to remove hexosan constituents by extraction with organic solvents furnishes an independent confirmation of the findings of O'Dwyer[6] and Anderson and co-workers[7] that anhydrohexose units are probably chemically combined with xylan in certain types of hemicelluloses.

Experimental

Preparation of Corn Cob and Lima Bean Pod Holocelluloses.—Corncobs and dried lima bean pods of normal canning maturity were reduced to twenty mesh and extracted successively with benzene–ethanol (2:1) for twelve hours in a large Soxhlet extractor, twice with thirty parts of boiling 0.5% ammonium oxalate solution for two-hour periods, and twice with thirty parts of boiling water. Delignification was accomplished by the sodium chlorite procedure of Wise, Murphy and D'Addieco[10] as follows: Two hundred grams of air-dried extracted material was heated to 70° with four liters of water in a six-liter flask in a fume hood. Glacial acetic acid (15 ml.) and technical sodium chlorite (30 g.) were added and the suspension held at 68–70° for an hour. Addition of acetic acid and sodium chlorite was repeated and heating was continued for another hour. This treatment produced a white fibrous holocellulose from the lima bean pods. A third addition

---

(8) The hemicelluloses were precipitated according to the directions of Angell and Norris (*Biochem. J.*, **30**, 2155 (1936)).

(9) The hemicellulose was treated according to the directions of Steiner and Guthrie (*Ind. Eng. Chem., Anal. Ed.*, **16**, 736 (1944)), who showed that quantitative extraction of starch from various plant materials can be accomplished with boiling calcium chloride solution.

(10) Wise, Murphy and D'Addieco, *Paper Trade J.*, **122** [2], 35 (1946).

of reagents and an additional hour of heating was required to produce a white product from the corn cobs. The suspension was cooled to room temperature, filtered on a cloth mat in a Buchner funnel, and the white holocellulose was washed repeatedly with large quantities of distilled water, 95% ethanol and acetone. Corncob and lima bean pod holocelluloses were obtained in yields of 81 and 90%, respectively. The yields were based on the dry extractive-free material.

Extraction of Hemicellulose Fractions from the Holocelluloses.—Four hundred grams of air-dried holocellulose was heated for two hours with six liters of boiling water, filtered, and then steeped for forty-eight hours in eight liters of 2% sodium carbonate (in the absence of oxygen), refiltered and washed with a liter of distilled water. The filter cake from the carbonate extraction was steeped for two hours in eight liters of 5% potassium hydroxide at 20–22°. Nitrogen was bubbled through the mixture to assist in mixing and removal of oxygen. The pale amber-colored suspension was filtered on hardened paper, and the filter cake was washed with two liters of distilled water without drawing air through the funnel. The hemicellulose fraction was isolated as a white curdy precipitate when the filtrate was poured into two volumes of 95% ethanol. The suspension was acidified (*p*H 4.5–5.0) with acetic acid and filtered. The hemicellulose was washed successively with 70% ethanol—5% acetic acid, 70, 85, and 95% ethanol and acetone, and air dried.

A second fraction was isolated by extracting the filter cake from the 5% potassium hydroxide extraction in the same general way but with four liters of 24% potassium hydroxide solution.

Hemicellulose Diacetate, Dipropionate and Dibutyrate.—Twelve grams of hemicellulose from corn cob or lima bean pod (dried *in vacuo* at 70°) was gelatinized by stirring for one hour at 63–65° with 250 g. of formamide. Pyridine (250 ml.) was added and the mixture was cooled to 25°. The appropriate acid anhydride (0.7–0.9 mole) was added in four equal portions over a four-hour period. The reaction mixture was stirred for six hours at 25–30° and allowed to stand overnight at room temperature. The esters were isolated by pouring the reaction mixture into 3 liters of water containing a kilogram of chopped ice. The esters, which precipitated either as flocs or as grainy precipitates, were filtered and washed successively with cold 2% aqueous hydrochloric acid, distilled water, 95% ethanol and ether. They usually had acyl contents one or two per cent. below the theoretical and were esterified a second time by treatment with pyridine and acid anhydride for several days at room temperature to yield the diesters in quantitative yields with maximum esterifications.

Hemicellulose Benzoate.—Eight grams of corncob hemicellulose (anhydrous) was stirred for one hour in 100 ml. of water at 80–85° and a smooth suspension was obtained. To the cooled mixture 100 ml. of 25% sodium hydroxide solution was added and the resulting clear amber solution was cooled to 5° with an ice-bath. Forty grams of benzoyl chloride was added in small quantities with vigorous stirring over a three-hour period and stirring was continued for two more hours at 7–10°. Xylan benzoate which precipitated as a white granular material was filtered and washed successively with 2% aqueous hydrochloric acid, hot (70°) distilled water, 95% ethanol and ether. Hemicellulose benzoate, 17.5 g., was obtained which had a benzoyl content of 55.8%, equivalent to 1.7 benzoyl groups per anhydroxylose repeating unit. A second esterification with pyridine and benzoyl chloride for two days at 22–25° yielded a benzoate containing approximately 1.8 benzoyl groups per repeating unit.

Hemicellulose Caprate, Laurate, Myristate and Palmitate.—These esters could not be prepared satisfactorily in formamide dispersion because of extensive side reactions between the acid chlorides and formamide. In a typical preparation, ten grams of hemicellulose was dispersed to a smooth paste by heating for fifteen minutes at 90° with 70 ml. of water in a 3-neck liter, round-bottom flask. To the paste 150 ml. of anhydrous pyridine was added, and the mixture was stirred mechanically and heated while pyridine and water were distilled off azeotropically. Fresh pyridine was added at intervals and the distillation continued until the distillation temperature reached 114° at which point the polysaccharide was practically free of water. The reaction mixture was cooled to 40°, additional pyridine was added to give a total volume of approximately 400 ml. and 0.3 mole of acid chloride was added in three equal quantities over a three-hour period. The reaction mixture was stirred for a total of six hours at 43–45°, allowed to stand overnight, and the esters recovered as waxy or resinous aggregates by pouring into two liters of ice water. In order to remove completely excess fatty acid, it was usually necessary to swell and partially dissolve the ester in dioxane and to re-precipitate into ethanol.

Acknowledgment.—The authors are grateful to Miss Nylan Jeung for analysis of methoxyl and uronic anhydride.

Summary

The acetate, propionate, butyrate, caprate, laurate, myristate, palmitate and benzoate of a corncob hemicellulose and the acetate, propionate, and butyrate of a lima bean pod hemicellulose have been prepared and their solubility characteristics studied.

Fractionation of the acetate, propionate and butyrate of the lima bean pod hemicellulose with organic solvents into soluble and insoluble fractions failed to accomplish an appreciable change in xylan content of the regenerated hemicellulose, which indicated that the non-pentosan part is probably chemically combined with the xylan in agreement with earlier observations of hemicelluloses extracted from sapwood tissue.

ALBANY, CALIFORNIA RECEIVED JULY 26, 1947

[Contribution from the Department of Chemistry of the Massachusetts Institute of Technology]

Aryl Carbamates of Cellulose Acetate

By W. M. Hearon and Jules L. Lobsitz

Phenyl and α-naphthyl isocyanates have been found to react readily with partially hydrolyzed cellulose acetates to produce colorless fibrous mixed esters with good solubilities in a variety of solvents.[1] The carbamate groups thus introduced are very resistant to acid hydrolysis and are only partially removed in alkaline media.[2] Recently, the reaction of chlorophenyl isocyanates with methyl cellulose has also been studied.[3]

We have now extended the study of the condensation of aryl isocyanates with partially hydrolyzed cellulose acetate to determine their relative rates of reaction, the solubilities of the products, and the ease of alkaline hydrolysis of the different carbamate groups. The relative rates of reaction of the isocyanates used at 2.5 times the theoretical with cellulose acetate containing 38.8% acetyl[3a] at 60° in order of increasing speed were as follows: *o*-tolyl, *p*-tolyl, phenyl, α-naphthyl, *o*-chlorophenyl and *p*-bromophenyl (see Fig. 1). The completely carbamated products were all soluble in acetone, pyridine, ethyl acetate, acetic acid, 1,4-dioxane, and chloroform, insoluble in methanol, and swollen in 75% ethyl aclohol. The phenyl, *p*-bromophenyl, and *o*-tolyl carbamates of cellulose acetate were soluble in cellosolve, while the *o*-chlorophenyl, *p*-tolyl, and α-naphthyl carbamates were merely swollen in the cold and soluble in that solvent hot.

Determination of acetyl by the Eberstadt method[4] in cellulose acetate carbamates has been modified[2] to compensate for the carbamyl lost during the alkaline conditions. After the usual saponification, the excess alkali is back-titrated to an end-point, excess acid then added and the carbon dioxide removed by boiling. A second alkaline titration is then carried out to a second end-point. The carbamate hydrolyzed corresponds to the carbon dioxide lost while the acetyl accounts for the rest of the alkali consumed. Using this method on the acetate aryl carbamates formed, the acetyl values were determined and on the assumption, previously found true,[1] that no acetyl is lost during carbamation, the amount of carbamyl which entered has been calculated. The acetyl determinations have also indicated the amount of carbamyl hydrolyzed during the acetyl determination and these values are given in Table I. The values reported are, however, probably more a function of physical form of the ester than nature of the carbamate.

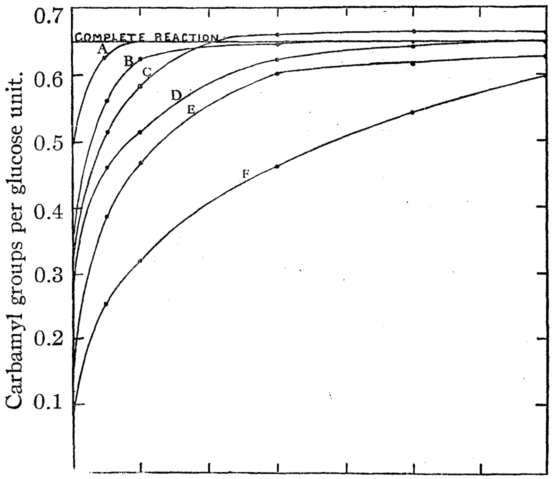


Fig. 1.—Rates of carbanilation of cellulose acetate (38.8% acetyl) with A, *p*-bromophenyl isocyanate; B, *o*-chlorophenyl isocyanate; C, α-naphthyl isocyanate; D, phenyl isocyanate; E, *p*-tolyl isocyanate; and F, *o*-tolyl isocyanate.

Table I

Hydrolysis of Carbamyl from Cellulose Acetate Carbamates after Forty-eight Hours of Saponification with 0.5 *N* Sodium Hydroxide

Cellulose acetate carbamates	% Carbamyl hydrolyzed	% Carbamyl originally	% of total carbamyl hydrolyzed
Phenyl	1.66	23.0	7.25
o-Chlorophenyl	9.45	27.8	34.0
p-Bromophenyl	1.98	33.2	5.97
o-Tolyl	2.37	25.1	9.46
p-Tolyl	1.24	25.1	4.96
α-Naphthyl	4.56	29.8	15.30

Experimental

Preparation of Carbamates.—The same procedure was followed for all rate studies. A 12.5-g. sample of cellulose acetate containing 38.8% acetyl, dried at 100° for forty-eight hours, was dissolved in 100 g. of dry pyridine and allowed to remain at 60° overnight in a tightly stoppered and previously dried flask. To the clear dope was added 2.5 times the theoretical of the isocyanate and the mixture was thoroughly shaken and left at 60 ± 0.5°. Samples were then withdrawn after 0.5, 1, 3, 5 and 7-hour intervals. Each sample was treated at once with 10 ml. of methanol to stop the reaction and precipitated into 600 ml. of rapidly stirred methanol. Purification of the white, fibrous product was completed by two additional precipitations into methanol from acetone dopes. The products were finally washed with water for two hours and dried at 60° for four hours. The yields in all cases were essentially quantitative. Acetyl analyses were carried out by the Eberstadt method[4] modified for carbamate[2] and gave the values listed in Table II.

---

[1] Hearon, Hiatt and Fordyce, This Journal, **65**, 829 (1943).

[2] Hearon, Hiatt and Fordyce, *ibid.*, **65**, 833 (1943).

[3] Dyer and McCormick, *ibid.*, **68**, 986 (1946).

[3a] Kindly furnished by the Eastman Kodak Company, Rochester, New York.

[4] Genung and Mallatt, *Ind. Eng. Chem.*, *Anal. Ed.*, **13**, 369 (1941).

TABLE II

ANALYSES OF CELLULOSE ACETATE CARBAMATES FROM CELLULOSE ACETATE OF 38.8% ACETYL 2.352 acetyls/glucose unit and 0.648 hydroxyls/glucose unit

Cellulose acetate carbamates	0.5 Hours		1 Hour		3 Hours		5 Hours		7 Hours		% Ac calcd. for complete reaction
	% Ac	Carb./ g. u.	% Ac	Carb./ g. u.	% Ac	Carb./ g. u.	% Ac	Carb./ g. u.	% Ac	Carb./ g. u.	
Phenyl	32.02	0.465	31.45	0.512	30.28	0.620	30.13	0.635	29.98	0.648	29.90
o-Chlorophenyl	29.15	.561	28.40	.624	28.20	.640	28.20	.640	28.05	.654	28.10
p-Bromophenyl	26.33	.627	26.10	.644	26.10	.644	26.10	.644	26.10	.644	26.00
o-Tolyl	34.48	.246	33.40	.317	31.40	.466	30.43	.536	29.80	.596	29.10
p-Tolyl	32.40	.388	31.35	.470	29.72	.600	29.56	.616	29.52	.619	29.10
α-Naphthyl	29.18	.512	28.17	.583	27.17	.665	27.17	.665	27.17	.665	27.30

Summary

1. Phenyl, *o*-chlorophenyl, *p*-bromophenyl, *o*-tolyl, *p*-tolyl, and α-naphthyl isocyanates reacted readily with 38.8% cellulose acetate at 60°.

2. The order of relative reaction rates of these isocyanates was as follows: *p*-bromophenyl (fastest), *o*-chlorophenyl, α-naphthyl, phenyl, *p*-tolyl, and *o*-tolyl (slowest).

3. The completely carbamated esters showed good solubilities in a variety of organic solvents.

4. All cellulose acetate carbamates formed hydrolyzed partially during deacetylation with aqueous alkali at room temperature.

RECEIVED AUGUST 2, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Methyl Glucoside Carbanilates. II. α-Methyl-*d*-glucoside-2,3,6-tricarbanilate

BY W. M. HEARON

Carbanilates are excellent derivatives of methyl glucoside since they are readily formed, high melting, insoluble in water, readily crystallized and resistant to hydrolysis.

To the partially substituted methyl glucoside carbanilates previously reported[1] is now added the 2,3,6-tricarbanilate, which is of special interest because of its relation to carbanilated cellulose[2] and starch. The series of reactions for its preparation is given below

α-methyl-*d*-glucoside-2,3-dicarbanilate (I)
↓
6-trityl-α-methyl-*d*-glucoside-2,3-dicarbanilate (II)
↓
6-trityl-α-methyl-*d*-glucoside-2,3-dicarbaniliate-4-acetate (III)
↓
α-methyl-*d*-glucoside-2,3-dicarbanilate-4-acetate (IV)
↓
α-methyl-*d*-glucoside-2,3,6-tricarbanilate-4-acetate (V)
↓
α-methyl-*d*-glucoside-2,3,6-tricarbanilate (VI)

As with methyl-*d*-glucoside,[3] tritylation and acetylation of α-methyl-*d*-glucoside-2,3-dicarbanilate could be carried out without isolation of the intermediate. That no migration of acetyl to the primary hydroxyl[4] occurred during detritylation was proved by retritylation of IV to III. No migration of acetyl occurred during carbanilation since (V) melted sharply about 70° below α-methyl-*d*-glucoside-2,3,4-tricarbanilate-6-acetate which was prepared by acetylation of the 2,3,4-tricarbanilate.[1] Finally, no inversions or loss of methoxyl occurred during this series of reactions since carbanilation of VI gave the previously reported α-methyl-*d*-glucoside tetracarbanilate.[5]

Experimental

6-Trityl-α-methyl-*d*-glucoside-2,3-dicarbanilate (II).—A solution of 3.0 g. of α-methyl-*d*-glucoside-2,3-dicarbanilate[1] and 1.93 g. of trityl chloride in 6 ml. of dry pyridine was heated in a stoppered flask on a steam-bath for one hour. After cooling the solution was diluted with 20 ml. of ordinary pyridine and poured into cold water. The white precipitate, amounting to 4.8 g. or 98%, was recrystallized from hot methanol giving 3.1 g. or 63% yield melting at 121–122°; $[\alpha]^{25}\text{D}$ +57.3° (acetone, *C* 0.1).

Anal. Calcd. for $C_{40}H_{38}O_8N_2$: C, 71.2; H, 5.63; N, 4.16; trityl, 36.1. Found: C, 71.1; H, 5.75; N, 4.15; trityl, 36.2.

6-Trityl-α-methyl-*d*-glucoside-2,3-dicarbanilate-4-acetate (III). A. By Acetylation of 6-Trityl-α-methyl-*d*-glucoside-2,3-dicarbanilate.—A solution of 2.0 g. of 6-trityl-α-methyl-*d*-glucoside-2,3-dicarbanilate and 4.5 ml. of acetic anhydride in 10 ml. of dry pyridine was heated in a stoppered flask on a steam-bath for thirty minutes. After cooling to room temperature water was added to a permanent cloudiness and the mixture was poured into cold water. The precipitate, amounting to 2.1 g. or 99%, crystallized from hot alcohol giving 1.9 g. or a 90% yield, m. p. 134–135°, $[\alpha]^{25}\text{D}$ +77.8° (acetone, *C* 0.1).

Anal. Calcd. for $C_{42}H_{40}O_9N_2$: C, 70.4; H, 5.58; N, 3.91; trityl, 33.9. Found: C, 70.0; H, 5.80; N, 3.75; trityl, 33.8.

---

[1] Hearon, Hiatt, and Fordyce, THIS JOURNAL, **66**, 995 (1944).

[2] Hearon, Hiatt and Fordyce, *ibid.*, **65**, 829 (1943).

[3] Helferich, Klein and Snyder, *Ber.*, **59**, 81 (1926).

[4] Compare Helferich and Bredereck, *ibid.*, **64**, 2413 (1931); Helferich and Müller, *ibid.*, **63**, 2146 (1930); Robertson, *J. Chem. Soc.*, **1933**, 737.

[5] Wolfrom and Pletcher, THIS JOURNAL, **62**, 1151 (1940).

B. By Tritylation and Acetylation of 6-Trityl-α-methyl-*d*-glucoside-2,3-dicarbanilate.—A mixture of 15 g. of α-methyl-*d*-glucoside-2,3-dicarbanilate and 9.7 g. of trityl chloride in 30 ml. of dry pyridine was heated in a stoppered flask on a steam-bath for one hour. After cooling 15 ml. of acetic anhydride was added and the solution allowed to stand at room temperature for fifteen hours. After dilution with 45 ml. of ordinary pyridine the mixture was poured into cold water. The white precipitate was crystallized from hot alcohol giving 23.7 g. or 95.7% yield, m. p. 134–135°; mixed melting point with the material from A, above, 134–135°.

α-Methyl-*d*-glucoside-2,3-dicarbanilate-4-acetate (IV).—A cold solution of 6.2 g. of 6-trityl-α-methyl-*d*-glucoside-2,3-dicarbanilate in 18 ml. of glacial acetic acid was treated with 18 ml. of hydrobromic acid in acetic acid (made by adding 11 ml. of 42% hydrobromic acid to 46 ml. of cooled acetic anhydride). The heavy precipitate of trityl bromide (2.3 g.) was sucked off and the filtrate run immediately into ice water. The white precipitate was sucked off, washed with water and dried; weight, 3.9 g., or 95%. Crystallization from alcohol and water gave 3.8 g. or 93%. Recrystallization by dissolving in chloroform and precipitating with *n*-butyl ether gave 3.5 g. or 85% yield melting at 119–120°, $[\alpha]^{25}\text{D}$ +85.3° (acetone, *C* 0.1).

Anal. Calcd. for $C_{23}H_{26}O_9N_2$: C, 58.2; H, 5.48; N, 5.90. Found: C, 58.3; H, 5.50; N, 5.89.

A small amount of the product, when treated in pyridine with the theoretical quantity of trityl chloride, gave a precipitate in water which melted at 133–134° (from alcohol) and did not depress the melting point of 6-trityl-α-methyl-*d*-glucoside-2,3-dicarbanilate-4-acetate.

α-Methyl-*d*-glucoside-2,3,6-tricarbanilate-4-acetate (V).—A solution of 1.5 g. of α-methyl-*d*-glucoside-2,3-dicarbanilate-4-acetate in 3 ml. of dry pyridine was treated with 0.5 g. of phenyl isocyanate (1.4 times theory) and heated in a stoppered flask on a steam-bath for one hour. After cooling, the solution was diluted with 1 ml. of methanol and allowed to stand ten minutes. Five ml. of ordinary pyridine was then added and the mixture poured into cold water. The precipitate was sucked off, washed and dried. After washing with hot ligroin to remove methyl carbanilate the precipitate weighed 1.7 g. or 91%. Crystallization from *n*-butanol gave 1.2 g. or 64% melting at 166–167°, $[\alpha]^{25}\text{D}$ +75.0° (acetone, *C* 0.1).

Anal. Calcd. for $C_{30}H_{31}O_{10}N_3$: C, 60.7; H, 5.22; N, 7.08. Found: C, 60.6; H, 5.36; N, 6.98.

α-Methyl-*d*-glucoside-2,3,6-tricarbanilate (IV).—A solution of 1.0 g. α-methyl-*d*-glucoside-2,3,6-tricarbanilate-4-acetate in 20 ml. of methanol containing 0.5% hydrochloric acid was refluxed for two hours. After cooling the hydrochloric acid was removed with barium carbonate, and the solution evaporated to dryness by an air stream. The white solid was purified by solution in acetone, addition of benzene and heating to remove most of the acetone. On cooling the product crystallized out and was sucked off. This purification, when repeated, gave 0.8 g. or 86% melting at 190–191°; $[\alpha]^{25}\text{D}$ +56.0° (acetone, *C* 0.1).

Anal. Calcd. for $C_{28}H_{29}O_9N_3$: C, 61.0; H, 5.27; N, 7.62. Found: C, 60.8; H, 5.32; N, 7.56.

α-Methyl-*d*-glucoside-2,3,4-tricarbanilate-6-acetate.—Acetylation of 1.5 g. of α-methyl-*d*-glucoside-2,3,4-tricarbanilate[1] in 10 ml. of dry pyridine with 5 ml. of acetic anhydride at room temperature for fifteen hours gave 1.5 g. crude (94%) and 1.0 g. pure (63%) of white crystals from hot alcohol melting at 235–237°; $[\alpha]^{25}\text{D}$ +71.0° (acetone, *C* 0.1).

Anal. Calcd. for $C_{30}H_{31}O_{10}N_3$: C, 60.7; H, 5.22; N, 7.08. Found: C, 60.7; H, 5.35; N, 7.16.

α-Methyl-*d*-glucoside-2,3,4,6-tetracarbanilate.—A small quantity of α-methyl-*d*-glucoside-2,3,6-tricarbanilate in pyridine with an excess of phenyl isocyanate was heated on a steam-bath for one hour. After cooling a little methanol was added to remove excess isocyanate and the mixture poured into cold water. The resulting white precipitate, after recrystallization twice from hot acetic acid, melted at 227° and did not depress the melting point of an authentic sample of α-methyl-*d*-glucoside-2,3,4,6-tetracarbanilate.[5]

Summary

1. Crystalline α-methyl-*d*-glucoside-2,3,6-tricarbanilate has been prepared by a five-step series of reactions from α-methyl-*d*-glucoside-2,3-dicarbanilate.

2. The intermediates in this synthesis, all crystalline, have been described and identified.

CAMBRIDGE, MASSACHUSETTS RECEIVED AUGUST 2, 1947

[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY, VANDERBILT UNIVERSITY]

Branched-Chain Fatty Acids. V. The Synthesis of Optically Active 10-Methyloctadecanoic Acids[1]

BY FRANKLIN S. PROUT,[2,3] JAMES CASON[4] AND A. W. INGERSOLL

The synthesis of 10-methyloctadecanoic acid was undertaken as a continuation of the program to synthesize and compare the properties of the complete series of methyloctadecanoic acids.[5] The 10-methyl member of this series is particularly interesting, moreover, since tuberculostearic acid, a C_{19} branched-chain fatty acid isolated from the lipids of tubercle bacillus by Anderson and Chargaff,[6] has been assigned this structure.[7] The assignment of structure by Spielman was based on oxidative degradation of the natural acid and the synthesis of *dl*-10-methyloctadecanoic acid. The synthetic acid melted some ten degrees higher (20–21°) than the melting point (10–11°) reported for tuberculostearic acid. There was, however, close agreement in other properties, and it appeared probable that tuberculostearic acid, although reported to be optically inactive,

---

[1] Preceding paper in this series: Cason, THIS JOURNAL, **68**, 2078 (1946).

[2] Constructed from a thesis submitted by Franklin S. Prout in partial fulfilment of the requirements for the Ph.D. degree, Vanderbilt University, March, 1947.

[3] Present address: Department of Chemistry, Northwestern University, Evanston, Illinois.

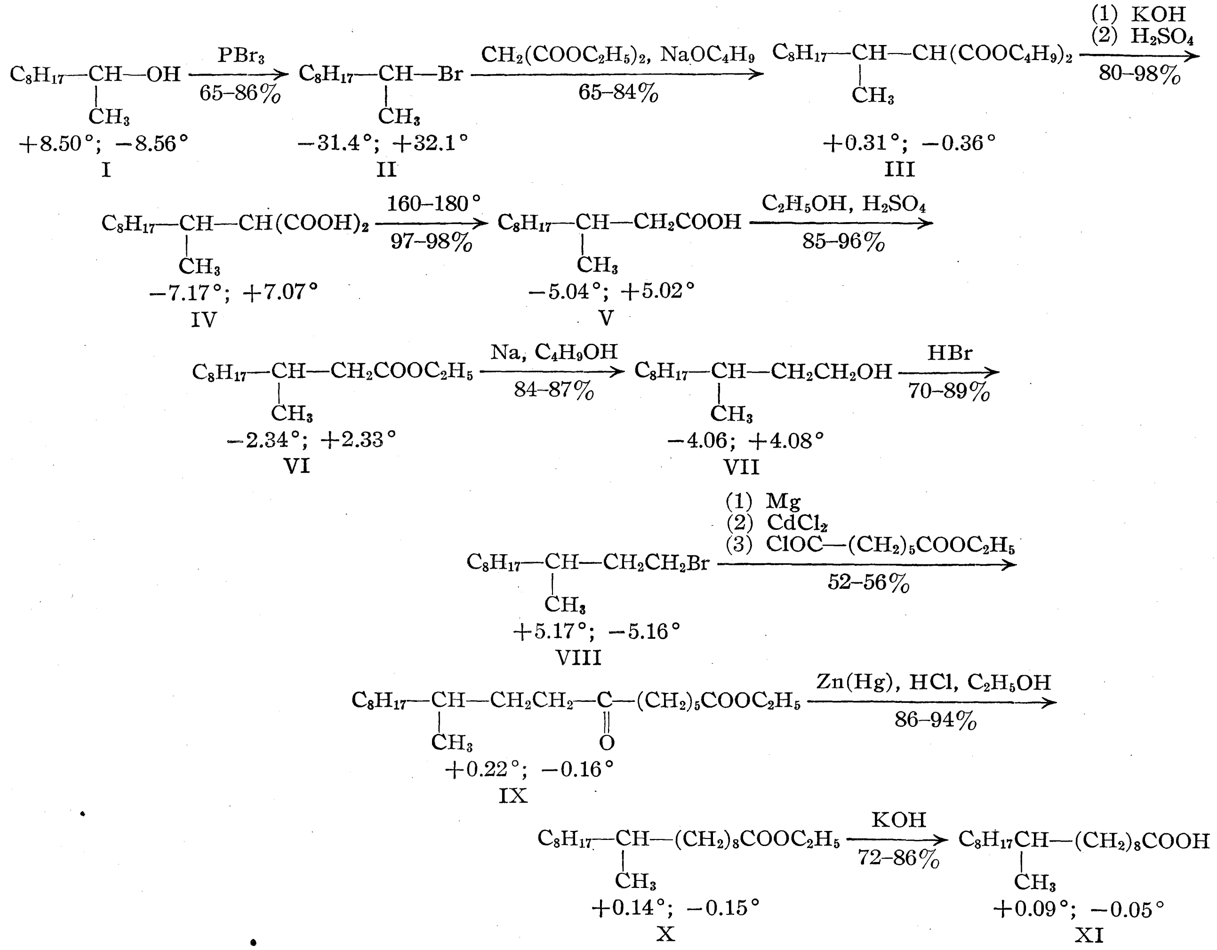
[4] Present address: Department of Chemistry, University of California, Berkeley, California.

[5] (a) Cason, THIS JOURNAL, **64**, 1106 (1942); (b) Cason and Prout, *ibid.*, **66**, 46 (1943); (c) Cason, Adams, Bennett and Register, *ibid.*, **66**, 1764 (1944).

[6] Anderson and Chargaff, *J. Biol. Chem.*, **85**, 77 (1929).

[7] Spielman, *ibid.*, **106**, 87 (1934).

SCHEME FOR THE SYNTHESIS OF 10-METHYLOCTADECANOIC ACIDS



$$C_8H_{17}-\underset{CH_3}{CH}-OH \xrightarrow[65-86\%]{PBr_3} C_8H_{17}-\underset{CH_3}{CH}-Br \xrightarrow[65-84\%]{CH_2(COOC_2H_5)_2,\ NaOC_4H_9} C_8H_{17}-\underset{CH_3}{CH}-CH(COOC_4H_9)_2 \xrightarrow[80-98\%]{(1)\ KOH\ (2)\ H_2SO_4}$$

+8.50°; −8.56° I; −31.4°; +32.1° II; +0.31°; −0.36° III

$$C_8H_{17}-\underset{CH_3}{CH}-CH(COOH)_2 \xrightarrow[97-98\%]{160-180°} C_8H_{17}-\underset{CH_3}{CH}-CH_2COOH \xrightarrow[85-96\%]{C_2H_5OH,\ H_2SO_4}$$

−7.17°; +7.07° IV; −5.04°; +5.02° V

$$C_8H_{17}-\underset{CH_3}{CH}-CH_2COOC_2H_5 \xrightarrow[84-87\%]{Na,\ C_4H_9OH} C_8H_{17}-\underset{CH_3}{CH}-CH_2CH_2OH \xrightarrow[70-89\%]{HBr}$$

−2.34°; +2.33° VI; −4.06; +4.08° VII

$$C_8H_{17}-\underset{CH_3}{CH}-CH_2CH_2Br \xrightarrow[52-56\%]{(1)\ Mg\ (2)\ CdCl_2\ (3)\ ClOC-(CH_2)_5COOC_2H_5}$$

+5.17°; −5.16° VIII

$$C_8H_{17}-\underset{CH_3}{CH}-CH_2CH_2-\underset{\overset{\|}{O}}{C}-(CH_2)_5COOC_2H_5 \xrightarrow[86-94\%]{Zn(Hg),\ HCl,\ C_2H_5OH}$$

+0.22°; −0.16° IX

$$C_8H_{17}-\underset{CH_3}{CH}-(CH_2)_8COOC_2H_5 \xrightarrow[72-86\%]{KOH} C_8H_{17}\underset{CH_3}{CH}-(CH_2)_8COOH$$

+0.14°; −0.15° X; +0.09°; −0.05° XI

might be an active form with a very small rotation.

In view of this situation it was decided to prepare *dl*-10-methyloctadecanoic acid by a different method and also to prepare both active forms of this acid. It was expected that comparison of the isomeric acids with each other and with tuberculostearic acid might provide decisive evidence on the points at issue.

The results of this phase of the work have already been briefly reported.[8] It has been found that carefully purified *dl*-10-methyloctadecanoic acid melts at 25.4–26.1°, while the pure active forms melt at 13.0–13.5° and have specific rotations in the range 0.05–0.09°. A sample of tuberculostearic acid, derived from a sample of the methyl ester kindly supplied by Dr. R. J. Anderson[9] and purified by one crystallization from acetone, melted at 10.3–11.7° and showed a small but definite levo rotation. A mixture of this acid with approximately an equal amount of the synthetic levorotatory acid melted at 11.0–12.4°, while a similar mixture with the synthetic dextrorotatory acid melted at 19.4–20.1°. A mixture of the two synthetic acids melted at 21.0–25.8°. Further comparisons of the amides and tribromoanilides of the natural and synthetic acids (Table I) es-

TABLE I

COMPARISON OF TUBERCULOSTEARIC ACID WITH 10-METHYLOCTADECANOIC ACIDS

	Melting points, °C. Acid	Amide	Tribromo-anilide
Tuberculostearic	10.3–11.7[a]	71.5–75.6	94.5–95.4
dl-10-Methyloctadecanoic	25.4–26.1	77.5–79.2	93.4–93.9[b]
	20–21[c]	75.2–78.1[c]	93–94[c]
(+)-10-Methyloctadecanoic	13–13.5	75.5–76.4	93.2–95.2
(−)-10-Methyloctadenoic	12.8–13.4	75.1–76.3	94.0–95.3
(+)-10)-Methyloctadecanoic (−)-10-Methyloctadecanoic [a]	21–25.8	74.8–78.7	93.1–94.4[b]
(+)-10-Methyloctadecanoic Tuberculostearic [d]	19.4–20.1	73.6–77.8	93.3–94.0[b]
(−)-10-Methyloctadecanoic Tuberculostearic [d]	11.0–12.4[a]	72.5–76.3	93.9–95.5[b]

[a] These melts were slightly cloudy owing to the presence of small amounts of stearic acid. [b] These data are remelting points. The initial m.p.'s are less definitive. [c] Spielman's data, ref. 7. [d] Mixtures contained as nearly as possible equal amounts of the components.

---

(8) Prout, Cason and Ingersoll, THIS JOURNAL, **69**, 1233 (1947).

(9) The methyl tuberculostearate was material purified by fractional distillation by Dr. Sidney F. Velick. Samples of the amide and tribromoanilide prepared by Dr. M. A. Spielman (ref. 7) were also supplied.

tablished beyond reasonable doubt the identity of tuberculostearic acid with levorotatory 10-methyloctadecanoic acid.[10]

Scheme of Synthesis

The scheme of synthesis and data on yields and specific rotations of active forms are shown in the accompanying chart. The first rotation value in each instance refers to the series of products derived from (+)-2-decanol. The purposes of the work required the selection of a combination of optical resolution and synthetic procedures which would assure not only structural and chemical purity of the desired 10-methyloctadecanoic acids, but also complete antipodal purity of both active forms. The plan adopted involved the preliminary preparation of both active forms of a suitable intermediate, namely, 3-methylhendecanoic acid (V), which would permit subsequent chain extension without racemization. This intermediate was selected rather than 2-methyldecanoic acid or 2-methyl-1-decanol. Both of these have the requisite 2-decyl terminal structure but appeared unlikely to permit satisfactory resolution into both forms[11] or chain extension without serious racemization.[11,12] It appeared improbable also that resolution of 3-methylhendecanoic acid itself would be satisfactory.[13]

The resolution step was carried out upon *dl*-2-decanol, the (+)-form being obtained by the method of Pickard and Kenyon[14] and the (−)-form by an original method. The conditions for the steps through the 3-methylhendecanoic acids were chosen to minimize racemization,[13,15] but this amounted to some 10–15% at the 2-decylmalonic acid stage. The key to complete antipodal purity of the 3-methylhendecanoic acids was the fact that fractional crystallization of the partially racemized 2-decylmalonic acids afforded a sharp separation of the more sparingly soluble active forms (m. p. 100.5°) from the *dl*-form (m. p. 75.5°). Decarboxylation of the pure malonic acids and all succeeding steps proceeded without racemization.

Configurative Relationships

The synthesis of the 3-methylhendecanoic acids from the 2-decanols appears to involve inversion of configuration accompanied by slight racemization in the bromination stage and again in the alkylation of malonic ester.[16,17] The remaining steps involve no further inversions. Hence (−)-10-methyloctadecanoic acid (tuberculostearic acid) has the same configuration as (−)-2-decanol and (+)-3-methylhendecanoic acid. The latter acid should have the same configuration as (−)-2-methylbutanoic acid[11b,13] which has been related to (−)-2-butanol[18] and to D-(+)-glyceraldehyde.[19,20] Accordingly, (−)-10-methyloctadecanoic acid may be assigned to the D-series but this classification is regarded as provisional since the correlation of (−)-2-methylbutanoic acid with (+)-glyceraldehyde is still somewhat uncertain.

Acknowledgment.—We are indebted to Professor R. J. Anderson of Yale University and his associates who kindly supplied us with the methyl tuberculostearate and other derivatives used for the comparisons with our synthetic materials.

Experimental[21]

Resolution of *dl*-2-Decanol

***dl*-2-Decanol (I).**[14,22]—The Grignard reagent from 970 g. of 1-bromoöctane,[23] b. p. 106–106.5° (35 mm.), in 1500 cc. of ether was treated with 220 g. of acetaldehyde in 750 cc. of ether at −5° to 5° to form 2-decanol in a yield of 634 g. (80.0%); b. p. 124–126° (31 mm.) (95% at 124.5–125.5° at 31 mm., column V45)[24]; f. p. −2.4°; $n^{25}\text{D}$ 1.4327. A forerun of 38.7 g., b. p. 43–40° (43–32 mm.), was presumably *n*-octane. A small fraction (9.2 g.) of b. p. 126–127° (31 mm.), was rejected. A 0.5-mole run using 0.9 equivalent of acetaldehyde gave the same yield (80.9%).

The **3,5-dinitrobenzoate** was obtained in 65% yield by reaction of 2-decanol with 3,5-dinitrobenzoyl chloride in the presence of powdered sodium carbonate; m. p. 49.8–51.5°. Two crystallizations from ligroin or 95% ethanol furnished the pure ester; m. p. 52.0–52.9°. Heilbron, Jones and Raphael[22b] give m. p. 44°.

***dl*-2-Decyl hydrogen phthalate** was prepared in a 2-mole run in 92.7% yield by essentially the procedure of Kenyon[25] for the preparation of *dl*-2-octyl hydrogen phthalate, except that the product was extracted with hexane.[26] The crude half ester melted at 26–38.6°. After three crystallizations from pentane[26] the m. p.

---

[10] After our previous communication (ref. 8) had been submitted it was learned (private communication) that Stina Stallberg-Stenhagen (Uppsala, Sweden) has recently prepared levorotatory 10-methyloctadecanoic acid by a completely different synthesis. From the information supplied the properties of her acid and ours are in close agreement.

[11] (a) Levene and Mikeska, *J. Biol. Chem.*, **84**, 571 (1929); (b) Levene and Marker, *ibid.*, **98**, 1 (1932).

[12] Whitmore and Karnatz, THIS JOURNAL, **60**, 2533 (1938); Whitmore and Olewine, *ibid.*, **60**, 2570 (1938).

[13] Levene and Marker, *J. Biol. Chem.*, **91**, 77, 405 (1931).

[14] Pickard and Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

[15] Hsueh and Marvel, THIS JOURNAL, **50**, 855 (1928); Shriner and Young, *ibid.*, **52**, 3332 (1930); Rose and Haller, *ibid.*, **58**, 2648 (1936); Brink, Lane and Wallis, *ibid.*, **65**, 943 (1943).

[16] Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1252 (1937).

[17] Gerrard, *ibid.*, 85 (1944); 106, 848 (1945); 741 (1946); Gerrard and Richmond, *ibid.*, 853 (1945).

[18] Kenyon, Phillips and Pittman, *ibid.*, 1072 (1935).

[19] Levene, Walti and Haller, *J. Biol. Chem.*, **71**, 465 (1926); Levene, *Chem. Rev.*, **2**, 180 (1925).

[20] S. Stenhagen and E. Stenhagen, *Arkiv Kemi, Mineral. Geol.*, **B24**, No. 9 (1947).

[21] The melting points are corrected and the boiling points are uncorrected. Densities were taken in a 5-cc. pycnometer unless otherwise specified.

[22] (a) Adamson and Kenner, *J. Chem. Soc.*, 838 (1934); (b) Heilbron, Jones and Raphael, *ibid.*, 264 (1943); (c) Petrov, Shchupina and Ol'dekop, *J. Gen. Chem.* (*U. S. S. R.*), **14**, 498 (1944); *C. A.*, **39**, 4585 (1945).

[23] Kamm and Marvel, "Organic Syntheses," Coll. Vol. I, 2nd ed., p. 30.

[24] Three columns with electrically heated jackets were used in this work. Columns V45 and V90 were of Vigreux type, 0.8 × 45 cm. and 1.2 × 90 cm., respectively; P45 was 0.6 × 45 cm. and contained a tantalum wire spiral of the Podbielniak type.

[25] Kenyon, *J. Chem. Soc.*, **121**, 2540 (1922); "Organic Syntheses," Coll. Vol. I, 2nd ed., p. 418.

[26] The solvents herein called hexane and pentane are redistilled fractions of Skellysolve B and Skellysolve F boiling at 63–69° and 36–38°, respectively.

remained constant at 38.0–39.4°. A sample prepared later by recrystallizing a mixture of equal amounts of the pure *l*- and *d*-forms had m. p. 37.4–39.5°. Pickard and Kenyon[14] give 48–49° as the melting point of the unrecrystallized half ester.

Resolution with Brucine.—The resolution of the crude *dl*-2-decyl hydrogen phthalate with brucine followed the procedures of Pickard and Kenyon[14] and Kenyon.[25] The salt of brucine (733 g.) and *dl*-2-decyl hydrogen phthalate (569 g.) was crystallized from 1200 cc. of acetone to give 477 g. of the crude brucine salt of the dextrorotatory half ester; m. p. 129–134.5°. Systematic recrystallization of this crop and the second crop (219 g.) furnished finally 456 g. (70% yield) of the pure salt; m. p. 135.2–137.1° (gas); $[\alpha]^{25}\mathrm{D}$ −5.48° (95% ethanol, *c*, 9.07); literature,[14] m. p. 136–138°; $[\alpha]\mathrm{D}$ −6.01° (alcohol, *c*, 5). The mother liquor was reserved for recovery of the levorotatory form of the half ester.

(+)-2-Decyl Hydrogen phthalate was obtained by dissolving 200 g. of the brucine salt of the dextrorotatory half ester ($[\alpha]^{24}\mathrm{D}$ −5.64°) in 250 cc. of ethanol and adding 100 cc. of concentrated hydrochloric acid in 1200 cc. of water. The ester was extracted by two portions of hexane (200 and 150 cc.). After these extracts had been washed twice with water and once with saturated sodium chloride solution and filtered through sodium sulfate, removal of solvent gave 87.2 g. (99%) of substantially pure half ester. Three recrystallizations of a sample of this ester from hexane (cooling at 5°) furnished product of high purity; m. p. 33.4–36.2°; $[\alpha]^{25}\mathrm{D}$ +47.1° (95% ethanol, *c*, 4.42); $[\alpha]^{25}\mathrm{D}$ +40.5° (acetone, *c*, 4.77); $[\alpha]^{25}\mathrm{D}$ +39.1° (hexane, *c*, 4.26). Pickard and Kenyon[14] give m. p. 38–39°; $[\alpha]\mathrm{D}$ +45.19° (alcohol).

(+)-2-Decanol.[14]—Crude (+)-2-decyl hydrogen phthalate (197 g.), as obtained directly by decomposition of pure brucine salt, was heated under reflux for thirty minutes with 144 g. of potassium hydroxide in 350 cc. of water and 700 cc. of 95% ethanol. The decanol was extracted from the diluted alkaline solution with hexane and distilled from a Claisen flask: yield, 99.0 g. (97.5%); b. p. 127–129° (35 mm.); f. p. 1.7°; $\alpha^{25}\mathrm{D}$ +6.98°[27]; $[\alpha]^{25}\mathrm{D}$ +8.50° (d^{25} 0.821[14]). The literature[14] value is $[\alpha]^{26.4}\mathrm{D}$ +8.55°.

(+)-2-Decyl 3,5-dinitrobenzoate was prepared in 33% yield by direct reaction between the active alcohol and the acid chloride; m. p. 41–44°. Crystallization from 95% ethanol furnished the purified ester. It softens at 49.5° and melts at 55.8–56.8° when heated at 1.8°/minute, hence is probably polymorphic. The rotation is $[\alpha]^{25}\mathrm{D}$ +34.4° (chloroform, *c*, 2.04).

Recovery of Partially Resolved (−)-2-Decyl Hydrogen Phthalate.—The brucine salts remaining in the mother liquors of the initial resolution were obtained in four successive fractions. The first (98 g.) crystallized from mother liquors of the recrystallization of the brucine (+)-phthalate. The combined mother liquors were concentrated *in vacuo* to about 1 liter and diluted with 2 liters of dry ether; 439 g. of salts separated after two days at room temperature and a further 200 g. after chilling at 5° for several days. The final fraction (not weighed) was residue from evaporation of solvents. The partially resolved half ester was obtained from each fraction as already described, the amounts being 43, 186, 88 and 19 g., respectively. The corresponding rotations ($[\alpha]^{25}\mathrm{D}$, hexane, *c*, 9–10) were −19.0, −27.6, −13.1 and −9.4°.

(−)-2-Decyl Hydrogen Phthalate.—In efforts to obtain the pure levorotatory half ester, resolutions of the partially resolved levorotatory ester were unsuccessfully attempted with cinchonidine, cinchonine and quinine. The cinchonidine salt crystallized, but was too soluble for satisfactory fractionation.[14] A process based upon fractional crystallization of the mixed hydrogen phthalates from hexane (*cf.* Kenyon[25]) gave a small yield of the pure (−)-phthalate but the method was too tedious for satisfactory use. The purification of the (−)-phthalate was readily effected by crystallization of the (+)-α-phenylethylamine salts.

Resolution with (+)-α-Phenylethylamine.—In a typical run 131 g. of 2-decyl hydrogen phthalate ($[\alpha]^{25}\mathrm{D}$ −15.1°, hexane; calculated (−)-form, 70%) was combined with 50.8 g. of (+)-α-phenylethylamine in 350 cc. of acetone. The initial crop (103 g., m. p. 98–113°) crystallized at room temperature as a loose mass of small nodules. Concentration of the mother liquor and cooling at 5° furnished two more crops: 29.7 g., m. p. 103–112.4° and 2.9 g., m. p. 65–96°, and a dark sirupy mother liquor. The solid fractions were recrystallized systematically; usually four or five crystallizations were required to furnish the pure salt of the levorotatory half ester as a mass of soft hair-like needles; m. p. 118.4–120.7°; $[\alpha]^{25}\mathrm{D}$ −19.2° (95% ethanol, *c*, 8.02). For analysis a sample was dried at 56° *in vacuo* and showed no loss in weight in two hours.

Anal. Calcd. for $C_{26}H_{37}O_4N$: N, 3.28. Found: N, 3.26 (Kjeldahl).

The yield of pure salt in this run was 92.1 g., corresponding to recovery of 74.3% of the total (−)-form originally present. Similar results were obtained in other runs. The fractionation is most satisfactorily followed by observation of the melting point and crystal habit of the salt. The separation of initial crops should be carried through promptly because in the presence of the amine acetone condenses fairly rapidly, forming eventually a black viscous mother liquor.

To obtain a sample of pure (−)-2-decyl hydrogen phthalate, 19.2 g. of the above (+)-α-phenylethylamine salt was decomposed with hydrochloric acid and the half ester extracted with hexane.[28] The extracts were concentrated to a volume of 60 cc. and the solution was cooled at 5° to furnish 8.49 g. of half ester; m. p. 33.4–36.5°. An additional 3.8 g. was obtained from the mother liquors: total yield, 89.3%. After one recrystallization the ester had m. p. 33.3–35.8°; $[\alpha]^{25}\mathrm{D}$ −46.6° (95% ethanol, *c*, 4.04); $[\alpha]^{25}\mathrm{D}$ −39.5° (acetone, *c*, 4.37); $[\alpha]^{25}\mathrm{D}$ −39.1° (hexane, *c*, 4.19). These properties agree closely with those of the dextrorotatory half ester.

(−)-2-Decanol was obtained by saponification of either the pure crystalline half ester or the half ester obtained, without crystallization, from the pure salt of (+)-α-phenylethylamine. Both methods gave *pure* optically active alcohol. A sample of pure crystalline (−)-2-decyl hydrogen phthalate (31.1 g., m. p. 33.6–35.9°, $[\alpha]^{25}\mathrm{D}$ −39.7° (hexane, *c*, 4.79)) was saponified and the product purified by the procedure used to obtain (+)-2-decanol. The yield was 15.1 g. (93.7%); b. p. 122° (28 mm.); f. p. 2.8°; $\alpha^{25}\mathrm{D}$ −7.03°; $[\alpha]^{25}\mathrm{D}$ −8.56°.

A sample of crude levorotatory ester (91.3 g. from 126 g. of amine salt) was saponified to furnish 46.4 g. (99.3%) of (−)-2-decanol; b. p. 119–121° (22–25 mm.); f. p. 2.2°; $\alpha^{25}\mathrm{D}$ −7.03°; $[\alpha]^{25}\mathrm{D}$ −8.56°.

(−)-2-Decyl 3,5-dinitrobenzoate was prepared from (−)-2-decanol and the acid chloride by boiling in a benzene solution containing dimethylaniline and crystallized three times from pentane and once from ethanol. The high yield (91.3%) by this procedure is noteworthy. The ester had m. p. 55.8–56.7° after sintering at 49.5° and is probably polymorphic; $[\alpha]^{25}\mathrm{D}$ −32.6° (chloroform, *c*, 4.09). A sample of dinitrobenzoate prepared similarly from partially resolved (−)-2-decanol showed no signs of separation on repeated crystallization.

The 3-Methylhendecanoic Acids

***dl*-2-Bromodecane (II).**[22c]—This bromide was made by the phosphorus tribromide procedure of Hsueh and Marvel[15] for the preparation of the active 2-bromo-octanes; except that the final hour of heating was omitted and potassium carbonate was used for drying instead of calcium chloride. From 31.7 g. of *dl*-2-decanol and 59.6 g. of

---

[27] In this paper observed rotations, $\alpha\mathrm{D}$, for liquids (without solvent) refer to 1 dm. The accompanying density value was used for calculation of specific rotation. Densities are given in absolute units (g./cc.).

[28] The (+)-α-phenylethylamine was recovered in 90% yield from the aqueous layers of the above extraction.

phosphorus tribromide there was obtained 35.0 g. (82.9%) of *dl*-2-bromodecane. A similar run with an hour of heating at 100° gave 84.3% yield. A run using less phosphorus tribromide (20% over equivalence) gave a much lower yield (59.9%). The product had b. p. 111° (11 mm.); d^{20} 1.0512, d^{25} 1.0470, d^{30} 1.0426, d^{35} 1.0375; $n^{25}\mathrm{D}$ 1.4526.

Anal. Calcd. for $C_{10}H_{21}Br$: Br, 36.13. Found: Br, 35.95.

(−)-2-Bromodecane.—The procedure used to make *dl*-2-bromodecane was employed with 36.9 g. of (+)-2-decanol ($[\alpha]^{28}\mathrm{D}$ +8.54°) and 69.7 g. of phosphorus tribromide. The yield was 33.6 g. (65.2%); b. p. 117–119° (20 mm.); $\alpha^{27}\mathrm{D}$ −32.8°; $[\alpha]^{27}\mathrm{D}$ −31.4° (d^{27} 1.045). The reaction proceeds with inversion of configuration.[16] In another preparation the yield was increased to 86.2% but the specific rotation was lowered to $[\alpha]^{25}\mathrm{D}$ −29.0°. Although no simple explanation of these variations is apparent, the results are in general accord with the reaction mechanism proposed by Gerrard[17] in which a small part of the product is formed with retention of configuration. There was no indication that racemization resulted from migration of halogen.[29]

(+)-2-Bromodecane was made using 47.7 g. of (−)-2-decanol ($[\alpha]^{25}\mathrm{D}$ −8.56°) and 89.9 g. of phosphorus tribromide. The yield was 50.2 g. (75.5%); b. p. 122–125° (24 mm.); $\alpha^{25}\mathrm{D}$ +32.4°; $[\alpha]^{25}\mathrm{D}$ +31.0°. Another run using (−)-2-decanol with a specific rotation of −8.63° furnished the bromide in 66.2% yield; $\alpha^{25}\mathrm{D}$ +33.7°; $[\alpha]^{25}\mathrm{D}$ +32.1°. This rotation value is probably close to maximum.

***dl*-2-Iododecane.**—Fifty grams of *dl*-2-decanol, 30 g. of red phosphorus and 120 g. of powdered iodine were stirred together at 0 to 5° for eight hours and then for nine hours longer while the temperature rose to 29°. The reaction mixture was poured into 300 g. of cracked ice, stirred with 200 cc. of ether and filtered by suction to remove the excess phosphorus. After extracting, drying over potassium carbonate and removing the ether, distillation furnished 78 g. (92%) of almost colorless iodide; b. p. 150–152° (44 mm.); d^{20} 1.2466, d^{25} 1.2412, d^{30} 1.2362, d^{35} 1.2308; $n^{25}\mathrm{D}$ 1.4831.

Anal. Calcd. for $C_{10}H_{21}I$: I, 47.32. Found: I, 47.13.

(−)-2-Iododecane.—Fifty grams of (+)-2-decanol ($[\alpha]^{25}\mathrm{D}$ +8.50°) furnished 81 g. (95%) of the levorotatory iodide; b. p. 146–147° (33 mm.); $\alpha^{25}\mathrm{D}$ −37.8°; $[\alpha]^{25}\mathrm{D}$ −30.4°. In view of the low rotation as compared to the reported values ($[\alpha]\mathrm{D}$ ±40°) for the *d*- and *l*-2-iodoöctanes,[14] it is clear that our iodide was considerably racemized. Because of this and further racemization in the malonic ester step (see below), the use of the iodide was abandoned. The dextrorotatory iodide was not prepared.

Dibutyl *dl*-2-Decylmalonate (III).—Sodium butoxide[30] was prepared from 85 cc. of dry butanol and 3.9 g. of sodium in a three-necked flask fitted with a condenser and stirrer and arranged for a nitrogen atmosphere. Diethyl malonate (27.0 g.) and *dl*-2-bromodecane (25.0 g.) were added and the mixture was heated at 100° for five hours. The cooled reaction mixture was washed twice with water and once with saturated sodium chloride solution. The aqueous washes were twice extracted with ether. After filtering the extracts through sodium sulfate and removing the solvent the product was distilled (V90). After removal of 8.9 g. of forerun (boiling mainly at 153–160° (24 mm.)), 30.8 g. (76.4%) of essentially pure dibutyl *dl*-2-decylmalonate was obtained; b. p. 170–188° (95% at 184–187°) (3 mm.). The analytical sample (center cut from the redistillation of a similar run) boiled at 178° (1 mm.); d^{20} 0.9186, d^{25} 0.9147, d^{30} 0.9113, d^{35} 0.9072; $n^{25}\mathrm{D}$ 1.4403.

Anal. Calcd. for $C_{21}H_{40}O_4$: sapn. equiv., 178.3. Found: sapn. equiv., 181.7.[31]

Redistillation of the forerun gave 3.2 g. of dibutyl malonate; b. p. 151–152° (26–24 mm.); $n^{26}\mathrm{D}$ 1.4234. In later preparations additional malonic ester (2.5 equiv.) gave no improvement in yield and shortening the heating to one hour reduced the yield somewhat. Toluene was an unsatisfactory solvent. With *dl*-2-iodododecane the yield of 2-decylmalonic ester was 81.2%.

Dibutyl (+)-2-decylmalonate was prepared from 100 cc. of butanol, 5.1 g. of sodium, 35.5 g. of diethyl malonate and 32.5 g. of (−)-2-bromodecane ($[\alpha]^{25}\mathrm{D}$ −31.3°). The yield was 43.9 g. (83.8%); b. p. 147–177° (90% at 165–176°) (0.5 mm.); $\alpha^{27}\mathrm{D}$ +0.28°; $[\alpha]^{27}\mathrm{D}$ +0.31° (d^{27} 0.914).

In another run with the bromide the yield was only 65.3%. When the reaction was run with (−)-2-iododecane ($[\alpha]^{25}\mathrm{D}$ −30.4°) the yield of ester was 87.5%; $[\alpha]^{25}\mathrm{D}$ +0.34°. The (−)-2-decylmalonic acid derived from this ester was considerably racemized (see below).

Dibutyl (−)-2-decylmalonate was prepared in 81.7% yield from 220 cc. of butanol, 8.6 g. of sodium, 60 g. of diethyl malonate and 55.2 g. of (+)-2-bromodecane ($[\alpha]^{25}\mathrm{D}$ +32.1°). The product (72.9 g.) was distilled at 2 mm. pressure; b. p. 160–182° (85% at 178–182°); $\alpha^{25}\mathrm{D}$ −0.33°; $[\alpha]^{25}\mathrm{D}$ −0.36°. A yield of 78.6% was obtained in another run.

2-Decylmalonic Acids (IV). Preliminary Chemical Purification.—In order to prepare the active 3-methylhendecanoic acids in maximum antipodal purity from intermediates containing small amounts of the *dl*-form it was necessary to employ fractional crystallization of the intermediate 2-decylmalonic acids, depending upon the markedly greater crystallizing power and lower solubility of the active acids as compared with the *dl*-form. This crystallization was best preceded by a double extraction designed to remove neutral materials and incidental impurities which tended to impede crystallization.

Dibutyl 2-decylmalonate (72 g.) was saponified by heating under reflux for an hour in a solution of 45 g. of potassium hydroxide, 300 cc. of 95% ethanol and 25 cc. of water. This mixture was diluted with 1200 cc. of water, acidified and the crude acid extracted with three portions of hexane (150, 100, 100 cc.). The extracts were washed with two 100-cc. portions of half-saturated sodium chloride solution and the crude malonic acid was extracted with 700 cc. of 10% sodium bicarbonate solution. The extract was filtered to remove traces of solid material, and acidified. The 2-decylmalonic acid, which sometimes partially solidified, was extracted with three portions of ether. The residue of crude acid (contaminated with some butanol), which remained after removal of solvent, solidified slowly and was usually slightly more than the theoretical amount. This material was fractionally crystallized from hexane.

***dl*-2-Decylmalonic Acid.**—The crude acid obtained by saponification of 34 g. of dibutyl *dl*-2-decylmalonate crystallized sluggishly at 5° from 100 cc. of hexane. The first crop of 12.4 g. (53.4%), m. p. 68.1–71.3°, was used for characterization of this acid. Four recrystallizations from hexane (cooling at room temperature) furnished the *dl*-acid as a microcrystalline powder; m. p. 73.6–75.5°. (A mixture of equal amounts of the purified active forms after one crystallization melted at 70.5–72.8°.)

Anal. Calcd. for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90; equiv. wt., 122.2. Found: C, 64.14; H, 9.89; equiv. wt., 122.8.

(−)-2-Decylmalonic Acid. Antipodal Purification.—Saponification of 62.5 g. of dibutyl (+)-2-decylmalonate furnished 39.6 g. (92.8%) of crude acid. The initial series of crystallization of this acid from hexane afforded 34.45 g. (80.8%) of crystalline acid in four crops. The first crop (26.14 g., m. p. 94.3–97.3°) already had a high degree of antipodal purity ($[\alpha]^{25}\mathrm{D}$ −6.22° (acetone, *c*,

---

(29) Sherrill, Otto and Pickett, THIS JOURNAL, **51**, 3023 (1929); Sherrill, Baldwin and Haas, *ibid.*, **51**, 3034 (1929).

(30) Reid and Ruhoff, "Organic Syntheses," Coll. Vol. II, p. 474.

(31) Analytical saponification with 1 *N* alcoholic potassium hydroxide required three hours; preparative saponifications with stronger solutions were complete in one hour.

8.30), 88% of maximum value). The remaining crops had progressively much smaller rotations and lower melting points. From the rotation values (assuming −7.1° as maximum) the original mixture was estimated to contain about 89% of the (−)-form.

Systematic recrystallization was carried out with hexane containing about 4% acetone for the purer fractions. Foot fractions rich in the *dl*-form could be enriched in the active form by crystallization from hexane alone. The fractionation was followed by the melting point rise and by the change in crystal habit from a microcrystalline powder to distinct translucent blades characteristic of the active forms. The yield of pure levorotatory acid from this fractionation was 26.26 g.; m. p. 99.3–100.6°; $[\alpha]^{25}\mathrm{D}$ −7.17° (acetone, *c*, 8.18). This amounts to 61.7% of the acid present in the starting ester or to nearly 98% of the levorotatory acid calculated to be present in excess of the *dl*-form in the original crystalline fractions.

Anal. Calcd. for $C_{13}H_{24}O_4$: equiv. wt., 122.2. Found: equiv. wt., 122.2, 122.3.

One specimen of (−)-2-decylmalonic acid was prepared from partially racemized (−)-2-iododecane. Acid from this source had an initial calculated content of 72.5% (−)-form. The fractionation of this crude acid nevertheless gave pure (−)-acid amounting to 34% of the theoretical total.

(+)-2-Decylmalonic Acid. Antipodal Purification.—The saponification of 72.8 g. of dibutyl (−)-2-decylmalonate gave 54.2 g. (106%) of the crude acid. Recrystallization from 125 cc. of hexane gave a first crop of 40.40 g.; m. p. 96.2–98.3°; $[\alpha]^{25}\mathrm{D}$ +6.86° (acetone, *c*, 8.50). Two more crops (8.75 g.) having lower melting points and rotations were obtained: total yield, 49.15 g. (98.5%). The combined crops were calculated to contain 94% of the (+)-form. Systematic recrystallization of this acid by procedures described for the levorotatory antipode furnished 43.53 g. (87.1%) of pure acid; m. p. 99.6–100.5°; $[\alpha]^{25}\mathrm{D}$ +7.07° (acetone, *c*, 8.21).

Anal. Calcd. for $C_{13}H_{24}O_4$: equiv. wt., 122.2. Found: equiv. wt., 122.7.

In one run it was shown that partially resolved levorotatory 2-decanol could be used for the preparation of pure (+)-2-decylmalonic acid. (−)-2-Decanol ($[\alpha]^{25}\mathrm{D}$ −4.93°, 79% (−)-form) was converted to the dextrorotatory bromide, $[\alpha]^{25}\mathrm{D}$ +17.6° (*ca.* 78% (+)-form). This bromide was used to prepare (+)-2-decylmalonic acid (73.5% (+)-form). Systematic crystallization of this acid gave pure (+)-2-decylmalonic acid corresponding to 72% of the excess of this form initially present.

***dl*-3-Methylhendecanoic Acid (V).**—The crude malonic acid from 89.5 g. of the butyl ester was heated at 175–185° for an hour. Distillation then gave 51.3 g. (102%) of crude 3-methylhendecanoic acid; b. p. 147–153° (5 mm.). This acid, which contained some of its butyl ester, was used without further purification for conversion to the ethyl ester (below). A sample of pure acid was recovered from the unreduced portion remaining after reduction of the ester (below). The acid (3.3 g.) was distilled (P45); b. p. 147.5–148.5° (2 mm.); d^{20} 0.8906, d^{25} 0.8868, d^{30} 0.8832, d^{35} 0.8795; $n^{25}\mathrm{D}$ 1.4389. Rupe and Willi[32] give b. p. 165.5° (10 mm.).

Anal. Calcd. for $C_{12}H_{24}O_2$: equiv. wt., 200.3. Found: equiv. wt., 199.2.

The **amide** was obtained by a previously described method[5b] in 89% yield; m. p. 67–77°. After four crystallizations from acetone it appeared as long needles; m. p. 88.3–89.3°.

Anal. Calcd. for $C_{12}H_{25}ON$: C, 72.30; H, 12.64. Found: C, 72.54; H, 12.75.

The **tribromoanilide** was obtained in 79% yield[5a]; m. p. 106.4–109.9°. Four recrystallizations from methanol furnished feather-like crystals; m. p. 108.0–111.9°.

Anal. Calcd. for $C_{18}H_{27}Br_3ON$: C, 42.13; H, 5.30. Found: C, 42.03; H, 5.55.

(−)-3-Methylhendecanoic Acid.—Thirty-seven grams of carefully purified (−)-2-decylmalonic acid ($[\alpha]^{25}\mathrm{D}$ −7.17°) was heated at 165–180° for twenty minutes and the product distilled to yield 29.7 g. (97.7%) of acid; b. p. 142.5–138° (2–1 mm.); $\alpha^{25}\mathrm{D}$ −4.47°; $[\alpha]^{25}\mathrm{D}$ −5.04°; $[\alpha]^{25}\mathrm{D}$ −6.87° (acetone, *c*, 8.50).

The **amide** was prepared[5b] in 85% yield; m. p. 75–85°. Three crystallizations from acetone gave soft, long needles; m. p. 87.3–88.4°; $[\alpha]^{25}\mathrm{D}$ −2.54° (acetone, *c*, 2.51). A mixture of the *l*- and *dl*-amides had m. p. 88.9–91.5°.

The **tribromoanilide** was prepared[5a] in 84% yield; m. p. 121.3–128.2°. Three crystallizations from methanol gave soft needles; m. p. 128.8–129.6°; $[\alpha]^{25}\mathrm{D}$ −2.20° (chloroform, *c*, 4.19).

(+)-3-Methylhendecanoic Acid.—(+)-2-Decylmalonic acid (64.8 g., $[\alpha]^{25}\mathrm{D}$ +7.07–7.12°) was decarboxylated by heating at 165–180° for fifteen minutes and the product was distilled to give 52.4 g. (98.3%) of acid; b. p. 140–149° (0.5 mm.); $\alpha^{25}\mathrm{D}$ +4.45°; $[\alpha]^{25}\mathrm{D}$ +5.02°; $[\alpha]^{25}\mathrm{D}$ +7.13° (acetone, *c*, 7.95).

The **amide** was prepared in 93% yield; m. p. 87.6–88.6°; $[\alpha]^{25}\mathrm{D}$ +2.76° (acetone, *c*, 4.02). A mixture of the *d*- and *dl*-amides melted at 89.3–91.5°.

The **tribromoanilide** was made in 90% yield; m. p. 128.7–129.5°; $[\alpha]^{25}\mathrm{D}$ +1.99° (chloroform, *c*, 4.53).

The 10-Methyloctadecanoic Acids

Ethyl *dl*-3-Methylhendecanoate (VI).—The crude acid (51.3 g. obtained as previously described from 89.5 g. of dibutyl *dl*-2-decylmalonate) was heated under reflux for two hours with 400 cc. of absolute ethanol and 20 cc. of concentrated sulfuric acid. The ester was distilled (P45); yield 48.5 g. (84.6%); b. p. 118.5–120.5° (2 mm.). A sample of b. p. 122° (2.5 mm.) was used for analysis and constants: d^{20} 0.8605, d^{25} 0.8571, d^{30} 0.8532, d^{35} 0.8492; $n^{25}\mathrm{D}$ 1.4287.

Anal. Calcd. for $C_{14}H_{28}O_2$: sapn. equiv., 228.4. Found: sapn. equiv., 224.3.

Ethyl (−)-3-Methylhendecanoate.—Pure (−)-3-methylhendecanoic acid (44.16 g., $[\alpha]^{25}\mathrm{D}$ −5.04° to −5.05°) was esterified as described for the *dl*-ester. Distillation (P45) gave 46.96 g. (93.6%); b. p. 108.5–110.2° (1.5 mm.); $\alpha^{25}\mathrm{D}$ −2.01°; $[\alpha]^{25}\mathrm{D}$ −2.34°.

Ethyl (+)-3-Methylhendecanoate.—Pure (+)-3-methylhendecanoic acid (52.27 g., $[\alpha]^{25}\mathrm{D}$ +5.02°) was esterified as described for the *dl*-ester. Distillation (P45) gave 57.31 g. (96.0%); b. p. 104.5–107° (0.5–1 mm.); $\alpha^{25}\mathrm{D}$ +2.00°; $[\alpha]^{25}\mathrm{D}$ +2.33°.

***dl*-3-Methyl-1-hendecanol (VII).**—Fifty grams of ethyl *dl*-3-methylhendecanoate was reduced with 26.9 g. of sodium in 435 cc. of dry butanol.[33] After addition of water, the alcohol was extracted from the alkaline solution with hexane and distilled (P45). Besides a small forerun (0.24 g., b. p. 100–118° (3.5–2.5 mm.)) there was obtained 34.3 g. (84.5%) of the alcohol; b. p. 118–117° (2.5–2 mm.). A center cut boiling at 117° (2 mm.) was used for analysis and constants: d^{20} 0.8341, d^{25} 0.8309, d^{30} 0.8275, d^{35} 0.8241; $n^{25}\mathrm{D}$ 1.4409.

Anal. Calcd. for $C_{12}H_{26}O$: C, 77.35; H, 14.07. Found: C, 77.29; H, 13.90.

A non-volatile, water-soluble residue remained after distillation. A similar product, presumably the sodium salt of the acid corresponding to the ester reduced, was reported by Reid and his co-workers[33] from the reduction of butyl oleate. A sample of pure *dl*-3-methylhendecanoic acid (3.3 g.) was recovered from the aqueous phases as previously described.

The **3,5-dinitrobenzoate** was prepared in 76% yield by the method described for the dinitrobenzoate of (−)-2-decanol. Two crystallizations from pentane gave pure ester as clumps of short needles; m. p. 46.0–47.1°.

Anal. Calcd. for $C_{19}H_{26}O_6N_2$: C, 60.40; H, 6.93. Found: C, 60.36; H, 7.01.

---

[32] Rupe and Willi, *Helv. Chim. Acta*, **15**, 842 (1932).

[33] Reid, Cockerille, Meyer, Cox and Ruhoff, "Organic Syntheses," Coll. Vol. II, p. 468.

(−)-3-Methyl-1-hendecanol was obtained from 46.76 g. of ethyl (−)-3-methylhendecanoate ($[\alpha]^{25}_{D}$ −2.34°), 24.6 g. of sodium and 410 cc. of butanol. Distillation gave 32.76 g. (85.8%); b. p. 119° (3–2 mm.); α^{25}_{D} −3.37°; $[\alpha]^{25}_{D}$ −4.06.

The **3,5-dinitrobenzoate** was prepared in 78% yield. Two recrystallizations from pentane furnished the pure product; m. p. 39.9–40.6°; $[\alpha]^{25}_{D}$ −2.71° (acetone, *c*, 8.12).

(+)-3-Methyl-1-hendecanol was prepared from 57.3 g. of ethyl (+)-3-methylhendecanoate ($[\alpha]^{25}_{D}$ +2.33°), 30 g. of sodium and 500 cc. of butanol. Distillation gave 39.7 g. (86.7%); b. p. 118.5–116° (3–1.5 mm.); α^{25}_{D} +3.39°; $[\alpha]^{25}_{D}$ +4.08°.

The **3,5-dinitrobenzoate** was prepared in 84% yield; m. p. 39.5–40.5°; $[\alpha]^{25}_{D}$ +3.09° (acetone, *c*, 8.10).

***dl*-1-Bromo-3-methylhendecane (VIII).**—*dl*-3-Methyl-1-hendecanol (27.1 g.) was treated with gaseous hydrobromic acid by the procedure of Reid, Ruhoff and Burnett.[34] The product was distilled (P45) to give 30.4 g. (86.2%); b. p. 112–112.5° (1.5 mm.). A small forerun of 0.26 g., b. p. 112.5° (2 mm.), was discarded. A center cut, b. p. 112–112.2° (1.5 mm.), was used for analysis and constants: d^{20} 1.0421, d^{25} 1.0379, d^{30} 1.0334, d^{35} 1.0290; n^{25}_{D} 1.4569.

Anal. Calcd. for $C_{12}H_{25}Br$: Br, 32.07. Found: Br, 32.04.

(+)-1-Bromo-3-methylhendecane was prepared in 89.4% yield from 30.4 g. of (−)-3-methyl-1-hendecanol ($[\alpha]^{25}_{D}$ −4.06°) and gaseous hydrogen bromide. The product was distilled (P45) to give 36.4 g.; b. p. 102–105° (1 mm.); α^{25}_{D} +5.36°; $[\alpha]^{25}_{D}$ +5.17°.

(−)-1-Bromo-3-methylhendecane was prepared similarly in 69.7% yield from 37.5 g. of (+)-3-methyl-1-hendecanol ($[\alpha]^{25}_{D}$ +4.08°); yield 34.9 g.; b. p. 104–108° (1 mm.); α^{25}_{D} −5.36°; $[\alpha]^{25}_{D}$ −5.16°.

ω-Carbethoxycaproyl Chloride.[35a,d]—Ethyl hydrogen pimelate[35] was prepared by adaptation of the partial esterification method of Swann, Oehler and Buswell.[36] Distillation of the product (V90) gave the half ester in 44% yield (or 60% yield deducting the recovered diester); b. p. 159.5–160° (4 mm.). The half ester was treated with phosphorus pentachloride[5a] to give the ester acid chloride in 94% yield; b. p. 125–121° (6–3 mm.).

Ethyl *dl*-7-Keto-10-methyloctadecanoate (IX).—The preparation followed the general procedure for the synthesis of keto esters by the reaction of a dialkylcadmium compound with an ester acid chloride.[1,5a,5b,37] The preparation employed 2.43 g. of magnesium, 24.92 g. of *dl*-1-bromo-3-methylhendecane, 11 g. of cadmium chloride and 16.54 g. (0.8 equiv.) of ω-carbethoxycaproyl chloride. Distillation (P45) at 0.5 mm. gave: (a) 3.12 g., b. p. 49.58°; (b) 1.32 g., b. p. 90–95°; (c) 19.13 g., b. p. 175–193° (95% at 185–193°). There was 3.7 g. of residue. The yield (fraction (c)) was 56.2%, based on the bromide, or 70.3%, based on the acid chloride. A center cut was used for analysis and constants: d^{20} 0.896, d^{25} 0.893, d^{30} 0.889, d^{35} 0.886; n^{25}_{D} 1.4477.

Anal. Calcd. for $C_{21}H_{40}O_3$: sapn. equiv., 340.6. Found: sapn. equiv., 348.7, 350.6 (center cut); 368.7 (sample taken at end of fraction (c)).

The presence in fraction (c) of 9,14-dimethyldocosane (see below) from coupling of the Grignard reagent caused the divergence from theoretical saponification equivalents. Since it was expected that the hydrocarbon could be separated more readily at a later stage no effort was made to effect complete purification of the keto ester.

Fraction (a), principally **3-methylhendecane**, was washed with concentrated sulfuric acid and distilled; 1.8 g., b. p. 109–110° (32 mm.), n^{25}_{D} 1.4213.

Anal. Calcd. for $C_{12}H_{26}$: C, 84.61; H, 15.39. Found: C, 85.41; H, 15.26.

Fraction (b) was mainly diethyl pimelate. The acid (0.5 g.) obtained after saponification had m. p. 101.3–104.6°, alone or mixed with authentic pimelic acid.

***dl*-7-Keto-10-methyloctadecanoic acid** was obtained from the ester in 96% yield; m. p. 28–37°. Five crystallizations from pentane gave iridescent short blades, m. p. 38.6–39.9°. A sample of *dl*-acid later prepared by crystallizing equal amounts of both active antipodes melted at 38.3–39.3°.

Anal. Calcd. for $C_{19}H_{36}O_3$: equiv. wt., 312.6. Found: equiv. wt., 311.0.

The **semicarbazone** of the *dl*-keto acid was prepared in 89% yield.[38] Three crystallizations from acetone gave small cubic crystals; m. p. 97.8–98.6°.

Anal. Calcd. for $C_{20}H_{39}O_3N_3$: C, 65.01; H, 10.64. Found: C, 65.14; H, 10.68.

Ethyl (+)-7-Keto-10-methyloctadecanoate was prepared[1,5a] from 36.1 g. of (+)-1-bromo-3-methylhendecane ($[\alpha]^{25}_{D}$ +5.17°), 3.52 g. of magnesium, 16 g. of cadmium chloride and 24.0 g. of ω-carbethoxycaproyl chloride. Distillation of the product (V45) at *ca.* 0.5 mm. gave three fractions: (a) 6.39 g., b. p. 53–56°; (b) 1.74 g., b. p. 96–99°; (c) 25.60 g., b. p. 165–198° (80% at 190–198°), α^{25}_{D} +0.20°; $[\alpha]^{25}_{D}$ +0.22°. There was 7.0 g. of residue.

Fraction (c) contained the keto ester; yield 51.7% (based on bromide) or 64.8% (based on acid chloride). This fraction, however, contained 10–11% of (+)-9,14-dimethyldocosane (see below) which probably caused the observed rotation values to be somewhat greater than those of the pure keto ester.

Fraction (a), chiefly **(−)-3-methylhendecane**, was washed with sulfuric acid and distilled: 3.73 g.; b. p. 101.5–102.5° (20 mm.); α^{26}_{D} −5.95° (micro tube,[39] d^{25} 0.748 (1-cc. pycnometer)); $[\alpha]^{26}_{D}$ −7.96°.

(+)-7-Keto-10-methyloctadecanoic acid was obtained from the ester in 85% yield; m. p. 27–31°. Three crystallizations from pentane gave soft feather-like crystals; m. p. 30.7–32.2°; $[\alpha]^{26}_{D}$ +0.13° (acetone, *c*, 37.6, micro tube).[39]

The **semicarbazone** was prepared in 77% yield; m. p. 73–88°. Three crystallizations from acetone gave small plates; m. p. 94.8–95.4°.

Ethyl (−)-7-keto-10-methyloctadecanoate was prepared from 34.7 g. of (−)-1-bromo-3-methylhendecane ($[\alpha]^{25}_{D}$ −5.16°), 3.39 g. of magnesium, 15 g. of cadmium chloride and 23.0 g. of ω-carbethoxycaproyl chloride. Distillation gave three fractions: (a) 5.44 g., b. p. 61–55° (2–1 mm.); (b) 2.44 g., b. p. 100–102° (*ca.* 0.5 mm.); (c) 25.54 g. (53.9%, based on the bromide, and 67.5%, based on the acid chloride), b. p. 175–195° (*ca.* 0.5 mm.), α^{25}_{D} −0.15°; $[\alpha]^{25}_{D}$ −0.16°. There was 6.6 g. of residue.

Fraction (a), chiefly **(+)-3-methylhendecane**, was washed with sulfuric acid and redistilled: 3.54 g.; b. p. 97–98° (17 mm.); α^{26}_{D} +5.60° (micro tube[39]); $[\alpha]^{26}_{D}$ +7.49°.

(−)-7-Keto-10-methyloctadecanoic acid was prepared from the ester in 92% yield; m. p. 29–31°. Two crystallizations from pentane gave pure acid; m. p. 31.1–32.1°; $[\alpha]^{26}_{D}$ −0.07° (acetone, *c*, 27.9, micro tube[39]).

The **semicarbazone** was prepared in 46% yield; m. p. 71–89°. Three crystallizations from acetone gave small plates; m. p. 94.8–95.4°. The mixture with an approximately equal amount of the dextrorotatory antipode melted at 93.5–96°.

Ethyl *dl*-10-Methyloctadecanoate (X).—Ethyl *dl*-7-keto-10-methyloctadecanoate (11.36 g.) was reduced with

---

(34) Reid, Ruhoff and Burnett, ref. 33, p. 246.

(35) (a) Blaise and Koehler, *Bull. soc. chim.*, [4] **7**, 215 (1910); (b) Fourneau and Sabatay, *ibid.*, [4] **45**, 839 (1929); (c) Walker and Lumsden, *J. Chem. Soc.*, **79**, 1197 (1901); (d) Morgan and Walton, *ibid.*, 290 (1935).

(36) Swann, Oehler and Buswell, "Organic Syntheses," Coll. Vol. II, p. 276.

(37) Cason, *Chem. Rev.*, **40**, 15 (1947).

(38) Shriner and Fuson, "Identification of Organic Compounds," 2nd. ed., John Wiley and Sons, New York, N. Y., 1940, p. 142.

(39) Smith and Ehrhardt, *Ind. Eng. Chem.*, *Anal. Ed.*. **18**, 81 (1946).

alcoholic hydrogen chloride and amalgamated zinc by the general procedure of Schneider and Spielman.[40] The ester was extracted from the diluted alcoholic mixture and distilled at *ca.* 0.5 mm. (P45). After a forerun of 1.25 g., b. p. 81–160°, was removed the main fraction (9.33 g., 85.7%) distilled at 160–172°.

The main product was contaminated with about 10% of unsaponifiable material as shown by analytical saponification of an intermediate fraction, b. p. 168.5–169° (*ca.* 0.5 mm.) (calcd.: sapn. equiv., 326.6. Found: sapn. equiv., 359.2). Purified ethyl ester was prepared later by esterification of the acid remaining in the combined mother liquors after crystallization of the *dl*-10-methyloctadecanoic acid (below). This ester (2.15 g.), formed and worked up by essentially the procedure used to make the esters of 3-methylhendecanoic acids, was distilled from a Claisen flask; b. p. 178–182° (2 mm.); d^{20} 0.862, d^{25} 0.858, d^{30} 0.854, d^{35} 0.852 (all densities in 1-cc. pycnometer); n^{25}_{D} 1.4447.

Anal. Calcd. for $C_{21}H_{42}O_2$: sapn. equiv., 326.6. Found: sapn. equiv., 323.7.

Ethyl (+)-10-methyloctadecanoate was prepared by reduction[40] of 21.72 g. of ethyl (+)-7-keto-10-methyloctadecanoate ($[\alpha]^{25}_{\mathrm{D}}$ +0.22°). The ester was distilled (V45) at *ca.* 0.5 mm. pressure. A forerun of 2.56 g., b. p. 91–160°, was removed and the main product (18.01 g., 86.5%) distilled at 160–182° (90% at 169–182°); α^{25}_{D} +0.12°; $[\alpha]^{25}_{\mathrm{D}}$ +0.14°. The saponification equivalent was 382 (theory, 326.6) indicating the presence of 14% unsaponifiable impurity.

Ethyl (−)-10-methyloctadecanoate was obtained similarly by the reduction of 20.11 g. of ethyl (−)-7-keto-10-methyloctadecanoate ($[\alpha]^{25}_{\mathrm{D}}$ −0.16°); yield, 16.87 g. (94.2%); b. p. 169–183° (*ca.* 0.5 mm.), (90% at 173–181°); α^{25}_{D} −0.13°; $[\alpha]^{25}_{\mathrm{D}}$ −0.15°; sapn. equiv., 370 (theory, 326.6, hence 12% impurity). A forerun of 2.05 g., b. p. 91–169°, was also obtained.

***dl*-10-Methyloctadecanoic Acid (XI)**.[7]—Ethyl *dl*-10-methyloctadecanoate (7.66 g.) was saponified with 100 cc. of 3% alcoholic potassium hydroxide and the solution was then diluted with an equal volume of water. The solution was extracted with three 35-cc. portions of hexane to extract unsaponifiable material. The extracts were washed successively with four 50-cc. portions of water, with addition of a little ethanol to break up emulsions. The hexane extracts were combined and reserved for the isolation of *dl*-9,14-dimethyldocosane (below).

The acid obtained from the combined aqueous phases was solid at 22° but liquid at 25°; yield, 5.38 g. (77.2%). This acid was crystallized once from pentane and three times from acetone (cooling in a mixture of hydrochloric acid and ice) to furnish 2.42 g. of purified acid as fine hard crystals; m. p. 25.4–26.1°; n^{25}_{D} 1.4512 (supercooled melt). (A mixture of approximately equal amounts of the *d*- and *l*-forms prepared later and crystallized from acetone had m. p. 21–25.8°.) For an unrecrystallized sample of *dl*-10-methyloctadecanoic acid prepared by another method Spielman[7] reported m. p. 20–21°, n^{25}_{D} 1.4512.

Anal. Calcd. for $C_{19}H_{38}O_2$: equiv. wt., 298.5. Found: equiv. wt., 298.8.

The **amide** was made by a previously described method[5b] and crystallized three times from hexane. It then had m. p. 77.5–79.2°. A sample of the amide prepared by Spielman[7] and kindly furnished by Dr. R. J. Anderson had m. p. 75.2–78.1° (Spielman[7] reported m. p. 76–77°).

The **tribromoanilide** was made by the method employed by Cason[5a] and after two crystallizations from methanol and five from acetone had m. p. 93.4–93.9°. Spielman[7] recorded m. p. 93–94°.

(+)-10-Methyloctadecanoic Acid.—Ethyl (+)-10-methyloctadecanoate (17.87 g., $[\alpha]^{25}_{\mathrm{D}}$ +0.14°) was saponified and the neutral material extracted in the manner described for the *dl*-form. From the combined aqueous layers there was obtained 11.8 g. (72.4%) of crude acid. Recrystallization of this acid once from acetone and once from pentane, preferably working in a cold room at 0–5°, furnished 8.16 g. of pure acid; m. p. 13–13.5° (uncor., mass method); f. p. 13° (uncor.), n^{25}_{D} 1.4512; α^{26}_{D} +0.08° (micro tube[39]); $[\alpha]^{26}_{\mathrm{D}}$ +0.09° (d^{25} 0.88[7]).

Anal. Calcd. for $C_{19}H_{38}O_2$: equiv. wt., 298.5. Found: equiv. wt., 300.8.

The amide, prepared as before,[5b] was crystallized five times from acetone: m. p. 75.5–76.4°; $[\alpha]^{25}_{\mathrm{D}}$ +0.10° (chloroform, *c*, 5.65, micro tube[39]).

The tribromoanilide, after three crystallizations from methanol and four from acetone, melted at 93.2–95.2°; $[\alpha]^{25}_{\mathrm{D}}$ +0.15° (chloroform, *c*, 15.3, micro tube[39]).

(−)-10-Methyloctadecanoic Acid.—Ethyl (−)-10-methyloctadecanoate (15.80 g., $[\alpha]^{25}_{\mathrm{D}}$ −0.15°) was saponified and the neutral material extracted as described for the *dl*-ester; yield, 13.1 g. (85.7%) of crude acid; f. p. 10.5°. The acid was recrystallized once from pentane and three times from acetone to give 7.15 g. of purified acid; m. p. 12.8–13.4°; n^{25}_{D} 1.4514, α^{26}_{D} −0.045° (micro tube[39]); $[\alpha]^{26}_{\mathrm{D}}$ −0.05°.

Anal. Calcd. for $C_{19}H_{38}O_2$: equiv. wt., 298.5. Found: equiv. wt., 299.2.

The **amide** was crystallized five times from acetone; m. p. 75.1–76.3°; $[\alpha]^{24}_{\mathrm{D}}$ −0.09° (chloroform, *c*, 25.4, micro tube[39]).

The **tribromoanilide** was obtained pure only after four recrystallizations from methanol and eight from acetone; m. p. 94.0–95.3°; $[\alpha]^{26}_{\mathrm{D}}$ −0.11° (chloroform, *c*, 28.2, micro tube[39]).

***dl*-9,14-Dimethyldocosane**.—The neutral extract from the saponification of ethyl *dl*-10-methyloctadecanoate was concentrated and the residue distilled as a yellow oil; b. p. 195–200° (4 mm.). After treatment with concentrated sulfuric acid the hydrocarbon was redistilled to furnish 1.14 g.; b. p. 186–188° (2 mm.); n^{25}_{D} 1.4475.

Anal. Calcd. for $C_{24}H_{50}$: C, 85.12; H, 14.88. Found: C, 85.35; H, 14.29.

(+)-9,14-Dimethyldocosane, similarly obtained as the neutral material from the saponification of ethyl (+)-10-methyloctadecanoate, weighed 1.85 g., b. p. 195–198° (3 mm.); α^{26}_{D} +0.50° (micro tube[39]); $[\alpha]^{26}_{\mathrm{D}}$ +0.63° (d^{25}, see (−)-form).

(−)-9,14-Dimethyldocosane, obtained as the neutral material from the saponification of ethyl (−)-10-methyloctadecanoate, weighed 1.26 g., b. p. 190–195° (2 mm.); α^{25}_{D} −0.48° (micro tube[39]); d^{25} 0.800 (1-cc. pycnometer); $[\alpha]^{25}_{\mathrm{D}}$ −0.60°.

Summary

1. A method for the total resolution of 2-decanol has been worked out. The use of this alcohol for the preparation of the active 3-methylhendecanoic acids by way of the malonic ester synthesis has afforded a means to prepare these acids in maximum antipodal purity.

2. The synthesis of the three stereoisomeric forms of 10-methyloctadecanoic acid has been accomplished by extension of the chain of the three stereoisomers of 3-methylhendecanoic acid.

3. Tuberculostearic acid has been shown to be (−)-10-methyloctadecanoic acid by comparison of the acid, amide and tribromoanilide with the (+)- and (−)-forms of 10-methyloctadecanoic acid and their corresponding derivatives.

NASHVILLE, TENN. RECEIVED AUGUST 4, 1947

---

(40) Schneider and Spielman, *J. Biol. Chem.*, **142**, 345 (1942).

[CONTRIBUTION FROM THE DIVISION OF PLANT NUTRITION, COLLEGE OF AGRICULTURE, AND THE DEPARTMENT OF BACTERIOLOGY, UNIVERSITY OF CALIFORNIA]

The Structure of an Enzymatically Synthesized Reducing Disaccharide D-Glucosido-L-arabinose

BY W. Z. HASSID, M. DOUDOROFF, A. L. POTTER AND H. A. BARKER

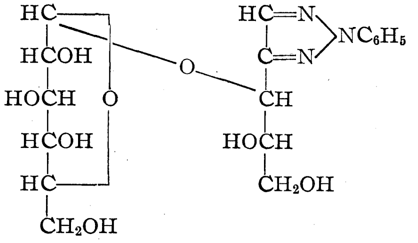
It has been shown that sucrose phosphorylase preparations from *Pseudomonas saccharophila* catalyze the reversible reaction between glucose-1-phosphate and certain ketose sugars forming disaccharides with the liberation of inorganic phosphate. Thus, sucrose and several other non-reducing disaccharides, namely, D-glucosido-L-sorboside, D-glucosido-D-xyloketoside, and D-glucosido-L-araboketoside[1,2,3,4] were prepared.

It appeared at first as though this enzyme were only capable of catalyzing the reaction between ketose monosaccharides and glucose-1-phosphate. Since these disaccharides are non-reducing and their ketose constituents exist in the furanose form, they can be considered as analogs of sucrose. However, it was later discovered that the same enzyme will catalyze a reaction between glucose-1-phosphate and L-arabinose to form a reducing disaccharide having no obvious structural relation to sucrose or to any of the previously prepared sucrose analogs.[4]

The present investigation is concerned with the structural configuration of the crystalline reducing disaccharide formed from α-D-glucose-1-phosphate and L-arabinose under the influence of the enzyme from *Pseudomonas saccharophila.*

This disaccharide reduces Fehling and alkaline ferricyanide solutions. It contains two molecules of water of crystallization and has a specific rotation $[\alpha]_D$ in water of +156°. On hydrolysis with acid it produces one mole of D-glucose and one mole of L-arabinose. The phenylosotriazole derivative of the disaccharide prepared according to Hudson, *et al.*,[5] is readily hydrolyzed with acid to D-glucose and L-arabinose phenylosotriazole, showing that the L-arabinose constitutes the free reducing unit in the disaccharide. Like the previously isolated disaccharides, it is formed by the agency of phosphorylase from *Pseudomonas saccharophila* as a result of "de-phosphorolytic" condensation involving α-D-glucose-1-phosphate, indicating that glucose exists in the disaccharide as the α-form.

On oxidation of the phenylosotriazole derivative of the disaccharide with sodium periodate, three moles of periodate are consumed with the formation of one mole each of formic acid and formaldehyde per mole of phenylosotriazole derivative. The structure of this compound is, therefore, 3-[α-D-glucopyranosido]-L-arabinose phenylosotriazole in which D-glucose is attached through carbon atom 1 to carbon atom 3 of L-arabinose as shown by Formula (I).



1. 3-[α-D-Glucopyranosido]-L-arabinose phenylosotriazole

If the D-glucose in the D-glucopyranosido-L-arabinose phenylosotriazole were attached to carbon atom 4 of the L-arabinose derivative, oxidation of this compound with sodium periodate would require two moles of periodate and would liberate one mole of formic acid with no formaldehyde production. Junction of D-glucose to carbon atom 5 of the L-arabinose phenylosotriazole would require three moles of periodate whereby one mole of formic acid would be produced, and no formaldehyde formed.

On methylation of the disaccharide with dimethyl sulfate and sodium hydroxide a hexamethylmethyl derivative of the carbohydrate was obtained. When this fully methylated derivative (II) was hydrolyzed with acid, 2,3,4,6-tetramethyl-D-glucose (III) and dimethyl-L-arabinose (IV) were produced. Since position 3 in the L-arabinose component (I) was shown to be occupied in glycosidic linkage with D-glucose, the dimethyl-L-arabinose could be either the 2,5- or 2,4-dimethyl derivative (IV), depending on whether the L-arabinose unit originally exists in the disaccharide in the furanose or pyranose form. The ring type of the L-arabinose was ascertained by subjecting the dimethyl-L-arabinose to oxidation with sodium periodate, after it had been oxidized with hypoiodite to the corresponding lactone (V) and subsequently hydrolyzed to the straight chain, dimethyl-L-arabonic acid (VI).

If the dimethyl derivative were the 2,5-dimethyl-L-arabonic acid, it would possess a pair of adjacent hydroxyls, on positions 3 and 4, which on oxidation with sodium periodate would consume one mole of periodate in the reaction. On the other hand, the 2,4-dimethyl-L-arabonic acid (VI), lacking a pair of adjacent hydroxyls, cannot

---

(1) W. Z. Hassid, M. Doudoroff and H. A. Barker, THIS JOURNAL, **66**, 1416 (1944).

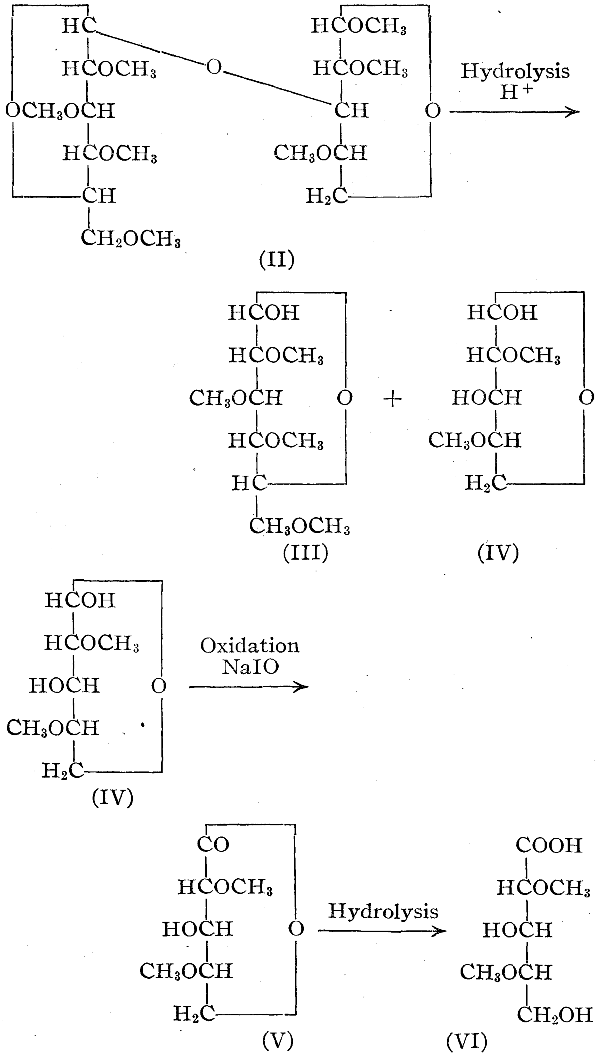
(2) W. Z. Hassid, M. Doudoroff, H. A. Barker and W. H. Dore, *ibid.*, **67**, 1394 (1945).

(3) W. Z. Hassid, M. Doudoroff, H. A. Barker and W. H. Dore, *ibid.*, **68**, 146 (1946).

(4) M. Doudoroff, W. Z. Hassid and H. A. Barker, *J. Biol. Chem.*, **168**, 733 (1947); M. Doudoroff, H. A. Barker and W. Z. Hassid, *ibid.*, **168**, 725 (1947).

(5) R. M. Hann and C. S. Hudson, THIS JOURNAL, **66**, 735 (1944); W. T. Haskins, R. M. Hann and C. S. Hudson, *ibid.*, **67**, 939 (1945).

be oxidized. Actually, no periodate was consumed when the dimethyl-L-arabonic acid was treated with this reagent. This shows that the dimethyl derivative is 2,4-dimethyl-L-arabonic acid. The free hydroxyl in position 3 is obviously restored in the dimethyl-L-arabinose when the methylated disaccharide is hydrolyzed; the hydroxyl in position 5 is formed when its internal ring is broken in the process of hydrolysis of the lactone to dimethyl-L-arabonic acid, which is a straight chain compound.



A more direct confirmation that the dimethyl-L-arabinose possesses a pyranose configuration was obtained from the study of the rate with which its lactone derivative is hydrolyzed to the open chain acid. Haworth, *et al.*,[6] found that the six-membered ring sugar lactones hydrolyze in water to their corresponding straight chain acids at a distinctly greater rate than the five-membered ring sugar lactones. The gamma lactones require approximately two weeks for complete opening of the ring, while the delta lactones are converted completely into the open chain acids within a few hours. It is thus possible to determine whether a given lactone has a furanose or pyranose configuration.

When the dimethyl-L-arabono lactone was dissolved in water, it was found to be almost completely hydrolyzed within four hours. This was indicated by a change of its rotation from $[\alpha]_D$ + 60 to 24° (Fig. 1). A constant value of $[\alpha]_D$ +17° was reached within less than twenty-four hours. Since the rate of change in rotation of this methylated lactone due to hydrolysis is high, it strongly indicates that the lactone possesses a pyranose configuration. This observation confirms the periodate oxidation data, showing that the dimethyl derivative is 2,4-dimethyl-L-arabonic acid.

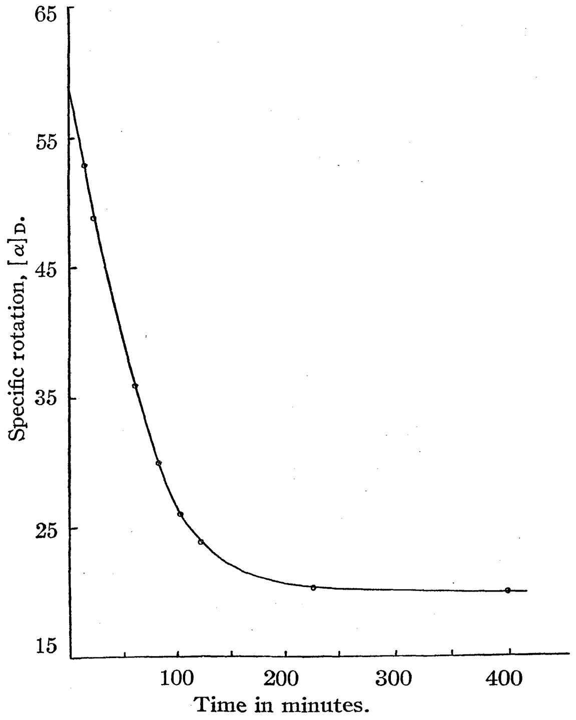


Fig. 1.—Hydrolysis of dimethyl-L-arabonolactone.

On the basis of these results the structural formula for this reducing disaccharide may be written as in Fig. 2.

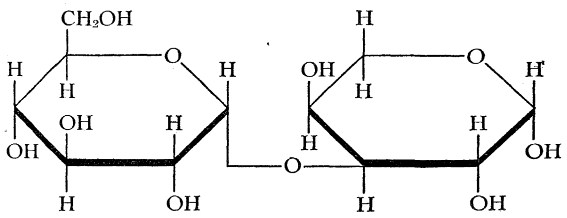


Fig. 2.

---

[6] W. N. Haworth, "The Constitution of Sugars," Edward Arnold and Company, London, 1929, p. 24; S. Baker and W. N. Haworth, *J. Chem. Soc.*, **127**, 365 (1925).

Experimental

Enzymatic Synthesis of D-Glucosido-L-arabinose.—A mixture of 30 g. of glucose-1-phosphate, 16 g. of L-arabinose and 400 ml. of 0.1 *M* barium acetate was incubated for eighteen hours at *p*H 7.0 and 35° in the presence of enzyme extracted from the bacteria *Pseudomonas saccharophila* by the method previously described.[1,2] The unused glucose-1-phosphate was removed by precipitation with alcohol and the unused L-arabinose by fermentation with a selected strain of *Escherichia coli*.[7] After passage through ion exchange columns and concentration of the solution *in vacuo*, the sugar was crystallized from absolute alcohol in the usual manner.[2,3] The yield was 5.4 g.

Properties of the Disaccharide.—The disaccharide is hygroscopic, very soluble in water and has a sweet taste. It reduces Fehling or alkaline ferricyanide solution and after hydrolysis with acid and subsequent neutralization gives the orcinol–hydrochloric acid reaction (Bial), characteristic for pentose sugars. This reducing disaccharide does not give the diazouracil reaction[8] specific for sucrose and the other synthetic disaccharides[2,3] which apparently contain the type of glycosidic glucose–fructose linkage existing in sucrose.

The carbohydrate is practically unaffected by yeast invertase and has a much greater resistance to acid hydrolysis than the previously synthesized non-reducing disaccharides, containing ketose units. Its rate of hydrolysis with acid is about one-third as great as that of maltose.

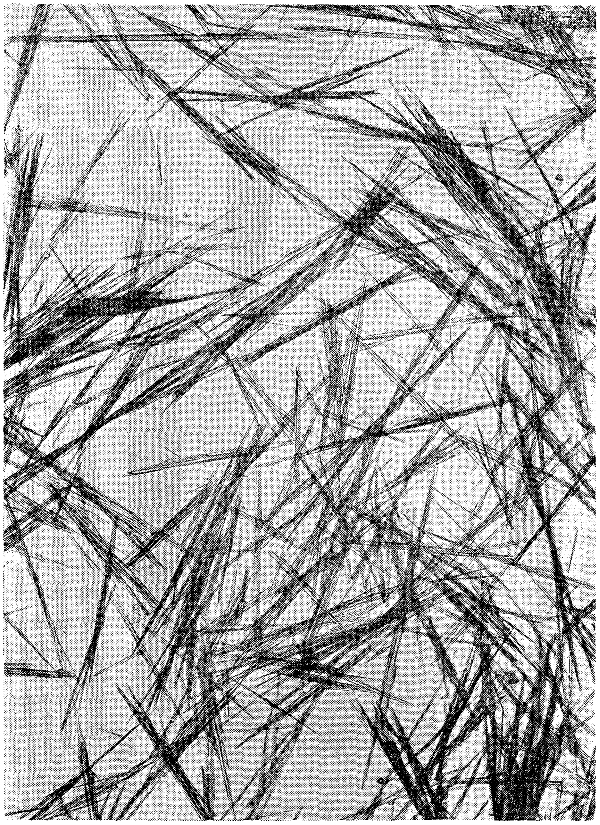


Fig. 3.—Phenylosazone of D-glucosido-L-arabinose (× 93).

Anal. Calcd. for $C_{11}H_{20}O_{10}\cdot 2H_2O$: C, 37.93; H, 6.90. Found: C, 38.26; H, 6.89; specific rotation $[\alpha]_D$ +156°, (in water, *c*, 2).

Hydrolysis of the Disaccharide and Identification of Products.—A 0.02-g. sample of the disaccharide was hydrolyzed with 0.5 *N* hydrochloric acid at 100° for six hours. Analysis of the hydrolyzed solution for reducing sugars by oxidation with ferricyanide,[9] showed a reducing value of 96% calculated on the basis of an equimolar mixture of glucose and L-arabinose and taking into consideration that the disaccharide contains two molecules of water of crystallization. After removal of the glucose from the hydrolyzate by fermentation with *Tortula monosa*, an osazone was prepared which was identified as arabosazone. Determination of pentose on an original sample of the disaccharide gave the theoretical value of L-arabinose.[10] A 2% solution of the disaccharide in 0.5 *N* hydrochloric acid hydrolyzed at 100° gave a final specific rotation $[\alpha]_D$ +71.0°. The calculated rotation of a hydrolyzed disaccharide consisting of D-glucose and L-arabinose and containing two molecules of water of crystallization is $[\alpha]_D$ +72.3°.

Rate of Hydrolysis of the Disaccharide.—The hydrolysis of a 2% solution of the D-glucosido-L-arabinose in 6 *N* hydrochloric acid was followed by observing the change of rotation at 50°. The rate of hydrolysis was compared with that of a similar solution of maltose under identical conditions. The course of hydrolysis of this disaccharide was represented by a logarithmic curve, indicating a first order reaction. The velocity constant *K* of the reaction is 4.37×10^{-3}. The velocity constant *K* of a 2% maltose solution, determined under the same conditions, is 1.28×10^{-2}, showing that the rate of hydrolysis of the D-glucosido-L-arabinose with acid is approximately one-third as great as that of maltose.

Phenylosazone.—One gram of the D-glucosido-L-arabinose was mixed in a test-tube with 2 g. of phenylhydrazine hydrochloride and 3 g. of sodium acetate. The mixture was dissolved in 14 ml. of water and heated on a steam-bath for thirty minutes. Upon cooling to room temperature crystals of the phenylosazone separated out, which appeared under the microscope as yellowish-green needles (Fig. 3). After placing the test-tube with the contents in the refrigerator for several hours at 4° the osazone was filtered, recrystallized from 50% alcohol and dried *in vacuo* at 30°. The yield was 0.735 g.

D-Glucosido-L-arabinose Phenylosotriazole.—A suspension of 0.50 g. of phenylosazone derivative of the new disaccharide was dissolved in 50 ml. of water, heated to the boiling point and a solution of 0.265 g. of copper sulfate pentahydrate (1.1 molecular equivalents) in 5 ml. of water was added. The mixture was heated under a reflux condenser for thirty minutes from the time of addition of the copper sulfate solution, then cooled and filtered. The filtrate, after neutralization with 0.20 g. of calcium carbonate, was extracted with ether to remove aniline. The solution was then run through ion exchange columns (Duolite C-3 and A-3, obtained from the Chemical Process Co., San Francisco) to remove inorganic impurities and evaporated to dryness *in vacuo* at 50°. The residue was extracted with hot alcohol, filtered, and the extract evaporated *in vacuo* to a small volume. Upon the addition of petroleum ether and upon stirring, crystals of the phenylosotriazole derivative were obtained. After cooling to 0°, the crystals were filtered on a sintered glass filter, washed with petroleum ether three times and dried *in vacuo* at 40°. The product was then recrystallized from 3 ml. of hot alcohol. A yield of 0.276 g. was obtained.

Anal. Calcd. for $C_{17}H_{23}N_3O_8$: C, 51.37; H, 5.83; N, 10.58. Found: C, 50.89; H, 5.82; N, 10.38; specific rotation, $[\alpha]_D$ +80° (in water, *c*, 2); melting point, 126.5°.

Oxidation of the D-Glucosido-L-arabinose Phenylosotriazole with Sodium Periodate.—A 0.0397-g. sample

---

[7] The removal by extraction of its osazone derivative was precluded by the reducing nature of the synthesized carbohydrate.

[8] H. W. Raybin, This Journal, **55**, 2603 (1933); **59**, 1402 (1937).

[9] W. Z. Hassid, *Ind. Eng. Chem., Anal. Ed.*, **9**, 228 (1937).

[10] W. Mejbaum, *Z. physiol. Chem.*, **258**, 117 (1939).

(0.1 millimole) of the derivative was oxidized at room temperature with 0.5 *M* sodium periodate. The amount of periodate consumed in the reaction and the amount of formic acid liberated was estimated by the usual procedure.[11] The formaldehyde produced in the reaction was determined photocolorimetrically with 1,8-dihydroxynaphthalene-3,6-disulfonic acid by the method of MacFayden.[12]

The results showed that three moles of periodate were consumed, giving rise to one mole of formic acid and one mole of formaldehyde in the oxidation of one mole of the phenylosotriazole derivative.

Acetylation.—A 0.1-g. sample of the disaccharide was acetylated with 0.46 ml. of acetic anhydride in the presence of pyridine at 0° as previously described.[1] The acetylated derivative was insoluble in water but soluble in chloroform and acetone. The yield was 0.11 g.

Anal. Calcd. for $C_{11}H_{13}O_{10}(CH_3CO)_7$: CH_3CO, 49.67. Found: CH_3CO, 48.88; specific rotation, $[\alpha]_D$ +111° (in chloroform, *c*, 2).

Methylation of D-Glucosido-L-arabinose.—The disaccharide was methylated by the method of Haworth and Leitch[13] as follows: One gram of the sugar was dissolved in a minimum of hot water (approximately 1 ml.) and the solution cooled to 30°. A total of 3.8 ml. of methyl sulfate and 8 ml. of 30% sodium hydroxide were added in eight equal portions with vigorous stirring. The first portion (0.5 ml.) of the methyl sulfate and that of the sodium hydroxide (1 ml.) were added at 30°. It is important that the sodium hydroxide be added very slowly so as not to allow the solution to become alkaline at any time during the methylation procedure. The temperature was then raised to 40° and the treatment was repeated with similar portions of methyl sulfate and sodium hydroxide solution. The mixture was then kept overnight at room temperature and on the following day tested for its reducing value. It was found to have no reducing property. Thereafter the temperature was raised to 60° and a third portion corresponding to one-eighth of the original volume of methyl sulfate was introduced and a similar proportion of sodium hydroxide was added drop by drop, with vigorous stirring. The remainder of the reagents was added at 70° in the same order and in similar fractions, stirring being continued throughout the addition. Finally the temperature was raised to 100° for a period of half an hour and the solution allowed to cool to room temperature. The solution was dried with anhydrous sodium sulfate, filtered and the chloroform distilled off. The yield was 1.03 g.

The incompletely methylated product was further methylated by the method of Pacsu and Trister[14] by dissolving in ether and treating with sodium and then methyl iodide. The yield obtained of the hexamethylmethyl D-glucosido-L-arabinose was 0.58 g.

Anal. Calcd. for $C_{18}H_{34}O_{10}$: OCH_3, 52.91. Found: 51.70; specific rotation, $[\alpha]_D$ +122° (in water, *c*, 2.34).

Hydrolysis of the Methylated Disaccharide and Separation of the 2,3,4,6-Tetramethyl-D-glucose and Dimethyl-L-arabinose.—The methylated D-glucosido-L-arabinose (0.56 g.) was dissolved in 20 ml. of 2 *N* hydrochloric acid and the solution was heated on a steam-bath for three hours. The hydrolyzate was cooled and extracted six times with equal volumes of chloroform. The solution was evaporated to a small volume on the steam-bath and dried by contact with a mixture of anhydrous sodium sulfate and anhydrous magnesium sulfate for forty minutes. A small amount of charcoal was then added and after fifteen more minutes the mixture was filtered. After evaporating this solution to dryness *in vacuo*, a yield of 0.31 g. (Fraction I) of crude 2,3,4,6-tetramethyl-D-glucose was obtained. The specific rotation of this product (in water, *c*, 1.67) was $[\alpha]_D$ +87°.

The tetramethylglucose was purified as follows: The crude product (Fraction I) was dissolved in 20 ml. of water, extracted six times with equal volumes of chloroform and the chloroform dried with a mixture of anhydrous sodium sulfate and anhydrous magnesium sulfate. A small amount of charcoal was then added and after a few minutes the solution was filtered. Upon evaporation of the chloroform solution to dryness, a yield of 0.27 g. of 2,3,4,6-tetramethyl-D-glucose was obtained.

Anal. Calcd. for $C_6H_8O_2(OCH_3)_4$: OCH_3, 52.6. Found: OCH_3, 51.6; specific rotation, $[\alpha]_D$ +81° (in water, *c*, 2).

The aqueous solution left after Fraction I was separated was again extracted six times with equal volumes of chloroform and the chloroform was evaporated, dried and clarified as before. Upon evaporation to dryness, 0.02 g. (Fraction II) of sirup was obtained. This small amount of sirup, probably dimethylarabinose, was discarded.

The aqueous solution contained practically all the dimethyl-L-arabinose, inasmuch as the dimethyl arabinose derivative is greatly in favor of the aqueous phase. The aqueous solution was passed through a 140-ml. capacity Duolite A-3 column to adsorb the hydrochloric acid. The column was washed with six volumes of water and the combined solutions evaporated to dryness *in vacuo*. The residue was then extracted with chloroform, clarified with charcoal, filtered and evaporated to dryness again. The yield of dimethyl-L-arabinose sirup was 0.180 g. (Fraction III).

Anal. Calcd. for $C_5H_8O_3(OCH_3)_2$: OCH_3, 34.8. Found: OCH_3, 34.2; specific rotation, $[\alpha]_D$ +61° (in alcohol, *c*, 1.56).

Oxidation of Dimethyl-L-arabinose to its Lactone.—The oxidation of the dimethyl-L-arabinose was carried out by a modified method of Goebel.[15] The sirup (0.165 g.) was dissolved in 33 ml. of 0.3 *N* barium iodide–iodine solution (7.5 g. of barium iodide and 3.81 g. of iodine dissolved in 100 ml. of water) to which 50 ml. of 0.4 *N* barium hydroxide was added in three minutes at constant rate of flow while stirring. The mixture was allowed to stand for fifteen minutes and was then acidified with 0.925 ml. of concentrated sulfuric acid which was diluted with 7.5 ml. of water. An excess of lead carbonate (7.5 g.) was immediately added and the mixture was rapidly stirred until it became neutral to congo red. The precipitate was permitted to settle and the supernatant liquid decanted. The precipitate was washed several times by decantation. The supernatant liquid and the washings, containing the methylated arabonate, was evaporated *in vacuo*, thus removing the iodine, and the concentrated solution filtered and the residue washed with water. The filtrate was then treated with 0.1 g. of silver sulfate to precipitate the iodide. The precipitate was filtered and the filtrate was treated with hydrogen sulfide to remove the excess silver and lead and filtered again. The solution was neutralized with barium hydroxide, allowed to stand for a few hours and filtered. It was then passed through a 25-ml. capacity Duolite C-3 column and washed with several volumes of water. The solution was concentrated *in vacuo* to dryness, adding water several times during the course of distillation, in order to remove any volatile acids that might be present. The dry residue was extracted with hot alcohol and the alcohol evaporated to dryness *in vacuo*. The yield of dimethyl-L-arabonic lactone was 0.14 g. When a sample of 0.0295 g. of the lactone was neutralized with 0.1 *N* sodium hydroxide, 1.50 ml. of this reagent was consumed. The theoretical requirement is 1.68 ml. of 0.1 *N* sodium hydroxide.

Anal. Calcd. for $C_5H_6O_3(OCH_3)_2$: OCH_3, 35.2. Found: OCH_3, 35.2.

Hydrolysis of Dimethyl-L-arabonolactone.—A sample of 0.0492 g. of the lactone was dissolved in 5 ml. of water and its rate of hydrolysis was followed by observing the

---

[11] E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 994 (1937); **62**, 958 (1940); R. M. Hann, W. D. Maclay and C. S. Hudson, *ibid.*, **61**, 2432 (1939).

[12] D. A. MacFayden, *J. Biol. Chem.*, **158**, 107 (1945).

[13] W. N. Haworth and G. C. Leitch, *J. Chem. Soc.*, **113**, 195 (1918).

[14] E. Pacsu and S. M. Trister, THIS JOURNAL, **61**, 2442 (1939).

[15] W. F. Goebel, *J. Biol. Chem.*, **72**, 809 (1927).

change of rotation in a polariscope. It was found that the lactone was almost completely hydrolyzed to the acid within four hours. A change from the initial rotation of [α]D +60° to +24° occurred within that time. After twenty-four hours the rotation had reached [α]D +17°, which remained constant thereafter (Fig. 1). Since the rate of change in the rotation of this lactone due to hydrolysis is high, it is concluded that this methylated lactone, and therefore also the original pentose unit, possesses the pyranose configuration.

Oxidation of the Dimethyl-D-arabonic Acid.—A 0.017-g. sample of the lactone was oxidized by allowing it to remain at room temperature with 0.5 *M* sodium periodate[11] for thirty hours. In aqueous solution the lactone is converted to the straight chain acid in a few hours. Analysis of the solution showed that no periodate was used up, indicating that the substance was not oxidized, apparently, due to the fact that it did not contain any adjacent free hydroxyl groups. When a similar sample of 2,3,6-trimethylgluconic acid was oxidized with periodate under the same conditions, one mole of periodate was consumed in the reaction.

Acknowledgment.—The work reported in this paper was supported in part by a grant from the Corn Industries Research Foundation.

Summary

A reducing crystalline disaccharide consisting of D-glucose and L-arabinose has been synthesized from glucose-1-phosphate and L-arabinose by the agency of a phosphorylase from the organism *Pseudomonas saccharophila.*

On oxidation of the phenylosotriazole derivative of this disaccharide with sodium periodate, three moles of periodate are consumed with the formation of one mole each of formic acid and formaldehyde per mole of phenylosotriazole derivative. These data indicate that in the disaccharide D-glucose is linked through carbon atom 1 to carbon atom 3 of L-arabinose.

Methylation of the disaccharide produced a hexamethylmethyl derivative, which on hydrolysis with acid gave rise to 2,3,4,6-tetramethyl-D-glucose and 2,4-dimethyl-L-arabinose.

Evidence that the dimethyl-L-arabinose possesses the pyranose configuration was obtained from the rate of hydrolysis of the dimethyl-L-arabonolactone derivative to its acid and also from periodate oxidation of this lactone.

On the basis of these data, the new reducing disaccharide may be designated as 3-[α-D-glucopyranosido]-L-arabopyranose.

BERKELEY, CALIFORNIA RECEIVED AUGUST 25, 1947

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

1,5-Anhydro-4-(β-D-glucopyranosyl)-D-glucitol,[1] 1,5-Anhydro-6-(β-D-glucopyranosyl)-D-glucitol and 1,5-Anhydro-D-galactitol[2]

BY HEWITT G. FLETCHER, JR., AND C. S. HUDSON

The palladium–catalyzed addition of hydrogen to the double bond of an acetylated 2-hydroxyglycal may, because of the new asymmetry introduced at carbon two, give rise to either or both of the predicted diastereomeric sugar alcohol anhydrides. Thus Zervas[3] reduced 2,3,4,6-tetraacetyl-2-hydroxy-D-glucal in a 61% yield to an anhydrohexitol which later was demonstrated[4] to be 1,5-anhydro-D-mannitol (styracitol), while Richtmyer, Carr and Hudson[4c] have more recently succeeded in obtaining a 4% yield of 1,5-anhydro-D-glucitol (polygalitol) by the same process.

The catalytic reduction of 2,3,4-triacetyl-2-hydroxy-D-xylal, which might lead to either 1,5-anhydro-xylitol or 1,5-anhydro-D-arabitol or to both, has recently been investigated[5]; only 1,5-anhydro-xylitol, isolated as its triacetate in a yield of 83%, was obtained.

In addition to the two cases above, the reduction of three other acetylated 2-hydroxy-glycals has been reported in the literature. Maurer and Plötner[6] reduced both heptaacetyl-2-hydroxy-cellobial (I) and heptaacetyl-2-hydroxy-gentiobial (V) in the presence of palladium to corresponding heptaacetyl-1,5-anhydro-(β-D-glucopyranosyl)-hexitols in yields, respectively, of 62 and 53%. The free anhydrides were termed "1.4-glucosido-styracitol" and "1.6-glucosido-styracitol," that is, as derivatives of an anhydride (styracitol) which is now known to have the mannitol configuration. Apparently these names were chosen solely on the assumption that the course of the reduction of the acetates of the two substituted 2-hydroxy-glycals had been similar to that of 2,3,4,6-tetraacetyl-2-hydroxy-D-glucal, which, as mentioned above, appears to give predominantly 1,5-anhydro-D-mannitol. Definitive proof, such as might have been obtained by the hydrolysis of the 1,5-anhydro-(β-D-glucopyranosyl)-hexitols, was apparently not adduced.

A third acetylated 2-hydroxy-glycal, 2,3,4,6-tetraacetyl-2-hydroxy-D-galactal (IX), was reduced in the presence of palladium by Freuden-

---

[1] By D-glucitol we denote the hexitol corresponding in configuration to D-glucose and commonly termed sorbitol.

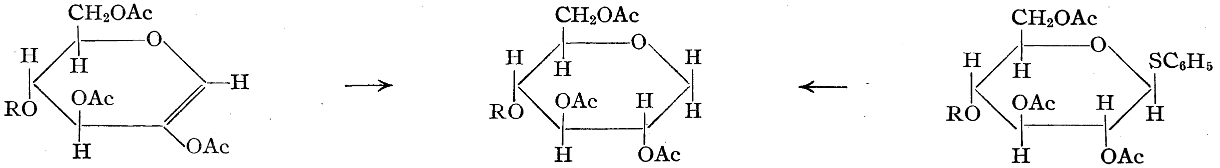
[2] This communication represents a portion of a paper presented before the Division of Sugar Chemistry and Technology at the Atlantic City meeting of the American Chemical Society, April 15, 1947.

[3] L. Zervas, *Ber.*, **63**, 1689 (1930).

[4] (a) L. Zervas and I. Papadimitriou, *Ber.*, **73**, 174 (1940); (b) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **65**, 64 (1943); (c) N. K. Richtmyer, C. J. Carr and C. S. Hudson, *ibid.*, **65**, 1477 (1943); (d) R. C. Hockett and Maryalice Conley, *ibid.*, **66**, 464 (1944).

[5] H. G. Fletcher and C. S. Hudson, *ibid.*, **69**, 921 (1947).

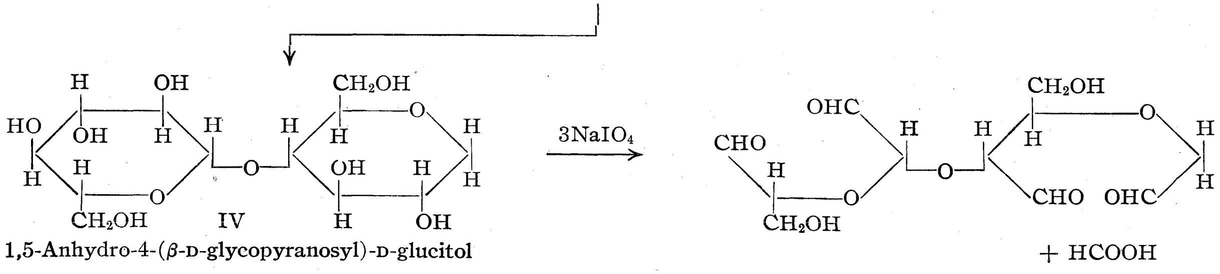
[6] K. Maurer and K. Plötner, *Ber.*, **64**, 281 (1931).



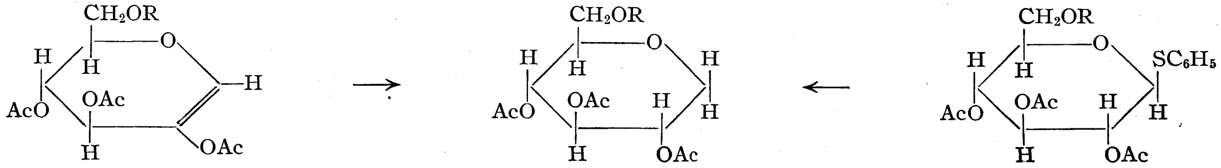
I
Heptaacetyl-2-hydroxy-cellobial
R = tetraacetyl-β-D-glucopyranosyl

II
Heptaacetyl-1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol

III
Phenyl 1-thio-β-cellobioside heptaacetate



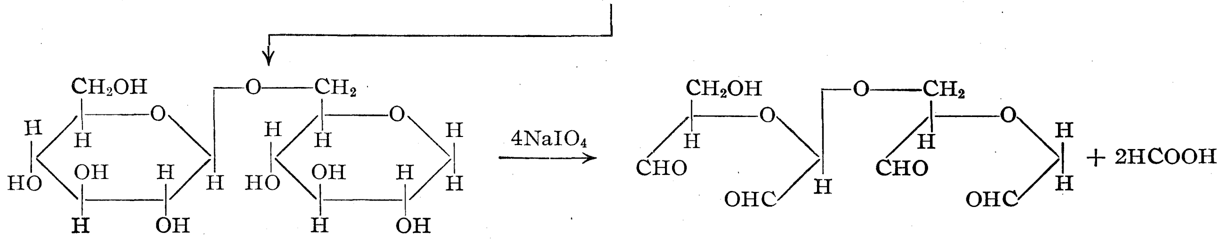
IV
1,5-Anhydro-4-(β-D-glycopyranosyl)-D-glucitol



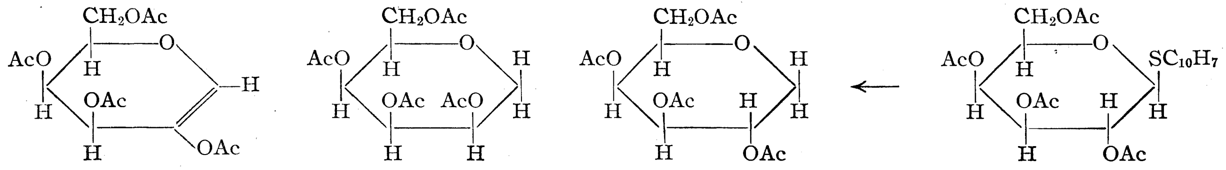
V
Heptaacetyl-2-hydroxy-gentiobial

VI
Heptaacetyl-1,5-anhydro-6-(β-D-glucopyranosyl)-D-glucitol

VII
Phenyl 1-thio-β-gentiobioside heptaacetate



VIII
1,5-Anhydro-6-(β-D-glucopyranosyl)-D-glucitol

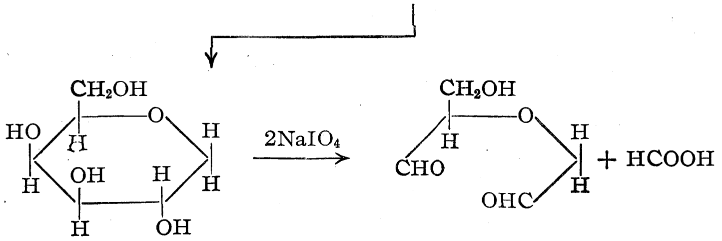


IX
2,3,4,6-Tetraacetyl-2-hydroxy-D-galactal

X
Tetraacetyl-1,5-anhydro-D-talitol

XI
Tetraacetyl-1,5-anhydro-D-galactitol

XII
2′-Naphthyl 1-thio-β-D-galactopyranoside tetraacetate



XIII
1,5-Anhydro-D-galactitol

berg and Rogers[7] to give, in 70% yield, the tetraacetate of an anhydro-hexitol whose structure as either 1,5-anhydro-D-galactitol (XI) or 1,5-anhydro-D-talitol (X) remained uncertain.

The reductive desulfurization of acetylated 1-thio-aldose derivatives with Raney nickel which has recently been applied to the synthesis of 1,5-anhydro-D-glucitol,[4c,8a] 1,5-anhydro-xylitol[5] and 1,5-anhydro-D-arabitol,[8b] furnishes an easy method for preparing sugar-alcohol 1,5-anhydrides of unequivocal configuration. The present research was designed to afford such authentic anhydrides for comparison with the three reduction products of uncertain configuration mentioned above.

Phenyl 1-thio-β-cellobioside heptaacetate (III), prepared originally by Purves[9] through the condensation of heptaacetyl-α-cellobiosyl bromide with potassium thiophenolate, was subjected in warm ethanolic solution to the action of freshly prepared Raney nickel. The resulting crystalline heptaacetyl-1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol (II), as well as its parent polyalcohol (IV), obtained by catalytic deacetylation, was produced in satisfactory yield and they possessed melting points and rotations (Table I) which were at little variance from the corresponding values reported by Maurer and Plötner for the reduction product of heptaacetyl-2-hydroxy-cellobial. It appears, therefore, that the "1,4-glucosido-styracitol" of these authors is not a mannitol derivative as this name now implies but is 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol, a substituted polygalitol (4-(β-D-glucopyranosyl)-polygalitol).

TABLE I

HEXITOL 1,5-ANHYDRIDES AND DERIVATIVES

	Fletcher and Hudson M. p., °C.	Fletcher and Hudson [α]D	Maurer and Plötner[6] M. p., °C.	Maurer and Plötner[6] [α]D
1,5-Anhydro-4-(β-D-glucopyranosyl)-D-glucitol heptaacetate	194–195	+ 4.0°[a]	187	+ 7.0°[a]
1,5-Anhydro-4-(β-D-glucopyranosyl)-D-glucitol	172	+29.3°[b]	173	+29.01°[b]
1,5-Anhydro-6-(β-D-glucopyranosyl)-D-glucitol heptaacetate	153	+13.0°[a]	152	+17.2°[a]
1,5-Anhydro-6-(β-D-glucopyranosyl)-D-glucitol	239–240	+ 3.6°[b]	223	+ 2.44°[b]
			Freudenberg and Rogers[7]	
1,5-Anhydro-D-galactitol tetraacetate	75–76	+49.1°[a]	108	−15.31°[a]
1,5-Anhydro-D-galactitol	114–115	+76.6°[b]	(sirup)	− 7.34°[b]

[a] In chloroform solution. [b] In aqueous solution.

In accord with its structure, 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol (IV) was found on a molar basis to consume three moles of periodate with the simultaneous formation of one mole of formic acid.

Phenyl 1-thio-β-gentiobioside heptaacetate was obtained from β-gentiobiose octaacetate in a manner similar to its cellobiose analog; the substance is classed as a β-pyranose derivative by comparison of its rotation with that of methyl β-gentiobioside heptaacetate and on the strength of the analogy with the similar pair of substances in the cellobiose series (Table II).

TABLE II

COMPARISON OF SOME MOLECULAR ROTATIONS IN THE CELLOBIOSE AND GENTIOBIOSE SERIES

	Mol. wt.	[α]D (CHCl$_3$)	[M]D	Difference
Methyl β-cellobioside heptaacetate	651	−25.1°	−16300	4600
Phenyl 1-thio-β-cellobioside tetraacetate	729	−28.7°	−20900	
Methyl β-gentiobioside heptaacetate	651	−18.9°	−12300	4200
Phenyl 1-thio-β-gentiobioside heptaacetate	729	−22.7°	−16500	

Phenyl 1-thio-β-gentiobioside heptaacetate was also treated with Raney nickel to yield heptaacetyl-1,5-anhydro-6-(β-D-glucopyranosyl)-D-glucitol (VI). The physical constants of this crystalline compound, together with those of its unacetylated parent (Table I), approached quite closely the constants for the corresponding compounds which Maurer and Plötner obtained through the reduction of heptaacetyl-2-hydroxy-gentiobial (V). It therefore appears that the "1,6-glucosido-styracitol" which these authors recorded is actually 1,5-anhydro-6-(β-D-glucopyranosyl)-D-glucitol, a substituted polygalitol (6-(β-D-glucopyranosyl)-polygalitol).

In conformity with its structure, 1,5-anhydro-6-(β-D-glucopyranosyl)-D-glucitol (VIII) reduces on a molar basis four moles of periodate with the simultaneous liberation of two moles of formic acid.

Reductive desulfurization with Raney nickel of 2′-naphthyl 1-thio-β-D-galactopyranoside tetraacetate (XII), prepared as recently reported by Haskins and Hudson,[10] gave tetraacetyl-1,5-anhydro-D-galactitol (XI). The physical constants of this latter compound as well as of the free crystalline 1,5-anhydro-D-galactitol (Table I) were found to differ markedly from those reported by Freudenberg and Rogers[7] for the comparable substances which they obtained by the reduction of 2,3,4,6-tetraacetyl-2-hydroxy-D-galactal (IX). The optical rotations of the two substances, for instance, were opposite in sign as well as numerically different from those reported by Freudenberg and Rogers. It would therefore appear that the anhydride of these authors is probably 1,5-anhydro-D-talitol (corresponding to X). A study directed to the synthesis of authentic 1,5-anhydro-D-talitol is at present being pursued in this Laboratory.

One of us (H. G. F.) held the Chemical Foundation Research Associateship while carrying out this research. We are indebted to Mr. Charles A.

---

[7] W. Freudenberg and E. F. Rogers, THIS JOURNAL, **59**, 1602 (1937).

[8] (a) H. G. Fletcher, *ibid.*, **69**, 706 (1947); (b) H. G. Fletcher and C. S. Hudson, *ibid.*, **69**, 1672 (1947).

[9] C. B. Purves, *ibid.*, **51**, 3619 (1929).

[10] W. T. Haskins and C. S. Hudson, *ibid.*, **69**, 1668 (1947).

Kinser and Mrs. Betty Mount for combustion analyses.

Experimental[11]

1,5-Anhydro-4-(β-D-glucopyranosyl)-D-glucitol Heptaacetate (II).—Ten grams of phenyl 1-thio-β-cellobioside heptaacetate prepared according to the method of Purves,[9] melting at 225–226°[12] and rotating −28.7° in chloroform (*c*, 1.36), was suspended in 100 ml. of absolute alcohol, treated with approximately 100 g. of freshly prepared Raney nickel in absolute alcohol and then boiled gently for one hour. After cooling, the supernatant solution was decanted and the nickel washed by decantation with three successive 100-ml. portions of boiling absolute alcohol. The combined decantates, after filtration through a fine sintered glass plate, were concentrated at 80° (bath) under a slight vacuum to a volume of 125 ml.; crystallization of the product as a mass of very fine needles was spontaneous. Concentration of the mother liquor afforded a very small quantity of additional material: yield 5.9 g. or 69%. Two recrystallizations from warm 95% ethanol furnished with little loss material melting at 194–195° and rotating +4.0° in chloroform (*c*, 1.39).

1,5-Anhydro-4-(β-D-glucopyranosyl)-D-glucitol heptaacetate is readily soluble in acetone, chloroform and hot alcohol, and relatively insoluble in cold alcohol, water and pentane.

Anal. Calcd. for $C_{26}H_{36}O_{17}$: C, 50.32; H, 5.85. Found: C, 50.51; H, 5.73.

1,5-Anhydro-4-(β-D-glucopyranosyl)-D-glucitol (IV).—Three grams of 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol heptaacetate was deacetylated catalytically with barium methylate to give 1.4 g. (89%) of 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol as minute prismatic needles. Recrystallized from aqueous alcohol, the pure substance melted at 172° and appeared to decompose very slowly at this temperature. In water the compound showed a rotation of +29.3° (*c*, 4.64). It is readily soluble in water, somewhat soluble in alcohol and insoluble in ethyl acetate and pentane.

Anal. Calcd. for $C_{12}H_{22}O_{10}$: C, 44.17; H, 6.79. Found: C, 44.44; H, 6.72.

Sodium Metaperiodate Oxidation of 1,5-Anhydro-4-(β-D-glucopyranosyl)-D-glucitol.—The technique of Jackson and Hudson[13] was employed. The 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol (0.1013 g.) was dissolved in a little water, treated with 5.0 ml. of 0.480 *M* sodium metaperiodate solution and the solution diluted to 25.0 ml. with water. After twenty-four hours at room temperature a 5.0-ml. sample was titrated for formic acid and residual oxidant. On a molar basis the compound consumed 2.99 moles of oxidant while 1.22 moles of formic acid was liberated.

Phenyl 1-Thio-β-gentiobioside Heptaacetate (VII).—The procedure which Purves[9] devised for the preparation of phenyl 1-thio-β-cellobioside heptaacetate gave phenyl 1-thio-β-gentiobioside heptaacetate in a yield of 33% from β-gentiobiose octaacetate. The very fine needle-like crystals obtained by repeated recrystallization from 8 parts of alcohol melted at 172° and rotated in chloroform −22.7° (*c*, 1.64). Comparison of this rotation with that of methyl β-gentiobioside heptaacetate (Table II) indicates that the glycoside is of the β-configuration.

Phenyl 1-thio-β-gentiobioside heptaacetate is readily soluble in acetone, chloroform and boiling alcohol, very sparingly soluble in cold alcohol, and relatively insoluble in water and pentane.

Anal. Calcd. for $C_{32}H_{40}O_{17}S$: C, 52.74; H, 5.53; S, 4.40. Found: C, 52.54; H, 5.35; S, 4.15.

1,5-Anhydro-6-(β-D-glucopyranosyl)-D-glucitol Heptaacetate (VI).—Six grams of phenyl 1-thio-β-gentiobioside heptaacetate was desulfurized with Raney nickel in a manner similar to that described above for its cellobiose analog. Three recrystallizations of the crude product (3.7 g.; 72%), first from 7 parts of warm alcohol, then from a mixture of 1 part acetone and 3 parts of ether, and finally from seven parts of warm alcohol, gave with little loss pure 1,5-anhydro-6-(β-D-glucopyranosyl)-D-glucitol heptaacetate melting at 153° and rotating in chloroform +13.0° (*c*, 1.27).

The compound is soluble in methyl cellosolve, dioxane and ethyl acetate. At elevated temperature it dissolves in *n*-butanol, benzene and alcohol.

Anal. Calcd. for $C_{26}H_{36}O_{17}$: C, 50.32; H, 5.85. Found: C, 50.49; H, 5.80.

1,5-Anhydro-6-(β-D-glucopyranosyl)-D-glucitol (VIII).—Two grams of 1,5-anhydro-6-(β-D-glucopyranosyl)-D-glucitol heptaacetate was deacetylated in the customary manner with sodium methylate to give 0.6 g. (57%) of material as minute clusters of thin prisms. Recrystallized from a mixture of 1.7 parts of water and 2.5 parts of alcohol the 1,5-anhydro-6-(β-D-glucopyranosyl)-D-glucitol melted at 239–240° and rotated in water +3.6° (*c*, 4.43).

The compound is insoluble in benzene, acetone, ethyl acetate and alcohol. It may be recrystallized by solution in a limited quantity of warm water.

Anal. Calcd. for $C_{12}H_{22}O_{10}$: C, 44.17; H, 6.79. Found: C, 43.86; H, 6.93.

Sodium Metaperiodate Oxidation of 1,5-Anhydro-6-(β-D-glucopyranosyl)-D-glucitol.—The oxidation was carried out in the same manner as that of its isomer described above. On a molar basis 1,5-anhydro-6-(β-D-glucopyranosyl)-D-glucitol was found to consume 4.04 moles of oxidant with the concomitant liberation of 1.96 moles of formic acid.

1,5-Anhydro-D-galactitol Tetraacetate (XI).—Ten grams of 2′-naphthyl 1-thio-β-D-galactopyranoside tetraacetate (m. p. 113–114°; $[\alpha]^{20}D$ +6.55° ($CHCl_3$, *c*, 1.37)), prepared as recently reported by Haskins and Hudson,[10] was desulfurized with Raney nickel in absolute alcoholic solution and yielded 4.91 g. (73%) of nearly pure product. Recrystallized first from a mixture of 1.2 parts of ether and 0.6 parts of pentane and then from a mixture of 1.3 parts of absolute alcohol and 0.94 parts of pentane, the material melted at 75–76° and rotated in chloroform +49.1° (*c*, 0.82). 1,5-Anhydro-D-galactitol tetraacetate is soluble in acetone, ether and hot alcohol, and relatively insoluble in cold alcohol, pentane and water.

Anal. Calcd. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.67; H, 6.17.

1,5-Anhydro-D-galactitol (XIII).—Five grams of 1,5-anhydro-D-galactitol tetraacetate was deacetylated catalytically with barium methylate, the product (2.37 g., 96%) being precipitated from its concentrated solution in methanol by the addition of ethyl acetate. Recrystallized once from 7 parts of boiling absolute alcohol and once from aqueous alcohol, the small, clear prisms melted at 114–115° and rotated in water +76.6° (*c*, 1.08).

1,5-Anhydro-D-galactitol is readily soluble in water, sparingly soluble in alcohol, and relatively insoluble in ethyl acetate, benzene and pentane.

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 44.18; H, 7.38.

Sodium Metaperiodate Oxidation of 1,5-Anhydro-D-galactitol.—The quantitative oxidation of 1,5-anhydro-D-galactitol with sodium metaperiodate was carried out in the same manner as described for the two anhydrides above. On a molar basis the substance consumed 2.00 moles of oxidant while 0.97 mole of formic acid was liberated.

---

[11] Melting points below 200° were taken with a calibrated Anschütz-type thermometer completely immersed in the bath liquid; those above 200° were measured in a Berl and Kullmann copper block, the thermometer readings being corrected for stem exposure. Rotations are specific rotations for sodium light at 20°; concentration is expressed in g. of substance per 100 ml. of solution.

[12] Purves (ref. 9) reported that this compound "decomposed in the neighborhood of 295°." A sample of his material was found to melt at 225–226° either alone or in admixture with that prepared in the course of the present research.

[13] E. L. Jackson and C. S. Hudson, This Journal, **59**, 994 (1937).

Summary

Reductive desulfurization of phenyl 1-thio-β-cellobioside heptaacetate with Raney nickel has furnished 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol heptaacetate. The physical constants of this substance, as well as of the 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol obtained from it by deacetylation, conform quite closely with the constants which are recorded in the literature for the corresponding products obtained through the palladium catalyzed reduction of heptaacetyl-2-hydroxy-cellobial.

1,5-Anhydro-6-(β-D-glucopyranosyl)-D-glucitol and its heptaacetate have similarly been obtained through the reductive desulfurization of phenyl 1-thio-β-gentiobioside heptaacetate and found to possess physical constants in substantial agreement with those reported in the literature for the comparable substances arising through the palladium-catalyzed reduction of heptaacetyl-2-hydroxy-gentiobial.

1,5-Anhydro-D-galactitol and its tetraacetate have been prepared through the reductive desulfurization of 2′-naphthyl 1-thio-β-D-galactopyranoside tetraacetate. The physical constants of these two compounds depart markedly from those reported for the corresponding substances, derived through the palladium-catalyzed reduction of 2,3,4,6-tetraacetyl-2-hydroxy-D-galactal.

The behavior of 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol, 1,5-anhydro-6-(β-D-glucopyranosyl)-D-glucitol and 1,5-anhydro-D-galactitol toward sodium metaperiodate has been examined and found in each case to conform to the assigned structure.

BETHESDA, MARYLAND RECEIVED JUNE 14, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Deacetylation of Acetylated Carbohydrate Derivatives with Potassium Alkoxides

BY WILLIAM A. BONNER AND WAYNE L. KOEHLER

Fischer and Bergmann[1] were apparently the first to extend the catalytic deacylation of esters with sodium ethylate to the sugar acetates. In succeeding years Zemplén and his co-workers[2] gave a mechanistic interpretation to this reaction and extended it widely in the field of carbohydrates. Today the Zemplén–Pacsu deacylation, using a catalytic amount of sodium in methanol, is one of the standard tools employed by workers in this field.

One disadvantage inherent in deacylations with sodium methylate is the retention in solution of sodium ions. This is not serious where the deacylated product crystallizes directly from the methanol solvent and the sodium ion remains in the mother liquor. However it constitutes a source of non-removable impurity in cases where the deacylated product does not crystallize and must be isolated by distillation of the solvent and volatile constituents of the reaction mixture.

A procedure capable of obviating this difficulty is found in the use of barium methylate, a modification introduced by Weltzien and Singer[3] and subsequently extended by others.[4] In this technique the barium ion is quantitatively precipitated by addition of an equivalent amount of sulfuric acid. While excellent in principle, this method suffers from the colloidal nature of the precipitated barium sulfate and consequent added difficulties in its removal, as well as from the extra trouble involved in the preparation and standardizations of the solutions employed.

It became desirable to develop a simple and rapid procedure which would permit the isolation of sirupy deacetylation products in a substantially ash-free state. The procedure developed employs a potassium methylate or ethylate in place of the sodium or barium methylates used previously, followed by a quantitative precipitation of potassium ion as perchlorate on potentiometric titration with concentrated perchloric acid.

This procedure was tested by application to several known acetylated sugar derivatives. After deacetylation was complete and potassium was removed as perchlorate, the free sugar derivative was isolated from the filtrate by evaporation *in vacuo* of the volatile constituents. Physical constants and ash analyses were determined on the crude residues to determine their purity. The data obtained, tabulated in the Experimental Part, indicate that the method can be applied to instances where sirupy deacetylation products result with assurance that reasonably pure sirups will be obtained in substantially quantitative yield.

Although methanol has been the solvent commonly employed by previous workers, we have studied the efficacy of higher alcohols as solvents in deacetylations employing both sodium and potassium alkoxides as catalysts. Primary alcohols, whether straight-chained or branched, gave yields of deacetylated products very close to theoretical, but secondary and tertiary alcohols gave yields up to 55% high. This is apparently due to a decrease in the rate of deacetylation in these cases and, on grounds of steric hindrance, is in

---

[1] Fischer and Bergmann, *Ber.*, **52**, 852 (1919).

[2] Zemplén and Kunz, *ibid.*, **56**, 1705 (1923); Zemplén, *ibid.*, **59**, 1258 (1926); **60**, 1555 (1927); Zemplén and Pacsu, *ibid.*, **62**, 1613 (1929).

[3] Weltzien and Singer, *Ann.*, **443**, 104 (1925).

[4] Brauns, THIS JOURNAL, **48**, 2784 (1926); Mitchell, *ibid.*, **63**, 3534 (1941); Isbell, *Natl. Bur. Standards J. Res.*, **5**, 1185 (1930).

TABLE I

DEACETYLATION OF ACETYLATED SUGAR DERIVATIVES WITH POTASSIUM ALKOXIDES

Acetate	Solvent	Yield, %	Deacetylated derivative M. p., °C. Obs.	M. p., °C. Lit.	$[\alpha]_D$ Obs.[a]	$[\alpha]_D$ Lit.[b]	Ash, %
Phenyl tetraacetyl-β-D-glucoside	Methanol	101.3	172–172.5	171–172[5]	−63.3	−71.0[6]	0.15
	Ethanol	98.6	171–172		−74.6	−65.5[5]	0.21
Methyl tetraacetyl-α-D-glucoside	Methanol	103.1	163–165	166[7]	151.5	158.9[7]	0.14[d]
	Ethanol	101.0[c]	163–165.5[c]		151.0[c]		0.23[c,d]
Phenyl tetraacetyl-β-D-thioglucoside	Methanol	99.3	129.5–130	133[8]	−68.3	−70.3[8]	0.13
	Ethanol	101.9	126–131		−67.1		2.75

[a] All rotations were taken in water at 23° at concentrations around 3%. [b] Rotations here were reported in water at 20°, with the exception of ref. 5 which was at 18°. [c] Deacetylation in ethanol gave rise to direct crystallization of about 75% of the methyl α-D-glucoside, The crystalline material, dried in the usual fashion, had m. p. 165.5–167° and $[\alpha]^{23}D$ 158.2° (c, 3.790; H_2O). The constants given in the table apply to the 25% of product remaining in the mother liquors. The yield is based on the total weight of both fractions. [d] It is interesting to calculate that, had the potassium not been removed in this case by precipitation, the quantities of inorganic impurity present would be about 6 to 7%, weighed as potassium alkoxide.

accord with the mechanism of deacetylation proposed by Zemplén.

It was believed possible to simplify the barium methylate deacetylation used previously[4] by a potentiometric titration of the barium ion with sulfuric acid. The method failed, however, since the pH required for complete precipitation of the barium was too low, and hydrolysis of the sugar derivatives occurred during subsequent processing. When pH values high enough to prevent hydrolysis were employed as an end-point in the titration, precipitation of barium was incomplete and the crude products contained excessive quantities of ash.

In applying the potassium methylate procedure to a typical deacetylation giving a sirupy product, we have deacetylated tetraacetyl-β-D-glucosylbenzene. β-D-Glucosylbenzene proved to be a clear, thick, non-reducing glass, isolable as an alcoholate. This substance, its tetrapropionate, and its tetrabenzoate are herein reported for the first time.

Experimental Part

Deacetylations with Potassium.—A sample of the acetylated sugar derivative (*ca.* 2 g.) was placed in a 50-ml. Erlenmeyer flask and methanol or ethanol added (10 ml. per gram of solute). A small chip of freshly cut potassium (20–35 mg.) was added, and the flask placed on the steam-bath for five minutes, removed, stoppered and permitted to stand at room temperature for about twenty-four hours. After this period the potassium was precipitated by titration with commercial 60% perchloric acid to a potentiometrically determined end-point using a Beckman pH meter. The pH value used for the end-point in methanol was 8.15 and in ethanol 7.55. These pH values were found in separate experiments when potassium perchlorate was permitted to stand with intermittent shaking for several hours in contact with these alcohols. Care must be taken in approaching the end-point, since it is easily passed when titrating with concentrated perchloric acid. Occasionally it was found expedient to titrate to one pH unit above the end-point with concentrated acid, and to approach the final end-point using perchloric acid diluted with solvent. It was found that the use of dilute perchloric acid during the entire titration led to a colloidal precipitate of potassium perchlorate which proved difficult to filter.

The precipitated potassium perchlorate was filtered and rinsed with a small amount of solvent, and the filtrate and washings placed in a small beaker. The beaker was placed under a micro bell jar and the latter evacuated with an aspirator. A fine stream of air, controlled by a pinch clamp, was directed onto the surface of the liquid through a capillary entering the top of the bell jar through a rubber stopper. The bell jar plate was warmed to 55° by controlled heating on a hot-plate. In this fashion the solvent and volatile products (methyl or ethyl acetates) were removed by vacuum evaporation under low heating.

The residual deacetylated sugar derivative was dried in a vacuum desiccator over phosphorus pentoxide for seventy-two hours, then in an oven at 60° for an additional twenty-eight hours. Melting points, rotations and ash analyses were taken on the resulting crude, dried, unrecrystallized products. Ash analyses were conducted by cautiously igniting 0.1 to 0.2 g. of the deacylated derivative in a platinum crucible.

Data on the known derivatives deacetylated in this manner are tabulated in Table I. The particular acetates employed were selected because preliminary experiments showed that their products would not precipitate directly from the solvent on deacetylation. This was desirable here, since the procedure was to be applied to acetates giving sirupy deacetylation products.

Deacetylations in Various Solvent Media.—Two sets of experiments were conducted, the first studying the completeness of deacetylations using sodium and potassium in three alcohols, and the second studying the completeness of deacetylation using potassium in ten alcohols.

In the first set approximately 2 g. of phenyl tetraacetyl-β-D-glucoside (weighed to mg.) was dissolved in 20 ml. of the solvent and a known weight (20–30 mg.) of freshly-cut sodium or potassium added. The solution was heated to 80–90° on the water-bath for five minutes, then allowed to stand for one day. The solvent was removed by vacuum evaporation, and the residue dried *in vacuo* over phosphorus pentoxide for seventy-two hours. The dried residue was weighed and the yield determined. The results are given in Table II; the yields are based on weights corrected for the amounts of metal alkoxides present in the residue.

TABLE II

DEACETYLATIONS WITH SODIUM AND POTASSIUM IN METHANOL, ETHANOL AND 2-PROPANOL

Solvent	Phenyl β-D-glucoside, % yield Sodium	Potassium
Methanol	98.8	99.4
Ethanol	102.1	100.7
2-Propanol	103.1	111.6

---

(5) Helferich, Bäuerlein and Wiegand, *Ann.*, **447**, 27 (1926).

(6) Fischer and Armstrong, *Ber.*, **34**, 2885 (1901).

(7) Riiber, *ibid.*, **57**, 1797 (1924).

(8) Purves, THIS JOURNAL, **51**, 3626 (1929).

In the second set of experiments a known weight of phenyl tetraacetyl-β-D-glucoside (weighed to mg.) was dissolved in the alcohol (10 ml. per gram of acetate). The solution was treated with a known weight of potassium, then permitted to react and processed exactly as above. The dried residue was weighed (mg.) and the yield determined, correcting for the quantity of potassium alkoxide remaining in the residue. The data for these experiments appear in Table III. It is seen that the yield of phenyl β-D-glucoside is close to the theoretical in the case of primary alcohols but far above the theoretical in the cases of secondary and tertiary alcohols, indicating incomplete deacetylation in these latter cases.

TABLE III

DEACYLATIONS WITH POTASSIUM IN VARIOUS ALCOHOLS

Alcohol	Type	Phenyl β-D-glucoside, % yield
Methyl	Primary	99.4
Ethyl		100.7
n-Propyl		98.0
n-Butyl		101.5
Isobutyl		100.2[a]
n-Amyl		105.4[a]
Isoamyl		98.2[a]
Isopropyl	Secondary	111.6
s-Butyl		153.3[a]
t-Amyl	Tertiary	154.9[a]

[a] In these experiments the product crystallized directly from the reaction mixture, confirming the expected decrease in solubility of the free glucoside in higher alcohols.

Attempted Deacetylations with Barium.—This describes the attempted extension of the potentiometric titration method to barium deacetylations. Samples of phenyl tetraacetyl-β-D-glucoside, methyl tetraacetyl-α-D-glucoside and phenyl tetraacetyl-β-D-thioglucoside were dissolved in methanol and ethanol. A small chip of barium metal (*ca.* 20 mg.) was added to each of the six solutions. These were then heated for five minutes and allowed to stand for twenty-four hours. They were next titrated with alcoholic sulfuric acid (*ca.* 1 *N*) with the aid of a *p*H meter. The *p*H found for pure barium sulfate in methanol was 2.00 and for ethanol 2.63. (The same barium sulfate gave a *p*H of 6.3 when shaken with water.) These values were used as end-points in the present titrations. On filtration of the barium sulfate and vacuum evaporation of the filtrate, each of the samples underwent marked decomposition.

When the end-point of one such titration was taken as *p*H 7.4 methyl α-D-glucoside was recovered in a yield of 106.3% from methanol. This crude product, however, proved to contain 7.8% ash.

β-D-Glucosylbenzene.—Crystalline tetraacetyl-β-D-glucosylbenzene[9] (5.925 g.) was dissolved in methanol (30 ml.) and a small chip of freshly-cut potassium added. The mixture was warmed on the steam-bath for five minutes and the resulting amber solution permitted to stand at 25° for twenty-four hours. It was then decolorized by filtration through a small bed of Norit over Super-cel. The filtrate was potentiometrically titrated to the usual *p*H with 60% perchloric acid, and the solid filtered and rinsed with methanol. The product was isolated as before by vacuum evaporation, and was dried for several weeks *in vacuo* over phosphorus pentoxide. The product was a clear, non-reducing glass weighing 3.548 g. (89.9%). It proved to be an alcoholate, retaining one mole of methanol. Rotation: $[\alpha]^{23}\text{D}$ 18.25° (*c*, 2.740, H_2O). *Anal.* Calcd. for $C_{13}H_{20}O_6$: C, 57.35; H, 7.41. Found: C, 57.40, 57.15; H, 7.06, 7.64. When 0.228 g. of the product was ignited in a platinum crucible, there remained 0.2 mg. of residue; ash, 0.09%.

Tetrapropionyl-β-D-glucosylbenzene.—β-D-Glucosylbenzene methanolate (1.00 g.) was dissolved in pyridine (15 ml.) and propionic anhydride (15 ml.) added. The mixture stood for three days at room temperature with no color change. It was then poured into water (100 ml.) and allowed to stand for nine hours with intermittent shaking. A sirupy lower layer resulted. This was extracted into ether, and the extract washed with water, 4 *N* hydrochloric acid, water (twice), saturated sodium bicarbonate solution and finally water. The clear extract was dried over anhydrous sodium sulfate, filtered and the solvent distilled, last traces *in vacuo*. There resulted 1.76 g. (102%) of a clear, amber sirup which crystallized slowly on standing. This was recrystallized three times by dissolving in 2-propanol, adding water until faintly turbid and placing at 0°. The product, fine white needles, had m. p. 69.5° and $[\alpha]\text{D}^{25}$ −14.12° (*c*, 3.183; $CHCl_3$). *Anal.* Calcd. for $C_{24}H_{32}O_9$: C, 62.08; H, 6.94. Found: C, 62.68; H, 7.11.

Tetrabenzyl-β-D-glucosylbenzene.—β-D-Glucosylbenzene methanolate (0.80 g.) was dissolved in pyridine (20 ml.) and benzoyl chloride (10 ml.) added. Considerable warming and darkening occurred, and a thin paste resulted. This stood for three days and was thrown into water. On standing for nine hours with occasional shaking an oily second phase resulted. The aqueous layer was decanted and the oil treated with ether. The oily product crystallized to give 1.91 g. (98.5%) of white solid, m. p. 181–182.5°. The residual ether was used to extract the aqueous layer, and the extract processed as above. Removal of the solvent after decolorization of the extract gave 3.54 g. of a thin, amber liquid. This had a negligible rotation and was not investigated. The white solid proved very insoluble in 2-propanol, and was purified by extracting with 2-propanol in a Soxhlet extractor for several hours. The undissolved residue had m. p. 184.5–185.5°. A small amount of material crystallized from the pot solvent, m. p. 183.5–185.5°. The purer sample had $[\alpha]^{25}\text{D}$ −22.93° (*c*, 0.960; $CHCl_3$). *Anal.* Calcd. for $C_{40}H_{32}O_9$: C, 73.20; H, 4.91. Found: C, 73.10, 73.30; H, 4.97, 5.10.

Summary

1. Potassium methylate and ethylate have been found useful for the catalytic deacetylation of acetylated sugar derivatives. After reaction the potassium is removed as perchlorate, permitting isolation of substantially ash-free products, even if the latter are sirups.

2. Such deacetylations have been studied using a wide variety of alcohols as solvent. Primary alcohols generally gave good results, but incomplete deacetylation was noted when secondary or tertiary alcohols were used under comparable conditions.

3. β-D-Glucosylbenzene methanolate, tetrapropionyl-β-D-glucosylbenzene, and tetrabenzoyl-β-D-glucosylbenzene are described.

STANFORD UNIV., CALIFORNIA RECEIVED JUNE 30, 1947

---

[9] Hurd and Bonner, THIS JOURNAL, **67**, 1972 (1945).

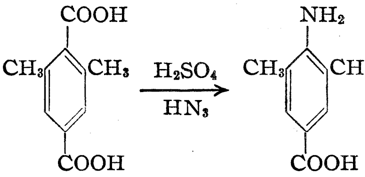
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

The Mechanism of the Schmidt Reactions and Observations on the Curtius Rearrangement[1]

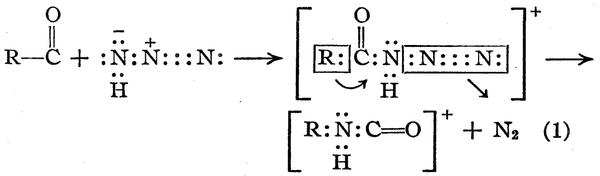
BY MELVIN S. NEWMAN AND HYMAN L. GILDENHORN[2]

During studies on the synthesis of 4-amino-2,6-dimethylbenzoic acid we made an observation which gave us a clue as to the mechanism of the Schmidt reactions[3] and led us to predict that the Curtius rearrangement should be acid catalyzed. In this paper we present mechanisms for the reactions of hydrazoic acid with acids and other compounds and also demonstrate that the Curtius rearrangement is catalyzed by protonic and nonprotonic acids.

The original observation which gave the impetus to this work was the fact that 2,6-dimethylterephthalic acid, I, yielded 4-amino-3,5-dimethylbenzoic acid, II, in the Schmidt reaction. Since the hindered carboxyl group reacted exclusively we were struck by the similarity between this Schmidt reaction and the sulfuric acid esterification of 2,4,6-trimethylbenzoic acid.[4] Since the mechanism for this esterification involves an oxocarbonium ion,[4,5] it seemed logical to propose a similar intermediate for the Schmidt reaction. Accordingly we submit that the Schmidt reaction with acids may proceed by an electrophilic attack of an oxocarbonium ion on nitrogen accompanied by a rearrangement.[6] The function of the sulfuric acid is to convert the acid, RCOOH, into an oxocarbonium ion, R—C⁺=O, or a dihydroxycarbonium ion, $R—C^+(OH)_2$.[7] The carbonium ion then attacks the nitrogen atom in hydrazoic acid which is attached to hydrogen. The unstable initial adduct loses nitrogen as a molecule of N_2 leaving the remaining nitrogen electronically deficient. This in turn sets up forces which cause the R group originally attached to the carbonium–carbon to rearrange to the nitrogen. In this migration the R group carries with it the pair of electrons which originally bound it to the carbonium–carbon. The final resulting electron-deficient complex may either remain as such in the reaction medium or, on dilution with water, react with water to yield the final products.

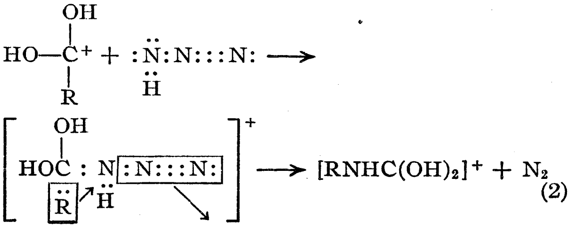


I II



$$R{-}\overset{\displaystyle O}{\overset{\|}{C}} + :\underset{H}{\overset{-}{\ddot{N}}}:\overset{+}{N}:::N: \longrightarrow \left[\boxed{R:}\overset{\displaystyle O}{\overset{\|}{C}}:\underset{H}{\ddot{N}}\boxed{:N:::N:}\right]^+ \longrightarrow \left[R:\underset{H}{\ddot{N}}:C{=}O\right]^+ + N_2 \quad (1)$$

$$[RNHCO]^+ + H_2O \longrightarrow RNH_3^+ + CO_2 \quad (1a)$$



$$HO{-}\underset{R}{\overset{OH}{C^+}} + :\underset{H}{\ddot{N}}:N:::N: \longrightarrow \left[HO\overset{OH}{\underset{\boxed{\ddot{R}}}{C}}:\underset{H}{N}\boxed{:N:::N:}\right]^+ \longrightarrow [RNHC(OH)_2]^+ + N_2 \quad (2)$$

$$RNH\overset{+}{C}(OH)_2 \longrightarrow RNH_3^+ + CO_2 \quad (2a)$$

Evidence supporting the first alternative was obtained by showing that with sulfuric and hydrazoic acids: (A) methyl 2,4,6-trimethylbenzoate, which has been shown to yield $(CH_3)_3C_6H_2C^+{=}O$ ions in the cold in sulfuric acid solution,[8] is converted into mesidine (2,4,6-trimethylaniline) at 0°; (B) 2,4,6-trimethylbenzoic acid which likewise yields $(CH_3)_3C_6H_2C^+{=}O$ ions in the cold in sulfuric acid solution[8] is converted into mesidine, even at 0°; (C) benzoic acid, which yields mainly $C_6H_5C^+(OH)_2$ ions in the cold in sulfuric acid, does not yield aniline in the cold. This evidence indicates that oxocarbonium ions[5] react readily with hydrazoic acid but does not exclude the pos-

---

[1] Part of the material herein presented is contained in the M.S. thesis presented by H. L. G. to the Ohio State University in June, 1947. This also formed the basis for part of the address given by M. S. N. to the Organic Symposium in Boston, Massachusetts, June 12, 1947. Additional work on the Schmidt reaction carried out in the Department of Chemistry of the Massachusetts Institute of Technology by Dr. Conrad Schuerch with Professor E. H. Huntress, executed independently of but concurrently with the present paper, will shortly be presented to THIS JOURNAL.

[2] Present address: Cornell University Medical School, New York, N. Y.

[3] Wolff in Adams "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 309–310. Under the heading of Schmidt reactions are included the reactions of organic compounds with sulfuric and hydrazoic acids.

[4] Newman, THIS JOURNAL, **63**, 2431 (1941).

[5] As a suitable system for the nomenclature of simple carbonium ions we propose that the central electron deficient carbon atom be used as a root and that the attached groups be named as usual. Thus $(CH_3)_3C^+$ would be called trimethylcarbonium ion, $CH_3C^+(OH)_2$ would be called methyl dihydroxy carbonium ion, and $CH_3—C^+{=}O$, methyl oxo carbonium ion. For more complicated carbonium ions a more systematic nomenclature would be necessary.

[6] It is to be understood throughout our discussion that the intermediate stages pictured in formulas have no significance other than to indicate formation and loosening of the bonds involved and to indicate driving forces for the reactions.

[7] The activated form for hydrazoic acid proposed by Hurd in Gilman's "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1938, p. 699, is merely one of the contributing resonance structures and does not require sulfuric acid for its existence. See Hendricks and Pauling, THIS JOURNAL, **47**, 2904 (1925); Langseth and Nielsen, *Phys. Rev.*, **44**, 326 (1933); and Brockway and Pauling, *Proc. Natl. Acad. Sci.*, **19**, 860 (1933).

[8] Newman, Kuivila and Garrett, THIS JOURNAL, **67**, 704 (1945).

sibility that dihydroxycarbonium ions[5] may also react as shown in equation 2. However, the reaction with dihydroxycarbonium ions is undoubtedly much slower. This difference in reactivity of these two types of carbonium ions is strikingly illustrated by the course of the reaction in the case of I. Findings B and C (above) are also to be noted.

The fragments, $(RNHCO)^+$ and $[RNHC(OH)_2]^+$, react with water to yield the amine and carbon dioxide. In some cases, at least, carbon dioxide is evolved directly from the sulfuric acid solution. We noticed that the fragment $(RNHCO)^+$ should also be the species first formed when an isocyanate is dissolved in sulfuric acid. When we added phenyl isocyanate to sulfuric acid there was an immediate evolution of carbon dioxide and aniline was isolated from the reaction mixture.

The reaction pictured in equation (1) takes place at a temperature determined by the ease with which the acid in question yields appreciable quantities of oxocarbonium ion, $R—C^+{=}O$. In the case of 2,6-dimethylterephthalic acid, I, and 2,4,6-trimethylbenzoic acid, a temperature of 10° or lower is sufficient because of the tendency of these acids to undergo complex ionization[8,9] in sulfuric acid according to equation (3).[10]

$$RCOOH + 2H_2SO_4 \rightleftarrows R—C^+{=}O + H_3O^+ + 2HSO_4^- \quad (3)$$

But in the case of benzoic acid and many other acids, a temperature of 35 to 50° is required for the Schmidt reaction (equation 2). Acids of this type ionize according to equation 4 in sulfuric acid.[10]

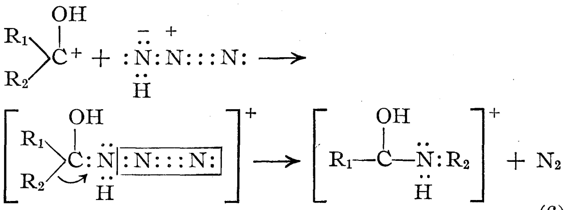
$$RCOOH + H_2SO_4 \rightleftarrows RC^+(OH_2) + HSO_4^- \quad (4)$$

The dihydroxycarbonium ions,[5] $RC^+(OH_2)$, thus formed evidently do not react with hydrazoic acid as easily as do the oxocarbonium ions,[5] $R—C^+{=}O$. The higher reaction temperature required for many Schmidt reactions may be needed to shift the equilibrium shown in equation 5 to the right or to provide a higher temperature for the reaction of the less reactive dihydroxycarbonium ions as shown in equation (2).

$$RC^+(OH)_2 \rightleftarrows R—C^+{=}O + H_2O \quad (5)$$

Should it prove possible to produce appreciable concentrations of oxocarbonium ions from acids of the benzoic type at lower temperatures by altering the reaction medium, we would expect reaction with hydrazoic acid. Thus it may be that reaction at low temperatures of a system with hydrazoic acid to yield nitrogen will prove to be a means of determining the presence of oxocarbonium ions, barring complications involving hydrazoic acid.

In the case of Schmidt reactions with aldehydes and ketones a similar mechanism has been used to account for the products formed.[11] The reaction of the hydroxycarbonium ion[5] formed from aldehydes and ketones in sulfuric acid[10] with hydrazoic acid is shown in equation 6.

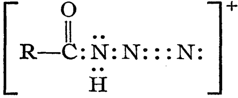


(6)

It should be pointed out that many of these reactions proceed at low temperatures. The complex ion formed loses a proton to yield an amide. In this connection it should prove interesting to compare the migration aptitudes of various groups in the Schmidt reaction with those obtained by Bachmann in the case of the rearrangement of symmetrical pinacols.[12] The qualitative results reported for a few ketones show that the migration aptitudes are roughly what one would expect using data from pinacol rearrangements.[11,12]

Further application of the principles outlined above allow reasonable mechanisms to be postulated for the reaction of a variety of other compounds with hydrazoic acid under acid conditions.[13]

If we return to the first reaction stage of equation 1, it is readily seen that this intermediate,



$$\left[R—\overset{\overset{\displaystyle O}{\|}}{C}:\underset{\underset{\displaystyle H}{..}}{\overset{..}{N}}:N:::N:\right]^+$$

, could likewise be obtained by the addition of a proton to an acid azide. Therefore, since the Schmidt reaction takes place readily at 35 to 50° and most azides decompose in solvents only at higher temperatures, we were led to predict that the Curtius reaction should be acid catalyzed.[14] This prediction was verified by showing that the rate of decomposition of benza-

---

(9) Raymond A. Craig has shown in unpublished work that acid I has an i factor of 2.4. Although the exact i factor for this acid could not be predicted its magnitude is in the region expected if one considers that the i factor of 2,4,6-trimethylbenzoic acid is 4 and that for 2,6-dimethylbenzoic acid is about 3.5. Thus substitution of the 4-methyl group by hydrogen causes a decrease in i factor (see Treffers and Hammett, THIS JOURNAL, **59**, 1708 (1937)). Further substitution of a carboxyl group in the 4-position, as in I, would be expected to produce a further decrease in the i factor.

(10) See Hammett "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 45–56.

(11) See Sanford, Blair, Arroya and Sherk, THIS JOURNAL, **67** 1941 (1945), for a comparison of mechanisms involving hydrazoic acid and hydroxylamine-O-sulfuric acid.

(12) See Wallis in Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 969–970. Dr. P. A. S. Smith, University of Michigan, has informed us that he is studying this problem now.

(13) See the entire chapter of ref. 3 above.

(14) No mention of acid catalysis in the Curtius reaction is made either in the chapter on this reaction by Smith in "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 337, *et seq.*, or in the chapter by Wallis and Lane, *ibid.*, p. 267, *et seq.* Since this article was written, Dr. Smith (see ref. 12) pointed out that Th. Curtius, *J. prakt. Chem.*, [2] **50**, 291 (1894), mentions briefly the decomposition of azides in ether containing hydrogen chloride.

zide in acetic acid was increased progressively by separate additions of chloroacetic, dichloroacetic, trichloroacetic and sulfuric acids. The rate of decomposition of benzazide in dioxane was also markedly increased by hydrogen chloride and by boron trifluoride.[15] We are now studying some quantitative aspects of this catalytic reaction.

Experimental[16]

3,5-Dimethyl-4-aminobenzoic Acid, II.—To a stirred mixture of 4.7 g. of pure 2,6-dimethylterephthalic acid[17] in 20 cc. of 100% sulfuric acid and 15 cc. of chloroform at 25° was added 1.05 g. of sodium azide over a period of two and one-half hours. After stirring for another fifteen minutes, the mixture was poured on ice and neutralized with sodium hydroxide. The chloroform layer was separated and the aqueous layer acidified with dilute hydrochloric acid. The white solid which separated was collected and dried. It weighed 2.3 g. (87% based on azide used) and melted with darkening and decomposition from 240 to 250°. After two recrystallizations from alcohol white crystals of pure II were obtained. The melting point of 251 to 252° with decomposition[18] was determined in a copper block by heating from 30 to 200° in ten minutes and then heating at a rate of 4° per minute.

Anal. Calcd. for $C_9H_{11}O_2N$: C, 65.4; H, 6.7; N, 8.5. Found: C, 64.9, 65.0; H, 6.6, 6.8; N, 8.5, 8.7.

This amino acid was diazotized and coupled with β-naphthol to yield a brilliant orange-red product, m. p. 285.5 to 288° with decomposition, when recrystallized from absolute alcohol (m. p. procedure same as for II).

Anal. Calcd. for $C_{19}H_{16}O_3N_2$: C, 71.2; H, 5.0; N, 8.8. Found: C, 71.0, 71.0; H, 5.2, 5.4; N, 8.8, 8.9.

In another experiment, the diazonium solution was heated with added copper sulfate[19] to yield a small amount of colorless crystals, m. p. 222–224°, of 3,5-dimethyl-4-hydroxybenzoic acid[20] on crystallization from benzene.

Further evidence for the structure of II was obtained in decarboxylation experiments. Our amino acid decarboxylated with difficulty whereas Noyes[17] reported that the isomeric 2,6-dimethyl-4-aminobenzoic acid decarboxylates readily. On heating our acid with a little copper carbonate[21] a small amount of an amine was obtained which formed an acetate, m. p. 170–174° after crystallization from alcohol and from benzene. The melting point of the acetate of *sym-m*-xylidine is 140.5°[22] whereas that of *vic-m*-xylidine melts at 177°.[23]

Schmidt Reactions at Low Temperature.—In two parallel experiments 5 g. of benzoic and 2,4,6-trimethylbenzoic acids were dissolved in 100% sulfuric acid and the solutions were cooled at 0°. Equivalent amounts of sodium azide were added to each solution during one hour. From the former no gas was evolved but from the latter a brisk evolution of nitrogen took place. Carbon dioxide was also formed but no carbon monoxide. After stirring an additional half hour the solutions were poured on ice. From the former a negligible amount of aniline was isolated but from the latter 51% of mesidine was obtained. The mesidine was identified as its formyl derivative, m. p. 175.5–176.5°.[24] We also prepared the 1,3,5-trinitrobenzene addition product of mesidine and found it to form deep reddish-brown needles, m. p. 133.5–134.0°.[25]

Anal. Calcd. for $C_{15}H_{16}O_6N_4$: C, 51.7; H, 4.6; N, 16.1. Found: C, 51.7, 51.9; H, 4.8, 5.0; N, 16.1, 16.2.

Mesidine from Methyl 2,4,6-Trimethylbenzoate.—To a solution of 5.2 g. of methyl 2,4,6-trimethylbenzoate in 40 cc. of concentrated sulfuric acid at 40° was added slowly 1.56 g. of sodium azide. The gases evolved amounted to 1020 cc., almost twice the theory for nitrogen. No tests on this gas were made other than to show it contained carbon dioxide and did not contain carbon monoxide. The reaction mixture was poured on ice and the mesidine formed was extracted from the alkaline solution and distilled. It boiled at 80° at 2 mm. and was isolated in 79% yield (based on azide). From the acid portion of the reaction mixture was recovered 13% of 2,4,6-trimethylbenzoic acid.

Acid Catalyzed Curtius Rearrangements.[26]—Qualitative experiments on the effect of acids on the decomposition of benzazide at 75° were carried out in a 500-cc., three-necked flask fitted with a sealed stirrer and dropping funnel and connected to an azotometer. Various acids were added to the acetic acid to make 50 mole per cent. solutions. The apparatus was equilibrated at 75° and was then pinched off and the flask cooled. A solution of benzazide in 10 cc. of acetic acid was then sucked in through the separatory funnel, followed by a rinse with 5 cc. of acetic acid. The pinchcock was then removed and the flask heated to 75°. The times required for collection of one-half of the total volume of gas evolved were as follows: acetic acid, 20 minutes; chloroacetic acid, 13 minutes; dichloroacetic acid, 10 minutes; trichloroacetic acid, 7 minutes; 2.5 cc. of 100% sulfuric acid in 50 cc. of acetic acid, 10 minutes; 50 mole per cent. sulfuric in acetic, 6 minutes. When benzazide was added to 100% sulfuric acid, an explosion occurred.[15] In three experiments in dioxane, the time for dioxane was 60 minutes, for a solution of 9 g. of boron trifluoride in 50 cc. of dioxane, 7 minutes, and for 2.3 g. of hydrogen chloride in 65 cc. of dioxane, 6 minutes.

Summary

A mechanism for the Schmidt reactions of acids and certain esters with hydrazoic acid in sulfuric acid solution is proposed.

Catalysis of the Curtius rearrangement of benzazide by protonic and non-protonic acids has been demonstrated.

COLUMBUS 10, OHIO RECEIVED AUGUST 1, 1947

---

[15] The following references mention explosions or catalysis of decomposition of azides by acids: *Ber.*, **58**, 1221 (1925); *Ann.*, **469**, 44 (1929); *Helv. Chim. Acta.*, **15**, 935 (1932), **16**, 349 (1933); *Rec. trav. chim.*, **53**, 988 (1934).

[16] All melting points corrected. Microanalyses by W. J. Polglase, O. S. U.

[17] Noyes, *Am. Chem. J.*, **20**, 789 (1898).

[18] Fittig and Brueckner, *Ann.*, **147**, 40 (1868), give a m. p. of 235° and Wheeler and Hoffman, THIS JOURNAL, **44**, 120 (1922), 242° for this compound.

[19] Lassar-Cohn "Arbeitsmethoden," Leipzig, 1923, p. 136.

[20] Thiele and Eichwede, *Ann.*, **311**, 372 (1900). The isomeric 2,6-dimethyl-4-hydroxybenzoic acid melts at 185°, Rabe and Spence, *Ann.*, **342**, 351 (1905).

[21] Fieser "Experiments in Organic Chemistry," D. C. Heath Co., New York, N. Y., 1941, p. 201.

[22] Wroblewski, *Ann.*, **207**, 96 (1881).

[23] Hodgkinson and Limpach, *J. Chem. Soc.*, **77**, 67 (1900).

[24] Hantzsch and Lucas, *Ber.*, **28**, 751 (1895).

[25] Noelthing and Sommerhof, *ibid.*, **39**, 77 (1906), give 120–122° as the melting point of this derivative.

[26] For a study of solvent effect on the rate of Curtius rearrangement of benzazide, see Newman, Lee and Garrett, THIS JOURNAL, **69**, 113 (1947).

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Schmidt Reaction: Experimental Conditions and Mechanism

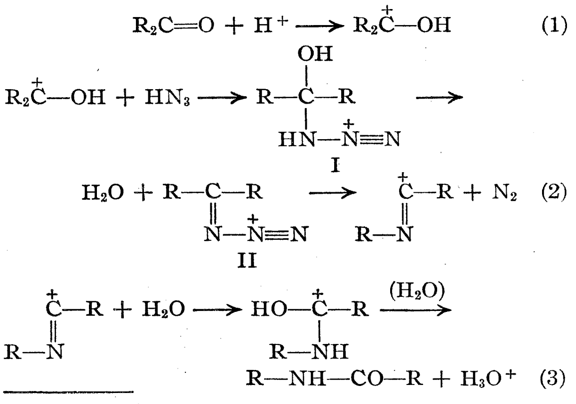
BY PETER A. S. SMITH

In 1944[1] we proposed a mechanism for the amination of the benzene ring by hydrazoic acid involving the radical NH or NH_2^+. On the other hand, we felt that the amination of carbonyl compounds by the same reagents, known as the Schmidt reaction,[2] proceeded by a carbonium ion mechanism,[3] but publication has been withheld pending more complete experimental confirmation. Recently, Newman proposed essentially the same mechanism,[4] and it seemed desirable, therefore, to present our work as it now stands. A review of other mechanisms which have been proposed for the Schmidt reaction through 1945 is available elsewhere.[2] Since then an oxatriazole intermediate has been suggested.[5]

The stoichiometry of the Schmidt reaction is represented by

$$R{-}CO{-}R + HN_3 = R{-}NH{-}CO{-}R + N_2$$

The reaction is carried out with the aid of at least equimolar quantities[2] of catalysts which are strong Lewis acids.[6] The mechanism now proposed consists of the formation of a carbonium ion from the carbonyl group and the acid catalyst; this is the initial step recently proposed by Sanford, Blair, Arroya and Sherk[7] for an otherwise somewhat different mechanism. The carbonium ion and hydrogen azide form a transitory intermediate (I), which loses water and undergoes *trans* rearrangement with loss of nitrogen, as detailed below.



$$R_2C{=}O + H^+ \longrightarrow R_2\overset{+}{C}{-}OH \qquad (1)$$

$$R_2\overset{+}{C}{-}OH + HN_3 \longrightarrow R{-}\underset{HN-\overset{+}{N}\equiv N}{\overset{OH}{\overset{|}{\underset{|}{C}}}}{-}R \longrightarrow$$

I

$$H_2O + R{-}\underset{N-\overset{+}{N}\equiv N}{\underset{\|}{C}}{-}R \longrightarrow \underset{R-N}{\underset{\|}{\overset{+}{C}}}{-}R + N_2 \qquad (2)$$

II

$$\underset{R-N}{\underset{\|}{\overset{+}{C}}}{-}R + H_2O \longrightarrow HO{-}\underset{R-NH}{\underset{|}{\overset{+}{C}}}{-}R \xrightarrow{(H_2O)} R{-}NH{-}CO{-}R + H_3O^+ \qquad (3)$$

It can be seen that this mechanism implies: (1) that the occurrence of the Schmidt reaction is dependent upon both the extent to which the carbonyl compound undergoes step (1) and the polarizing power of the particular carbonium ion in step (2); and (2), that insofar as the intermediate (II) has a finite existence, there should be a geometrical effect influencing the apparent "migration aptitudes" of the two groups in unsymmetrical ketones. In this paper a series of Schmidt reactions are described in which the carbonyl compound, the acid catalyst, and the solvent were varied in order to test the first conclusion. The investigation of the second conclusion by determining the ratios of the isomeric amides formed from unsymmetrical ketones is now in progress, and will be the subject of a future communication.

The occurrence and rate of the Schmidt reaction should depend on the equilibrium concentration of carbonium ion produced by step (1) if step (2) is rate-determining. As a first approximation, one may say that the more basic the carbonyl compound and the more acidic the reaction medium, the faster the reaction will go. Our experiments with nineteen carbonyl compounds of different types in solvents of varying basicity and with catalysts of different acid strength bear this out. Only a qualitative agreement would be expected, however, since each carbonium ion will of course have its own specific reaction rate in step (2).

The available data on the basic strengths of carbonyl compounds[8] permit as a rough generalization the assumption of the following order: cycloalkyl ketones > dialkyl ketones > aryl alkyl ketones > diaryl ketones > carboxylic acids. Cycloalkyl and dialkyl ketones were found to undergo the Schmidt reaction even in such basic solvents as water, alcohols, and ethers, but with the less basic types of carbonyl compounds the use of these solvents inhibited the reaction largely or completely.[9] Catalysts which are strong enough acids to bring about the Schmidt reaction with the more basic carbonyl compounds may not be strong enough to be effective with the less basic ones. Thus trichloroacetic acid was found to be an efficient catalyst for alkyl and aryl alkyl ketones, but it was only partially effective on diaryl ketones, and failed completely with all acids but formic. The carboxyl group of trichloroacetic acid itself does not show a measurable tendency to

---

[1] R. N. Keller and P. A. S. Smith, THIS JOURNAL, **66**, 1122 (1944).

[2] *Cf.* H. Wolfe, "The Schmidt Reaction," in R. Adams, "Organic Reactions," Vol. III, John Wiley and Sons, New York, N. Y., 1946.

[3] P. A. S. Smith, Thesis, "Reaction Mechanisms Involving the Radical NH," University of Michigan, 1944.

[4] (a) M. S. Newman, Organic Chemistry Symposium, Boston, Mass., 1947; (b) M. S. Newman and H. Gildenhorn, THIS JOURNAL, **70**, 317 (1948).

[5] A. A. Morton, "The Chemistry of Heterocyclic Compounds," McGraw-Hill Book Co., New York, N. Y., 1946, p. 371.

[6] G. N. Lewis, "Valence and the Structure of Atoms and Molecules," Chemical Catalog Co., New York, N. Y., 1923, p. 142.

[7] J. K. Sanford, F. T. Blair, J. Arroya and K. W. Sherk, THIS JOURNAL, **67**, 1941 (1945).

[8] *Cf.* W. Gordy and S. C. Stanford, *J. Chem. Phys.*, **8**, 170 (1940).

[9] *Cf.* the published observation[10] that the use of ether in place of chloroform reduces the yield of aniline from benzoic acid from 85% to 24%.

[10] L. H. Briggs, G. C. De Ath and S. R. Ellis, *J. Chem. Soc.*, 61 (1942).

form carbonium ions.[11] It is thus understandable that no catalyst was found strong enough to bring about the Schmidt reaction with it; and trichloroacetic acid is accordingly a satisfactory solvent in which to carry out the Schmidt reaction on other carbonyl compounds, using sulfuric acid as the catalyst if necessary. Trifluoroacetic acid has been reported[12] to be similarly resistant.

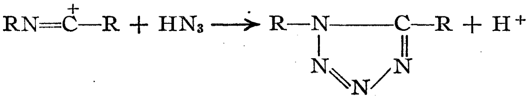
Our experiences lead us to some recommendations about the choice of experimental conditions. In general, the least strongly acid medium which will bring about reaction in a reasonable time gives the purest products. Concentrated aqueous hydrochloric acid has been found to be a useful solvent and catalyst for the reaction with aliphatic ketones; its use minimizes the formation of both tars and tetrazoles. Benzylacetone, for example, gave an 87% yield of mixed amides (consisting of 5% of N-methylphenylpropionamide and 95% of N-(β-phenylethyl)-acetamide when treated with sodium azide in hydrochloric acid, whereas with sulfuric acid[10] a yield of only 62% has been reported. Solutions of hydrogen chloride in alcohol[13] or dioxane are useful with relatively insoluble ketones, but most aliphatic ketones dissolve sufficiently in aqueous acid. While aqueous hydrochloric acid is not strong enough to bring about the Schmidt reaction on the less basic aryl alkyl ketones, the more acid medium provided by molten trichloroacetic acid gives excellent results. Acetophenone, β-acetonaphthone and α-tetralone gave yields of N-aryl amides of 89, 95 and 85%, respectively, whereas yields of 77,[14] 70 and 70%[14] were given by the unnecessarily strong catalyst sulfuric acid; in addition, purification of the products may be more difficult when sulfuric acid is used. Sulfuric acid appears to be the best catalyst for the even less basic diaryl ketones and carboxylic acids, but the use of only two molar equivalents of sulfuric acid with one of the carbonyl compound in trichloroacetic acid as a solvent provides a homogeneous and fluid reaction medium and lessens the danger of sulfonation. Work at present under way indicates that strong aprotic acids, such as aluminum chloride, in inert solvents favor tetrazole formation.

Among numerous applications of the mechanism here presented, which cannot be reviewed here, it is interesting to consider Götzky's[15] observation that benzhydrylidene diazide gives benzanilide in 98% yield when treated with 70% sulfuric acid. This reaction may be formulated in an analogous manner

$$\mathrm{Ar_2C(N_3)_2} \xrightarrow{(\mathrm{H^+})} \mathrm{HN_3} + \mathrm{Ar_2C{=}N{-}\overset{+}{N}{\equiv}N} \longrightarrow$$

$$\mathrm{N_2} + \mathrm{Ar{-}N{=}\overset{+}{C}{-}Ar} \xrightarrow{(\mathrm{H_2O})} \mathrm{Ar{-}NH{-}CO{-}Ar} + \mathrm{H_3O^+}$$

The imino-carbonium ion[16] resulting from step (2) may give rise to products other than amides in step (3) if it encounters a species other than water capable of forming a permanent attachment. If it should encounter a second molecule of hydrogen azide, a tetrazole would be produced



If a large quantity of alcohol is present, an imido-ester results instead of an amide. The same type of imino-carbonium ion probably arises[17] in the Beckmann rearrangement of oximes, and it is significant that tetrazoles and imido-esters result from the Beckmann rearrangement also when it is carried out in the presence of azide or alcohols, respectively. Most of the catalysts used in the Schmidt reaction cannot generate an imino-carbonium ion from amides and, accordingly, amides, once formed, do not react further with hydrogen azide. It is expected that we will be able to present a more detailed treatment of tetrazole formation at the completion of present work.

In view of the additional evidence presented by Newman and Gildenhorn, the carbonium ion mechanism seems to be fairly well established. A quantitative study of the rate of the Schmidt reaction as influenced by substrate, solvent, and catalyst is nevertheless felt to be a suitable addition to this work, and has recently been begun.

It was felt of interest to confirm the report[10] that methyl azide does not take part in a Schmidt reaction as does hydrogen azide. No N-methyl products could be detected in experiments with acetophenone, and the principal effect of mixtures of ketones and acids on alkyl azides appeared to be catalysis of their decomposition according to other paths.

Experimental

In the accompanying table the results of a number of Schmidt reactions are summarized. In the method usually employed, powdered sodium azide was added to the mixture of solvent, catalyst, and carbonyl compound. In certain experiments, indicated by a footnote, benzene solutions of hydrogen azide were used. In many experiments where the yield of product would be of little significance or preparative value, yields were not determined. These experiments are listed just before the table, or, for carbonyl compounds which do appear in the table, are mentioned in footnotes. Nitrogen evolution was used as the criterion of reaction in these cases, and the results were confirmed by a qualitative test for the products. All reactions were run at room temperature unless noted otherwise by a footnote. The organic chemicals used were Eastman Kodak Co. products, except monochloro- and trichloroacetic acids, which were Mallinckrodt products, and α-tetralone, phenylacetone, benzylacetone, and cyclohexanone-α-carboxylic ester, which were synthesized

---

[11] L. P. Hammett and A. J. Deyrup, THIS JOURNAL, **55**, 1900 (1933); M. Ussanovich and V. Tartakovskaya, *J. Gen. Chem.* (*U. S. S. R.*), **16**, 1987 (1946); T. Sumarokova and Z. Grishkun, *ibid.*, **16**, 1991 (1946).

[12] H. Gilman and R. G. Jones, THIS JOURNAL, **65**, 1458 (1943).

[13] The use of alcohols gives rise to imido-esters.

[14] L. H. Briggs and G. C. De Ath, *J. Chem. Soc.*, 456 (1937).

[15] S. Götzky, *Ber.*, **64**, 1555 (1931).

[16] We are pleased to adopt the nomenclature for carbonium ions suggested by Newman and Gildenhorn, ref. 4.

[17] W. A. Waters, "Physical Aspects of Organic Chemistry," D. Van Nostrand Co., New York, N. Y., 1936, p. 354, *et seq.*

TABLE I

YIELDS AND PRODUCTS OF SOME SCHMIDT REACTIONS

Carbonyl compd.	Solvent	Cat.	Product	Yield, %
Cyclohexanone	H_2O[b]	HCl	ε-Caprolactam	63
Cyclohexanone	CH_3COOH[c]	HBr	ε-Caprolactam	56
Cyclohexanone-α-carboxylic ester	H_2O	HCl	α-Aminopimelic acid	20
Benzylacetone	H_2O	HCl	Mixed amides[d]	87
Acetoacetic ester	H_2O	HCl	Glycine·HCl	56
α-Tetralone	Cl_3CCOOH[a]		Homodihydrocarbostyryl[e]	85
Acetophenone	CH_3COOH[f]	HBr	Acetanilide	21
Acetophenone	Cl_3CCOOH[a]		Acetanilide	89
Acetophenone	$C_6H_5NO_2$[g]	$AlCl_3$	1-Phenyl-5-methyltetrazole	42[h]
α-Acetonaphthone	Cl_3CCOOH[a]		α-Acetnaphthalide	90
β-Acetonaphthone	Cl_3CCOOH[a,i]		β-Acetnaphthalide	95
β-Acetonaphthone	H_2SO_4		β-Acetnaphthalide	55
β-Acetonaphthone	$C_6H_5NO_2$[j,g]	$AlCl_3$	1-β-Naphthyl-5-methyltetrazole	73[h]
β-Acetonaphthone	$CHCl_3$	$POCl_3$	β-Acetnaphthalide	42
Benzophenone	Cl_3CCOOH[a,i]		Benzanilide	59
Benzophenone	Cl_3CCOOH[a]	H_2SO_4	Benzanilide	99
Fluorenone	Cl_3CCOOH[a,k]		Phenanthridone	55
Fluorenone	H_2SO_4		Phenanthridone	99[l,m]
m-Toluic acid	Cl_3CCOOH	H_2SO_4	*m*-Toluidine	43

[a] Temperature between 55 and 65°. [b] Also reacts vigorously in dioxane or ether solution with hydrogen chloride as catalyst. [c] No reaction in acetic acid alone; moderate reaction in acetic acid with trichloroacetic acid as catalyst and in monochloroacetic acid alone; moderate to vigorous reaction in dichloroacetic acid alone and in trichloroacetic acid alone. [d] Consisted of N-β-phenylethylacetamide, 95%, and N-methylphenylpropionamide, 5%, as determined from hydrolysis products. [e] As its trichloroacetic acid salt. [f] No reaction in water or dioxane with hydrogen chloride catalyst. [g] Benzene solution of hydrogen azide used. [h] Based on hydrogen azide; these two preparations will be described in a forthcoming communication. [i] No reaction in dioxane with hydrogen chloride catalyst. [j] Almost no reaction in nitrobenzene with stannic chloride catalyst. [k] No reaction in dioxane, ethanol, or acetic acid with hydrogen chloride or bromide catalyst. [l] This experiment performed by Mr. Jerome Horwitz. [m] A yield of 70% has been obtained by L. P. Walls, *J. Chem. Soc.*, 1405 (1935), by adding an aqueous solution of sodium azide to fluorenone dissolved in sulfuric acid.

by standard procedures. Yields are reported for products purified only to the point where their identity could be definitely established by comparison, usually by mixed melting point, with known samples; in other cases, the products were in turn converted into identifiable derivatives. Following the tabulation, a more detailed description of selected typical experiments is given.

The following carbonyl compounds were treated with sodium azide in the solvents and with the catalysts named, without determining the yields: Methyl ethyl ketone in water or dioxane with hydrogen chloride catalyst reacted at a moderate rate; phenylacetone in aqueous hydrochloric acid reacted vigorously; formic acid alone did not react, nor did it in aqueous hydrochloric acid, but with trichloroacetic acid catalyst it reacted at a moderate rate; acetic acid did not react alone nor with trichloroacetic acid catalyst, but reacted vigorously with hydrogen bromide catalyst; benzoic acid did not react with aqueous hydrochloric acid, but reacted very slowly in molten trichloroacetic acid alone, and moderately rapidly in trichloroacetic acid with sulfuric acid catalyst; molten chloroacetic acid alone reacted very slowly, dichloracetic acid alone reacted slowly, and trichloroacetic alone or with sulfuric acid catalyst reacted not at all.

β-Acetnaphthalide from β-Acetonaphthone: A. With Trichloroacetic Acid.—To a solution of 1.70 g. (0.01 mole) of β-acetonaphthone in 15 g. of trichloroacetic acid at 60° was added 1.0 g. (0.015 mole) of powdered sodium azide all at once. After four hours at 60° with occasional stirring, the mixture was diluted with 75 cc. of water and alkalized with 10 cc. of concd. ammonium hydroxide. The nearly white product was filtered from the cooled solution and washed with water and warm petroleum ether; wt. 1.75 g. (95%), m.p. 125–130°. Recrystallization of a portion from aqueous alcohol gave snow-white crystals, m.p. 132–134° (lit.[18], 132°).

B. With Sulfuric Acid.—To a solution of 1.70 g. of β-acetonaphthone in 20 cc. of concd. sulfuric acid overlaid with 10 cc. of chloroform was added with stirring 0.9 g. of sodium azide in small portions over a five-hour period. When further addition caused no fresh gas evolution, the pasty mixture was poured on ice, alkalized with concd. ammonium hydroxide, and the organic material was taken up in ether. Evaporation of the extracts left a waxy solid, which was successively extracted with petroleum ether and recrystallized from benzene–petroleum ether. There was obtained 1.02 g. (55%) of impure β-acetamidonaphthalene; the filtrates yielded 0.17 g. (10%) of recovered β-acetonaphthone.

ε-Caprolactam from Cyclohexanone.—To a solution of 2.0 g. of cyclohexanone (0.02 mole) in 10 cc. of concd. hydrochloric acid at room temperature was added 2.0 g. (0.031 mole) of sodium azide in portions as fast as the vigor of the reaction permitted. After standing for several hours, the mixture was distilled to dryness *in vacuo*, and the residue taken up in a little water and alkalized with excess 50% sodium hydroxide solution. The yellow oil which separated was extracted with three portions of chloroform, and the extracts washed with a very little water and evaporated to a mass of crystals; wt. 1.3 g. (63%). Recrystallization from benzene–petroleum ether produced a colorless product, m.p. 63–64° (lit.,[19] 68–70°), with very little loss.

Acetophenone in Acetic Acid with Hydrogen Bromide.—To a solution of 2.4 g. of acetophenone in 15 cc. of 30% hydrogen bromide in acetic acid was added with stirring 1.0 g. of sodium azide in portions over thirty minutes. When the gas evolution subsided, the mixture was poured on ice, neutralized with ammonium hydroxide, and the excess acetophenone was removed by steam distillation. From the cooled residue was obtained 0.18 g. of acetanilide, and, on treatment with bromine water, 0.40 g. of *p*-bro-

---

(18) C. Liebermann and F. Scheiding, *Ann.*, **183**, 267 (1876).

(19) O. Wallach, *ibid.*, **312**, 187 (1900).

moacetanilide, m.p. 164–165° (lit.,[20] 167–168°); total yield 21%, based on sodium azide.

Phenanthridone from Fluorenone: A. With Trichloroacetic Acid.—On treatment with the same quantities of reagents under the same conditions as described above for β-acetonaphthone, 1.80 g. of fluorenone yielded 1.08 g. (56%) of crude phenanthridone; m.p. *ca.* 220° with sublimation, and 0.86 g. (48%) of crude recovered fluorenone.

B. With Sulfuric Acid.[21]—To a solution of 1.80 g. of fluorenone in 20 cc. of concd. sulfuric acid at room temperature was added with stirring 1.0 g. of sodium azide in portions over half an hour. The mixture was then poured on ice, and the precipitated phenanthridone was filtered off and washed with water and petroleum ether; wt. 1.93 g. (99%), m.p. 290–293° with sublimation (lit.,[22] 293°).

Methyl Azide and Acetophenone.—Solutions of methyl azide in petroleum ether or chloroform were prepared from methyl sulfate and 3.25 g. of sodium azide, according to the method of Dimroth and Wislicenus[23]; the methyl azide was passed in the gas phase through a long tube of soda-lime and potassium hydroxide pellets to remove completely any trace of hydrogen azide. The purity of the product so obtained was confirmed by testing liberal portions with alcoholic silver nitrate and with ferric chloride solution; no opalescence of silver azide was obtained with the first reagent, and no color developed with the second. Mixtures of the methyl azide solutions with 5 cc. of acetophenone and 10 cc. of concd. sulfuric acid foamed vigorously at room temperature. When the reaction subsided, the mixture was poured on ice, and the organic material extracted with ether and steam-distilled. Treatment of the residue in the still-pot with bromine water gave 0.1 to 0.28 g. of *p*-bromoacetanilide in different runs (0.9–2.6%), m.p. 166–168° (lit.,[23] 168°). In an experiment in which aluminum chloride in nitrobenzene was used in place of sulfuric acid, nitrogen evolution was vigorous, but only resinous products were isolated.

Homodihydrocarbostyryl from α-Tetralone.—A mixture of 1.46 g. (0.01 mole) of α-tetralone, 15 g. of trichloroacetic acid, and 1.0 g. (0.015 mole) of sodium azide was heated at 60° for six hours. Pouring the mixture into *ca.* 75 cc. of cold water deposited a brownish, crystalline solid; wt. 2.75 g. (85%), m.p. 109–113°, after washing with water and petroleum ether. Recrystallization from benzene gave an analytical sample; rectangular prisms, m.p. 126°, insol. water and petroleum ether, sol. other organic solvents.

Anal.[24] Calcd. for $C_{10}H_{11}ON{\cdot}Cl_3CCOOH$: C, 44.45; H, 3.70; Cl, 32.85. Found: C, 44.61; H, 3.88; Cl, 32.67.

This substance could be titrated sharply to a methyl orange end-point, and then left as residue pure homodihydrocarbostyryl, m.p. 139–141° (lit.,[14] 141°), with only mechanical losses. The same addition product was produced at room temperature when equimolar amounts of the components were mixed in concentrated benzene solution.

An attempt to prepare this addition product from α-tetralone oxime by causing it to rearrange in trichloroacetic acid at 60° produced only **α-tetralone oxime trichloroacetate**, silky needles m.p. 113–115°, insol. water and petroleum ether, sol. other organic solvents. Titration with sodium hydroxide to a methyl orange end-point gave an equivalent weight of 323 (calcd. 324.5) and regenerated α-tetralone oxime, m.p. 101–102° (lit.,[25] 102.5–103.5°), with only mechanical losses.

Summary

1. A qualitative study of the effect of solvents and catalysts on the Schmidt reaction has been made.

2. The occurrence of the Schmidt reaction appears to be governed by the acidity of the medium as determined by the acid strength of the catalyst and the basic strength of the solvent, and by the basic strength of the carbonyl compound undergoing the reaction.

3. Some improvements in carrying out the Schmidt reaction are suggested.

4. The factors influencing the Schmidt reaction are correlated with a carbonium ion mechanism.

ANN ARBOR, MICHIGAN RECEIVED AUGUST 22, 1947

---

(20) H. Hübner, *Ann.*, **209**, 355 (1881).

(21) See *footnote l in table.*

(22) C. Graebe and C. A. Wander, *Ann.*, **276**, 248 (1893).

(23) O. Dimroth and W. Wislicenus, *Ber.*, **38**, 1573 (1905).

(24) Microanalysis by Micro-Tech. Laboratories, Skokie, Illinois.

(25) F. S. Kipping and A. Hill, *J. Chem. Soc.*, **75**, 151 (1899).

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

Ketoxime-O-sulfonic Acids[1]

BY PETER A. S. SMITH

Recently,[2] Sanford, Blair, Arroya and Sherk reported on the reaction of hydroxylamine-O-sulfonic acid with ketones, finding that aryl alkyl ketones yield the same amide as obtained from the Beckmann rearrangement of the corresponding oxime, and that aliphatic ketones yield only the oximes. An explanation of these facts was suggested involving the addition of hydroxylamine-O-sulfonic acid to the carbonyl group, subsequent loss of sulfuric acid, and final rearrangement of the organic fragment either to an oxime or to an amide. A different course for this reaction was suggested to the writer by an observation by Sommer, Schulz and Nassau[3] that salts of ketoxime-O-sulfonic acids can be made by the interaction of ketones with neutralized aqueous solutions of hydroxylamine-O-sulfonic acid.

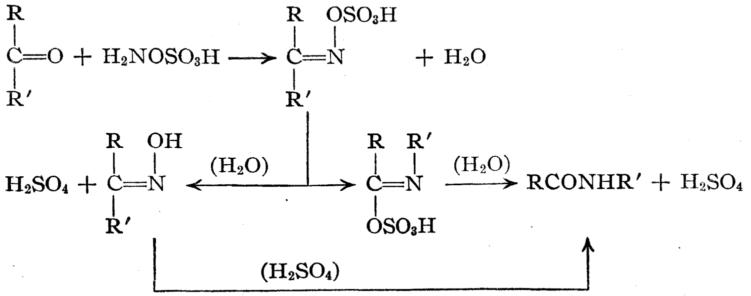
If the initial reaction between a ketone and hydroxylamine-O-sulfonic acid is the elimination of water to form a ketoxime-O-sulfonic acid, then an oxime might arise by hydrolysis of the sulfonyl group, or an amide might arise by direct rearrangement of the sulfonic acid, as indicated below. Some amide might also arise by the Beckmann rearrangement of the oxime under the influence of the sulfuric acid produced by the hydrolysis.

---

[1] Presented before the Division of Organic Chemistry at the 111th meeting of the American Chemical Society, Atlantic City, April, 1947.

[2] J. K. Sanford, F. T. Blair, J. Arroya and K. W. Sherk, THIS JOURNAL, **67**, 1941 (1945).

[3] F. Sommer, O. F. Schulz and M. Nassau, *Z. anorg. allgem. Chem.*, **147**, 142 (1925).



Continuing our studies[4] on derivatives of hydroxylamine-O-sulfonic acid to investigate this possibility, we have prepared the potassium ketoxime-O-sulfonates of cyclopentanone, cyclohexanone, heptanone-2, acetoacetic ester, phenylacetone, acetophenone, β-acetonaphthone, and α-tetralone. Because of the structural similarity to the O-arylsulfonyl ketoximes, $R_2C{=}NOSO_2Ar$, it was also felt to be of interest to compare the properties of these two classes of compounds.

The potassium ketoxime-O-sulfonates were found to be well-crystallized substances, indefinitely stable when pure and dry. Their solubility in water varies from large to very small, and all are somewhat soluble in boiling alcohol. All were found to oxidize hydriodic acid semiquantitatively, but with varying ease. The salts were caused to decompose by heating, either alone, in the presence of alcoholic alkali, or in the presence of moist or anhydrous hydrogen chloride. The aliphatic ketoxime-O-sulfonates yielded only the oximes when warmed with acid if water was present. In the complete absence of water, the derivatives of heptanone-2, cyclohexanone, and phenylacetone gave rise to basic products, which for the latter two ketones were found to be octahydrophenazine and 2,5-diphenyl-3,6-dimethylpyrazine, respectively; the derivatives of cyclopentanone and acetoacetic ester gave only tars. The aryl alkyl ketoxime-O-sulfonates gave amides in good yield when dry or nearly so, but increasing amounts of water favored hydrolysis to oxime and ketone.

The initial formation of ketoxime-O-sulfonic acids in the reaction of hydroxylamine-O-sulfonic acid with ketones is thus supported by two observations. The structure of the amides obtained from the few unsymmetrical ketones which have been subjected[2] to the reaction corresponds to the configuration of the oxime obtained by treatment of the ketone with hydroxylamine, strongly suggesting that here, too, *cis–trans* isomerism comes into play. That the ketoxime-O-sulfonic acids have the properties required of an intermediate in this reaction is shown by the observations reported in this paper that they can undergo hydrolysis to oximes and rearrangement to amides, and that the relative tendency to follow these respective courses is for different types of ketones the same as that observed in the direct reaction of hydroxylamine-O-sulfonic acid with ketones.

Neber and co-workers[5] have studied the behavior of O-arylsulfonyl ketoximes. These compounds give rise to amides, α-aminoketones, or pyrazines, according to the conditions to which they are exposed. We have found that ketoxime-O-sulfonates decompose to give qualitatively the same products under similar conditions; the reactions are usually not as clean, however. The yields of pyrazines obtained by treating ketoxime-O-sulfonates with alcoholic alkali were considerably lower than those obtained from the arylsulfonyl ketoximes. The ketoxime-O-sulfonates might nevertheless be useful for preparing pyrazines in cases where the corresponding arylsulfonyl ketoximes are too unstable to be handled easily; the isolation of some of the latter compounds is rendered inconvenient by the ease with which they deflagrate.

The mechanism by which pyrazines arise in the decomposition of ketoxime-O-sulfonates is not entirely clear, but is presumably similar to that which has been elucidated for the analogous reaction of arylsulfonylketoximes.[5] No evidence for the formation of a pyrazine from cyclopentanoxime-O-sulfonic acid could be obtained, which is reminiscent of the reported failure of α-chlorocyclopentanone to yield a pyrazine when treated with alcoholic ammonia,[6] although α-chlorocyclohexanone gave octahydrophenazine in 25% yield under this treatment.

Experimental

The potassium ketoxime-O-sulfonates were prepared by adding one-tenth equivalent of potassium carbonate or acetate in concentrated aqueous solution to an aqueous or methanolic solution of one-tenth equivalent each of hydroxylamine-O-sulfonic acid and ketone in an ice-bath. It is necessary first to allow sufficient time, usually about one minute, for the latter two reagents to react, as evidenced by the formation of a homogeneous solution. If this is not done, potassium hydroxylamine-O-sulfonate is obtained, which deflagrates with violence during subsequent operations. The desired salts crystallized on scratching, and were filtered and washed with water and/or methanol, followed by ether or benzene. Those salts which are appreciably soluble in water could not be freed of potassium sulfate by washing. Where purification could not be accomplished by recrystallization from water or alcohol, advantage was taken of the fact that potassium ketoxime-O-sulfonates as first formed are in highly supersaturated solution, but the contaminating potassium sulfate is present as a suspension in the alcoholic solution. Rapid filtration at this stage through a bed of Filter-Cel accomplished the desired purification. For the recrystallizations, it was found best to filter the hot solutions through

---

(4) R. N. Keller and P. A. S. Smith, THIS JOURNAL, **68**, 899 (1946).

(5) P. W. Neber and A. Friedolsheim *Ann.*, **449**, 109 (1926); P. W. Neber and H. Uber, *Ann.*, **467**, 52 (1928); P. W. Neber and A. Burgard, *Ann.*, **493**, 281 (1932); P. W. Neber and G. Huh, *Ann.*, **515**, 283 (1935); P. W. Neber, A. Burgard and W. Thier, *Ann.*, **526**, 277 (1936).

(6) M. Godchot and M. Mousseron, *Bul. soc. chim.*, [4] **51**, 360 (1932).

TABLE I

PROPERTIES OF POTASSIUM KETOXIME-O-SULFONATES

Parent ketone	Formula of sulfonate	K_2SO_4, %		Iod. eq. wt.		M. p., °C.	Yield, %	Solubility		Prod. from dry HCl treatment
		Calcd.	Found	Calcd.	Found			H_2O	EtOH	
Heptanone-2[a]	$C_7H_{14}O_4NSK$	35.20	36.05	123.5	139	180–185	55	v. s.	s. s.	Unident. basic oil b. p. 245° (735 mm.)
Acetoacetic ester[b]	$C_6H_{10}O_6NSK$	33.10	33.32	167.5	151	164–166	55	s.	i.	Unident. dark oil
Cyclopentanone[b]	$C_5H_8O_4NSK$	40.05	40.65	108.7	111	169 dec.	56	s.	i.	Tar[c]
Cyclohexanone[a,b]	$C_6H_{10}O_4NSK$	37.68	37.07	115.7	120	d. 155–180	52	s. s.	s. s.	Octahydrophenazine; m. p. 108–109°, >7%[d]
Phenylacetone[a]	$C_9H_{10}O_4NSK$	32.55	32.75	133.5	123	170–185	theo. 2	s. s.	i.	2,5-DiPh-3,6-di-Me-pyrazine, 14%[e]
Acetophenone[a,b]	$C_8H_8O_4NSK$	34.38	33.75			215–220	47	s.	s. s.	Acetanilide, 77%[f]
β-Acetonaphthone[a]	$C_{12}H_{10}O_4NSK$	29.70	29.35	151.7	145	205–210	40	i.	i.	β-Acetnaphthalide, m. p. 132–133°, 87%[g]
α-Tetralone[a]	$C_{10}H_{10}O_4NSK$	31.18	31.45	139.5	158	173–175	67	v. s.	i.	Largely α-tetralone, + <12% α-naphthylamine[h]

[a] Prepared from potassium acetate. [b] Prepared from potassium carbonate. [c] In the presence of moisture, cyclopentanoxime, 55%. [d] In the presence of moisture, cyclohexanoxime, 89%. When treated with alc. NaOH, only unident. oils produced. [e] When treated with alc. NaOH at T. > 40°, and worked up after Neber's[5] directions for *p*-tolylphenylacetoxime, there was produced 56% of 2,5-di-Ph-3,6-di-Me-pyrazine, m. p. 125–128°, or 22% of the acetate of 1-phenyl-1-aminoacetone diethyl acetal, m. p. 145–147°. [f] In the presence of moisture, 36% of acetophenoxime plus a smaller amount of acetanilide plus a little acetophenone. The dry salt heated alone gave 47% of acetanilide, m. p. 112–114°. [g] In the presence of several equivs. of water, β-acetonaphthoxime, 85%, plus a little β-acetonaphthone. [h] When heated in dry pyridine, a little dihydrohomocarbostyryl, m. p. 143–144°, was formed. When heated with alc. NaOH, only dark, nonbasic oils were formed.

a preheated, sintered-glass filter with the aid of compressed air, because of the sharp temperature gradient of the solubilities in the neighborhood of the boiling point. Yields on recrystallization were generally about 50–60%.

The hydroxylamine-O-sulfonic acid was prepared from hydroxylamine sulfate and chlorosulfonic acid.[3] α-Chlorocyclohexanone was obtained from Farchan Laboratories; heptanone-2, phenylacetone, α-tetralone, and cyclohexanoxime were prepared by standard procedures; and the remainder of the organic chemicals used were Eastman Kodak Co. products.

The potassium ketoxime-O-sulfonates were analyzed for potassium by fuming to dryness with sulfuric acid, and in addition were titrated iodometrically. The equivalent weights given by the latter determination are subject to an error of as much as 10%, because of the long time, usually about forty-eight hours, required for complete reaction with the iodide.

In the accompanying table are listed the principal properties of the potassium ketoxime-O-sulfonates prepared.

Rearrangement of Ketoxime-O-sulfonates.—Approximately 4 *N* solutions of hydrogen chloride in dioxane were prepared from tank hydrogen chloride dried successively over sulfuric acid and phosphorus pentoxide, and dioxane freshly distilled from sodium. Mixtures of the ketoxime-O-sulfonates and several equivalents of the acid solutions were heated near the boiling point for periods of from ten minutes to an hour, after which they were treated with water and worked up for the neutral, acidic and basic components. The products obtained are listed in the accompanying table; products obtained from other ways of decomposing the compounds are described in footnotes to the table.

Octahydrophenazine.—The product, m. p. 108–109°, which was extracted with some difficulty from the tars obtained as above from potassium cyclohexanoxime-O-sulfonate was identified with the octahydrophenazine, m.p. 107–108°, obtained in 25% yield by Godchot and Mousseron[6] by the action of ammonia on α-chlorocyclohexanone. Because these authors neglected to publish analytical data either for octahydrophenazine or its picrate, we repeated their preparation. The product was obtained in 37% yield using a six-day reaction time and a rapid addition of ammonia; separation of the product from tar was facilitated by precipitation from the acidified reaction mixture with ammonia instead of alkali, and recrystallizing alternately from acetone and petroleum ether, in which the tar is respectively very soluble and almost insoluble. *Anal.*[7] Calcd. for $C_{12}H_{16}N_2$: C, 76.60; H, 8.58; N, 14.92, mol. wt., 188. Found: C, 76.60; H, 8.55; N, 14.65; mol. wt. (ebullioscopic in benzene[8]), 192, 193.

A picrate was obtained as yellow prisms from ethanol; m. p. 162–163°. *Anal.*[7] Calcd. for $C_{12}H_{16}N_2{\cdot}2C_6H_3O_7N_3$: C, 44.60; H, 3.42; N, 17.35. Found: C, 44.58; H, 3.55; N, 16.83, 16.77. Godchot and Mousseron reported m.p. 163–164° for a "monopicrate" for which they gave no analysis.

A chloroaurate was obtained as tiny yellow needles from water; m.p. 145–146° after recrystallization from absolute ethanol. *Anal.*[7] Calcd. for $C_{12}H_{16}N_2{\cdot}HAuCl_4{\cdot}C_2H_5OH$: C, 29.28; H, 4.04; Au, 34.4. Found: C, 28.55; H, 4.14; Au, 36.05. No formulation for this compound which gives a more satisfactory agreement with the analytical data is immediately apparent.

Because of the singular reactions by which octahydrophenazine is formed, it was felt desirable to confirm its structure. An attempt to dehydrogenate it to phenazine by means of iodine in acetic acid[9] gave only an insoluble, black resin. But oxidation of 0.19 g. with potassium permanganate in alkaline solution gave 0.035 g., 14%, of a water-soluble, amphoteric solid, identified by its m.p. of 206–208° and the red-violet color given with ferrous sulfate solution as the expected pyrazine-2,3,5,6-tetracarboxylic acid.[10]

***p*-Toluenesulfonylcyclohexanoxime.**—A solution of 9.5 g. of *p*-toluenesulfonyl chloride in 15 cc. of pyridine was added dropwise with stirring to one of 5.6 g. of cyclohexanoxime in 10 cc. of pyridine in an ice–methanol-bath. The mixture was kept at 0° for four hours and then poured

---

(7) Analyses for C, H, N and Au by Micro-Tech Laboratories, Skokie, Ill.

(8) A. W. C. Menzies, THIS JOURNAL, **43**, 2309 (1921).

(9) G. R. Clemo and H. McIlwain, *J. Chem. Soc.*, 1993 (1934).

(10) L. Wolff, *Ber.*, **26**, 722 (1893).

on a slurry of ice and dilute sulfuric acid. The oil which separated in large amount crystallized in a few seconds, but upon warming to room temperature during filtration and washing, it deflagrated vigorously. In subsequent preparations, it was therefore taken up in cold benzene and dried and handled in that solvent. Treatment of such a benzene solution with hydrogen chloride in dioxane gave no crystallizable product. Treatment with alcoholic sodium hydroxide yielded less than 5% of octahydrophenazine. *p*-Toluenesulfonylphenylacetoxime likewise gave no crystalline products when treated with hydrogen chloride in dioxane.

Summary

1. The potassium oxime-O-sulfonates of eight ketones have been prepared.

2. Aqueous acid hydrolyzes these compounds to the corresponding oximes; anhydrous hydrogen chloride converts aryl alkyl ketoxime-O-sulfonates to amides by a Beckmann-type rearrangement, and converts some dialkyl ketoxime-O-sulfonates to pyrazines in low yield.

3. These reactions are related to the direct reaction of hydroxylamine-O-sulfonic acid with ketones, and to the reactions of O-arylsulfonyl ketoximes.

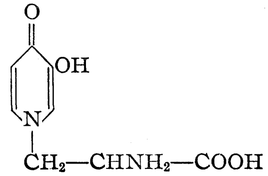
ANN ARBOR, MICH. RECEIVED SEPTEMBER 8, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE]

On the Structure of Leucaenine (Leucaenol) from *Leucaena Glauca* Bentham. III

BY A. F. BICKEL[1]

According to the experimental evidence now available, the most probable structure of leucaenine, an amino acid occurring in the tropical plant, *Leucaena glauca* Bentham, is β-[N-(3-hydroxypyridone-4)]-α-aminopropionic acid (I). The formation of 3,4-dihydroxypyridine on pyrolysis[2,3,4] and of N-methyl-3-methoxy-pyridone-4 on degradative methylation[5,6,7] proved the presence of a 3,4-dihydroxypyridine ring in leucaenine. These two reactions made it very probable that the part of the molecule containing the amino-acid residue is *not* bound to one of the carbon atoms of the pyridine ring. Since leucaenine is not split by treatment with 48% hydrobromic acid,[2] the alanine side-chain can*not* be bound to one of the hydroxyl groups of the ring. Hence, structure I was assumed to be the most probable.



I

The object of the present investigation was to attempt to provide definite proof of the existence of an alanine side-chain and to demonstrate its position in the molecule. It is known that a compound of a structure comparable to that of leucaenine, N-methyl-3-hydroxypyridone-4, yields methylamine[5] on oxidation with potassium permanganate. Should the oxidation of leucaenine proceed in the same way, formation of α,β-diaminopropionic acid may be expected. This diamino acid is, however, oxidized by potassium permanganate. Thus it was imperative to find an oxidizing agent capable of breaking the ring, while leaving the diamino acid unattacked. An aqueous solution of bromine proved to be a suitable reagent; hence the reaction of leucaenine with this oxidizing agent has been investigated more closely.

Upon oxidation of an aqueous suspension of leucaenine with bromine, a small amount of a compound $C_3H_9O_2N_2Br$ is formed. The specific rotation is $[\alpha]^{27}\mathrm{D}$ +13° (33 mg. dissolved in 5 cc. of 0.37% hydrochloric acid). Aqueous solutions of this substance as well as of *dl*-α,β-diaminopropionic acid hydrobromide, prepared by synthesis, show an acid reaction (*p*H of the saturated solution in both cases, 4), react with an acidified aqueous solution of silver nitrate to yield silver bromide, and show a strong ninhydrin reaction. On heating in a melting point capillary, both compounds (as well as their mixture) gradually turn brown above 200° and melt above 236° with decomposition.

Geiger counter spectrometer diffraction patterns of the two substances were prepared with CuKα radiation. These patterns both show a large number of sharp diffraction lines, identical in positions and intensities in both cases.

Ultraviolet absorption spectra of aqueous solutions were found to be essentially the same for both compounds; they showed gradually increasing absorption with decreasing wave length, but no characteristic maxima.[8] The shape of the curves obtained closely resembles that found by Ley and Vanheiden[9] for *dl*-α,β-diaminopropionic acid hydrochloride.

The above facts clearly prove that the substance isolated is α,β-diaminopropionic acid hydrobro-

---

(1) Visiting Fellow, Netherland–America Foundation.

(2) Adams, Cristol, Anderson and Albert, THIS JOURNAL, **67**, 89 (1945).

(3) Bickel, *ibid.*, **69**, 1805 (1947).

(4) Adams, Jones and Johnson, *ibid.*, **69**, 1810 (1947).

(5) Bickel and Wibaut, *Rec. trav. chim.*, **65**, 65 (1946).

(6) Wibaut and Kleipool, *ibid.*, **66**, 24 (1947).

(7) Bickel, THIS JOURNAL, **69**, 1801 (1947).

(8) The author is indebted to Dr. Harold P. Klug, Dr. Alfred L. Marston and Mr. Joseph H. Lieblich, all of the Department of Research in Chemical Physics at Mellon Institute, for carrying out the physical determinations.

(9) Ley and Vanheiden, *Z. anorg. allgem. Chem.*, **188**, 251 (1930).

mide; hence an alanine side-chain is bound to the nitrogen atom of the pyridine ring in leucaenine. This evidence establishes formula I as the correct structure for leucaenine.

The α,β-diaminopropionic acid *hydrochloride* showing a positive rotation is structurally related to the natural $l(-)$-serine.[10] Since the *hydrobromide* isolated also shows a positive rotation, it is very probable that leucaenine has the same stereochemical configuration as the other naturally-occurring amino acids. Natural leucaenine should therefore tentatively be designated as $l(-)$-leucaenine. (This result should be confirmed by comparison of the hydrochloride of the oxidation product with $l(+)$-α,β-diaminopropionic acid hydrochloride.)

Crystal structures of a racemic compound and of the corresponding *l*- and *d*-compounds are in general not the same; hence, one may expect a difference in melting points and X-ray diffraction patterns. The identity of these properties in the case of *dl*-α,β-diaminopropionic acid hydrobromide and the optically-active compound obtained on oxidation suggests, therefore, the absence of a racemic compound.

Another product obtained on oxidation of leucaenine by means of aqueous bromine solution is oxalic acid. It was isolated as the diammonium salt.

The optical rotation of leucaenine has been carefully re-determined and found to be $[\alpha]^{24}\text{D}\ -22°$, in good accord with the value for mimosine given by Renz.[11]

With sulfuric acid, leucaenine forms a sulfate of the composition $C_8H_{10}O_4N_2{\cdot}H_2SO_4{\cdot}1.5\ H_2O$.

Experimental

All melting points given are corrected.

α,β-Diaminopropionic Acid Hydrobromide. (A) From Leucaenine.—Leucaenine (2 g.) was suspended in 60 cc. of water, and bromine was added at room temperature until the color persisted (2.5 cc., or 5 moles of bromine per mole of leucaenine). After an hour the brown solution was evaporated *in vacuo* until the excess bromine had been removed, and then boiled with a great excess of lead carbonate until the evolution of carbon dioxide ceased. During this process the precipitate of lead bromide turned brown and a strong, aldehydic odor developed. After addition of Nuchar W, the reaction mixture was kept in the refrigerator overnight, and the lead bromide then filtered off and washed with ice-water. The yellow filtrate (*p*H 3) was treated with hydrogen sulfide, and the lead sulfide filtered off and washed with water. The final filtrate was evaporated *in vacuo* to dryness and the residue was dissolved in a small amount of water. After filtration, the brown solution was brought to *p*H 6 with 28% ammonia (0.5 cc.), again filtered, evaporated on the steam-bath until brown crystals separated, and filtered after cooling. One recrystallization from water (Nuchar W) gave colorless crystals which were dried in a vacuum desiccator over phosphorus pentoxide. Yield was 11 mg. (0.6%); m. p., above 236° with decomposition. In a second experiment the yield was 34 mg. (from 3 g. of leucaenine) or 1.2%.

Anal.[12] Calcd. for $C_3H_9O_2N_2Br$: C, 19.47; H, 4.90; N, 15.14; Br, 43.19. Found: C, 19.82; H, 4.64; N, 14.97; Br, 43.42.

(B) **From α,β-Dibromopropionic Acid.**—The preparation was carried out according to the directions of Winterstein.[13] Yield was 48%; m. p., above 236° with decomposition.

Anal. Calcd. for $C_3H_9O_2N_2Br$: C, 19.47; H, 4.90; N, 15.14; Br, 43.19. Found: C, 19.67; H, 4.71; N, 15.21; Br, 43.41.

A mixture of the hydrobromides from (A) and (B) melted above 236° with decomposition.

Ammonium Oxalate.—Leucaenine (1 g.) was dissolved in 5 cc. of 10% hydrobromic acid and bromine was added at room temperature until the color persisted. The excess bromine was removed *in vacuo* and the solution was evaporated in the vacuum desiccator over potassium hydroxide. The residue was dissolved in a small amount of water and the solution rendered neutral with 28% ammonia. On cooling, the needles which separated were filtered off, recrystallized once from water (Nuchar W), and dried at 110°. Yield was 50 mg.; m. p. 216–216.5° with decomposition.

Anal. Calcd. for $C_2H_8O_4N_2$: C, 19.36; H, 6.50; N, 22.58. Found: C, 19.71; H, 6.42; N, 22.78.

Ammonium oxalate prepared from oxalic acid and ammonia melted at 218–218.5° with decomposition; mixed melting point, 217.5–218° with decomposition.

Leucaenine Sulfate.—Leucaenine (0.99 g.) was dissolved in a warm solution of 0.52 g. of 95% sulfuric acid in 2 cc. of water. On cooling, the colorless crystals which separated were filtered off, and washed successively with water, ethanol, and ether. Yield was 1.53 g. (95%); m. p. 143–143.5°, with decomposition.

Anal. Calcd. for $C_8H_{10}O_4N_2{\cdot}H_2SO_4{\cdot}1.5H_2O$: C, 29.70; H, 4.68; N, 8.67. Found: C, 29.49; H, 4.79; N, 8.68.

Acknowledgment.—The author expresses his gratitude to Dr. E. R. Weidlein, Director of Mellon Institute, for enabling him to carry out this investigation, and to Dr. Leonard H. Cretcher, Head of the Department of Research in Pure Chemistry, for his interest and encouragement.

Summary

A compound, $C_3H_9O_2N_2Br$, obtained on bromine oxidation of *leucaenine* has been proved to be α,β-diaminopropionic acid hydrobromide. This result establishes the structure of leucaenine as β-[N-(3-hydroxypyridone-4)]-α-aminopropionic acid.

PITTSBURGH 13, PA. RECEIVED JULY 25, 1947

---

[10] See, among others, (a) Karrer, *Helv. Chim. Acta*, **6**, 411, 957 (1923); **9**, 301 (1926); (b) Schneider, *Ann.*, **529**, 1 (1937).

[11] Renz, *Z. physiol. Chem.*, **244**, 153 (1936).

[12] The microanalyses were carried out by Mr. G. L. Stragand of the University of Pittsburgh.

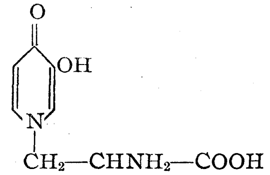
[13] Winterstein, *Z. physiol. Chem.*, **59**, 146 (1909).

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE]

On the Structure of Leucaenine (Leucaenol) from *Leucaena Glauca* Bentham. IV

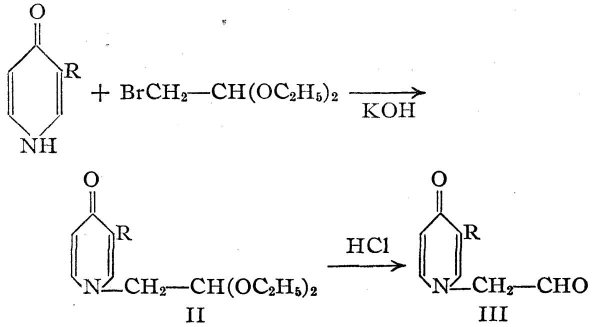
BY A. F. BICKEL[1]

In a number of investigations on the structure of leucaenine[2-6] it has been shown that this amino acid must be represented as β-[N-(3-hydroxypyridone-4)]-α-aminopropionic acid (I).



I

The object of the present investigation was to prepare [N-(3-methoxypyridone-4)]-acetaldehyde (IIIa), a compound which might serve as an intermediate in the synthesis of leucaenine by means of the Strecker reaction. IIIa might be prepared in the following manner.



(a) R = OCH_3 (b) R = H

The starting material for this synthesis, 3-methoxypyridone-4, is not easily available. Hence, in order to become acquainted with the reaction conditions, a similar synthesis, that of (N-pyridone-4)-acetaldehyde (IIIb) was first investigated. IIb was obtained in good yield by the reaction of pyridone-4, bromo-acetal and potassium hydroxide in alcoholic solution. The crude acetal was hydrolyzed to IIIb by boiling with dilute hydrochloric acid. The preparation of [N-(3-methoxypyridone-4)]-acetaldehyde (IIIa) was performed in the same manner. Although this aldehyde was not isolated in the pure state, its semicarbazone was prepared. Preliminary Strecker reactions carried out by the method of Cocker and Lapworth[7] have thus far been unsuccessful.

Experimental

All melting points given are corrected.

4-Hydroxypyridine was prepared according to the method of Königs and Greiner.[8]

(N-Pyridone-4)-acetaldehyde Diethyl Acetal.—A solution of 4.75 g. (0.05 mole) of 4-hydroxypyridine in 10 cc. of ethanol was mixed with 3.3 g. (0.05 mole) of 85% potassium hydroxide in 50 cc. of ethanol and 11.0 g. (0.055 mole) of bromoacetal was added. The resulting solution was heated in a sealed tube at 128–130° for seven hours, filtered from the separated potassium bromide (5.7 g. or 97% of the theoretical quantity), and evaporated *in vacuo*. The sirupy residue was dissolved in 30 cc. of water and rendered neutral with a few drops of concentrated hydrochloric acid.

The acetal was isolated as follows: The neutral aqueous solution was evaporated *in vacuo*. An alcoholic extract of the residue was filtered from a small amount of potassium chloride and concentrated *in vacuo*. On standing exposed to air, the resulting sirup yielded beautiful, colorless crystals of the acetal monohydrate, which were recrystallized from water, m. p., 87–89°. *Anal.*[9] Calcd. for $C_{11}H_{17}O_3N \cdot H_2O$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.44; H, 8.06; N, 6.18.

On drying over phosphorus pentoxide in a vacuum desiccator, the crystals lose water and revert to a sirup. The picrate was prepared by adding a small excess of picric acid dissolved in ethanol to a solution of the acetal in ethanol. Recrystallization was performed from the same solvent; m. p., 137–139°. *Anal.* Calcd. for $C_{11}H_{17}O_3N \cdot C_6H_3O_7N_3$: N, 12.72. Found: N, 12.49, 12.77.

(N-Pyridone-4)-acetaldehyde Hydrate.—The hydrolysis may be carried out after isolation of the acetal. It is simpler, however, to start with the aqueous solution of the original reaction mixture after neutralization with hydrochloric acid. This solution, treated with 8 cc. of 38% hydrochloric acid and 25 cc. of water, was refluxed for four hours. After evaporation *in vacuo*, a solution of the residue in 15 cc. of water was neutralized with sodium carbonate, a colorless crystalline precipitate of the aldehyde hydrate separating out. The product was collected, washed with small portions of ice-water until free from sodium chloride, and dried in the vacuum desiccator over phosphorus pentoxide. Yield was 4.3 g. (55% calculated on 4-hydroxypyridine). Recrystallization was performed from water. On heating, this compound turns brown above 110°, but does not melt.

Anal. Calcd. for $C_7H_7O_2N \cdot H_2O$: C, 54.19; H, 5.85; N, 9.03. Found: C, 53.98; H, 5.82; N, 8.97.

The picrate was prepared by adding an aqueous solution of picric acid to an aqueous solution of the aldehyde; recrystallization from water, m. p. 182.0–182.5° with decomposition.

Anal. Calcd. for $C_7H_7O_2N \cdot C_6H_3O_7N_3 \cdot H_2O$: C, 40.63; H, 3.15; N, 14.58. Found: C, 40.90, 40.94; H, 3.20, 3.38; N, 14.42.

The semicarbazone was obtained by evaporating an aqueous solution of 155 mg. of aldehyde hydrate, 112 mg. of semicarbazide hydrochloride, and 53 mg. of sodium carbonate on the steam-bath until needles separated. On cooling, the crystals were filtered off and washed with ice-water. Recrystallization was performed from 50% ethanol; m. p. 208–208.5° with decomposition.

Anal. Calcd. for $C_8H_{10}O_2N_4$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.63; H, 5.38; N, 28.61.

---

[1] Visiting Fellow, Netherland–America Foundation.

[2] Adams, Cristol, Anderson and Albert, THIS JOURNAL, **67**, 89 (1945).

[3] Bickel and Wibaut, *Rec. trav. chim.*, **65**, 65 (1946).

[4] Wibaut and Kleipool, *ibid.*, **66**, 24 (1947).

[5] Bickel, THIS JOURNAL, **69**, 1801, 1805 (1947); **70**, 326 (1948).

[6] Adams, Jones and Johnson, *ibid.*, **69**, 1810 (1947).

[7] Cocker and Lapworth, *J. Chem. Soc.*, 1391 (1931).

[8] Königs and Greiner, *Ber.*, **64**, 1049 (1931).

[9] The microanalyses were carried out by Mr. G. L. Stragand of the University of Pittsburgh.

[N-(3-Methoxypyridone-4)]-acetaldehyde.—3-Methoxypyridone-4, bromoacetal and potassium hydroxide were caused to react in the manner described for pyridone-4. More than 90% of the theoretical quantity of potassium bromide was formed. No attempts were made to isolate the acetal; instead, its aqueous solution was refluxed with hydrochloric acid. On neutralizing with sodium carbonate, the liquid turned a dark brown but no aldehyde separated. By reaction of the crude material with semicarbazide, however, a semicarbazone was formed; its yield indicated that the over-all yield of aldehyde, calculated on 3-methoxypyridone-4, was about 40%. The semicarbazone was recrystallized from water and dried over phosphorus pentoxide in the vacuum desiccator; m. p. 188–188.5° with decomposition.

Anal. Calcd. for $C_9H_{12}O_3N_4 \cdot 2H_2O$: C, 41.53; H, 6.20; N, 21.53; H_2O, 13.84. Found: C, 41.86; H, 6.30; N, 21.41; H_2O, 13.76.

The anhydrous compound, which may be prepared by drying over phosphorus pentoxide at 100° (1 mm.), is very hygroscopic.

Summary

(N-Pyridone-4)-acetaldehyde and [N-(3-methoxypyridone-4)]-acetaldehyde have been synthesized.

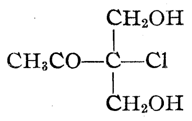
PITTSBURGH 13, PA. RECEIVED JULY 25, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY AND COMMERCIAL SOLVENTS CORPORATION]

The Condensation of Chloroacetone with Formaldehyde

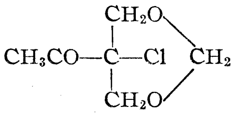
BY CHARLES D. HURD, WARREN D. MCPHEE[1] AND GLEN H. MOREY

While the condensation of formaldehyde with lower ketones has been studied extensively, the reaction of this aldehyde with chloroacetone has not previously been investigated. From the reaction of one mole of chloroacetone with 2.1 moles of formaldehyde, there are obtained three substances: A, a crystalline solid melting at 61–62°; B, a colorless oil distilling at 93.5° (10 mm.); C, a colorless oil distilling at 73–74.5° (10 mm.). From the evidence presented herein, it has been concluded that these substances are respectively 2-chloro-2-acetyl-1,3-propanediol, 2-chloro-2-acetyl-1,3-propanediol formal and 4-hydroxy-3,3-dichloro-2-butanone.



$$\mathrm{CH_3CO{-}\overset{\displaystyle CH_2OH}{\underset{\displaystyle CH_2OH}{C}}{-}Cl}$$

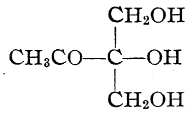
A



B

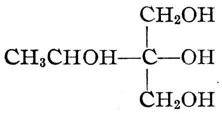
$\mathrm{CH_3COCCl_2CH_2OH}$

C



$$\mathrm{CH_3CO{-}\overset{\displaystyle CH_2OH}{\underset{\displaystyle CH_2OH}{C}}{-}OH}$$

D



$$\mathrm{CH_3CHOH{-}\overset{\displaystyle CH_2OH}{\underset{\displaystyle CH_2OH}{C}}{-}OH}$$

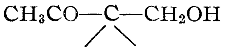
E

In determining the structure of substance A, it is apparent from the empirical formula that two hydroxymethyl groups have been introduced. It is necessary only to ascertain which α-carbon atom carries them. This was done by oxidation of A to acetic acid and by reaction with sodium hypoiodite with the formation of iodoform. ω-Chloroacetophenone is known to give a negative iodoform reaction,[2] and chloroacetone was found to give similar results. In view of these facts, A was assigned the structure shown.

Compound B differs from A only by the presence of one more carbon atom. It seemed logical that B should be the cyclic formal derived from A by reaction with a third mole of formaldehyde. Compound A was converted into B by means of dry formaldehyde in ether in the presence of a trace of acid, thus proving the structure of B. The compound so synthesized was shown to be identical with B.

The high chlorine content of C indicated that it was derived from dichloroacetone, which is generally present in small amounts in chloroacetone. Structure C, analogous to structure A, was selected because this compound gives a positive iodoform test. The formula was confirmed by synthesis of C from α,α-dichloroacetone and formaldehyde.

2-Chloro-2-acetyl-1,3-propanediol, A, was readily converted to its diacetate with ketene and to its dibenzoate with benzoyl chloride. Upon treatment with aqueous or alcoholic alkali, there is obtained a triol believed to be acetylglycerol, D. There is no evidence on the question whether this comes by direct saponification or by way of dehydrohalogenation to an ethylene oxide intermediate,



By the reaction of three moles of formaldehyde per mole of chloroacetone in the presence of one mole of sodium hydroxide, there is obtained substance D. The latter was identical with the triol obtained by alkaline hydrolysis of A. Substance D was reduced by sodium in alcohol to a tetrol, 2-hydroxymethyl-1,2,3-butanetriol, E.

Experimental

Reaction of Chloroacetone and Formaldehyde.—Chloroacetone (containing a little α,α-dichloroacetone) and formalin (40% solution) were mixed in a molar ratio of 1:2.1. The mixture was agitated at 25° for thirty minutes, during which time 2 *N* sodium hydroxide solution was added dropwise till 0.27 mole of the base was added. There was some heat of reaction during this addition, and the two-layer system gradually became homogeneous. The

---

[1] Holder of Commercial Solvents Corporation Fellowship, 1938–1940.

[2] Fuson and Tullock, THIS JOURNAL, **56**, 1638 (1934).

mixture was shaken three hours longer, then distilled. After the water was removed at 100°, colorless volatile products were collected at 140° (5–10 mm.). A nonvolatile tarry residue (weighing 8–9% of the initial reactants) remained in the flask and the distillate was found to comprise a colorless, sirupy liquid and a crystalline solid which were separated by filtration. The liquid represented 21% of the initial reactants and the solid 33%. The latter was shown to be 2-chloro-2-acetyl-1,3-propanediol. It melted at 61–62° after crystallization from heptane.

Anal. Calcd. for $C_5H_9ClO_3$: Cl, 23.25; mol. wt., 152.5. Found: Cl, 23.36; mol. wt., 149.

Two components, both colorless oils, were separated from the sirupy liquid by distillation: component C, b. p. 73° (10 mm.), d^{20}_{20} 1.371; component B, b. p. 93.5° (10 mm.), d^{20}_{20} 1.286.

Anal. of B. Calcd. for $C_6H_9ClO_3$: Cl, 21.57. Found: Cl, 21.45.

Haloform Reactions.—2-Chloro-2-acetyl-1,3-propanediol (A) was tested as follows:

Five-tenths gram of the substance was dissolved in a solution formed by adding 1.25 g. of iodine to 8 ml. of 10% sodium hydroxide solution, after which 1.25 g. of iodine was added in small amounts with sufficient alkali solution to discharge the brown color. A voluminous white precipitate of iodoform (2 g. or 78%) was formed, m. p. 119°.

In a similar way (A) gave a positive chloroform test by the following procedure: Ten cubic centimeters of 10% sodium hydroxide solution was saturated at 0° with chlorine, followed by addition of 10 cc. more alkali and 1 g. of substance A. The mixture was distilled and the distillate contained an oily layer of chloroform, which was separated and dried; n^{20}_D 1.4458.

4-Hydroxy-3,3-dichloro-2-butanone (C) gave iodoform positively by the above procedure using 1 ml. of C; yield 0.4 g. (25%), m. p. 118.5–119°.

2-Chloro-2-acetyl-1,3-propanediol diacetate (0.5 g.) gave a low yield of impure iodoform by mixing it with 5 ml. of sodium hypoiodite solution prepared by dissolving 2.5 g. of iodine in 16 ml. of 10% sodium hydroxide. The resulting suspension was shaken for fifteen minutes, during which time about 0.1 g. of iodoform melting at 114° was obtained.

Chloroacetone gave a negative iodoform test as follows: 0.6 ml. of chloroacetone was shaken for ten minutes with 8 ml. of sodium hypoiodite solution prepared as above. No iodoform was obtained.

Oxidation of 2-Chloro-2-acetyl-1,3-propanediol.—A sample of the 2-chloro-2-acetyl-1,3-propanediol weighing 1.505 g. (0.00986 mole) was dissolved in 100 g. of water and oxidized quantitatively by means of a chromic acid mixture prepared from 8.8 g. (0.03 mole) of potassium dichromate, 75 g. of water and 22 ml. of concentrated sulfuric acid. The mixture was refluxed in an all-glass apparatus until the evolution of carbon dioxide ceased (thirty minutes). It was then distilled slowly until crystals separated, whereupon 100 g. of water was added, and the distillation was continued. The combined distillate and washings were made up to 500 ml. and two 25-ml. samples were titrated with 0.0651 *N* sodium hydroxide. The ml. of alkali required were 5.36 and 5.34, respectively, representing a total of 0.00697 mole of acid distilled. This is 0.71 mole of acid per mole of 2-chloro-2-acetyl-1,3-propanediol oxidized. The sodium salt, obtained by evaporating the neutralized distillate, was converted into the *p*-bromophenacyl acetate, m. p. 85°.

Duclaux constants were taken on a fresh portion of the distillate: 6.0, 6.4, 6.8. These check fairly well with those for acetic acid, 6.8, 7.1, 7.4.

Conversion of 2-Chloro-2-acetyl-1,3-propanediol into its Formal.—Five grams of dry paraformaldehyde in a 125-cc. flask was heated to 170–180° in an oil-bath while a slow stream of nitrogen (dried with concentrated sulfuric acid) was passed through the flask. The outlet tube (12 mm.) led into a test-tube containing 30 ml. of anhydrous ether at −80°. The heating was continued until nearly all the polymer had disappeared. The gain in weight of the ether solution was 1.3 g., representing 0.04 mole of formaldehyde. To this cold (−80°) solution was added 2.2 g. (0.014 mole) of 2-chloro-2-acetyl-1,3-propanediol (A) and two drops of concentrated sulfuric acid. The solution was kept at −80° for twelve hours, then allowed to come to room temperature. After two days the ether was evaporated on the steam-bath. About 2.3 g. of colorless oil was left. This represents about a 95% yield of the cyclic acetal. The oil was not soluble in water, whereas the starting products were.

The 2,4-dinitrophenylhydrazones of the oil and of substance B (b. p. 93.5° at 10 mm.) both melted at 159–160° after recrystallization from alcohol. Their mixture also melted at 159–160°, but if either was mixed with formaldehyde 2,4-dinitrophenylhydrazone (m. p. 163°), the m. p. was depressed to 139–150°. Hence, the hydrazone is not that of formaldehyde. 2-Chloro-2-acetyl-1,3-propanediol, the starting product, gives no 2,4-dinitrophenylhydrazone when prepared in alcohol, since the hydrazone is soluble in alcohol.

Condensation of α,α-Dichloroacetone with Formaldehyde.—A mixture of 51 g. of α,α-dichloroacetone (55.01% Cl) and 65 ml. of 40% formalin was stirred mechanically while 5 g. of dry sodium carbonate was added slowly. After the initial vigorous reaction (the solution boils) the mixture was stirred at room temperature for eight hours. The lower organic layer was separated, dried with drierite, filtered and vacuum-distilled. The odor of formaldehyde was noticeable. A small forerun (4.5 g.) was obtained, b. p. 78–81° (20 mm.), n^{20}_D 1.4725, after which the main body of 4-hydroxy-3,3-dichloro-2-butanone was obtained, b. p. 81° (20 mm.), 105° (50 mm.), d^{20}_{20} 1.34, n^{20}_D 1.4727. There was no other volatile fraction. This product has the same physical constants as substance C (b. p. 79.5–80.5° (20 mm.), n^{20}_D 1.4724), isolated originally from the experiment with chloroacetone. These directions were modified for runs involving several kg. of product with yields consistently at about 75%.

Anal. Calcd. for $C_4H_6Cl_2O_2$: Cl, 45.21. Found: Cl, 44.96.

The semicarbazone of this substance melted with decomposition at 230–231° after recrystallization from alcohol. The semicarbazone of C, similarly prepared, also melted at 229–230°. The mixed m. p. of the two was 229–230°.

Esters of 2-Chloro-2-acetyl-1,3-propanediol

Diacetate.—This was made by passing a slight excess of ketene into an acetone solution of the diol. From 2 g. of (A), 1.5 g. of 2-chloro-2-acetyl-1,3-propanediol diacetate, b. p. 138–143° (18 mm.), was obtained.

Anal. Calcd. for $C_9H_{13}ClO_5$: Cl, 15.0. Found: Cl, 14.7.

Dibenzoate.—Reaction with boiling benzoyl chloride effected benzoylation in 85% yield. Crystallization was from ethanol or ligroin: m. p., 82–83°.

Anal. Calcd. for $C_{19}H_{17}ClO_5$: Cl, 9.84. Found: Cl, 10.0.

Bis-*p*-nitrobenzoate.—Treatment with *p*-nitrobenzoyl chloride and pyridine (boiling), and crystallization from ethyl acetate (or ethanol) resulted in a 36% yield, m. p. 161°.

Anal. Calcd. for $C_{19}H_{15}ClN_2O_9$: Cl, 7.89. Found: Cl, 8.11.

Acetylglycerol from (A).—Five grams of the solid 2-chloro-2-acetyl-1,3-propanediol was dissolved in 100 ml. of 95% ethanol containing 2.5 g. of potassium hydroxide. A precipitate of potassium chloride formed immediately. The mixture was neutralized with a solution of hydrogen chloride in absolute alcohol. The salt was filtered off and washed with absolute alcohol. The alcohol was removed at 20 mm. by heating in a bath at 60°. The residual yellow sirup was not distillable at 5 mm. from a Claisen flask with a bath temperature of 175°, but it distilled readily from a simple molecular still[3] connected to a pair of mercury pumps and heated by a bath at 120–125°. The colorless, non-viscous, water-soluble distillate (D_1) weighed 1.8 g.

Material possessing the same properties was obtained by treatment with an equivalent of aqueous (6 *N*) sodium hydroxide, removal of water by vacuum distillation, filtration to remove sodium chloride, and distillation from the molecular still. The liquid will be called D_2.

From Chloroacetone.—Five grams (0.055 mole) of chloroacetone and 0.16 mole of formaldehyde (as formalin) were mixed and maintained at 20° while 0.055 mole of 6 *N* sodium hydroxide solution was added little by little with stirring in the course of a day. The mixture was then heated to 60° for ten hours to consume the base. The water was removed by evaporation under reduced pressure up to 90° and sodium chloride was precipitated in quantitative yield. The sirupy material (6.5 g.) was not distillable in an ordinary Claisen flask up to 175° (bath) and 5 mm., but it came over readily from a molecular still with the conditions specified above. The limpid distillate, to be referred to as D_3, weighed 1.5–2 g. There was a red-brown, non-volatile residue in the still.

Anal. Calcd. for $C_5H_{10}O_4$: active hydrogen atoms, 3. Found (Zerewitinoff): active hydrogen atoms from D_1, 3.13, 3.09; from D_3, 3.06, 2.98.

***p*-Bromobenzoic Ester.**—A mixture of 0.5 g. of acetylglycerol, 4 g. of *p*-bromobenzoyl chloride and 30 ml. of dry pyridine was maintained at 0° for thirty-six hours, and subsequently treated with 40 ml. of 5% sodium carbonate solution for eight more hours at 0°. Fifty grams of water was added, and the mixture was filtered. The acetylglycerol tris-*p*-bromobenzoate was digested in ethanol and recrystallized from butyl ether; yield of white needles, 2 g. (79%). D_1, D_2 and D_3 all behaved identically, giving products melting at 215–216°. Mixed melting point determinations of these products were not lowered.

The same product was formed but in lower yield if a reaction temperature of 100–115° was maintained.

Anal. Calcd. for $C_{26}H_{19}Br_3O_7$: Br, 35.1. Found: Br, 35.9.

Reduction of Acetylglycerol.—Four grams of acetylglycerol was dissolved in 17 ml. of ethanol and 3 g. of water. Two grams of sodium was added in small pieces during two hours. At first, the mixture was cooled with ice; when the reaction became less vigorous, it was allowed to proceed at room temperature. After ninety minutes the reaction was very slow, so 10 ml. more of alcohol was added. The solution became a deep red and a yellow precipitate formed. After the sodium had been added, the mixture was neutralized with a saturated solution of dry hydrogen chloride in alcohol. The solution was filtered from the salt which precipitated, the solvent was removed, and the 5 cc. of dark residue was distilled in the molecular still with a bath temperature of 80–85°. The yield of colorless distillate was 0.91 g. or 23%.

Anal. Calcd. for $C_5H_{12}O_4$: active hydrogen atoms, 4. Found (Zerewitinoff): active hydrogen atoms, 3.84, 4.02.

Summary

Formaldehyde condenses with chloroacetone to yield 2-chloro-2-acetyl-1,3-propanediol and its cyclic formal. α,α-Dichloroacetone, similarly treated, gives rise to 4-hydroxy-3,3-dichloro-2-butanone. Various reactions of these compounds are developed.

EVANSTON, ILLINOIS
TERRE HAUTE, INDIANA
RECEIVED AUGUST 4, 1947

---

[3] Hickman and Sanford, *J. Phys. Chem.*, **34**, 643 (1930).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

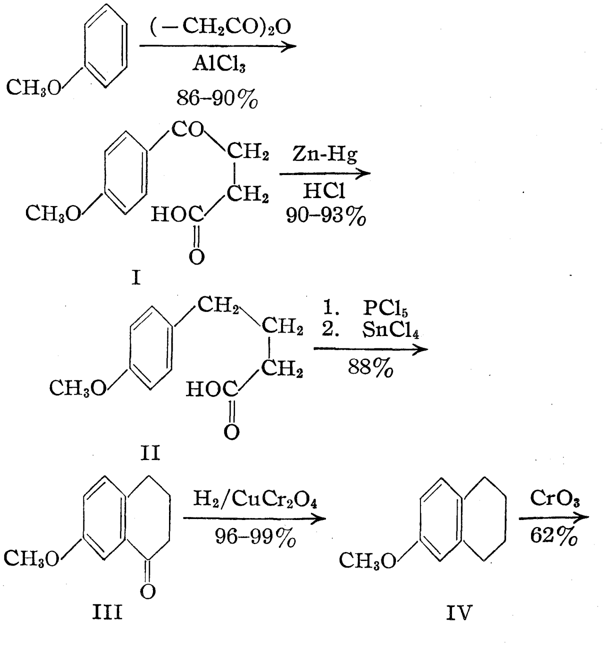
6-Methoxy-1-tetralone

BY DONALD G. THOMAS AND ALAN H. NATHAN

Of the various methods[1-6] described for the synthesis of 6-methoxy-1-tetralone (V), the one most generally used is that based on the chromic acid oxidation[5] of 6-methoxytetralin (IV), which usually has been obtained from tetralin by sulfonation, alkali fusion and methylation.[7,8] The over-all yield of 6-methoxy-1-tetralone by this method is about 30–35%.

An alternate route to 6-methoxy-1-tetralone is outlined below, and by this procedure we have obtained 6-methoxy-1-tetralone in over-all yields of 40–45%.

The reaction between anisole and succinic an-



---

[1] Thompson, *J. Chem. Soc.*, 2310 (1932).

[2] Robinson and co-workers, *ibid.*, 1285, 1288 (1935); 192, 747 (1936); 1581 (1937).

[3] Chuang and Huang, *Ber.*, **69**, 1505 (1936).

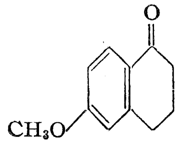
[4] Martin, THIS JOURNAL, **58**, 1438 (1936).

[5] Burnop, Elliott and Linstead, *J. Chem. Soc.*, 727 (1940).

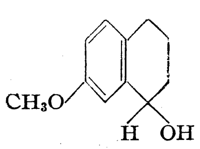
[6] Bachmann and Thomas, THIS JOURNAL, **64**, 94 (1942).

[7] Schroeter, *Ann.*, **426**, 83 (1922).

[8] Since this manuscript was submitted for publication, details of a superior method for the preparation of 6-methoxytetralin by catalytic hydrogenation of β-naphthyl methyl ether have been published by Stork, THIS JOURNAL, **69**, 576 (1947).

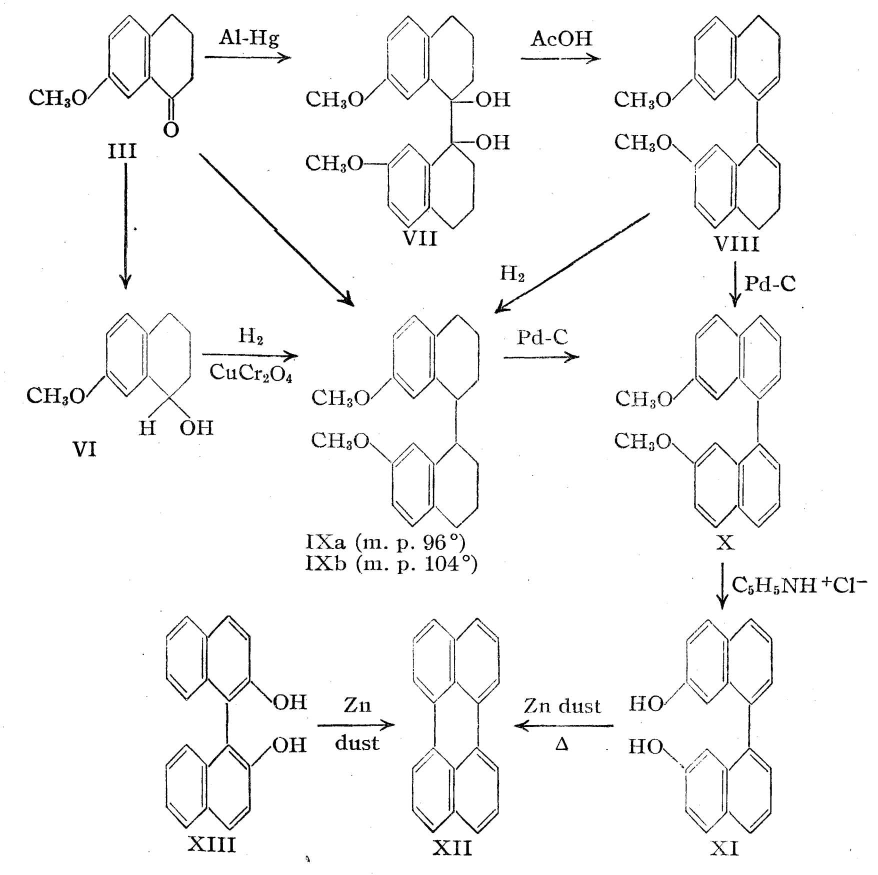


V



VI

hydride was carried out essentially as described,[9] with minor modifications that shortened the time required. Clemmensen reduction of the resultant β-(*p*-anisoyl)-propionic acid (I) was conducted as described.[10] Cyclization of the reduced acid (II) by treatment of the acid chloride with stannic chloride gave 7-methoxy-1-tetralone (III) in excellent yields. Hydrogenation of 7-methoxy-1-tetralone in the absence of solvent with a barium-free copper chromite catalyst up to 200° and under an initial pressure of 200 atmospheres gave practically quantitative yields of 6-methoxytetralin (IV). The success of the hydrogenation was dependent upon the purification of the ketone and the extent of the purification required was related to the amount of phosphorus pentachloride used in making the acid chloride of II. When the ratio of phosphorus pentachloride to acid was 1.1:1, the yield of purified 7-methoxy-1-tetralone was 83%, and it was essential to purify the ketone by distillation, refluxing with Raney nickel, and recrystallization before hydrogenation. Omission of any of these three steps resulted in only 55–70% yields of 6-methoxytetralin which was then accompanied by variable amounts of 7-methoxy-1-tetralol (VI) and occasionally by a crystalline bimolecular reduction product (see below). When the ratio of phosphorus pentachloride to acid was exactly 1:1, the yield of purified ketone was 88% and the treatment with Raney nickel could be omitted although in this case the yield of IV on hydrogenation was lowered to 92–94%.



The hydrogenation of either 7-methoxy-1-tetralone or 7-methoxy-1-tetralol in absolute alcohol with palladium–charcoal at room temperature and three atmospheres gave IV in 92–95% yield; the ketone did not have to be so rigorously purified. Clemmensen reduction of III gave IV in a maximum yield of only 77%.

Chromic acid oxidation of 6-methoxytetralin gave a 62% yield of distilled and recrystallized 6-methoxy-1-tetralone.

Hydrogenation of 7-methoxy-1-tetralol with copper chromite under the same conditions employed for 7-methoxy-1-tetralone gave a 58–62% yield of 6-methoxytetralin and, in addition, a 23–27% yield of a mixture which, by repeated fractional crystallization, was separated into two forms of 7,7′-dimethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-binaphthyl (IXa and b), which we conclude are the *cis* and *trans* forms. No attempt was made to determine the configurations of these two forms. The structure of IX was verified by the reactions outlined below.

7-Methoxy-1-tetralone was reduced with aluminum amalgam to the pinacol (VII), which was dehydrated to the diene (VIII).[11] Reduction of the diene with sodium and butyl alcohol gave a mixture from which both IXa and IXb were isolated; only IXb was isolated from the hydrogenation of the diene with Raney nickel. Dehydrogenation of VIII, IXa and IXb gave in each case 7,7′-dimethoxy-1,1′-binaphthyl (X).

The fact that these bimolecular reduction products were joined in the 1,1′-position was proved,

---

[9] Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936).

[10] Martin, "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942, p. 167.

[11] This diene was also obtained on distillation of the high-boiling residues from the Clemmensen reduction of 7-methoxy-1-tetralone.

not only by their formation via the pinacol reduction of 7-methoxy-1-tetralone,[12] but also by the formation from the binaphthol (XI) of perylene (XII), which has been previously prepared by a similar reaction from 2,2′-dihydroxy-1,1′-binaphthyl (XIII).[13]

Experimental

β-(*p*-Anisoyl)-propionic Acid (I).—A solution of 560 g. (4.2 moles) of aluminum chloride in 1 liter of 1-nitropropane[14] was added gradually to a mechanically stirred mixture of 216 g. (2 moles) of anisole and 210 g. (2.1 moles) of succinic anhydride in 500 cc. of 1-nitropropane while the temperature was kept at 0–5°. The mixture was kept at 3–8° for approximately twenty-four hours, allowed to reach 15° in about an hour and hydrolyzed with ice and hydrochloric acid. Isolation of the acid as described[9] gave 358–376 g. (86–90%) of almost colorless to cream-colored acid; m. p. (not recrystallized) 144.5–146.5°.

γ-(*p*-Anisyl)-butyric Acid (II).—Clemmensen reduction[10] of the above keto acid in amounts from 350–900 g. gave yields from 90–93.4%; b. p. 152–156° at 0.6 mm.; m. p. (not recrystallized) 59–61° with softening at 56°.

7-Methoxy-1-tetralone (III).—To a mechanically stirred solution of 194 g. (1 mole) of the reduced acid (II) in 1 liter of dry thiophene-free benzene was added 208.3 g. (1 mole) of phosphorus pentachloride while the temperature was kept at 5–10°. The resulting colorless solution was warmed to 50° for a few minutes and then chilled to 0 to −5°. To it was added rapidly (about forty seconds) a chilled solution of 175 cc. of anhydrous stannic chloride in 175 cc. of dry thiophene-free benzene. A blood-red color developed which quickly turned to a dark brown-green and in ten to fifteen minutes the reaction mixture set to a green semi-solid. Hydrolysis and isolation as described for a similar cyclization[15] followed by distillation from 115–120° at 0.6–0.8 mm. (160–165° at 11 mm.) gave 161.4 g. (91.7%) of colorless crystalline ketone. For hydrogenation with copper chromite the product was refluxed for an hour with about 5 g. of Raney nickel in absolute ethanol and then recrystallized from petroleum ether (60–75°) from which it separated as large colorless prisms; m. p. 61–62.5°; yield, 154.9 g. (88%).

6-Methoxytetralin (IV).—7-Methoxy-1-tetralone (70.4 g., 0.4 mole) was hydrogenated in the presence of 7.0 g. of barium-free copper chromite[16] at 200° without solvent and under an initial pressure (at room temperature) of 3000 pounds. Hydrogenation began at 125° and was complete after an hour at 200°.[17] The product was obtained as a colorless liquid; b. p. 121–128° at 11 mm.; yield, 62.2–64.2 g. (96–99%). Hydrogenation of ketone in whose purification the Raney nickel treatment was omitted gave 92–94% yields.

6-Methoxy-1-tetralone (V).—The oxidation of 113.4 g. (0.7 mole) of 6-methoxytetralin with chromic acid was carried out essentially as described[5] except that the tetralin was dissolved in a solvent consisting of 80% of acetic acid and 20% of propionic acid; this mixture prevented solidification when the solution was chilled. After oxidation, the solvent was removed, but instead of distilling the dark viscous residue with super-heated steam it was warmed with 5% sulfuric acid and the ketone was extracted with ether[18] which was then washed with water, 5% sodium hydroxide solution, water and dried. Distillation at 129–133° at 0.7 mm. (a fore-run of unchanged 6-methoxytetralin was collected) and recrystallization from petroleum ether (60–75°) gave V as large colorless prisms; m. p. 77–78.5°; yield, 76.4 g. (62%).

7-Methoxy-1-tetralol (VI).—Hydrogenation of 7-methoxy-1-tetralone in whose preparation 1.1 moles of phosphorus pentachloride was used and which was not subjected to the full purification procedure gave 55–72% yields of 6-methoxytetralin, 10–30% yields of 7-methoxy-1-tetralol and occasionally a bimolecular reduction product (IX) (see below); when IX was obtained little or no tetralol was isolated. 7-Methoxy-1-tetralol is a colorless viscous liquid; b. p. 118–120° at 0.3 mm. (164–166° at 10 mm.); $n^{23}D$ 1.5553.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.05; H, 7.97.

The *p*-nitrobenzoate crystallized from ethanol as pale yellow prisms; m. p. 73.5–74°.

Anal. Calcd. for $C_{18}H_{17}NO_5$: C, 66.04; H, 5.24; N, 4.28. Found: C, 65.95; H, 5.25; N, 4.29.

7,7′-Dimethoxy-1,1′-dihydroxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-binaphthyl (VII).—Eight and eight-tenths grams of 7-methoxy-1-tetralone was reduced with amalgamated aluminum foil in alcohol–benzene according to the procedure described by Newman[12] for 7-methyl-1-tetralone. The pinacol was isolated as a mixture of crystals and an oil which could not be obtained crystalline; both fractions could be converted to the diene (VIII). The crystals, after recrystallization from isopropanol, amounted to 3.9 g. (44%), m. p. 182–184°. After one further recrystallization from benzene–cyclohexane they melted at 183–184.5° and were analytically pure.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.56; H, 7.40. Found: C, 74.67, 74.77; H, 7.39, 7.37.

7,7′-Dimethoxy-3,3′,4,4′-tetrahydro-1,1′-binaphthyl (VIII).—Dehydration of the pinacol (VII) was accomplished by refluxing for two hours in about seven times its weight of glacial acetic acid. The diene crystallized from solution on cooling. Both the crystalline pinacol and the uncrystallizable oil gave the same diene, which was obtained as colorless octahedra from methanol, m. p. 147.8–148.2°.

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 82.99; H, 6.97. Found: C, 83.18; H, 7.15.

The pinacol was also converted to the diene by repeated recrystallization from alcohol. A mixed melting point with a product isolated from the Clemmensen reduction of 7-methoxy-1-tetralone was not depressed.

7,7′-Dimethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-binaphthyl (IXa and IXb).—Hydrogenation of 71.2 g. (0.4 mole) of 7-methoxy-1-tetralol (VI) under the same conditions employed for the hydrogenation of III gave 40.4 g. (62%) of 6-methoxytetralin and 17.5 g. (27%) of a very viscous yellow oil, b. p. 255–270° at 11 mm., which crystallized rather poorly when triturated in methanol. After a tedious series of fractional crystallizations from methanol two compounds were isolated. One (IXa) formed colorless rhomboidal plates, m. p. 95–96°; the other (IXb) formed colorless hexagonal prisms, m. p. 103–104.5°. Attempts to interconvert these two isomers failed.

Anal. Calcd. for $C_{22}H_{26}O_2$: C, 81.96; H, 8.13. Found: IXa, C, 82.00; H, 8.39. IXb, C, 81.98; H, 8.46.

To a solution of 1.75 g. of the diene (VIII) in 30 cc. of butanol at 60° was added 1.0 g. of sodium; after the reaction had subsided somewhat the mixture was heated until solution was complete. The cooled solution was washed with water until neutral, dried and evaporated. Fractional crystallization of the residue yielded both IXa and IXb.

---

[12] *Cf.* Newman, THIS JOURNAL, **62**, 1683 (1940). The reduction of 7-methyl-1-tetralone under identical conditions led to the synthesis of coronene.

[13] Marschalk, *Bull. soc. chim.*, [4] **43**, 1388 (1928).

[14] The 1-nitropropane was purified by treatment with aluminum chloride at room temperature followed by hydrolysis with ice, steam distillation, drying and distillation.

[15] Johnson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 136.

[16] Lazier and Arnold, "Organic Syntheses," Coll. Vol. II, p. 142.

[17] *Cf.* Mowry, Renoll and Huber, THIS JOURNAL, **68**, 1105 (1946), for the reduction of aryl methyl ketones with copper chromite.

[18] *Cf.* Schwenk and Papa, *ibid.*, **67**, 1432, ref. 13 (1945) for the use of butyl ether in the isolation.

A sample of the diene (VIII) in absolute alcohol was subjected to hydrogenation over Raney nickel at 50° and 160 atmospheres. The product after one recrystallization from methanol was pure IXb, m. p. 104–105°.

7,7′-Dimethoxy-1,1′-binaphthyl (X).—A mixture of the diene (VIII) with about 2.5% of its weight of palladized charcoal,[19] when heated at 290–300° for fifteen minutes, gave a practically quantitative yield of X which, after recrystallization from ethanol, formed colorless rectangular plates, m. p. 110.5–111.5°.

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.08; H, 5.77. Found: C, 83.73; H, 5.64.

Similar treatment of the bitetralyl (IXa and IXb) gave in each case the same compound, identified by mixed m. p.

7,7′-Dihydroxy-1,1′-binaphthyl (XI).—The methyl ether (X) was smoothly demethylated in practically quantitative yield by the method of Prey.[20] A mixture of X with three times its weight of pyridine hydrochloride was heated at 200° for six hours, then poured into water. For analysis, the compound was converted to its diacetate by standard methods, because the free phenol was difficult to purify. The diacetate formed white crystals from ethanol, m. p. 173.5–174.5°. After three recrystallizations the compound gave the following analytical values.

Anal. Calcd. for $C_{24}H_{18}O_4$: C, 77.82; H, 4.90. Found: C, 77.38; H, 4.66.

Perylene (XII).—A mixture of the binaphthol (XI) with five times its weight of zinc dust was heated in a distilling flask with a free flame. A yellow oil distilled out of the mixture and solidified in the cooler parts of the apparatus. This was removed and recrystallized from benzene; it formed yellow leaflets with a bronze luster, melting at 267–268°. This was identified as perylene by comparison with an authentic specimen prepared by heating 2,2′-dihydroxy-1,1′-binaphthyl (XIII)[21] with zinc, zinc chloride and water.[13] A mixture of the two samples melted at 267–268°. The picrate formed dark violet needles from benzene, m. p. 220° (reported[22] m. p. 221°). The sample of perylene obtained from XI gave the following analytical results.

Anal. Calcd. for $C_{20}H_{12}$: C, 95.21; H, 4.80. Found: C, 94.90; H, 4.65.

Summary

1. A procedure for the preparation of 6-methoxy-1-tetralone in 40–45% yields from anisole is described.

2. A by-product from the catalytic hydrogenation of 7-methoxy-1-tetralone or 7-methoxy-1-tetralol has been shown to be 7,7′-dimethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-binaphthyl.

Kalamazoo, Michigan Received[23] August 27, 1947

---

[19] Linstead and Thomas, *J. Chem. Soc.*, 1130 (1940).

[20] Prey, *Ber.*, **74B**, 1219 (1941).

[21] Julius, *Chem. Ind.*, **10**, 98 (1887).

[22] Brass and Tengler, *Ber.*, **64B**, 1650 (1931).

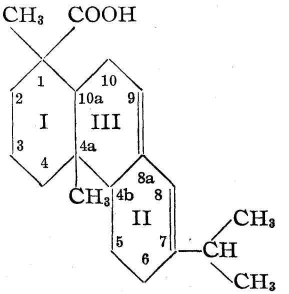
[23] Original manuscript received November 29, 1946.

[Contribution from the Hercules Experiment Station, Hercules Powder Company]

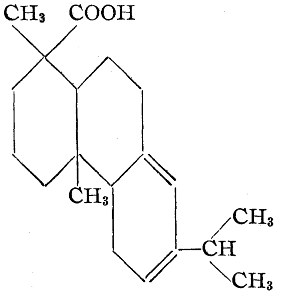
Resin Acids. I. An Improved Method of Isolation of Resin Acids; The Isolation of a New Abietic-Type[1] Acid, Neoabietic Acid

By George C. Harris and Thomas F. Sanderson

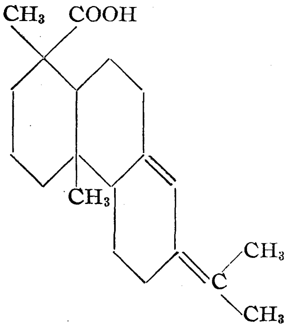
This is the first in a series of papers presenting recent developments made in these laboratories on the isolation and proof of structure of pure resin acids. This paper deals with improved methods of isolation of abietic acid (I)[2] and levopimaric acid (II)[3,4] the most familiar abietic-type acids; the isolation of neoabietic acid (III),[5] a new primary acid of this type, is also described.



I



II



III

Abietic Acid

The difficulty in separating abietic acid from isomeromorphic resin acids has made its isolation from rosin a difficult problem. However, Palkin and Harris[6] were able to obtain a pure abietic acid according to the following procedure: (1) isomerizing rosin by boiling in glacial acetic acid to increase the abietic acid content, (2) concen-

---

[1] We wish to designate by this term that type of resin acid that yields retene, 1-methyl-7-isopropylphenanthrene, upon complete dehydrogenation and has an isopropyl or isopropylidene group at C-7.

[2] L. Ruzicka, L. Sternbach and O. Jeger, *Helv. Chim. Acta*, **24**, 504 (1941).

[3] This word has purposely been written as one word since the compound is not stereoisomeric with dextropimaric acid as the prefixes *levo-* and *dextro-* would imply.

[4] L. Ruzicka and S. Kaufman, *Helv. Chim. Acta*, **23**, 1346 (1940); according to Ruzicka and Kaufman the double bonds may be at the positions indicated in Formula II or at positions 5–6 and 7–8, the former being preferred.

[5] G. C. Harris and T. F. Sanderson, Resin Acids. II., This Journal, **69**, 339 (1947).

[6] S. Palkin and T. H. Harris, *ibid.*, **56**, 1335 (1934).

trating the abietic acid in the form of "Steele's" acid[7] by crystallizing the isomerized rosin from glacial acetic acid, (3) further concentrating the abietic acid by the preparation and recrystallization of the acid sodium salts ($C_{19}H_{29}COONa\cdot 3C_{20}H_{30}O_2$), and (4) fractionating the regenerated acids by the preparation and recrystallization of the diamylamine salts, a method first employed by Balas.[8] This procedure is effective but somewhat tedious and gives a relatively low recovery (*ca.* 12%) of the pure acid compared with the total abietic acid which can be shown to be present by ultraviolt absorption spectra. We have now found that diamylamine, the amine used by Balas[8] and Palkin and Harris,[6] not only offers a means of purification of abietic acid, $[\alpha]^{24}\text{D}$ −98°, but is specific for the separation of abietic acid from the complex mixture of resin acids in rosin. Addition of a molar quantity of diamylamine to an acetone solution of isomerized rosin precipitates the crystalline amine salts high in abietic acid content from which the salt of abietic acid is readily separated by fractional crystallization. The pure acid, $[\alpha]^{24}\text{D}$ − 106°, m. p. 172–175°, was obtained by decomposition of the salt with a weak acid such as acetic or phosphoric to minimize isomerization of the regenerated acid. The yield amounted to 40% of the weight of the isomerized rosin which is in fair agreement with that indicated by the absorption spectra.

Ultraviolet absorption curves are of great value in determining the amount of abietic acid present in modified or unmodified rosins. Figure 1 shows the ultraviolet absorption spectra of pure abietic acid (curve 1) and isomerized rosin (curve 2) The difference, $\Delta\alpha$, in specific absorption coefficient between the maximum at 241 mμ and the inflection point at 248.5 mμ is a constant value characteristic of pure abietic acid and can well be used as a measure of the abietic acid content of a rosin. The ratio of this difference for isomerized rosin to that for the pure acid is a measure of the amount of pure acid in the isomerized rosin. On the basis of these ratios, isomerized rosin contains 47 ± 2% of abietic acid. This precision does not hold for a non-isomerized rosin which contains neoabietic acid whose most intense band of absorption is at 250 mμ.

The ultraviolet absorption spectrum of pure abietic acid was found to demonstrate its most intense band at 241 mμ, α (specific absorption coefficient)[8a] = 77.0. This value is in good accord with that reported by Sandermann[9] (240 mμ) and that calculated (242 mμ) according to a method postulated by Woodward[10] and in disagreement with the value of 237.5 mμ reported by Kraft.[11]

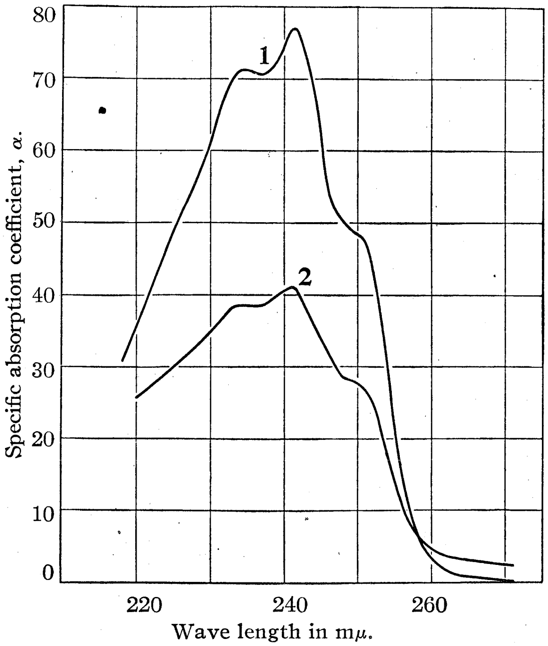


Fig. 1.—Ultraviolet absorption spectra: 1, abietic acid; 2, isomerized rosin.

Levopimaric Acid

Although levopimaric acid is the major constituent of the gum oleoresin of several conifers, its isolation has always been difficult with yields of the order of 1% having been obtained by Ruzicka, *et al.*,[12] and Palkin and Harris[13] from the "galipot"[13a] of *Pinus maritima* and *Pinus palustris*, respectively. The method employed was based on the fractional crystallization of the sodium salts.

The application of the amine salt technique in this instance resulted in the much increased yield of 20% of pure levopimaric acid $[\alpha]^{24}\text{D}$ −276°, from the "galipot" of *Pinus palustris*. The procedure is similar to that used for the isolation of abietic acid from rosin with the exception that butanolamine (2-amino-2-methyl-1-propanol, Commercial Solvents, Inc.) was used since it was found to be more specific for the precipitation of levopimaric acid than any other amine tried.

In the event that the whole oleoresin of *Pinus palustris* is used as the source of levopimaric acid, the total acids can be first separated from the turpentine by precipitation as amine salts. Cyclohexylamine was found most suitable for this purpose, since it results in a nearly quantitative precipitation of resin acids as the very insoluble cyclohexylamine salts from any medium in which they exist with non-resin acid material, *e. g.*, gum oleoresin or tall oil.[14] Formation of the butanol-

---

(7) L. L. Steele, This Journal, **44**, 1333 (1922).

(8) Fr. Balas, *Časopis Československeho Lěkárnictva*, **7**, 320 (1927).

(8a) Defined in the experimental section.

(9) W. Sandermann, *Ber.*, **74**, 154 (1941).

(10) R. B. Woodward, This Journal, **64**, 72 (1942).

(11) K. Kraft, *Ann.*, **520**, 133 (1935).

(12) L. Ruzicka and R. G. R. Bacon, *Helv. Chim. Acta*, **20**, 1542 (1937).

(13) S. Palkin and T. H. Harris, This Journal, **55**, 3677 (1933).

(13a) "Galipot" is a term used to describe the crystalline acids which settle out of the oleoresin, which, in turn, is a solution of resin acids in turpentine.

(14) G. C. Harris, U. S. Patent 2,419,211, April 22, 1947.

amine salt and regeneration of the acid as in the previous instance gave a yield of 15% based on the total acids or approximately 50% of the amount reported to be present. Recently, Fleck and Palkin[15] reported a value of 36% of levopimaric acid in the acids fraction of the oleoresin of *Pinus palustris* determined by the quantitative addition of maleic anhydride to levopimaric acid.

The ultraviolet absorption spectrum of pure levopimaric acid was found to demonstrate its most intense band at 272 mμ, $\alpha = 19.2$ (Fig. 2), in good agreement with that reported by Kraft.[11]

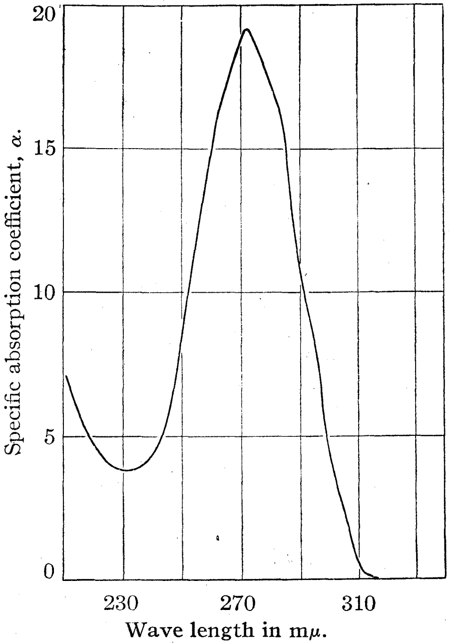


Fig. 2.—Ultraviolet absorption spectrum of levopimaric acid.

Neoabietic Acid

The presence of a dextrorotatory abietic-type acid in gum oleoresin has often been alluded to in the extensive literature on resin acids. The first serious attempt to isolate it was made by Kraft,[16] who was able to obtain only a mixture of acids with a positive rotation, $[\alpha]^{24}\text{D} + 11°$.[17] R. F. Cox, of this Laboratory, also isolated a resin acid with positive rotation, $[\alpha]^{24}\text{D} +83°$. This was obtained by the heat isomerization of abietic acid, $[\alpha]^{24}\text{D} -105°$, at 180° in accordance with a postulation by Ruzicka[18] that dextrorotatory acids are formed in equilibrium with levorotatory acids when the latter are isomerized at elevated temperatures. Cox's method of isolation of the dextro acid consisted of crystallizing the unaltered abietic acid from the mixture to concentrate the former in the residue from which it was fractionally crystallized. It is not surprising that further purification of the dextro acid was not obtained because fractional crystallization of mixtures of resin acids, as pointed out by Duffour,[19] always results in the isolation of mixed crystals rather than pure compounds. It was apparent, then, from the two instances cited above, that the lack of a workable technique for the isolation of pure resin acids from mixtures impeded progress in this direction.

Before employing the amine salt technique for the isolation of the dextrorotatory acid from the gum oleoresin of *Pinus palustris*, it was considered best to attempt its isolation from the simpler mixture of acids obtained in heat-isomerized abietic acid. Abietic acid, for this purpose, was heated[18] at 300° for twenty minutes, and the unreacted abietic acid (76%) separated from the mixture as its insoluble diamylamine salt. In this manner, a highly dextrorotatory residue was obtained which was treated with butanolamine in acetone to obtain two crops of crystalline salts. The first with rotation $[\alpha]^{24}\text{D} +24°$ was discarded, the second with rotation $[\alpha]^{24}\text{D} +100°$ was recrystallized from acetone to a constant rotation, $[\alpha]^{24}\text{D} +102°$. The salt was decomposed with boric acid to obtain a new resin acid, termed neoabietic acid, with rotation $[\alpha]^{24}\text{D} +159°$, and melting point 167–169°. Neoabietic acid, like levopimaric acid, was found to be highly susceptible to mineral acid and isomerizes almost completely to abietic acid in the presence of a trace of strong acid.

This acid was isolated in 5% yield from the resin acids of gum oleoresin by alternate fractional crystallization of the diethylamine and butanolamine salts. Neoabietic acid can also be prepared from commercial gum rosin of any color grade by using the diethylamine salt to obtain initial concentration and butanolamine to effect final purification.

The homogeneity of neoabietic acid was established by preparation and recrystallization of the methy ester, m. p. 61.5–62°, and also of the butanolamine salt, $[\alpha]^{24}\text{D} + 102°$, and regeneration in each case of acid identical with the original in optical rotation and ultraviolet absorption. The ultraviolet absorption spectrum of pure neoabietic acid demonstrates its most intense band at 250 mμ, $\alpha = 80.0$ (Fig. 3).

Experimental[20,21]

Abietic Acid

Acid Isomerization of Wood Rosin.—The extent to which rosin was isomerized to produce the maximum amount of abietic acid was determined as follows: A sample of rosin was heated under reflux in alcohol with concentrated hydrochloric acid. Samples were taken at intervals and the ultraviolet absorption characteristics and specific rotation of each determined. As shown in

---

[15] E. E. Fleck and S. Palkin, *Ind. Eng. Chem., Anal. Ed.*, **14**, 146 (1942).

[16] K. Kraft, *Ann.*, **524**, 1 (1936).

[17] The composition of Kraft's proabietic acid is the subject of a future publication; G. C. Harris and T. F. Sanderson, Resin Acids, VI.

[18] L. Ruzica and J. Meyer, *Helv. Chim. Acta*, **5**, 338, 342 (1922).

[19] M. A. Duffour, *Compt. rend.*, **175**, 109 (1922).

[20] All melting points are corrected.

[21] All rotations are of 1% solutions in absolute ethanol.

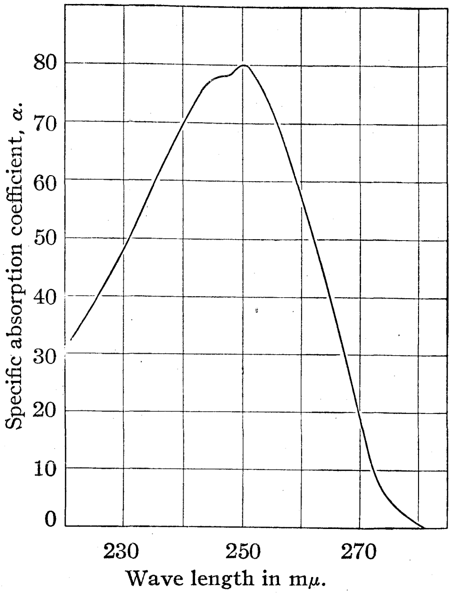


Fig. 3.—Ultraviolet absorption spectrum of neoabietic acid.

Fig. 4, the absorption curves of samples taken at one hour or after were the same and attained the highest value for specific absorption coefficient, α, at 241 mμ, indicating the production of the maximum amount of abietic acid, 47 ± 2%, at the end of one hour. The specific rotation of the samples, Fig. 5, also reached a constant value, $[\alpha]^{24}\mathrm{D}$ −35°, after one hour of heating, again indicating the formation of the equilibrium mixture at the end of this time.

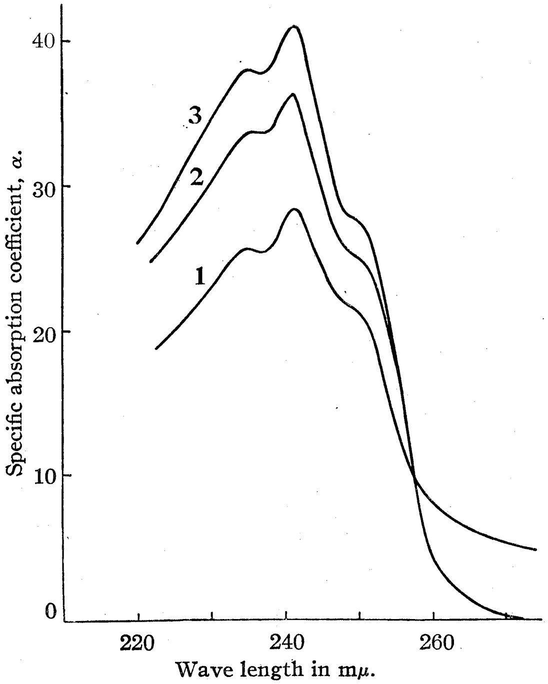


Fig. 4.—Ultraviolet absorption spectra: 1, N wood rosin; 2, rosin isomerized for half an hour; 3, rosin isomerized for one, two and three hours.

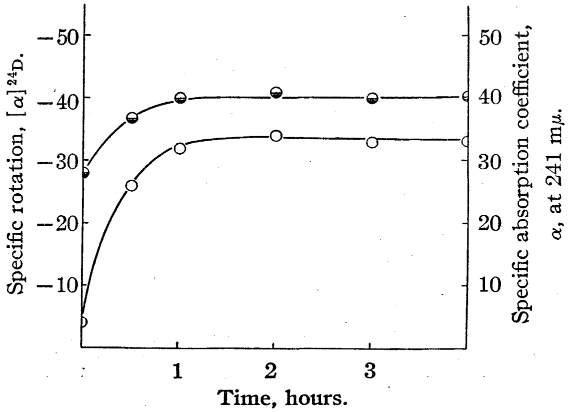


Fig. 5.—◓, Rate of change of specific absorption coefficient of isomerized rosin: ○, rate of change of specific rotation of isomerized rosin.

The sample used was prepared in the following manner. To a hot solution of 250 g. of wood rosin (color grades N to X, acid number 166) in 740 cc. of 95% ethanol was added 42 cc. of concentrated hydrochloric acid and the resulting solution boiled under reflux for one and one-half hours. A stream of carbon dioxide was passed over the surface of the solution during the reflux period and when the solution was being cooled to avoid discoloration due to atmospheric oxidation. At the end of the reaction time, the alcohol and acid were steam distilled, the water decanted, and the residue dissolved in ether. The ether solution was washed free of acid with water, dried over sodium sulfate, and the ether evaporated. The last traces of solvent were removed by melting the rosin in an oil-bath at 180 to 200° under water-pump vacuum. The molten rosin, blanketed continuously with carbon dioxide, was poured into a paper boat for ease of handling, to obtain 245 g. of material with rotation $[\alpha]^{24}\mathrm{D}$ −35°.

Preparation and Purification of the Diamylamine Salt.—To a solution of the isomerized rosin (245 g.) in 375 cc. of acetone at incipient boiling was added 127 g. of diamylamine (Sharples Company, Philadelphia, Pennsylvania) slowly with vigorous agitation. On cooling to room temperature, crystals appeared in the form of rosets. The mass was agitated, cooled in ice and filtered to obtain a cake of salts that was washed with 150 cc. of acetone. The latter was dried in a vacuum oven at 50° to obtain material with rotation $[\alpha]^{24}\mathrm{D}$ −18°. After four crystallizations, using a sufficient amount of acetone (*ca.* 4 liters for 200 g. of salt) to obtain an almost clear solution and evaporating to incipient precipitation (*ca.* 2 liters of solution), 118 g. of the pure amine salt of abietic acid was obtained with rotation $[\alpha]^{24}\mathrm{D}$ −60°. On recovery and recrystallization of the back crops to material with rotation $[\alpha]^{24}\mathrm{D}$ −60°, an additional 29 g. of pure salt was obtained, making a total of 147 g. In obtaining the later crops of salt by concentration of the mother liquors, some amine is lost by evaporation that should be replaced by the addition of a few drops to the concentrated solution.

Isolation of Abietic Acid.—To a cooled solution of the amine salt of abietic acid (147 g.) in one liter of 95% ethanol was added 39 g. of glacial acetic acid at once with stirring and 900 cc. of water slowly at first with vigorous agitation to incipient precipitation and then more freely. The crystals were filtered at once and washed with a liter of water to free them of traces of acetic acid. The acid was recrystallized from 750 cc. of 95% ethanol by the slow addition of 600 cc. of water as above and dried in a vacuum desiccator at room temperature over sodium hydroxide in an oxygen-free atmosphere. Undue exposure to higher temperatures will result in isomerization, and contact with air will result in the oxidation of the material. In this manner, 98 g. (40% by weight of isomerized rosin; theoretical 47%) of abietic acid was obtained with rotation $[\alpha]^{24}\mathrm{D}$ $-106°$. For storage purposes, the acid should be kept in vials under good vacuum.

Absorption Spectra.—The absorption spectrum data were obtained from measurements made with a Beckman ultraviolet spectrophotometer. The formulas employed in making the calculations use the term α, specific absorption coefficient.

$$\alpha = \log_{10} I_0/I/cl$$

I_0 = intensity of radiation transmitted by the solvent (95% ethanol)
I = intensity of radiation transmitted by the solution
c = concentration of solute in grams per liter
l = length in centimeters of solution through which the radiation passes

Levopimaric Acid

Preparation and Purification of the Butanolamine Salt.—To a solution of 125 g. of "galipot" in 250 g. of acetone was added 37 g. of butanolamine (2-amino-2-methyl-1-propanol) in 37 g. of acetone.[22] The suspension was cooled, the salt filtered, and a second crop taken by concentrating the solution to half its volume. The salt was fractionally crystallized from methyl acetate to obtain 31 g. of material with rotation $[\alpha]^{24}\mathrm{D}$ $-218°$.

Isolation of Levopimaric Acid.—The decomposition of the amine salt of levopimaric acid was carried out with boric acid.[23] The salt was suspended in ether and shaken vigorously with a saturated boric acid solution until the amine salt crystals had disappeared. To assure complete decomposition of the salt, the ether solution was washed twice more with boric acid. The ether solution containing the resin acid was washed free of boric acid with water, dried and the ether evaporated.[22] The acid was crystallized by dissolving it in warm ethanol and adding water to incipient turbidity, to obtain, upon cooling to room temperature, 24 g. of levopimaric acid (20% of the "galipot") with rotation $[\alpha]^{24}\mathrm{D}$ $-276°$.

Isolation of Primary Resin Acids from Gum Oleoresin. When the oleoresin is to be used as the source of levopimaric acid, the resin acids are separated from the turpentine according to the following procedure and used as in the following section. To a solution of 200 g. of the gum oleoresin of *Pinus palustris* in 600 g. of narrow-range gasoline (boiling range 90–100°) at 40° was added 41 g. of cyclohexylamine (Monsanto Chemical Co.) in 41 g. of gasoline.[22] The mass of crystalline salts was agitated and the suspension cooled in ice before the salts were filtered and washed with 200 g. of fresh solvent.

The salts were first air-dried overnight to remove the solvent and then decomposed in the same manner as the butanolamine salts taking the usual precautions for complete decomposition and rise in temperature of the concentrated solutions. The last traces of ether were evaporated by puffing the residue to a powder under water-pump vacuum. In this way was obtained 124 g. of resin acids (62% of the total oleoresin) with acid number 185 and neutral equivalent 302.

Preparation and Purification of Amine Salt and Isolation of Levopimaric Acid.—The butanolamine salts of the resin acids fraction (124 g.) were prepared as in the case of "galipot" using the same ratio of amine and solvent. The decomposition of the salts was carried out with the same precautions and the regenerated acid crystallized from ethanol and water to obtain 18.6 g. of pure levopimaric acid (15% of the total oleoresin acids) with rotation $[\alpha]^{24}\mathrm{D}$ $-276°$.

Neoabietic Acid

Heat Isomerization of Abietic Acid; Isolation of Amine Salt of Neoabietic Acid.—A 50.0-g. sample of abietic acid, $[\alpha]^{24}\mathrm{D}$ $-106°$, prepared according to the method described in this paper, was heated at 300° for twenty minutes under a stream of carbon dioxide gas. At the end of this time the molten material was poured in a paper boat to cool, chipped and dissolved in 100 cc. of acetone. Diamylamine (27 g.) was added to precipitate the unreacted abietic acid as its insoluble salt. Two successive crops of salts were obtained, totalling 58.1 g. and corresponding to 76% of unaltered abietic acid. The mother liquor was diluted with 50 cc. of acetone and treated with 3.6 g. of butanolamine to form the butanolamine salts of the residual resin acids combined as diamylamine salts. A first crop with rotation $[\alpha]^{24}\mathrm{D}$ $+24°$ was discarded, and the second, with rotation $[\alpha]^{24}$ $+100°$, obtained by concentrating the mother liquor to half the volume, was recrystallized from acetone to a constant rotation, $[\alpha]^{24}\mathrm{D}$ $+102°$.

Isolation of the New Abietic-Type Acid, Neoabietic Acid.—The butanolamine salt was suspended in ether and decomposed with a saturated solution of boric acid in the usual manner.[23] The ether solution containing the resin acid was washed free of boric acid with water, dried over sodium sulfate, and the ether evaporated.[22] The residue was crystallized from alcohol and water to obtain the pure neoabietic acid with rotation $[\alpha]^{24}\mathrm{D}$ $+159°$, melting point 167–169°, neutral equivalent 302, calcd. 302, in about 1% yield.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.39; H, 10.00. Found: C, 79.46, 79.40; H, 9.97, 9.97.

Isolation of Neoabietic Acid from the Gum Oleoresin.—The resin acids of the gum oleoresin of *Pinus palustris* were separated from the turpentine according to the method described in the previous section on levopimaric acid and used in the following manner for the isolation of neoabietic acid.

To a solution of the total acids, 124 g., in 248 g. of acetone was added 37 g. of butanolamine in 37 g. of acetone. The first three crops of salt, with rotations $[\alpha]^{24}\mathrm{D}$ -218, -210 and $-60°$, highly concentrated with the salt of levopimaric acid, were isolated. Further concentration of the mother liquor, with intermittent addition of small amounts (2 g.) of butanolamine to replace that lost by evaporation, resulted in the isolation of the two dextrorotatory crops, with rotations $[\alpha]^{24}\mathrm{D}$ $+12$ and $+15°$. Since no further increase in dextrorotation could be realized, these salts were combined and decomposed with boric acid in the usual manner. The more specific diethylamine was used to prepare the salts of the regenerated acids. Four recrystallizations from acetone resulted in the isolation of salts with rotation $[\alpha]^{24}\mathrm{D}$ $+70°$, which again could not be increased by further fractionation. These salts were then decomposed with boric acid, the butanolamine salts prepared, and the latter recrystallized from acetone to the top rotation of $[\alpha]^{24}\mathrm{D}$ $+102°$.

The pure salt of neoabietic acid (8.2 g.) was decomposed with boric acid to obtain 6.1 g. (5% of the total oleoresin acids) of pure acid with rotation, $[\alpha]^{24}\mathrm{D}$ $+159°$.

Preparation of the Methyl Ester of Neoabietic Acid.—Five grams of neoabietic acid, $[\alpha]^{24}\mathrm{D}$ $+159°$, was dissolved in 50 cc. of ether; the resulting water-white solution was treated with an excess of an ether solution of diazomethane as evidenced by a permanent yellow coloration. After standing for twenty minutes, the solution was evaporated to dryness.[22] The seed crystal was obtained by cooling a methanol solution of one drop of liquid ester to $-30°$ in an acetone–Dry Ice-bath. The ester, then, was readily crystallized from methanol with the aid of the seed crystal in excellent yield (5.0 g.) with a constant melting point, 61.5–62°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.70, 79.65; H, 10.07, 10.17.

The purity and homogeneity of neoabietic acid was established in the following manner. Material with rotation $[\alpha]^{24}\mathrm{D}$ $+159°$ was used to prepare the butanol-

---

(22) The formation of the amine salts is an exothermic reaction and great care must be taken that the temperature does not rise above 50° to alter the levopimaric acid (this applies to neoabietic acid as well) which is highly susceptible to isomerization by heat.

(23) Levopimaric acid (this applies to neoabietic acid as well) is highly susceptible to mineral acid and isomerizes almost completely to abietic acid in the presence of a trace of strong acid. Such precautions against acid isomerization must be taken in regenerating the resin acid from its amine salt. Boric acid, therefore, the weakest acid that can effect the decomposition of the amine salts, is always employed.

amine salt which was recrystallized several times to obtain the constant rotating salt (same as that from which the acid was isolated), $[\alpha]^{24}\mathrm{D}$ +102°. The resin acid was regenerated in the usual manner with the same rotation, $[\alpha]^{24}\mathrm{D}$ +159°, and the same ultraviolet absorption characteristics, particularly the height of the most intense band, 250 mμ, at $\alpha = 80.0$. The methyl ester, prepared with diazomethane as above, was obtained with the same constant melting point 61.5–62°. Saponification in alcoholic alkali with alkali in a sealed tube at 50° for ninety-six hours with subsequent acidification with carbon dioxide and boric acid resulted in the quantitative isolation of neoabietic acid with unchanged rotation, $[\alpha]^{24}\mathrm{D}$ +159°.

Isolation of Neoabietic Acid from Gum Rosin.—A 200-g. sample of gum rosin was dissolved in 400 g. of acetone and treated, at 50°, with 45 g. of diethylamine in an equal weight of acetone. The complete precipitation of salts was allowed to take place over a long period of time (twenty-four hours) at room temperature. No attempt was made to hasten the crystallization by cooling because the necessary fractionation was not obtained in this manner. The salts were fractionated from acetone to a rotation $[\alpha]^{24}\mathrm{D}$ +70° and converted to the butanolamine salts by dissolving in acetone and adding the necessary amount of butanolamine. The latter were, in turn, crystallized to a rotation $[\alpha]^{24}\mathrm{D}$ +102° and the pure neoabietic acid isolated in 5% yield (10.0 g.) with rotation $[\alpha]^{24}\mathrm{D}$ +159°.

Summary

1. An improved method, based on the amine salt technique, for the isolation of abietic acid from acid-isomerized wood rosin and levopimaric acid from the gum oleoresin of *Pinus palustris* is described.

2. The isolation of a new, abietic-type acid, termed neoabietic acid, from heat-isomerized abietic acid, the gum oleoresin of *Pinus palustris* and gum rosin is described.

3. The ultraviolet absorption spectra, utilizing specific absorption coefficients, α, have been determined for each of the three abietic-type acids.

WILMINGTON, DELAWARE RECEIVED[24] AUGUST 12, 1947

---

[24] Original manuscript received August 9, 1946.

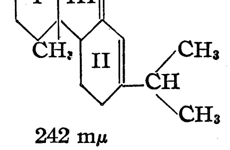
[CONTRIBUTION FROM THE HERCULES EXPERIMENT STATION, HERCULES POWDER COMPANY]

Resin Acids. II. The Structure of Neoabietic Acid

BY GEORGE C. HARRIS AND THOMAS F. SANDERSON

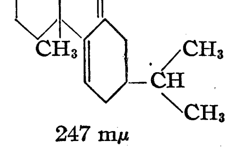
Neoabietic acid[1] has been isolated from the oleoresin and rosin of *Pinus palustris*. It has now been proved that this acid is an abietic-type acid since upon dehydrogenation with palladium–carbon catalyst retene, 1-methyl-7-isopropylphenanthrene, was isolated. The presence of two double bonds was shown by catalytic hydrogenation to the tetrahydro acids and by absorption in the ultraviolet region.[2] The intense band (Fig. 1, Curve 1) at 250 mμ, indicated also that the two double bonds are conjugated between two rings or that one is exocyclic with respect to the other in analogy with the absorption of abietic acid at 241 mμ and in contrast with that of levopimaric acid at 272 mμ. With this information, the structures I–V came into consideration.

From the work of R. B. Woodward[3] predictions can be made concerning the wave length of the most intense band of absorption of this type of conjugated system. These predictions are based on the degree of substitution of the double-bond carbon atoms; they are given below each formula. Since neoabietic acid demonstrates its most intense band at 250 mμ and since the predicted value for abietic acid, I, was so close to that found, 241 mμ, formula IV was at once suspected as that for neoabietic acid.



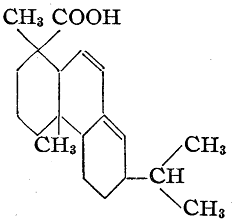
242 mμ

I



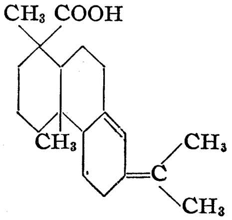
247 mμ

II



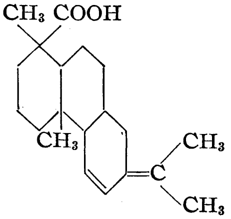
237 mμ

III



252 mμ

IV



242 mμ

V

If formula IV were that for neoabietic acid, ozonization and decomposition of the ozonide with water would result in the formation of acetone, as one of the products. The experiment was carried out and acetone was isolated as its 2,4-

---

[1] G. C. Harris and T. F. Sanderson, Resin Acids. I, THIS JOURNAL, **70**, 334 (1948).

[2] The ultraviolet absorption data were determined by Dr. Evelyn V. Cook of this Laboratory.

[3] R. B. Woodward, THIS JOURNAL, **64**, 72 (1942).

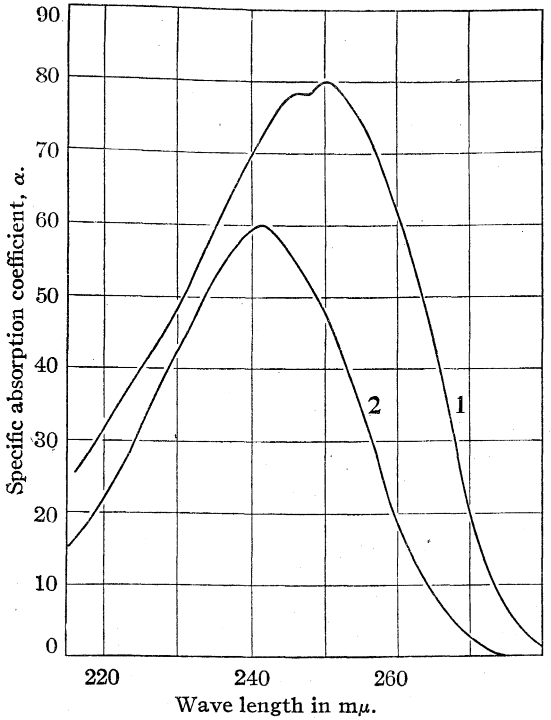
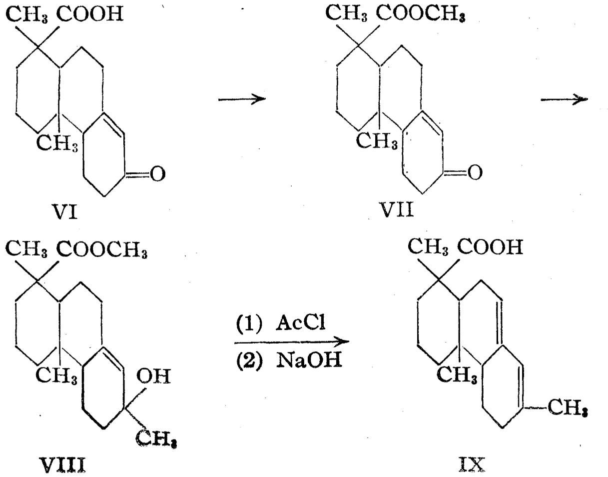


Fig. 1.—Ultraviolet absorption spectra: 1, neoabietic acid; 2, ketone (VI).

dinitrophenylhydrazone which was shown to be that of acetone after a mixed melting point with an authentic sample. After partial ozonolysis, that is, ozonization of only the exocyclic double bond of the isopropylidene group, in addition to acetone an α,β-unsaturated ketone would be obtained. This was found to be the case in the isolation of the ketone, VI, with melting point 187–188°. The functionality of the α,β-unsaturated keto acid was shown in the following manner. The neutral equivalent of the crystalline compound was 276, theory for the unsaturated keto acid 276. Its methyl ester, VII, was prepared with diazomethane and melted at 127–128°. The presence of the keto group was shown after the preparation of its 2,4-dinitrophenylhydrazone, m. p. 221–222°, and the isolation of the crystalline methyl Grignard addition product of the ester, VIII, m. p. 100–102°. The quantitative absorption of 1.0 mole of hydrogen of the latter in absolute ethanol with Adams catalyst indicated the residual unsaturation. Upon removal of the tertiary hydroxyl group of the Grignard product, VIII, with acetyl chloride or dry hydrogen chloride in benzene, hydrolysis of the ester group with alkali in diethylene glycol and redistribution of the double bonds, an abietic acid analog, IX, was obtained with rotation, $[\alpha]^{24}D$ − 125°, m. p. 187–190°, and specific absorption coefficient, α = 80.0 (Fig. 2).



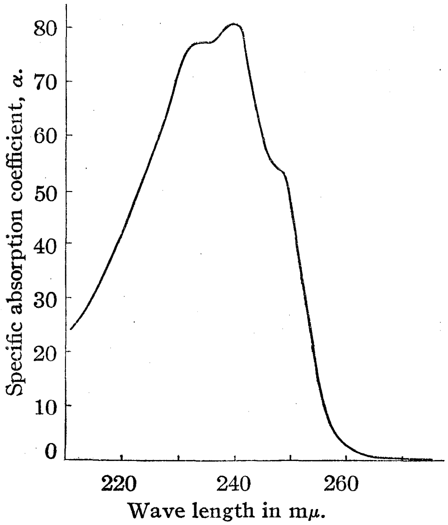
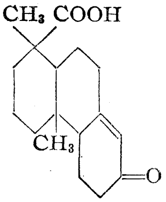
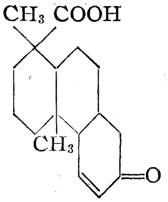


Fig. 2.—Ultraviolet absorption spectrum of an abietic acid analog.

If formula V were that for neoabietic acid (although very unlikely in view of its absorption at 242 mμ), a ketone with formula X would be obtained.



VI



X

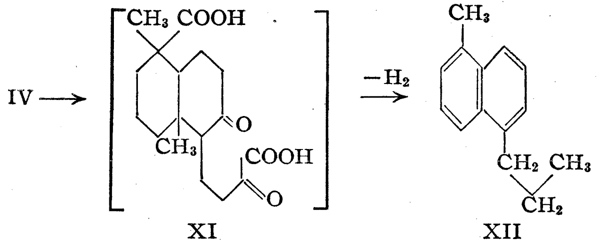
Using Woodward's[4] rules for predicting the most intense band of absorption of substituted α,β-unsaturated ketones, it is a simple matter to differentiate between the two ketones, VI and X. The ketone actually isolated demonstrated a maximum at 242 mμ (Fig. 1, Curve 2), a value that falls well within the limits,[4] 239 ± 5 mμ, set for a system with substitution similar to that of ketone VI and outside of those, 225 ± 5 mμ, set for a system similar to that of ketone X. Therefore

---

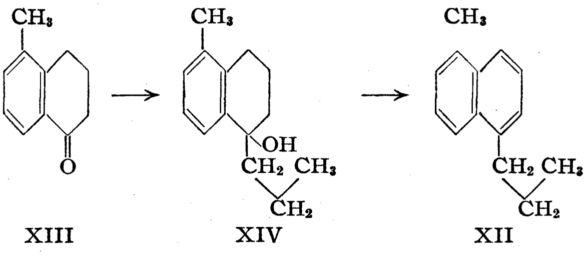
[4] R. B. Woodward, This Journal, 63, 1123 (1941).

formula VI is that for the ketone and formula IV that for neoabietic acid.

Further evidence for formula IV would be the isolation of a dialkylated naphthalene upon complete ozonization and dehydrogenation of the decomposed ozonide. In the case of the other structures, I through III, V having been eliminated, both rings II and III are split to result in the isolation of a substituted benzene nucleus or complete decomposition. Actually a 1,5-disubstituted naphthalene, XII, was isolated as proved by the similarity of the ultraviolet absorption curves of the trinitrobenzolate of this material with that of the synthetic sample and of an authentic sample of 1,5-dimethylnaphthalene[5] (Fig. 3). The hydrocarbon was isolated from the dehydrogenation mixture as its trinitrobenzolate and analyzed as the derivative and as the pure substance. From the analytical data it was determined to be 1-methyl-5-*n*-propylnaphthalene which could be obtained only from a compound with formula IV.



Hydrocarbon XII was synthesized in the following manner. The *n*-propyl Grignard product, of 5-methyl-1-tetralone,[5] XIII, was prepared and dehydrogenated with a palladium-on-carbon catalyst at 250°. The trinitrobenzolate of the hydrocarbon was prepared and found to melt at 82–84°. A mixed melting of the trinitrobenzolate of the hydrocarbon from the dehydrogenation mixture and this authentic sample showed no depression, m. p. 82–84°. The two derivatives also demonstrated identical X-ray diffraction patterns (Fig. 4).



For the sake of completeness and to eliminate the possibility of obtaining acetone from a structure such as that of abietic acid,[6] I, the same experiments were carried out with abietic acid. The failure to obtain acetone or a di- or tri-alkylated naphthalene upon complete ozonization both lends strength to the structure proof of neoabietic acid and eliminates the possibility of formula V as that of abietic acid in view of its absorption at 241 mμ wave length.

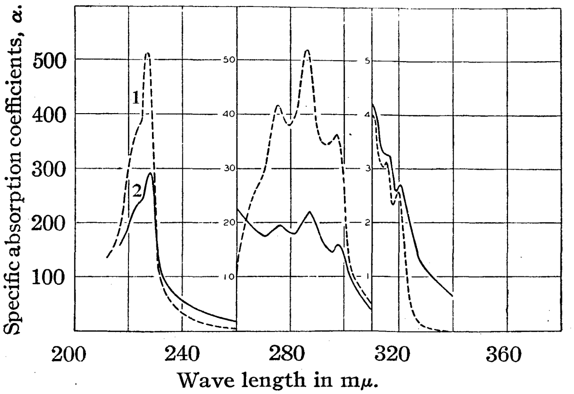


Fig. 3.—Ultraviolet absorption spectra: 1, the hydrocarbon, 1,5-dimethylnaphthalene; 2, the trinitrobenzolates of the isolated and synthetic 1-methyl-5-*n*-propylnaphthalene (identical curves for the two materials).

Experimental[7]

Dehydrogenation and Hydrogenation of Neoabietic Acid.—A 2.0-g. sample of neoabietic acid was mixed intimately with 2.0 g. of 5% palladium-on-carbon catalyst and the mixture heated at 300–330° for four hours. Carbon dioxide gas was passed over the reaction mixture to eliminate the reaction gases. After cooling to room temperature, the reaction products were dissolved in ether and separated from the catalyst by filtration. The oil was dissolved in ethanol and treated with a concentrated ethanol solution of trinitrobenzene to obtain 1.9 g. (65% yield) of constant melting derivative, m. p. 143–144°, that was shown to be that of retene when no depression was observed in a mixed melting point with an authentic sample.

Upon quantitative hydrogenation of neoabietic acid, 1.29% of hydrogen (H_2) was absorbed, calcd. for two double bonds 1.32%.

Ozonization of Neoabietic Acid.—The acid, rotation $[\alpha]^{24}\text{D}$ +159°,[8] was ozonized in 1.0-g. batches in 50 cc. of ethyl chloride at −60° to −70° using an oxygen flow of 20–25 liters per hour to obtain an oxygen solution of 5% of ozone. The gas was passed through the solution[9] until a purple coloration developed (*ca.* two hours) which indicated an excess of ozone. At the end of this time, the excess ozone was swept out with oxygen.

Decomposition of the Ozonide: Isolation of Acetone.—The ethyl chloride solution of the ozonide was added dropwise to hot water in an apparatus so designed that the ethyl chloride was evaporated and the acetone–water

---

[5] We wish to thank Dr. E. W. J. Butz of the Bureau of Animal Industry, U. S. Department of Agriculture, for a pure sample of this material; E. W. J. Butz, THIS JOURNAL, **62**, 2557 (1940).

[6] The structure was proved as that of formula I by L. F. Fieser and W. P. Campbell, *ibid.*, **60**, 159 (1938), and L. Ruzicka, L. Sternbach and O. Jeger, *Helv. Chim. Acta*, **24**, 504 (1941).

[7] All melting points are corrected.

[8] All rotations are of 1% solutions in absolute ethanol.

[9] The subsequent isolation of the hydrocarbon (XII) was indeed difficult until the technique for this type of ozonization was developed. When the solvent in the reaction was not anhydrous. the ozonide was decomposed in the medium and the intermediate ketone (XI) further attacked to form a lactone (A. Baeyer and V. Villiger, *Ber.*, **32**, 3625 (1899); **33**, 858 (1900). The active agent in Caro's acid is ozone). However, when the solvent was anhydrous, the ozonide remained intact during the ozonolysis to result in the formation of the ketone (XI) upon decomposition of the ozonide and the subsequent isolation of the hydrocarbon in good yield upon dehydrogenation.

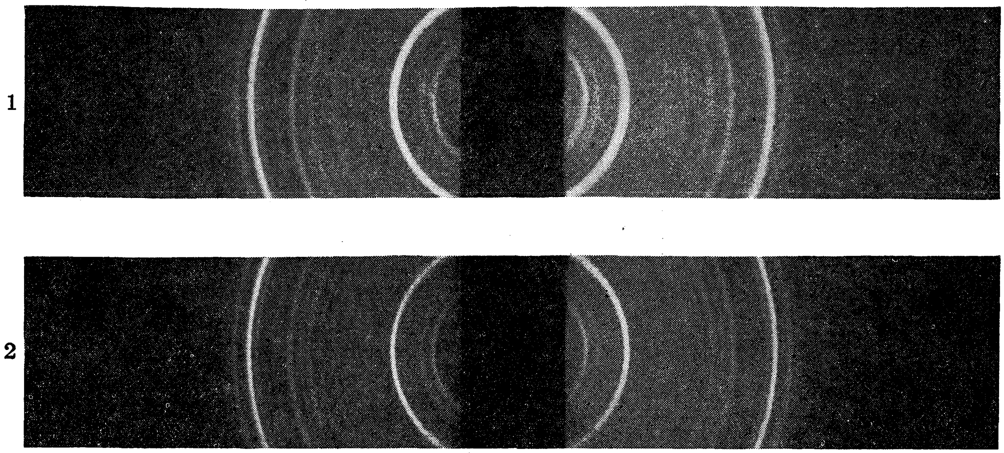


Fig. 4.—X-Ray diffraction patterns of trinitrobenzolates of 1-methyl-5-*n*-propylnaphthalene: 1, isolated; 2, synthesized.

azeotrope refluxed back to the receiver. After two hours of boiling, small portions of distillate were passed periodically for an hour through a saturated alcoholic solution of 2,4-dinitrophenylhydrazine. The alcoholic solution of the reagent (100 cc. of alcohol; 1.0 g. of reagent) was treated with 2 cc. of concentrated hydrochloric acid and boiled until a clear solution was obtained. Upon cooling, in addition to the dark red crystals of reagent, there appeared long, yellow needles which were recrystallized to a constant melting point of 124–126° and were proved to be the 2,4-dinitrophenylhydrazone of acetone when no depression was observed on melting with an authentic sample.

Isolation of 1-Methyl-5-*n*-Propylnaphthalene, XII.—The non-steam-volatile fraction of the decomposed ozonide was dissolved in ether and the bicarbonate-soluble fraction isolated (0.7 g. from 1.0 g. of acid). This was powdered, mixed intimately with 0.7 g. of 5% palladium–carbon catalyst, and dehydrogenated under carbon dioxide gas at 330–350° for four hours. The catalyst was filtered from an ether solution of the dehydrogenation product, the ether evaporated, and the residue dissolved in alcohol and treated with a saturated alcoholic solution of trinitrobenzene. The derivative precipitated and was crystallized to a constant melting point, 82–84°. The molecular weights were determined ebullioscopically, using acetone as solvent.

Anal. Calcd. for $C_{14}H_{16}\cdot C_6H_3N_3O_6$: C, 60.6; H, 4.8; N, 10.6; mol. wt., 199. Found: C, 59.8, 60.3; H, 4.8, 4.6; N, 10.3, 10.0; mol. wt., 201, 203.

The derivative in benzene was passed through a column of alumina to separate the hydrocarbon.

Anal. Calcd. for $C_{14}H_{16}$: C, 91.3; H, 8.7; mol. wt., 184. Found: C, 90.8, 91.0; H, 9.0, 9.2; mol. wt., 185, 188.

Preparation of 1-Methyl-5-*n*-propylnaphthalene, XII.—A 1.0-g. sample of 5-methyl-1-tetralone (XIII), m. p. 49.5–50.5°, was dissolved in dry ether and added to an ether solution of an *n*-propyl Grignard reagent prepared from 0.5 g. of magnesium and 3.3 g. of *n*-propyl iodide. The addition product was decomposed with saturated ammonium chloride and the tertiary alcohol, 1.3 g., isolated in ether. Attempts to crystallize the latter failed.

The oil was mixed intimately with 1.0 g. of 5% palladium-on-carbon catalyst and heated at 250° for two hours. The catalyst was filtered from an ether solution of the dehydrogenation mixture and the trinitrobenzolate of the hydrocarbon prepared in an alcoholic solution of the hydrocarbon using a saturated alcoholic solution of trinitrobenzene and crystallized to a constant melting point, 82–84°. A mixed melting point of the derivative from the dehydrogenation mixture with that of the synthetic sample showed no depression, m. p. 82–84°.

Isolation of Ketone VI.—For the ozonization of only the isopropylidene double bond the experiment was carried out in the same manner as for complete ozonization in respect to solvent, concentration, and temperature, but the time of ozonization was only thirty minutes. The ozonide was decomposed in the same manner and the product isolated in ether. The ketone was crystallized from the mixture from ether, and recrystallized to a constant melting point, 187–188°, and ultraviolet absorption curve with absorption coefficient, $\alpha = 60.2$.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 74.24; H, 8.72; neut. equiv., 276. Found: C, 74.04, 73.93; H, 8.96, 8.84; neut. equiv., 276.

The methyl ester, VII, was prepared in the usual manner with diazomethane and melted at 127–128°.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.45; H, 9.03. Found: C, 74.49, 74.45; H, 9.27, 9.19.

Derivatives of Ketone VI.—The 2,4-dinitrophenylhydrazone of the pure ketone was prepared in the usual manner in ethanol and recrystallized to a constant melting point, 221–222°.

The Grignard reaction product was prepared in the following manner. The reagent was prepared in a dropping funnel using 1.0 g. of magnesium turnings and 5.7 g. of methyl iodide in 25 cc. of dry ether and added dropwise to an ether solution of 5.8 g. of the ester, VII. A precipitate formed that remained insoluble after one hour of boiling of the mixture. After standing overnight, the reaction product was decomposed with saturated ammonium chloride and the product dissolved in ether. The ether solution was washed well with water, dried and the ether evaporated to obtain, upon recrystallization from ether–hexane, 3.0 g. of material with melting point 100–102°, VIII.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.52, 74.43; H, 9.84, 9.87.

Upon quantitative hydrogenation in absolute ethanol with Adams catalyst, the methyl ester of the Grignard addition product absorbed 0.63% of hydrogen, theory for one double bond 0.65%.

Isolation of the Abietic Acid Analog, IX.—A 5.0-g. sample of the Grignard product was dissolved in acetyl chloride at room temperature (same results obtained with dry hydrogen chloride in benzene). After standing for one hour, the reagent was evaporated under vacuum for a period of twenty-four hours. Attempts at crystallizing the ester were not successful; therefore, it was hydrolyzed in the usual manner with alkali (3.0 g.) in diethylene glycol. The acid was readily crystallized from alcohol and water to a constant melting point, 187–190°, $[\alpha]^{24}\text{D}$ − 125°, and specific absorption coefficient, α = 80.0.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.68, 78.69; H, 9.45, 9.50.

Summary

The structure of neoabietic acid has been proved with the aid of Woodward's rules for unsaturated systems, and by the isolation of acetone, a 1,5-dialkylated naphthalene, and a substituted α,β-unsaturated ketone.

WILMINGTON, DELAWARE RECEIVED[10] AUGUST 12, 1947

---

[10] Original manuscript received August. 9, 1946.

[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, MONSANTO CHEMICAL COMPANY]

N,N'N''-Triacylmelamines

BY WILLIAM S. EMERSON AND TRACY M. PATRICK, JR.

Ostrogovich[1] has reported that treatment of melamine with acetic anhydride gives 96% of diacetylmelamine and with benzoic anhydride gives 100% of tribenzoylmelamine. Diacetylmelamine can be further acetylated with a large excess of acetic anhydride to triacetylmelamine.[1] Triacetylmelamine also can be prepared by acetylating melamine with acetic anhydride in the presence of sodium acetate.[2]

We have found that aliphatic anhydrides above acetic give triacylmelamines as the sole products, and have prepared eleven such compounds by this method in 85–99% yields. We have also prepared diacetylmelamine by Ostrogovich's method.

Attempts to hydrolyze tripropionylmelamine to less highly acylated products were unsuccessful. The compound was unaffected by boiling water but was completely hydrolyzed to melamine by hot aqueous sodium hydroxide or sodium carbonate. Hot aqueous hydrochloric acid not only removed the propionyl groups but also hydrolyzed the melamine to what was probably a mixture of ammeline and ammelide.

Our tribenzoylmelamine melted at 201–203° in contrast to the 142–143° reported by Ostrogovich. His product was probably solvated.

Experimental

Preparation of Triacylmelamines.—These compounds were prepared by heating melamine with the appropriate acid anhydride. In the smaller runs a large test-tube (1 in. by 10 in.) with a thermometer as the stirrer, served as the reaction vessel. The larger runs were conducted in three-necked flasks of suitable dimensions. In all cases the temperature was raised by means of an oil-bath to the value indicated in the table and held there for five to thirty minutes. Upon cooling, the reaction mixture was diluted with some solvent such as methanol, ethanol, acetone or ethyl acetate, and filtered. The solid was washed with additional solvent and dried to obtain the crude yield. Further purification was effected by crystallization from glacial acetic acid or from the anhydride used in the preparation of the compound in question. The compounds prepared are summarized in Table I.

Hydrolyses of Tripropionylmelamine.—When 5 g. of tripropionylmelamine and 100 cc. of water were boiled under reflux for one hour the tripropionylmelamine was recovered unchanged, m. p. 275–276° (282°).

TABLE I

N,N',N''-TRIACYLMELAMINES

Acyl	Mol.[b] ratio	Reaction Temp., °C.	Reaction Time, min.	Yield, %	M. p.,[c] °C.	Nitrogen, % Calcd.	Nitrogen, % Found
Acetyl[a]	12	132	15	99[d]	312[e]	40.0	39.6
Propionyl	8.1	158	15	94	282	28.6	28.6[f]
n-Butyryl	12	160	30	98	258	25.0	24.6
n-Valeryl	10	172	30	94	228–229	22.2	22.4[f]
Isovaleryl	12	167	15	85	216–218	22.2	21.8
Caproyl	8.8	175	15	91	220	20.0	19.9
Oenanthyl	10	160	5	90	210	18.2	18.2
Caprylyl	9.3	175	15	94	209	16.7	16.7
Pelargonyl	6.3	185	5	88	194–195	15.4	15.3
Lauryl	6.5	192	15	99	178–179	12.5	12.5
Stearyl	3.5	200	30	93	159–161	9.08	9.66[f]
Oleyl	4.0	197	30	99	138–140	9.14	9.49
Benzoyl	8.3	172	60	84	201–203[g]	19.2	19.2

[a] Diacetylmelamine. [b] Molar ratio of anhydride to melamine. [c] All melting points corrected. [d] Ostrogovich[1] obtained a 96% yield, m. p. 305–306°. [e] Decomposed. [f] Microanalyses by the Oakwold Laboratories, Alexandria, Virginia. [g] Ostrogovich[1] gives m. p. 142–143°.

A 5-g. sample of tripropionylmelamine was boiled one hour with 100 cc. of 5% aqueous sodium hydroxide. Upon cooling, the mixture was neutralized with acetic acid and filtered. The 1.7 g. (81%) of dried solid proved to be melamine, m. p. 350° uncor. (347°).[1]

A similar experiment in which 100 cc. of 5% aqueous sodium carbonate was used yielded 1.7 g. (81%) of melamine, m. p. 353–354° uncor. (347°).[1]

A mixture of 5 g. of tripropionylmelamine and 100 cc. of 5% aqueous hydrochloric acid was boiled under reflux for one hour, cooled and neutralized with aqueous sodium bicarbonate. The solid was separated by filtration, washed with water and dried. It weighed 1.8 g. When heated on a spatula it did not melt but slowly decomposed and sublimed. It was soluble in dilute alkali.

Anal. Found: N, 50.8, 50.7. Calcd. for ammeline: N, 55.1. Calcd. for ammelide: N, 43.8.

Summary

Eleven new triacylmelamines have been prepared in 85–99% yield by treating melamine with the appropriate acid anhydride.

RECEIVED JULY 21, 1947

---

[1] Ostrogovich, *Gazz. chim. ital.*, **65**, 566 (1935).

[2] Cason, THIS JOURNAL, **69**, 495 (1947).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ST. LOUIS UNIVERSITY]

Dielectric Studies. IX. Studies with Gasoline[1]

BY NORMAN C. C. LI AND THOMAS D. TERRY

In earlier papers[2] it was shown that dipole moment studies can be made using solvents of unknown molecular weights, such as gasoline, kerosene and petroleum ether, and that the dipole moment values so obtained are in close agreement with values obtained using non-polar solvents of known molecular weights. The assumption is made, of course, that gasoline, kerosene and petroleum ether are non-polar. In this study this assumption is put to rigorous experimental tests by determining the dipole moment of gasoline and its fractions.

Experimental

The dielectric constants were obtained by determining the capacity difference between rotor positions of a variable cell by means of a heterodyne beat apparatus. It consisted of two oscillators, "The Ferret Model 600" manufactured by the Coastwise Electronics, a Model 200 Signal Tracer manufactured by the Precision Electronics Inc. of Chicago, a precision condenser, Type 722-D, made by General Radio Co. and a dielectric cell. Purified benzene, the dielectric constant of which was assumed to be 2.273 at 25° and 2.254 at 35°, was used in calibrating the dielectric cell.

Refractive indices were measured with an Abbe refractometer with thermostated prisms. Densities were determined by the usual pycnometer method. All such measurements were made in thermostats regulated to 25° and 35°.

For dipole moment determinations the gasoline samples used were taken at random, had a yellowish color and were used without purification. Sample A was separated into eight fractions. The molecular weights of gasoline and the fractions were determined by the usual cryoscopic method in benzene of 5.4° f. p. A summary of the results is presented in Table I.

TABLE I

RESULTS ON GASOLINE AND FRACTIONS AT 25°

Temp., °C.	Mean values aE_1	b	$P_{2(\infty)}$	P_{2D}	$\mu \times 10^{18}$
Gasoline, sample A boiling fraction: below 60	−0.58	−0.34	21.3	21.3	0
60–70	.43	.30	24.8	24.3	.15
70–100	.42	.26	30.8	30.6	.09
100–120	.40	.25	35.1	33.9	.22
120–140	.37	.21	35.7	35.2	.15
140–160	.26	.12	38.2	38.3	0
160–190	.25	.14	39.9	39.3	.17
Above 190	.18	.13	43.3	41.3	.31
Gasoline, sample B, undistilled	.34	.20	43.4	42.8	.17

In Table I the constants a and b are the dielectric constant and density coefficients, respectively, in the expressions

$$E = E_1(1 + aw_2) \qquad (1)$$

$$d = d_1(1 + bw_2) \qquad (2)$$

where E_1 and d_1 are the dielectric constant and density of the pure solvent; E and d are the dielectric constant and density, respectively, of a mixture of gasoline of weight fraction w_2 dissolved in benzene. The weight fractions of the solute, gasoline, vary from 0 to about 0.08. $P_{2(\infty)}$ is the molar polarization at infinite dilution and is given by the equation

$$P_{2(\infty)} = (p_1(1 - b) + CaE_1)M_2 \qquad (3)$$

where p_1 is the specific polarization of the solvent, $C = 3/d_1(E_1 + 2)^2$, and M_2 is the molecular weight of the solute.[3] The values of p_1 and C used in this paper are those for benzene and equal to 0.3412 and 0.1882, respectively.

As shown in Table I, with the exception of the highest boiling fraction which boils above 190°, the fractions from gasoline, sample A, have dipole moments ranging from 0 to 0.2×10^{-18} and are therefore essentially non-polar. The presence of the small apparent moment values in some of the fractions is understandable since the percentage error in $[P_{2(\infty)} - P_{2D}]$ is large when the difference is very small. Traces of polar impurities in the higher fractions, which are colored yellow, may also account for the small moments. In earlier papers where gasoline has been used for dipole moment determinations only the colorless grade was used and the assumption was made that it was non-polar. In this study we have used, for the first time, yellowish samples of gasoline and the result shows that the assumption is essentially correct and justifies the close agreement of dipole moments with those using non-polar solvents of known molecular weights.

The polarity of a compound is also indicated by the difference between the square of the refractive index and the dielectric constant. We have taken at random another sample of gasoline, fractionated it, determined the density, refractive index and dielectric constant of each fraction. The results are shown in Table II.

From the table it is seen that in three cases there is an exact equivalence between n^2_D and E and that the maximum difference between the two quantities is only 0.023 in the highest boiling fraction. This agrees with the results of Table I in

---

[1] Presented before Division of Physical and Inorganic Chemistry of the American Chemical Society, New York City Meeting, September, 1947.

[2] See for example Li and Chu, THIS JOURNAL, **69**, 558 (1947); Li, An and Wu, *ibid.*, **69**, 2558 (1947).

[3] For a discussion of these equations see ref. 1 of this paper.

TABLE II

DENSITY, SQUARE OF REFRACTIVE INDEX, DIELECTRIC CONSTANT OF GASOLINE AT 35°

Temp., °C.	d	n^2_D	E	$E - n^2_D$
Original sample of gasoline	0.7349	2.002	2.012	0.010
Boiling fraction: 60–90	.6782	1.909	1.909	0
90–100	.6933	1.937	1.937	0
100–120	.7164	1.960	1.960	0
120–140	.7257	1.987	1.990	0.007
140–160	.7449	2.008	2.021	.013
160–180	.7619	2.033	2.050	.017
Above 180	.7910	2.074	2.097	.023

that the highest boiling fraction has relatively the highest dipole moment of all fractions, namely, 0.31×10^{-18}. Benzene and carbon tetrachloride have frequently been used as non-polar solvents in dipole moment determinations. The difference in n^2_D and E for benzene and carbon tetrachloride at 25° are, however, 0.037 and 0.114, respectively. According to this criterion, gasoline should be more non-polar than benzene or carbon tetrachloride.

Table III lists the dipole moment values which have been obtained using gasoline and similar solvents of indefinite molecular weights and the values obtained for the same compounds using solvents of known molecular weights.

TABLE III

DIPOLE MOMENT AT 25°[a]

Castor oil	in gasoline 3.62×10^{-18}	in benzene 3.7×10^{-18}
Tung oil	kerosene 2.92	benzene 2.9
Di-*n*-butyl ether	kerosene 1.17	benzene 1.22 toluene 1.13
Ethyl-*n*-butyl ether	kerosene 1.19	benzene 1.24
Acetone	gasoline 2.8	benzene 2.72
Chloroform	gasoline 1.16	benzene 1.15
Acetonitrile	gasoline 3.33 kerosene 3.35 petroleum ether 3.35	benzene 3.37 toluene 3.38

[a] The values for castor oil and tung oil are taken from Li, *J. Chinese Chem. Soc.*, **13**, 8 (1946); the values for the ethers from Li and Hsü, *ibid.*, **13**, 11 (1946); the other values are from Ref. 1 of this paper.

Summary

Dipole moment can be measured using gasoline as solvent, a substance which has no definite molecular weight and whose physical properties may vary greatly with different samples. Experimental results indicate that gasoline and its fractions are essentially non-polar. A summary of the dipole moment values obtained using gasoline and similar solvents of indefinite molecular weights is given and shown to be in close agreement with values obtained using non-polar solvents of known molecular weights.

ST. LOUIS, MO. RECEIVED AUGUST 18, 1947

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Catalytic Decomposition of Ethane and Ethane–Hydrogen Mixtures

BY CHARLES KEMBALL[1] AND HUGH STOTT TAYLOR

The work of Morikawa, Benedict and Taylor[2,3] and of Morikawa, Trenner and Taylor[4] showed that the exchange reactions between the lower hydrocarbons and deuterium on supported nickel catalysts could be brought about at lower temperatures than the decomposition reactions. The energy of activation for the breaking of the carbon–hydrogen bond was some 15 kcal./mole less in the case of propane, than that for the breaking of the carbon–carbon bond. There is little doubt that the exchange reaction involves dissociative adsorption of the hydrocarbon, *e. g.*, as ethyl radical and hydrogen atom, and re-evaporation of the ethyl with a deuterium atom. Much less can be conjectured about the decomposition reaction and it was considered worthy of further study. Morikawa and his co-workers showed that, over a certain range of composition, the rate of production of methane from ethane and hydrogen depended inversely on the 2.5 power of the hydrogen pressure. This point required further investigation because it is difficult to see the kinetic interpretation of such a dependence. Accordingly it was decided to extend their investigation to a wider range of composition for the reacting mixture and further to study the decomposition of ethane in the absence of hydrogen.

Experimental

Analysis.—The reaction was followed by the withdrawal of a sample of gas and analysis by means of a mass spectrometer. The height of the mass 30 peak was determined solely by the ethane concentration and the mass 16 peak was almost entirely due to the methane. A small correction was made for the mass 16 in the ethane pattern; this amounted to 0.004 of the height of the "30 peak." In order to allow for fluctuations in the behavior of the instrument and to avoid the difficulty of using a constant pressure behind the leak of the spectrometer, the ratio of the "16 peak" to the "30 peak" was always measured. A series of known mixtures of ethane, methane and hydrogen were used to obtain calibration curves giving the ratio methane/ethane in terms of the ratio "16 peak"/"30 peak." The curve was linear up to 0.7 for methane/ethane, and was not greatly affected by the presence of hydrogen in the mixture. It was possible to estimate the amount of methane in a mixture to closer than 2% in this manner. A static system was used to follow the reaction and checks were made that the samples withdrawn were representative of the whole reacting gas.

---

[1] Commonwealth Fund Fellow, Princeton University, 1946–1947.

[2] Morikawa, Benedict and Taylor, THIS JOURNAL, **58**, 1445 (1936).

[3] Morikawa, Benedict and Taylor, *ibid.*, **58**, 1795 (1936).

[4] Morikawa, Trenner and Taylor, *ibid.*, **59**, 1103 (1937).

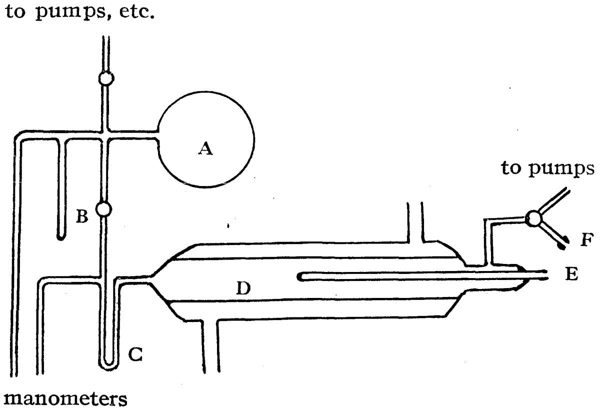


Fig. 1.—The apparatus.

Apparatus.—The essential part of the apparatus is shown in Fig. 1. The gases were allowed to mix in the bulb A. B could be cooled in liquid air to condense ethane during the admission of hydrogen. The trap C, maintained at −80°, prevented mercury out of the manometer from poisoning the catalyst, which was placed in the vessel D. The tube E was large enough to hold a thermometer. Sample bulbs could be fitted on to the ground joint F. The total volume of the reaction vessel was some 100 cc.; it was thermostated by means of the vapor jacket shown. Aniline, and, in the later experiments, naphthalene boiling under reduced pressure, were used for this purpose. The outside of the vapor jacket was wound with resistance wire and well lagged. The resistance unit served as an auxiliary heater and could also be used to bring the catalyst up to a high temperature for reduction or cleaning.

Preparation of Gases.—Cylinder hydrogen was purified by passing over heated copper at 400° and then dried over calcium chloride, Ascarite and finally phosphorus pentoxide. Cylinder ethane was passed over phosphorus pentoxide, condensed in liquid air and after two distillations the middle fraction was stored. Ethylene, which was required in some of the later experiments, was treated like ethane.

Catalyst.—The catalyst contained 15% Ni supported on kieselguhr. It was a specimen no. 330 prepared by the E. I. du Pont de Nemours Co., many years ago and was from the same batch of catalyst that was used by Morikawa[2,3,4]; 2.4 g. was used, being reduced in a stream of hydrogen at 430° and then evacuated. Between each experiment the catalyst was merely evacuated at the reaction temperature.

Experimental Results

Decomposition of Ethane–Hydrogen Mixtures.

A. Normal Kinetics.—The kinetic expression for the rate of production of methane from ethane and hydrogen depended on the composition of the reacting gases. At 182°, provided there was an excess of hydrogen (ratio > 1:1), the rate of reaction depended on $p_{C_2H_6}^{0.7} \times p_{H_2}^{-1.2}$ and the behavior of the catalyst was reproducible. The results of experiments of this type are given in Table I. Whenever the reacting gases were introduced into the reaction vessel there was a decrease in pressure of some 2 mm., taking place mainly in the first fifteen minutes. This was assumed to be due to adsorption of hydrogen but the correction it involved in the calculation of the mean pressures was small. In the last column of Table I the calculated rates of reaction for a given mixture (10 cm. ethane, 15 cm. hydrogen) based on the kinetic expression mentioned above, are listed. The constancy of these figures was the evidence for the expression $p_{C_2H_6}^{0.7} \times p_{H_2}^{-1.2}$. The reactions at 214° followed similar kinetics provided the hydrogen/ethane ratio was maintained at 2 or greater, see Table II. Neglecting the change in density of the gas between the two temperatures the mean rates gave an energy of activation of 52 kcal./mole.

B. Abnormal Kinetics.—With lower ratios of hydrogen to ethane (<1.0 at 182°, <2.0 at 214°) there was an increase in the rate of reaction above that expected from the kinetic expression. The results are tabulated in Table III which can be compared with Tables I and II. The behavior of the catalyst was not as reproducible for mixtures with low hydrogen content. Experiments 41, 42 and 43 showed unusually rapid reaction—this was attributed to the fact that the catalyst had been evacuated at a few degrees above the reaction temperature. Again while experiments 52 and 53 (ratio $H_2/C_2H_6 \approx 1$) showed normal kinetics, experiments 20, 21 and 22 were rapid. The deviation from normal behavior was greater the smaller the ratio of hydrogen to ethane and the smaller the total pressure. A kinetic expression for these reactions would have to contain a factor of the order $p_{H_2}^{-2}$ and it is interesting to note that it was in this region of composition that Morikawa, Benedict and Taylor found the factor $p_{H_2}^{-2.5}$. They worked with hydrogen/ethane ratios varying between 0.5 and 2.0 at 184°.

The Decomposition of Ethane Alone.—In experiments 22 and 24 a slight increase of pressure had been observed. This indicated that some of the ethane was decomposing to give carbon and methane. The rate of reaction of ethane in the absence of hydrogen was then examined. It was clear from the earlier work of Morikawa that the carbon so deposited might poison the surface; however, it was found that the carbon could be removed with hydrogen. The decomposition of ethane was followed by the increase of pressure, and the reaction was found to proceed to completion according to the equation $2C_2H_6 \rightarrow 3CH_4 + C$.

The data for three decompositions at 182° are shown in Fig. 2. Before each reaction the surface had been freed from carbon by hydrogenation as will be described in the next section. The small dip, experimentally observed, at the beginning of each curve was due to the adsorption of ethane. The experiments 27 and 29 were left overnight with little further change in pressure. The ratios of the final to initial pressure were, respectively, 1.49 and 1.51, indicating that the reaction $2C_2H_6 \rightarrow 3CH_4 + C$ was complete. A sample of the gas at the end of experiment 27 was analyzed on the mass spectrometer and the ratio of ethane to methane shown to be approximately 1/3,000. In experiment 31 there was a noticeable decrease in the rate of reaction after the pressure had increased by 2 cm. This was assumed to be due to the covering of surface with carbon and consequent lack of activity. It was found that the shape of the curves corresponded to an expression

$$\mathrm{d}p/\mathrm{d}t = k(p_\infty - p)^{0.7}$$

TABLE I

REACTIONS OF HYDROGEN AND ETHANE WITH NORMAL KINETICS AT 182°

Expt.	Time, hr.	Temp., °C.	Mean pressures, cm. Methane	Ethane	Hydrogen	Methane cm./hr.	Calcd. CH_4 cm./hr. for 10 cm. C_2H_6 15 cm. H_2
6	4	181.3	0.30	1.88	4.57	0.147	0.114
7	4	182.1	.06	2.09	15.27	.032	.098
8	4	182.6	.21	9.25	14.13	.104	.102
9	4	182.0	.45	1.95	2.94	.224	.099
10	4	181.8	.24	4.79	7.20	.122	.085
18	4	181.7	.16	3.75	10.92	.082	.111
19	4	181.8	.22	1.51	4.51	.109	.097
50	4	181.8	.23	5.42	10.57	.114	.115
51	4	181.1	.35	1.75	3.55	.176	.096
52	2	181.6	.14	9.96	9.75	.135	.081
53	2	181.5	.28	2.87	2.91	.279	.094
						Mean,	0.099

TABLE II

At 214°C.

11	1	214.3	3.05	3.70	6.48	6.10	4.47
12	1	214.3	0.56	4.83	30.29	1.11	4.27
13	1	214.3	0.92	0.92	7.81	1.84	4.45
16	1	214.0	1.60	3.27	11.04	3.21	4.84
17	1	214.0	1.65	3.40	11.51	3.29	5.10
						Mean,	4.63

TABLE III

REACTIONS OF HYDROGEN AND ETHANE WITH ABNORMAL KINETICS

Expt.	Time, hr.	Temp., °C.	Mean pressures, cm. Methane	Ethane	Hydrogen	Methane cm./hr.	Calcd. CH_4 cm./hr. for 10 cm. C_2H_6 15 cm. H_2
14	1	215.0	3.60	18.10	25.76	7.14	9.38
15	1	215.0	5.03	2.74	5.22	10.06	7.03
20	2	182.0	0.18	12.25	12.23	0.181	0.123
21	2	182.0	.67	4.09	4.12	0.333	.132
22	2	181.9	.74	1.70	1.86	0.743	.264
23	1	182.1	.65	7.91	3.99	1.30	.313
24	1	182.1	1.29	1.53	1.26	2.58	.491
41	1	182.0	0.87	24.30	11.75	1.74	.697
42	1	182.0	1.13	18.31	8.73	2.25	.769
43	1	182.5	1.95	11.21	5.11	3.90	.714
44	1	182.0	0.50	9.61	4.61	1.00	.250
45	1	182.2	.64	6.58	3.11	1.28	.260
46	1	181.9	.26	25.98	12.78	0.51	.216
47	1	181.9	.26	19.96	9.80	.51	.189
48	1	182.4	.31	14.93	7.28	.62	.196
49	1	182.9	.33	10.72	5.26	.66	.179
54	1	181.8	.29	10.44	4.97	.57	.148

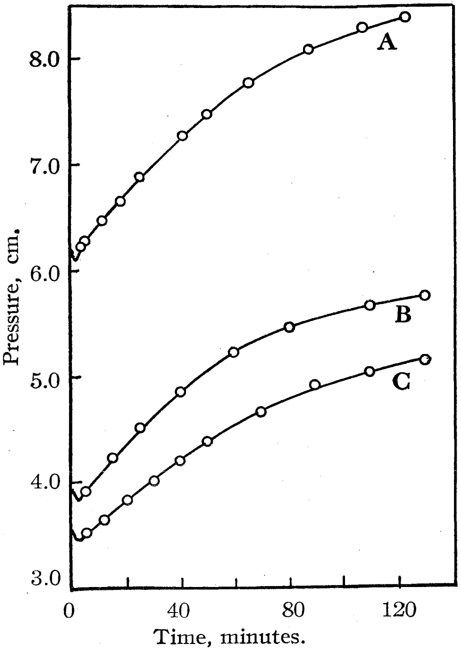


Fig. 2.—Ethane decompositions at 182°: A, Expt. 31, 182.8°; B, Expt. 29, 182.1°; C, Expt. 27, 182.0°.

where p_∞ is the final pressure, *i. e.*, the rate of reaction depended on a fractional power of the unchanged ethane. The plots of $(p_\infty - p)^{0.3}$ *versus* t, the integrated form of the equation, are shown in Fig. 3 and the values of k are listed in Table IV. The poisoning in experiment 31 is easily seen in Fig. 3.

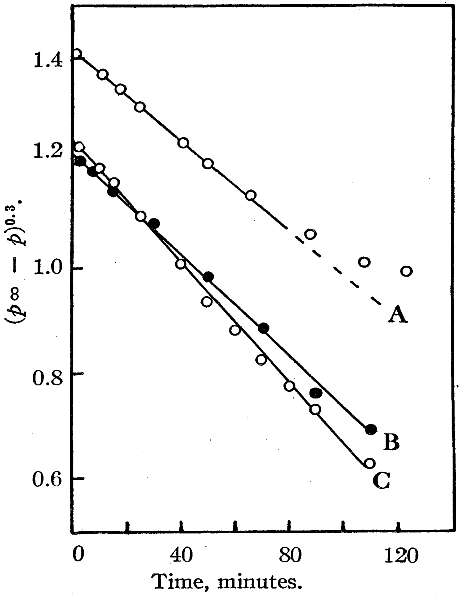


Fig. 3.—Ethane decompositions at 182°: A, Expt. 31, 182.8°; B, Expt. 27, 182.0°; C, Expt. 29, 182.1°.

Three experiments at 192° are recorded in Figs. 4 and 5 and the values of k are given in Table IV. The higher rate of reaction levelled out the dips

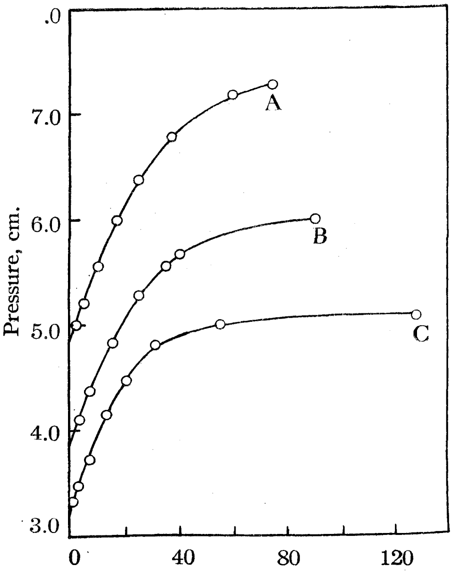


Fig. 4.—Ethane decompositions at 192°: A, Expt. 33, 194.2°; B, Expt. 35, 192.2°; C, Expt. 39, 192.0°.

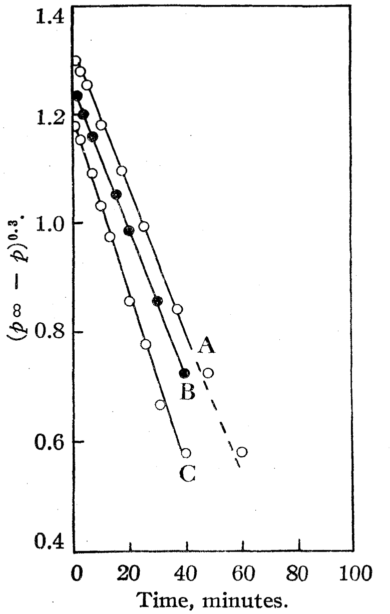


Fig. 5.—Ethane decompsitions at 192°: A, Expt. 33, 194.2°; B, Expt. 35, 192.2°; C, Expt. 39, 192.0°.

due to adsorption which were now only visible as smaller initial gradients. The energy of activation from the mean values of k was 40 kcal./mole.

The Removal of Deposited Carbon by Hydrogenation.—The ethane decompositions were alternated with carbon removal reactions according to the equation $C + 2H_2 \rightarrow CH_4$. The decrease in pressure observed on allowing hydrogen access to the catalyst (subject to a correction for adsorption) was therefore equivalent to the carbon removed and was found to correspond in each case to the rise in pressure in the previous ethane decomposition within the experimental error. This indicated that the carbon deposition was reversible, which was confirmed by the absence of any progressive poisoning. Two reactions are shown in Fig. 6. The decrease in rate of reaction with time was marked and it was not possible to fit a kinetic expression to the curves. The initial part could be fitted to a rate given by $-dp/dt = k(p - p_\infty)^3$, where $(p - p_\infty)$ represents the carbon still to be removed. However, a dependence of rate on the third power of the carbon to be removed is meaningless as regards a physical picture of the mechanism. The plot of $(p - p_\infty)^{-2}$ *versus* t enabled the initial rates of reaction to be estimated. Attempts were made to use rate expressions of the type

$$-dp/dt = k(p - p_\infty)(2p - p_0)^2$$

and

$$-dp/dt = k(p - p_\infty)(2p - p_0)^3$$

but without success; the term $(2p - p_0)$ is a measure of the hydrogen available. The rapid decrease in rate was more likely to be connected with the ease of removal of carbon from a heterogeneous surface.

TABLE IV

DECOMPOSITION OF ETHANE

Expt.	Temp., °C.	Initial pressure, cm.	k	
27	182.0	3.56	0.0160	0.0173
29	182.1	3.90	.0200	
31	182.8	6.22	.0159	
33	194.2	4.89	.043	0.047
35	192.2	4.01	.044	
39	192.0	3.32	.054	

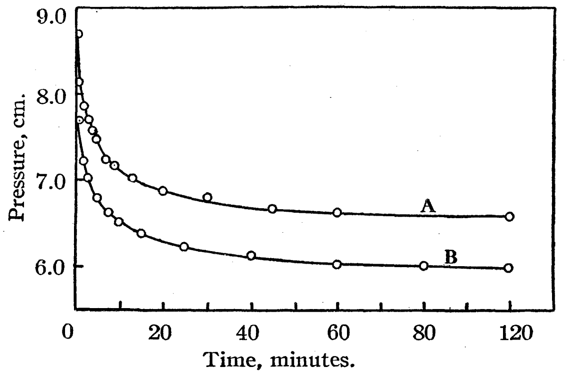


Fig. 6.—The reaction of hydrogen with adsorbed carbon to form methane: A, Expt. 32, 192.0°; B, Expt. 38, 182.1°.

Three experiments were carried out at 182° and four at 192°. There was always some difficulty in obtaining the value for the initial pressure especially at the higher temperature. The estimated initial rates of reaction are shown in Table V. They yielded an activation energy of 18 kcal./mole. However, a graphical comparison of the rates after five minutes indicated zero energy of activation which was further evidence for variation in the ease of carbon removal, *i. e.*, heterogeneity of the surface. These reactions with hydrogen were always left overnight and check experiments over a second night showed no further change in pressure.

TABLE V

REMOVAL OF CARBON BY HYDROGEN

Expt.	Temp., °C.	Initial pressure, cm.	Initial rate of reaction, cm./min.	
26	181.8	10.4	0.50	0.50
28	182.1	7.7	.67	
30	182.2	4.4	.32	
32	192.5	8.7	.87	0.76
34	192.0	10.2	.59	
36	192.0	11.5	.93	
38	191.7	10.5	.67	

Decomposition of Ethylene.—For reasons which will emerge from the subsequent discussion it was decided to study the formation of methane from pure ethylene. Preliminary experiments indicated that some methane was formed from ethylene, but that a similar amount of ethane would give more methane; the time of these experiments was either thirty or sixty minutes. Analysis with the mass spectrometer showed that the ethylene was converted to saturated hydrocarbons, probably quantitatively. It was difficult to detect traces of ethylene because the "28 peak" of ethane was large. However, by examination of the ratio "28 peak"/"30 peak" it was possible to show that there was little ethylene remaining. The carbon deposited in the early stages of the reaction of ethylene

$$3C_2H_4 \longrightarrow 2C_2H_6 + 2C$$
$$C_2H_4 \longrightarrow CH_4 + C$$

had a considerable poisoning action. Thus, the ethane formed would not decompose to methane nearly as rapidly as in the reactions described in a previous section. Once again the carbon was readily removable by hydrogenation to form methane. It became clear that if there was to be a fair comparison between the reactions with the two gases, the reaction time would have to be short. With longer times, the less poisoned surface under the ethane would lead to a greater yield of methane. The rapid formation of ethane from ethylene might have been accelerated by the hydrogen present on the surface (the surface was not normally pumped out above the reaction temperature and therefore was partially covered with hydrogen). An attempt was made to run some reactions on the catalyst relatively free from hydrogen. Before each of the six reactions in Table VI and Fig. 7 the catalyst was decarbonized overnight with hydrogen and then evacuated for two hours at 425° to remove the majority of the adsorbed hydrogen. The ratio "28 peak"/"30 peak" appeared to vary from day to day for ethane; part of this variation may have been due to the presence of differing amounts of methane. However, it will be observed that, in all three cases, the ratio, "28 peak"/"30 peak," is less for the mixture from ethylene than for the corresponding mixture from ethane. It was therefore most unlikely that there was any unchanged ethylene in the final product. Figure 7 shows clearly how the initial production of methane is faster from ethylene than from ethane. The slight induction period was presumably due to the time taken for the gas to come to reaction temperature and to permeate the catalyst. The greater poisoning of the surface with ethylene is also clear.

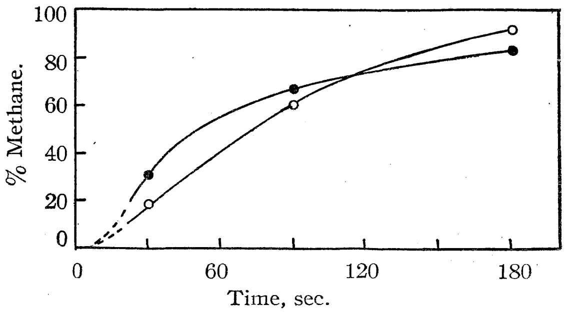


Fig. 7.—The formation of methane from ethane or ethylene: ○, ethane; ●, ethylene.

Interpretation of the Experimental Results

It is assumed that the breaking of the carbon–carbon bond is the slow reaction. In support of this there is the evidence of Morikawa, Benedict and Taylor that the ethane and deuterium exchange reaction proceeds at a temperature of 120°. They also reported 28 and 19 kcal./mole as the energies of activation for the methane exchange and the propane exchange. Thus, the carbon–hydrogen bond is easily broken and reformed and the large energy of activation in the decomposition reaction must be related to the breaking of the carbon–carbon bond. The experiments described in the preceding sections indicate that the equilibrium between methane, adsorbed methyl and methylene groups, etc., on the surface is quickly established. It is unlikely that a van der Waals adsorbed ethane will be sufficiently perturbed by the surface to lead to splitting of the C–C bond. It is possible that an adsorbed ethyl radical might dissociate into a methyl and a methylene group. However, it is more probable that the molecule has to be attacked at both ends, *i. e.*, as an adsorbed ethylene before dissociation can occur. If it is assumed that there will be an equilibrium established between the various species—van der Waals adsorbed ethane, chemically adsorbed ethyls, ethylenes and hydrogen—it is possible to use the device introduced by Temkin and Pyzhev[5] in the ammonia decomposition, namely, the use of a virtual equilibrium pressure.

---

(5) Temkin and Pyzhev, *Acta Physicochimica URSS*, **12**, 327 (1940).

$$\begin{tikzcd}
C_2H_6 \arrow[r, shift left, "\text{Virtual}"] \arrow[d, shift left] & C_2H_4 + {} \arrow[l, shift left] \arrow[d, shift left] & H_2 \arrow[d, shift left] \\
C_2H_{5ads} + H_{ads} \arrow[u, shift left, "\text{Established}"] \arrow[r, shift left] & C_2H_{4ads} + {} \arrow[l, shift left, "\text{Established}"] \arrow[u, shift left, "\text{Virtual}"] & 2H_{ads} \arrow[u, shift left, "\text{Established}"']
\end{tikzcd}$$

If $P^*_{C_2H_4}$ is the pressure of ethylene that would fulfil the gas phase equilibrium, then it would also be in equilibrium with the adsorbed ethylene. Let $\sigma_{C_2H_4}$ be the fraction of the surface covered by ethylene and let A be the fraction of the surface bare. Then

$$p^*_{C_2H_4}A = k_1\sigma_{C_2H_4}$$

Making an assumption similar to that of Temkin and Pyzhev, we write

$$p^*_{C_2H_4} = K\frac{p_{C_2H_6}}{p_{H_2}}$$

It is not possible to express A accurately in terms of the pressures of the gases. However, ignoring the dissociation of the ethane and the hydrogen and using Langmuirian equations of the type

$$p_{H_2}A = k_3\sigma_{H_2}$$
$$p_{C_2H_6}A = k_4\sigma_{C_2H_6}$$

then

$$A = \frac{1}{1 + ap_{C_2H_6} + bp_{H_2}}$$

Hence the rate of reaction, which is assumed proportional to $\sigma_{C_2H_4}$ but not fast enough to interfere with the equilibrium discussed above, is given by

$$\text{Rate} = \frac{kp_{C_2H_6}}{p_{H_2}\,(1 + ap_{C_2H_6} + bp_{H_2})}$$

This means that the rate will depend on some power slightly less than unity, of the ethane, and on some negative power of the hydrogen, slightly greater than unity. This is in good agreement with the observed $p_{C_2H_6}{}^{0.7}p_{H_2}{}^{-1.2}$.

In the decomposition of ethane alone the following equations will hold

$$p_{C_2H_6}(1 - \sigma_{C_2H_5} - \sigma_{C_2H_4} - \sigma_H) = k_1\sigma_{C_2H_5}\sigma_H$$
$$\sigma_{C_2H_4}\sigma_H = k_2\sigma_{C_4H_5}$$

Now there is evidence which will be discussed below to indicate that the surface is well covered with hydrogen and if it is assumed that σ_H is a constant it is possible to show that

$$\sigma_{C_2H_4} = k'p_{C_2H_6}/(1 + k''p_{C_2H_6})$$

which again would account for the rate of the decomposition being dependent on a fractional power of the ethane. It was in order to confirm the mechanism proposed, namely, the formation of methane through the breaking of the C–C bond in adsorbed ethylene that the reactions with ethylene were carried out.

The experiments with ethylene supported the possibility that the mechanism of the ethane–hydrogen and ethane decompositions involved adsorbed ethylene. It will be seen that the rates of reaction with a carefully cleaned surface, experiments 70, 78 and 80 were much faster than the decomposition rates on the "usual" surface, *i. e.*, experiments 27, 29 and 31. This was evidence that the "usual" surface, which was prepared by evacuation of the hydrogen and other gases at 182°, was greatly covered with hydrogen. This had two important results. First, it proved that the surface was definitely heterogeneous with respect to hydrogen adsorption, because the hydrogen could not all be removed by the standard evacuation at 182°. Consequently it is reasonable to suggest that the increase in the rate of reaction with ethane–hydrogen mixtures of low hydrogen content, described as "abnormal kinetics," was due to the uncovering of fresh areas of the surface as the hydrogen pressure was decreased. Second, the fact that the rate was so much faster on a clean surface provided justification for considering σ_H as a fixed quantity when examining the kinetics of the ethane decomposition by itself.

TABLE VI

THE PRODUCTION OF METHANE FROM ETHYLENE AND ETHANE

Expt.	Substance	Pressure, cm.	Temp., °C.	Time, sec.	"16 peak" "30 peak"	"28 peak" "30 peak"	Methane, %
68	C_2H_4	0.87	181.9	90	3.09	3.78	67.0
70	C_2H_6	1.06	182.0	90	2.26	3.85	59.7
76	C_2H_4	1.05	181.0	30	0.663	4.04	30.3
78	C_2H_6	1.12	182.0	30	0.333	4.15	17.9
80	C_2H_6	1.10	181.0	180	17.3	3.98	91.9
82	C_2H_4	1.14	182.1	180	7.82	3.85	83.7

It would be interesting to extend the work of Morikawa in following the decomposition of propane with greater pressures of hydrogen to see if normal kinetics were obtained in that case. Morikawa, Trenner and Taylor reported a rate dependent on $p_{C_3H_8}{}^{0.92}\ p_{H_2}{}^{-2.6}$ but this might turn over to a more normal expression with higher percentages of hydrogen present. If the mechanism was comparable to the present reaction, experiments with propylene would prove interesting.

The energy of activation found in the present work was 52 kcal./mole for the ethane–hydrogen reaction, which is slightly larger than the 43 kcal./mole given by Morikawa. The difference may be due to the region of composition in which the earlier work was done. As expected, the value for ethane decomposition in the absence of hydrogen was lower, being 40 kcal./mole. The decrease of 12 kcal./mole is reasonable when associated with a factor of $p_{H_2}{}^{-1.2}$.

It must be emphasized that little was known about the state of the catalyst except that its behavior was reproducible. It was certainly not yielding its maximum activity as shown by the later experiments with ethane and ethylene. The same sample of catalyst was used throughout and the reproducibility of the results is well illustrated in Table I where the experiments fall into three groups. The last group was carried out after the end of the ethane decomposition reactions and showed no loss in activity. A large fraction of the surface must have been permanently covered with hydrogen except in the last few experiments in which a carefully cleaned surface was used.

It would be interesting to try experiments with acetylene, to see whether it decomposed more readily than ethylene. It may well be that the breaking of the C–C bond would proceed through adsorbed ethylene rather than adsorbed acetylene. For, unless the latter was attached to four nickel atoms simultaneously there would be some double bond character in the C–C bond which should make it more difficult to break.

Acknowledgment.—One of us (C. K.) wishes to express his thanks to the Commonwealth Fund for the generous Fellowship which made this work possible.

Summary

1. The mass spectrometer can be used to follow the reaction of ethane and hydrogen producing methane using the ratio of the "16 peak" to the "30 peak."

2. The ethane–hydrogen decomposition on a supported nickel catalyst obeys the expression Rate = $kp_{C_2H_6}^{0.7}p_{H_2}^{-1.2}$ over a wide range of composition with an energy of activation of 52 kcal./mole.

3. At low ratios of hydrogen/ethane, abnormal kinetics, depending on a high inverse power of the hydrogen pressure, set in. This is ascribed to heterogeneity of the surface.

4. Ethane will decompose quantitatively over this catalyst to methane and carbon with a rate dependent on $p_{C_2H_6}^{0.7}$ and an energy of activation of 40 kcal./mole.

5. The carbon is reversibly deposited and can be converted to methane by hydrogen.

6. The rate-determining step of methane formation must be the breaking of the carbon–carbon bond. Both the ethane–hydrogen and the ethane decompositions can be interpreted by a mechanism involving the presence on the surface of adsorbed ethylene, in equilibrium with adsorbed ethyl radicals and hydrogen. This mechanism was supported directly by showing that the initial rate of production of methane is greater from ethylene than from ethane.

PRINCETON, NEW JERSEY RECEIVED JUNE 16, 1947

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF SARAH LAWRENCE COLLEGE]

Vapor Pressure of Isobutene over Dioxane as Basis of Manometric Kinetic Studies. The Dissociation of *t*-Butyl Benzoate

BY ROLF ALTSCHUL AND JOANNE HERBERT

This paper has as its primary objective the presentation of an improved method for kinetic measurements of liquid-phase reactions involving isobutene. Such an investigation was relevant to our present effort to expand a previous preliminary study of acid-catalyzed dissociations of tertiary esters.[1] In order to expedite this general project we tested a different analytical procedure, which, with equal accuracy, was to afford identical results with greater facility.

Vapor pressure measurements by a static method served as a basis for this alternate analysis. Two separate problems were involved to adapt this generally useful method to our particular needs: (a) A calibration to establish the vapor pressure of dioxane solutions as a function of their isobutene content. A constant and small amount of sulfuric acid (0.835 mole/liter), necessary to catalyze the subsequent kinetic runs, was included with these standardizations. (b) Application of these data to the reversible dissociation of *t*-butyl benzoate into benzoic acid and isobutene.[1] These manometric rate constants were then matched against parallel experiments resorting to acidimetric analysis by the orthodox procedure.

Since strong mechanical agitation was a prerequisite, a thermostated Van Slyke instrument appeared most opportune for this study.

Experimental

Materials.—Benzoic acid, *t*-butyl benzoate, isobutene, dioxane,[2] and 100% sulfuric acid were prepared, purified, and stored as before.[1] All gave the previous physical constants.

Manometric Determinations.—A Van Slyke instrument was equipped with a thermostated chamber which was maintained at 25 ± 0.05° by means of rapid circulation of water from a constant temperature bath. The detailed directions for this instrument were adapted from manometric analysis of insoluble gases[3] to our problem of measuring saturation pressures of soluble vapor. The optimum procedure described below was checked against pure dioxane, for which the vapor pressure at 25° has been accurately determined.[4] For our description we have adopted the terminology used by Peters and Van Slyke in their detailed outline.[5]

(a) **Calibration.**—Five cc. of 1.670 molar anhydrous sulfuric acid in dioxane is placed in the cup above the chamber, and, with the 3-way cock open and the mercury in the leveling bulb at slight negative pressure, the solution is drawn slowly into the chamber by careful opening and closing of the 4-mm. connecting stopcock. This is followed by the introduction of 5 cc. of an isobutene solu-

---

[1] Altschul, THIS JOURNAL, **68**, 2605 (1946).

[2] The solvent was purified by Mr. Jon J. Sugrue.

[3] Peters and Van Slyke, "Quantitative Clinical Chemistry," Volume II, The Williams and Wilkins Company, Baltimore, Md., 1932, Chapters 1, 3, 7.

[4] p_d = 3.55 cm.: Teague and Felsing, THIS JOURNAL, **65**, 485 (1943).

[5] See ref. 3, pp. 267–280. Figure 37 on p. 272 will be especially relevant to the following discussion. Descriptions of the manometric Van Slyke instrument have also been published in the literature: Van Slyke and co-workers, *J. Biol. Chem.*, **61**, 523 (1924); **73**, 121 (1927).

tion of indeterminate concentration in an identical manner. The 4-mm. cock is closed when the solution has been drained from the cup into the chamber except for a negligible residue remaining in the capillary of the cup. Degassing: after closing of the 3-way cock, the contents of the chamber is evacuated by lowering of the leveling bulb, with the 4-mm. cock open, until the mercury is about 2 cm. below the 50-cc. mark in the chamber. The 4-mm. cock is now closed and the solution is freed of air and some isobutene by rapid shaking for two to three minutes. Mercury is then slowly introduced from the raised leveling bulb by means of partial opening of the 4-mm. cock until the chamber is under very slight excess pressure. The extracted air is immediately expelled through the opened 3-way cock, with the liquid now again filling the capillary of the cup. Vapor pressure determination: the 4-mm. cock is closed, the leveling bulb lowered to slight negative pressure, and a drop of mercury placed into the cup of the chamber. This is slowly drawn into the capillary and into the bore of the 3-way cock by careful opening of the 4-mm. cock, to be turned off instantly when the desired adjustment is attained. With the 3-way cock closed and effectively sealed by means of the mercury, the chamber is evacuated as before, by means of the lowered leveling bulb with the 4-mm. cock temporarily open, until the mercury is again slightly below the 50-cc. mark in the chamber. After a brief period of shaking, the mercury is brought exactly to the 50-cc. mark *from below* by means of careful opening and closing of the 4-mm. cock, to be followed by a manometer reading. Shaking is resumed and the latter procedure repeated in order to assure equilibration of the system.

All our data seemed easily reproducible. The pressures are corrected for the weight of the liquid resting on the mercury in the chamber. The same total volume (10 cc.) was employed for *all* measurements.

Before the bromometric assay for isobutene,[1] the solution is forced back into the chamber by means of the raised leveling bulb with the 4-mm. cock open, until complete re-absorption has occurred. Aliquot samples are then withdrawn and titrated with thiosulfate as described before.[1] The concentrations in Table II are corrected for the constant and small fractions of isobutene present in the vapor phase by simple application of the ideal gas law.

To measure the vapor pressure of dioxane solutions containing varying quantities of sulfuric acid, a similar procedure is followed with these simplifications: Ten cc. of an acid solution is introduced into the chamber. After initial brief degassing shaking becomes superfluous for the measurement of the saturation pressure. Final re-absorption can of course be dispensed with. These preliminary studies are summarized in Table I.

(b) **Kinetic Studies.**—Five cc. of a 1.670 molar solution of anhydrous sulfuric acid in dioxane is introduced into the chamber, to be followed by 5 cc. of an ester solution of known molarity. The subsequent manipulations leading to expulsion of air follow the previous procedure exactly. This short degassing effects an inconsequential shift from the calculated zero point. With the dissolved air extracted and eliminated, the 3-way cock is sealed with mercury as above, and, with the 4-mm. cock temporarily open and the leveling bulb lowered, the mercury in the chamber is adjusted to the 50-cc. mark, or slightly below. Constant shaking is advisable, with brief interruptions for pressure recordings. These are taken on the manometer, at timed intervals, until equilibrium is attained, by careful and slow raising of the mercury to the 50-cc. mark, with the leveling bulb raised and the 4-mm. cock carefully opened until the desired point is reached.

At equilibrium, samples were withdrawn to be analyzed for benzoic acid by titration. They were always in good agreement with the values calculated from the manometric data and also with the known dissociation equilibrium constant.[6]

Acidimetric Runs.—To the *reversible* runs the previous sealed-ampoule technique was applied.[1]

Anhydrous nitrogen was saturated with dioxane vapor by bubbling through 0.83 molar sulfuric acid at 25° and was then passed through the reaction mixture contained in a loosely plugged vessel for the *irreversible* determinations. The stream was regulated to 1 to 2 bubbles per second. One cc. samples of the solutions were withdrawn at timed intervals and analyzed acidimetrically as usual. A blank run, containing 0.202 mole/liter of benzoic acid and no ester, established that the gas stream caused no concentration drifts for at least 2.5 hours, since the acid molarity remained unaltered within the experimental error over this period.

Results and Discussion

Preliminary measurements of the vapor pressure of dioxane, P_d, containing varying amounts of sulfuric acid, are presented in Table I. The values in the last column were computed for an ideal system (Raoult's law); N_d stands for the mole fraction of dioxane. The trend shows a deviation from ideality in the expected direction, emphasizing the formation of oxonium salt.

TABLE I

VAPOR PRESSURE OF SOLUTIONS OF SULFURIC ACID IN DIOXANE AT 25 ± 0.05°

(H_2SO_4), m./l.	N_d	Density	p_d, cm.	$N_d \times p_d{}^0$, cm.
0	1.000	1.03	3.56[a]	3.56
0.835	0.932	1.08	3.18	3.32
1.670	.866	1.12	2.98	3.18
1.941	.845	1.12	2.82	3.01

[a] See ref. 4.

In Table II there are contained the data for solutions of isobutene in 0.835 molar sulfuric acid. The partial pressures of the solute, P_i, were calculated by means of the equation

$$p_i = p_{\text{total}} - p_d \qquad (1)$$

assuming for p_d a constant value over the measured range (3.18 cm.). A simple check shows the error introduced through this approximation to be negative and to remain always below 0.5%. The values of the constant α in the last column illustrate how closely the data adhere to the ideal law

$$p_i = M_i \times \alpha \qquad (2)$$

into which the molarity of isobutene, M_i, rather

TABLE II

VAPOR PRESSURE OF ISOBUTENE OVER DIOXANE SOLUTIONS CONTAINING 0.835 MOLE/LITER OF H_2SO_4 AT 25 ± 0.05°

M_i	p_{total}, cm.	p_i, cm.	α cm. × liters/mole
0	3.18	0	..
0.043	5.35	2.17	50.5
.113	9.5	6.3	55.7
.234	16.8	13.6	56.9
.245	17.2	14.0	57.1
.382	25.4	22.2	58.6
.493	32.0	28.8	58.3
.606	37.4	34.2	56.5

---

(6) Blank tests established that comparable quantities of ester and benzoic acid had no effect on the vapor pressure of isobutene.

than its mole fraction, was substituted as is customary for dilute solutions.

The information above should clearly facilitate the manometric investigation of reactions in which isobutene is a participant, provided the other products and reactants are non-volatile. This surmise was put to the test of a kinetic inquiry. It was applied to the reversible dissociation of *t*-butyl benzoate in anhydrous dioxane solution with 100% sulfuric acid as a catalyst, a system which has been characterized before.[1,7]

$$C_6H_5COOC_4H_9 \underset{k_2}{\overset{k_1}{\rightleftarrows}} C_6H_5COOH + C_4H_8 \qquad (3)$$

The previously derived mathematical function for the dissociation rate constant k_1 can be adapted to the manometric process as follows

$$C + k_1 t = \frac{K_d}{(2p_e/\alpha) + K_d} \ln Q \qquad (4)$$

where

$$Q = \frac{(K_d\alpha) + p_e + p_i}{p_e - p_i} \qquad (5)$$

C is the usual integration constant, K_d is the known dissociation equilibrium constant (K_d = 0.68), and p_e stands for the equilibrium pressure of isobutene. The constant α serves to translate pressure, from cm., into concentration, moles/liter (α = 57.5).[8]

Table III contains the data for two representative manometric runs, while Fig. 1 emphasizes that the linear relationship postulated by Equation (4) is observed over their entire course.

TABLE III

MANOMETRIC RATES OF DISSOCIATION OF *t*-BUTYL BENZOATE IN DIOXANE CONTAINING 0.835 M./L. OF SULFURIC ACID AS A CATALYST, AT 25 ± 0.05°

Hr.	p_i, cm.	Q	Hr.	p_i, cm.	Q
Run no. 2A			Run no. 7		
0.12	0	2.31	0.28	0.82	2.93
.32	2.62	2.66	0.45	2.15	3.23
.56	6.27	3.32	0.64	4.42	3.85
.93	10.79	4.56	1.12	8.89	5.87
1.25	14.3	5.95	1.55	11.07	7.62
1.55	16.8	7.98	2.03	13.16	10.40
2.60	22.5	20.5	2.84	16.29	20.93
3.1	24.1	34.1	3.17	17.00	26.7
5.0	26.6	...	3.43	17.5	33.1
5.6	26.6	...	3.90	18.29	52.6
			6.16	19.67	...
			7.50	19.67	...

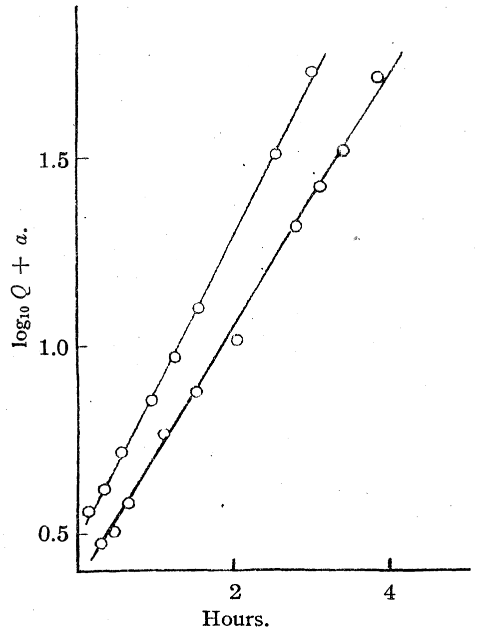


Fig. 1.—Manometric rates of sulfuric acid-catalyzed dissociations of *t*-butyl benzoate in dioxane at 25°: from left to right, no. 2A (a = 0.2) and no. 7 (a = 0).

Three separate approaches substantiated the measurements of the rate constant k_1, and, by implication, justified the manometric procedure. Thus, the ester decompositions were followed either manometrically in a reversible setting, as presented in Table III; or acidimetrically under reversible and under irreversible conditions. The latter was achieved by entraining the volatile olefin in a rapid stream of dry nitrogen, previously saturated with dioxane. The kinetic results obtained with these last experiments were interpreted by plotting the logarithm of ester concentration against the time, as is customary for first-order irreversible reactions. The results are summarized in Table IV. All runs were followed to completion with the exception of no. 4, for which only the initial 20% of its course was measured. Agreement among the diverse methods is obviously satisfactory. The manometric approach is clearly superior, since, with equal accuracy and reproducibility, it is more economic with respect to time and materials, dispensing as

TABLE IV

RATE CONSTANTS FOR THE DISSOCIATION OF *t*-BUTYL BENZOATE IN DIOXANE CONTAINING 0.835 M./L. OF SULFURIC ACID AS A CATALYST AT 25 ± 0.05°

Run	(Ester), m./l.	Method	k_1, (hr.$^{-1}$)
2A	1.112	Manometric	0.35
3A	0.552	Manometric	.33
7	0.787	Manometric	.34
1	1.112	Acidim., rev.	.33
3	1.112	Acidim., irrev.	.34
4	1.112	Acidim., irrev.	.33

---

(7) Additional instances of the breakage of the alkyl oxygen-bond in esters have recently been reported: Balfe, Downer, Evans, Kenyon, Poplett, Searle and Tarnoky, *J. Chem. Soc.*, 797 (1946); Balfe, Evans, Kenyon and Nandi, *ibid.*, 803 (1946); Balfe, Kenyon and Wicks, *ibid.*, 807 (1946).

(8) With a small and *constant* fraction of isobutene present in the vapor phase, its molarity in the dioxane solution is somewhat smaller than that of benzoic acid. This required an adjustment of the rate equation. Such a correction is embodied in the factor α, which, as indicated by Equation (2), is based on the concentration of *i*-butene in the *liquid* phase only. See the Experimental Part also.

it does with manipulations of aliquot portions and titrations.

Combined with the previous data at 35°, the new rate constant permits an estimate of the activation energy for the dissociation in 0.835 molar sulfuric acid, ΔE = 17 kcal./mole at 30°.

Summary

The partial pressure of isobutene over dilute solutions in dioxane containing 0.835 molar sulfuric acid was measured by a static method in a Van Slyke instrument at 25°. In its dependence on the concentration, the pressure adheres closely to the ideal law.

The data, applied to the acid-catalyzed reversible dissociation of *t*-butyl benzoate into benzoic acid and isobutene in dioxane solution, provide a basis for manometric kinetic studies and give a first-order rate constant for this reaction. This is in good agreement with the values obtained acidimetrically under reversible and under irreversible conditions.

The activation energy for this reaction is approximately 17 kcal./mole at 30°.

BRONXVILLE 8, NEW YORK

RECEIVED DECEMBER 21, 1946

[CONTRIBUTION NO. 50 FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF TENNESSEE]

The Salts of Perrhenic Acid. I. The Alkali Metals and Ammonium[1]

BY WM. T. SMITH, JR., AND SELMA HARMON LONG

Although the perrhenates of many of the metals have been prepared, in most cases the physical properties of these salts have been determined only approximately if at all. Of the perrhenates of the alkali metals and ammonium the potassium salt has been most thoroughly characterized, apparently due to the fact that this salt is precipitated in a common method for the recovery of rhenium[2] and that it is easily purified by recrystallization from water. The melting point,[3,4,5,6] boiling point,[6] solubility,[6,7,8,9] heat of solution[9,10] and crystal structure[11] have been reported. The density of the potassium salt was calculated from X-ray measurements of the crystal structure.[11] The density of no other perrhenate of this family has been reported. The only other melting point reported is for sodium perrhenate.[3] The solubilities at room temperature have been reported for all of these salts except lithium perrhenate.[7] The crystal structures of all of the salts except lithium perrhenate have been reported.[11,12,13,14]

Preparation of the Salts.—Rhenium was burned in a stream of oxygen at atmospheric pressure. The finely divided metal ignites under these conditions at approximately 300°. The heptoxide formed was dissolved in water to form perrhenic acid. The acid solution was then neutralized with the C. P. carbonate or hydroxide of the metal.[3] Litmus paper was used as an indicator. The salts so obtained were purified by several recrystallizations from water. They are all white in appearance. Evaporation of water from lithium perrhenate solutions was carried out at room temperature. The vapor from heated solutions of this salt was acidic and contained rhenium which indicated hydrolysis of the salt at elevated temperatures.

After each recrystallization the freezing point of the salt was determined. This was repeated until the same freezing point was observed after successive recrystallizations. The freezing points so obtained are listed in Table I.

The freezing points were obtained by cooling molten samples of 20 to 40 g. at a rate of approximately 2° per minute. The temperatures for the cooling curve for the dihydrate of lithium perrhenate were read on a mercury in glass thermometer while all others were read to 0.2° (0.01 millivolt) on a Brown Portable Potentiometer, Model 1117, using a Chromel–Alumel thermocouple which had been calibrated by direct comparison with a calibrated Iron–Constantan couple furnished by the Brown Instrument Company and guaranteed to give standard voltages corresponding to within 3°F. over the range 0–1200°F. Distinct "arrests" in the cooling curves were noted for each salt which could be melted at atmospheric pressure. The dihydrate of lithium perrhenate does not completely melt at 87.5° but undergoes a transition in which the hydrate decomposes to form a liquid and a white solid which will not completely dissolve in the liquid at 100°. Some of this white solid was separated from the liquid by decantation. The loss in weight of this wet solid on complete dehydration was not so great as the theoretical loss for the monohydrate to anhydrous salt. Apparently the equilibrium is $LiReO_4 \cdot 2H_2O(s) \rightleftarrows$ saturated solution(l) + $LiReO_4(s)$.

The purified salts were analyzed gravimetrically for rhenium as a check on the formula for the salt and its purity. The procedure outlined by Willard and Smith[15] was followed in general. It was found in washing the precipitate of tetraphenylarsonium perrhenate with ice water that precipitation occurred when the wash water was allowed to mix with the original filtrate. Whether this was due to the solubility of the precipitate in the wash water or to the decrease in solubility of the rhenium compound as the salt water filtrate was diluted was not definitely established. The procedure was modified by preparing the reagent, tetraphenylarsonium chloride, already mixed with the specified concentration of sodium

---

[1] This paper is based on a thesis presented by Selma Harmon Long to the Graduate School of the University of Tennessee in partial fulfillment of the requirements for the M.S. degree, May 26, 1947.

[2] Feit, *Z. angew. Chem.*, **43**, 459 (1930).

[3] I. and W. Noddack, *Z. anorg. allgem. Chem.*, **181**, 1–37 (1929).

[4] Biltz, *Z. angew. Chem.*, **46**, 271 (1933).

[5] Vorlander and Dalichau, *Ber.*, **66B**, 1534 (1933).

[6] Holemann and Klesse, *Z. anorg. allgem. Chem.*, **237**, 172 (1938).

[7] I. and W. Noddack, *Z. angew. Chem.*, **44**, 215 (1931).

[8] Puschin and Kovac, *Z. anorg. allgem. Chem.*, **199**, 369 (1931).

[9] Smith, THIS JOURNAL, **68**, 394 (1946).

[10] Roth and Becker, *Z. physik. Chem.*, **A159**, 27–39 (1932).

[11] Broch, *Z. physik. Chem.*, **6B**, 22–26 (1929).

[12] Beintema, *Z. Krist.*, **97**, 300–322 (1937).

[13] Jaeger and Bientema, *Proc. Acad. Sci. Amsterdam*, **36**, 523 (1933).

[14] Machatschki, *Z. Krist.*, **72**, 541 (1930).

[15] Willard and Smith, *Ind. Eng. Chem.*, *Anal. Ed.*, **11**, 305 (1939).

TABLE I

Salt	F. p., °C.	% of theoretical Re found	Density, g./cc.	Solubility (moles/100 g. H_2O × 10^2)			Heat of soln. ΔH (kcal./mole ± 0.02)
				0.0°	30.0°	50.3°	
$LiReO_4 \cdot 2H_2O$	87.5		3.69	100	140	140	+1.6 approx.
$LiReO_4 \cdot H_2O$	Dec.						
$LiReO_4$	426	99.8	4.61				
$NaReO_4$	414[a]	99.8	5.24	37.8	53.2	63.6	1.83
$KReO_4$	555[b]	100.0	4.38[d]	0.124	0.508	1.11[e]	7.68[f]
NH_4ReO_4	[c]	99.5	3.53	1.03	3.25	5.99	6.21
$RbReO_4$	598	99.8	4.73	0.116	0.468	1.05	7.70
$CsReO_4$	616	100.4	4.76	0.0861	0.287	0.640	7.69

[a] Melting point of 300° previously reported.[3] [b] Melting points previously reported 518°[6] and 552–553°.[5] [c] Decomposes around 365°. [d] Density of 4.887 previously reported.[11] [e] The values for the solubility of potassium perrhenate are calculated from previously published data.[9] The solubility of this salt in the 50.3° column is the solubility at 49.78°. [f] Roth and Becker[10] report 13.80 ± 0.03 kcal./mole at 21.7°.

chloride and saturated with tetraphenylarsonium perrhenate. The unknown samples were digested with this solution until they were completely converted to the tetraphenylarsonium perrhenate precipitate. During this digestion water was added, if necessary, to maintain the original volume. The precipitate was caught on a Gooch filter, sucked dry and then washed with a saturated solution of tetraphenylarsonium perrhenate. Excellent checks on duplicate samples were obtained in this manner and carefully purified samples of potassium perrhenate agreed with the theoretical rhenium content. The results of these analyses are presented in Table I.

The percentage of water removed from the hydrate of lithium perrhenate in a vacuum desiccator over anhydrous calcium chloride corresponded to the composition of a dihydrate. No further loss of water occurred even above the melting point of the dehydration product. The composition of the monohydrate of lithium perrhenate was established by following the loss in weight of a sample of the dihydrate and the gain in weight of an anhydrous sample of the lithium salt on standing over a 60% sulfuric acid solution in a desiccator at room temperature. After two months both samples were within 0.5% of the theoretical weight for the monohydrate.

Water Vapor Pressures of the Hydrates of Lithium Perrhenate.—In order to determine the conditions under which the hydrates of lithium perrhenate are stable, vapor pressure determinations on saturated solutions and on the solid–vapor systems were made over the approximate temperature range of 25 to 45°. A glass tube containing the sample was sealed to a closed mercury manometer and to a two-way stopcock through which the system was evacuated. The temperature of the sample tube was maintained by a water-bath which was controlled to ±0.05°. When the equilibrium pressure was established readings were made with a depth gage which could be read to 0.05 mm. Water vapor was pumped out of the apparatus after several pressure readings and new pressure readings were made. The pumping was continued periodically until no measurable pressure was found over the sample. The data so obtained are plotted in Fig. 1. Curve I is for the system which contained saturated solution in contact with solid salt. Curve II was obtained on the same samples after pumping off water vapor until lower equilibrium pressures were found. This system contained the two solid hydrates. Curve III was obtained by pumping off more water vapor from the above samples and also by admitting water vapor to anhydrous lithium perrhenate. The two solids in this system were anhydrous salt and monohydrate. The slopes of curves II and III give the following heats of hydration. $LiReO_4(s) + H_2O(v) \rightarrow LiReO_4 \cdot H_2O(s)$, $\Delta H = -13.7$ kcal. $LiReO_4 \cdot H_2O(s) + H_2O(v) \rightarrow LiReO_4 \cdot 2H_2O(s)$, $\Delta H = -12.4$ kcal. $LiReO_4(s) + 2H_2O(v) \rightarrow LiReO_4 \cdot 2H_2O(s)$, $\Delta H = -26.1$ kcal. Using 10.4 kcal. as the molar heat of vaporization of water at the mean temperature of the vapor pressure measurements, the heats of hydration using liquid water instead of vapor in the above reactions are $\Delta H = -3.3$, -2.0 and -5.3 kcal., respectively.

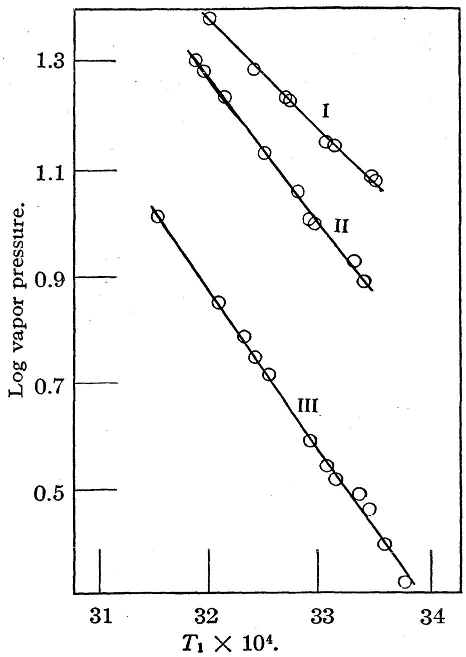


Fig. 1.—Plot of log vapor pressure against the reciprocal of the absolute temperature.

Density Determinations.—The densities of the solid salts were determined at room temperature in a pycnometer using benzene since it does not dissolve these salts and is volatile enough to be effectively removed from the sample without washing. The method was checked using sodium chloride and copper sulfate pentahydrate. The results were 1.4 and 3.5% lower, respectively, than published values[16,17] but duplicate determinations checked within 0.3% of the mean in all cases. Table I lists the densities of these salts.

Solubility Measurements.—The solubilities were determined at 0, 30 and 50.3 ±0.05°, using a method previously described.[9] Lithium perrhenate is so soluble that its solubility was measured only approximately by adding the minimum amount of water necessary to completely dissolve a weighed amount of the salt. Table I includes

(16) Baxter and Wallace, THIS JOURNAL, **38**, 259 (1916).

(17) Andreae, *Z. physik. Chem.*, **76**, 491 (1911).

the solubility of the salts and the heat of solution calculated from the slope of the line obtained when the logarithm of the solubility is plotted against the reciprocal of the absolute temperature. The method of least squares was used to find the best slope.

Microscopic Examination of Crystals.—All of the solid salts prepared were examined with a microscope using polarized light. They are all anisotropic. This has been previously reported[11,12,13,14] for all of these salts except anhydrous lithium perrhenate and its hydrates.

Freezing Point of Ammonium Perrhenate.—Although it was found that ammonium perrhenate decomposes rapidly at 365° at atmospheric pressure, its freezing point can be estimated from other properties. Plots of solubility, molar volume and radius of the cation against the freezing points of the alkali metal perrhenates indicate freezing points of 550, 605 and 580°, respectively, for ammonium perrhenate. The average value, approximately 580°, is predicted as the freezing point of this salt.

Summary

The perrhenates of the alkali metals and ammonium have been prepared and the formulas verified. The densities, freezing points and solubilities from 0 to 50° have been measured. The heats of solution have been calculated. The freezing point of ammonium perrhenate has been predicted.

KNOXVILLE, TENN. RECEIVED JUNE 14, 1947

CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1072]

Studies on the Denaturation of Antibody. III. Kinetic Aspects of the Inactivation of Diphtheria Antitoxin by Urea

BY GEORGE G. WRIGHT AND VERNER SCHOMAKER

Evidence has been presented[1,2] that the inactivation of antitoxin which takes place in urea solutions, as shown by the change in toxin-neutralizing activity, is a first-order reaction in antibody, since the specific rate of inactivation is independent of the initial concentration of antibody. This indicates that a polymolecular complexing reaction of the protein molecules[3-6] is not the mechanism of the inactivation under consideration, even though the occurrence of complexing as a result of the urea treatment could be inferred from the abnormalities of the quantitative flocculation reaction with toxin of the denatured samples.[2] The course of the reaction is not entirely typical of a classical first-order process, however, since the rate decreases more rapidly as the reaction proceeds than is predicted by the first-order law. Similar results have been obtained in the inactivation of antitoxin by heating in the neighborhood of 65°.[7,8] An understanding and a quantitative formulation of these deviations from first-order behavior are essential if the experimental results on antibody inactivation are to yield the maximum information regarding the chemical nature of the reactions and the structure and stabilizing forces of the combining region of the antibody.

In the present investigation we have studied the effects of *p*H, urea concentration, and temperature on the inactivation reaction, in order to explore the influence of these factors on its abnormalities. The experimental results are shown to be compatible with a simple kinetic mechanism.

Materials and Methods

The diphtheria antitoxin was the same globulin preparation used in previous work,[2] and consisted of the water-soluble portion of the protein precipitated from crude horse antitoxin plasma between 1.38 and 1.65 *M* ammonium sulfate. It contained 16% protein and had an activity of about 4000 units per ml. The urea was twice recrystallized from 70% alcohol. The denaturation reactions were carried out in buffered solutions at ionic strength about 0.1; acetate was used in the acid range and borate in the alkaline. The buffers were prepared by mixing various proportions of 0.2 *N* sodium hydroxide and a solution 0.2 *N* in the acid and 0.2 *M* in sodium chloride, so that the ionic strength remained approximately constant at different *p*H values. The *p*H measurements were made with a glass electrode. The buffers were effective in keeping the *p*H change during the experiment to less than 0.1 *p*H unit in practically every case; the recorded value represents the average of the initial and final *p*H measurements. The reactions were carried out in a thermostat constant to within a few hundredths of a degree, at 25.0° except where otherwise indicated.

The solutions for denaturation were prepared by weighing out the calculated amount of urea (using the density data of Dunstan and Mussel[9]), adding

---

[1] G. G. Wright, *J. Exptl. Med.*, **79**, 455 (1944).

[2] G. G. Wright, *ibid.*, **81**, 647 (1945).

[3] J. van der Scheer, R. W. G. Wyckoff and F. L. Clarke, *J. Immunol.*, **40**, 39 (1941).

[4] A. Kleczkowski, *Biochem. J.*, **37**, 30 (1943).

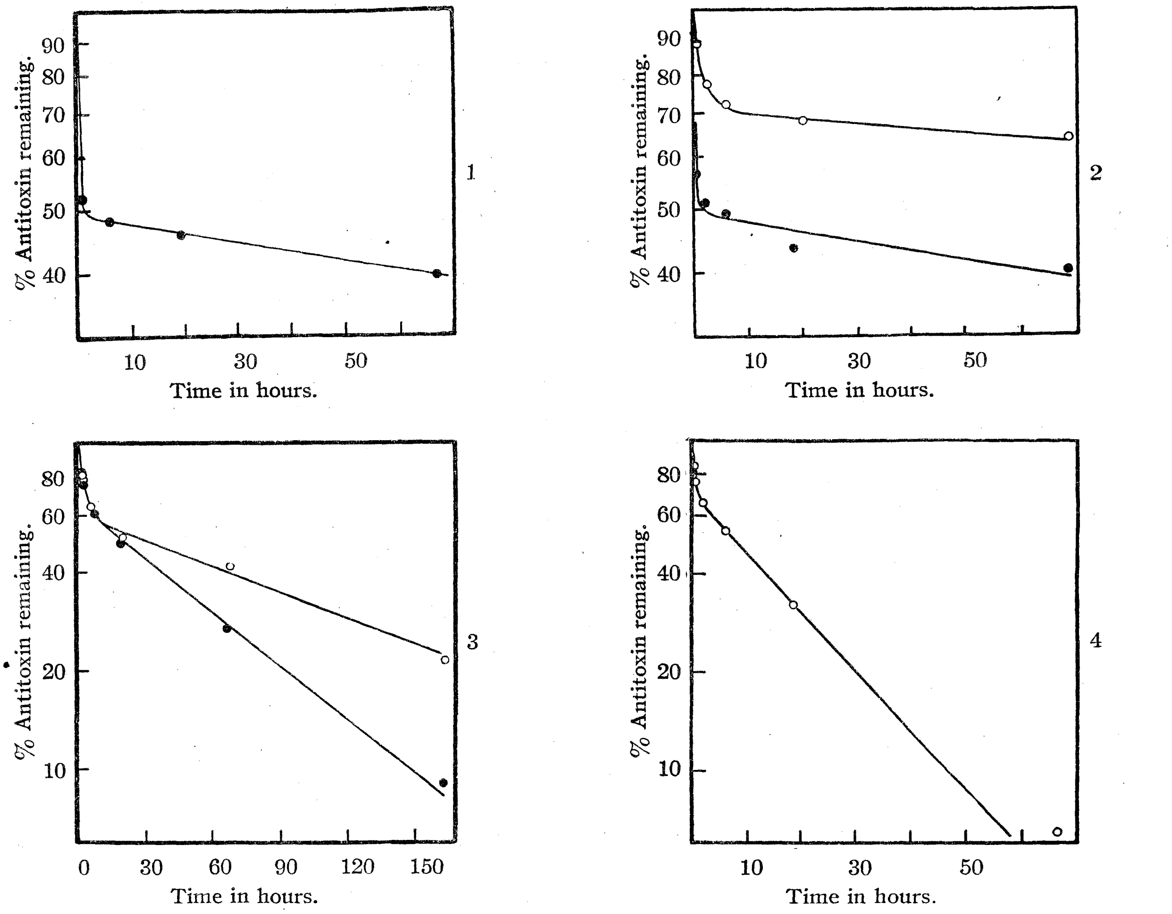
[5] B. D. Davis, A. Hollander and J. P. Greenstein, *J. Biol. Chem.*, **146**, 663 (1942).

[6] H. Smetana and D. Shemin, *J. Exptl. Med.*, **73**, 223 (1941).

[7] T. D. Gerlough and W. White, *J. Immunol.*, **27**, 367 (1934).

[8] F. H. Johnson and G. G. Wright, *Proc. Natl. Acad. Sci.*, **32**, 21 (1946).

[9] A. E. Dunstan and A. G. Mussel, *J. Chem. Soc.*, **97**, 1935 (1910).



Figs. 1–4.—Logarithm of antibody activity as a function of time of denaturation in 8 M urea at 25°, studied at various *p*H values. Fig. 1, *p*H 4.91. Fig. 2, filled circles, *p*H 5.38; open circles, *p*H 6.25. Fig. 3, open circles, *p*H 8.85; filled circles, *p*H 9.27. Fig. 4, *p*H 9.73.

an amount of buffer equal to half the final volume of the solution, and the required amount of water. After the urea had dissolved and the solution had come to temperature in the thermostat, the experiment was started by adding the antitoxic globulin. All the denaturation reactions reported in this paper were carried out at a protein concentration of 0.40%. At the desired intervals, 5-ml. samples were removed, diluted with an equal volume of saline to stop the reaction promptly, placed in cellophane tubing, and dialyzed against several large volumes of saline in the cold to removed the urea. The antitoxin in the samples was assayed by the Römer intracutaneous method in rabbits[10] and corrected for volume changes during the dialysis in accordance with the results of micro-Kjeldahl determinations as described previously.[2] Untreated antitoxin was included in each assay in addition to the partially inactivated samples, and the fraction of the antitoxin activity remaining in the samples was taken as the ratio of the largest amounts of untreated antitoxin and partially inactivated antitoxin which permitted a certain minimal skin reaction when added to the constant amount of toxin.

Experimental

A. The Effect of *p*H.—Previous results had shown that the degree of inactivation of antitoxin after urea treatment for a constant time was influenced markedly by the *p*H.[1] Accordingly, the course of the inactivation was investigated in 8 M urea at a series of *p*H values. Experiments were carried out in acetate buffer at *p*H 4.91, 5.38 and 6.25, and in borate buffer at *p*H 8.85, 9.29 and 9.73. The results are given in Figs. 1–4, where, as in Figs. 5–8, the curves represent the theoretical formulation advanced in the Discussion.

It is possible that specific salt effects may be involved in the variation of the experimental results with change in *p*H, even though the ionic strength was held approximately constant. Exploratory experiments suggested that such variations of ionic strength as did occur could not be of major importance in influencing the rate and course of the reaction. However, further experi-

---

[10] C. Jensen, *Acta Path. Microbiol. Scand., Suppl.*, 14 (1933).

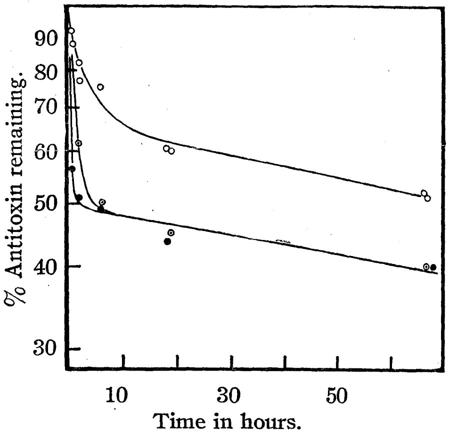


Fig. 5.—Logarithm of antibody activity as a function of time of denaturation in various concentrations of urea at *p*H 5.38 at 25°: open circles, 6 *M* urea (two different experiments); dotted circles, 7 *M* urea; filled circles, 8 *M* urea.

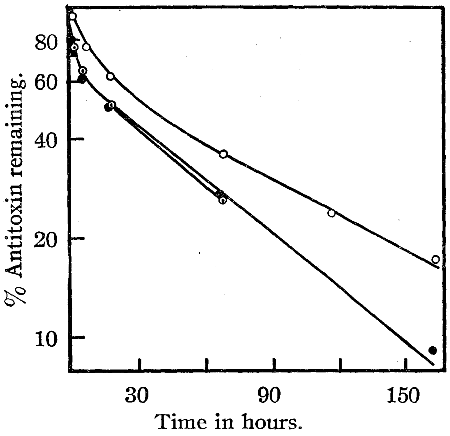


Fig. 6.—Logarithm of antibody activity as a function of time of denaturation in various concentrations of urea at *p*H 9.26 at 25°: open circles, 6 *M* urea; dotted circles, 7 *M* urea; filled circles, 8 *M* urea.

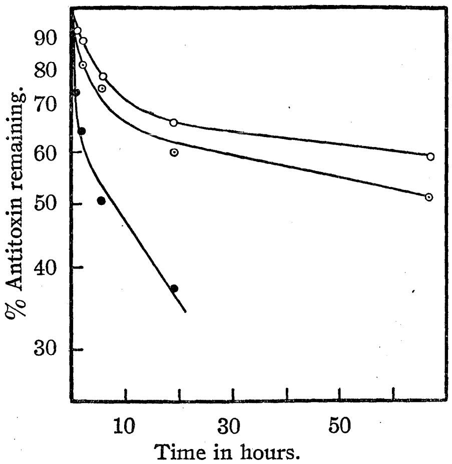


Fig. 7.—Logarithm of antibody activity as a function of time of denaturation in 6 *M* urea at *p*H 5.38 at various temperatures: open circles, 1.6°; dotted circles, 25°; filled circles, 35°.

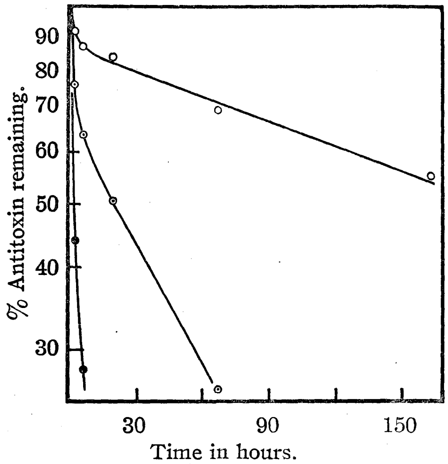


Fig. 8.—Logarithm of antibody activity as a function of time of denaturation in 7 *M* urea at *p*H 9.23 at various temperatures: open circles, 10°; dotted circles, 25°; filled circles, 40°.

ments on variation of the ionic strength and on the effects of specific buffer salts and buffer acids would be desirable.

In all of the Figs. 1–8 the fraction of the original antibody activity is plotted on a logarithmic scale and the time on a linear scale, a treatment which reduces the data for a simple first-order reaction to a straight line. Clearly, the reaction deviates from this behavior, and the degree of deviation is influenced markedly by the *p*H. Each of the curves, however, shows a definite tendency to approach linearity after the initial curved portion.

The possibility that the deviation from linearity might be due to some uncontrolled variable in the experimental method has been considered rather extensively. Although it is difficult to exclude this possibility entirely, considerable evidence now supports the conclusion that the deviation is in fact a property of the reaction under consideration. The solutions were adequately buffered, and no significant *p*H change occurred during the reaction. The curves were reproducible and seemed to show an orderly change with *p*H. No change was observed with different urea preparations, and, as noted below, a similar deviation was observed in guanidine hydrochloride inactivation. Perhaps most important, however, was the fact that the shape of the curve was independent of the initial concentration of protein,[2] for if the exhaustion of some contaminant or component of the solution not contributed by the antitoxin solution were responsible for the decrease in specific rate, it should in general occur more rapidly at high protein concentration. The same would be true even if such a substance originated in the antitoxin solution itself.

B. The Effect of Urea Concentration.—The effect of urea concentration was investigated at two representative *p*H values, one in the acid and the other in the alkaline region. Data were obtained for the reaction at 6 and 7 *M* concentrations of urea, and compared with the data already obtained at 8 *M* urea. Since the urea concentration influences the *p*H of the solution, small changes were made in the composition of the buffer used in the 6 and 7 *M* experiments, in order to keep the *p*H constant, as indicated by measurements with the glass electrode. The results are given in Figs. 5 and 6.

It is evident that the effect of increasing the urea concentration is not a uniform increase in the rate of over-all reaction, since the early part of the reaction is greatly speeded up by increase in urea and the latter part of the reaction is speeded up relatively slightly.

C. The Effect of Temperature.—An interesting aspect of the denaturation of proteins in urea is the frequent occurrence of a negative temperature coefficient.[11] Lauffer[12] found that the denaturation of tobacco mosaic virus shows a negative temperature coefficient below room temperature and a positive coefficient above; he advanced a quantitative formulation of this behavior. In a study of the urea denaturation of ovalbumin by measurement of the turbidity after removal of urea by dialysis, however, no negative coefficient was found from 4–40°.[13] It is reasonable that various phases of the denaturation reactions of different proteins with urea should have somewhat different activation energies, so that rather diverse temperature characteristics would be found depending upon the protein and the assay employed for the estimation of extent of denaturation. The results for our reaction, which are recorded in Figs. 7 and 8, show an over-all positive temperature coefficient through the region 0–40°, with, as in the case of ovalbumin, an indication that the reaction may have a minimum rate in the neighborhood of 0° and a negative temperature coefficient at lower temperatures. Although our data are too few and too scattered to demonstrate the existence of such a minimum in the rate of denaturation of antitoxin, they do show that if it does exist it must lie considerably below 25°, the temperature of minimum rate of denaturation of tobacco mosaic virus.[12]

The experiments were carried out under two conditions of urea concentration and *p*H, urea concentrations of less than 8 *M* being necessary because of the reduced solubility of urea at the lower temperatures. In each experiment a single mixture was divided into three parts which were quickly adjusted to the desired temperatures. Accordingly, the three solutions were identical at 25°, but no doubt there were minor differences in *p*H, etc., at the temperatures at which they were allowed to react.

D. Effect of Guanidine Hydrochloride.—The action of guanidine hydrochloride on proteins is generally rather similar to that of urea, but, at equimolar concentration, the denaturing action of the guanidine hydrochloride is considerably greater.[14] A preliminary experiment was carried out to explore the denaturing action of guanidine hydrochloride on antibody activity. Eight *M* guanidine hydrochloride was used, and no buffer or other electrolyte was added; otherwise the methods were the same as in the experiments with urea. The initial *p*H was 6.26, and after forty-eight hours had changed only to 6.28. The results resembled rather closely those for denaturation in 8 *M* urea at *p*H 4.91, but the deviation from linearity was even more extreme. The activity dropped to about 45% of the original in one hour, but after forty-eight hours was still 40%.

Discussion

Although the specific rate of inactivation of antitoxin by urea is independent of the initial concentration of antitoxin,[2] it is clear that the course of the reaction deviates from the typical behavior of a first-order reaction, the specific rate of inactivation decreasing as the reaction proceeds so as to produce a strong deviation from linearity of the log activity *vs.* time plots. The present work shows that this deviation varies greatly with the *p*H and to a lesser extent with the temperature and urea concentration even though it is independent of the protein concentration.[2] The kinetic situation appears in some of these respects to be the opposite of that for the denaturation of tobacco mosaic virus in urea as studied by the disintegration of the virus or by its insolubility on dilution.[12] Nearly straight lines were obtained when the log of the concentration of remaining virus was plotted against the time, but the specific rate varied considerably with the initial concentration of the virus. Preliminary results also suggest that the rate of inactivation of the antibody is less dependent on the ionic strength of the solution than is the rate of denaturation of the virus. It is not clear whether these differences in behavior are due to the very considerable differences in the proteins, or to the different properties of the proteins which were under consideration in the two cases.

It was suggested[1] that the deviation of the inactivation reaction from typical first-order behavior may be due to a heterogeneity of the antibody combining groups in their susceptibility to denaturation by urea. This view was strengthened when it was found to be possible to account quantitatively for the action of simple haptens in inhibiting the precipitin reaction by assuming a normal-error-curve distribution of the free energies of interaction of the antibody molecules with simple hapten.[15] For, although a heterogeneity of

---

[11] F. G. Hopkins, *Nature*, **126**, 328, 383 (1930).

[12] M. A. Lauffer, THIS JOURNAL, **65**, 1793 (1945).

[13] J. H. Clark, *J. Gen. Physiol.*, **27**, 101 (1943).

[14] J. P. Greenstein, *J. Biol. Chem.*, **125**, 501 (1938); **128**, 233 (1939); **130**, 519 (1939); **136**, 795 (1940).

[15] L. Pauling, D. Pressman and A. L. Grossberg, THIS JOURNAL, **66**, 784 (1944).

antibody molecules with respect to their interactions with hapten does not require that the molecules be correspondingly heterogeneous in their susceptibility to the denaturing action of urea, such a situation is definitely possible. Attempts were accordingly made to fit the data for antibody denaturation on the assumption, analogous to that adopted for the discussion of the hapten inhibition experiments, that the free energy of activation for the first-order denaturation process is distributed according to a normal-error-curve

$$N(E^*)\mathrm{d}E = \frac{1}{\sigma\sqrt{2\pi}}\, e^{-(E^*-E_0^*)^2/2\sigma_2}\,\mathrm{d}E^*$$

Tables and plots of the resulting expression

$$\text{Remaining fraction of antibody activity} = \frac{1}{\sqrt{\pi}}\int_{-\infty}^{\infty} e^{-k_0 t e^{-bx} - x^2}\,\mathrm{d}x$$

were prepared[16] for comparison with the observed curves. Here t is the time, k_0 is the specific rate of denaturation for antibody with activation energy E_0^* and b is $2^{1/2}\,\sigma/RT$. The fits were often unsatisfactory, since the tails of the plots of this function do not tend to approach straight lines, as seems to be required by the data, and the rapid decline in activity is predicted to amount always to about 50%, in very pronounced disagreement with some of the experimental curves (for example, the upper curve of Fig. 2). Although the shapes of the curves could, of course, be made to fit the data by the assumption of special, non-normal distribution functions for the free energy of activation—as will be seen below, they would indeed need to be simple bimodal distributions—the notion that heterogeneity of the antibody is the main reason for the peculiar kinetics of the reaction was discarded because the values of b required are sometimes greater by an order of magnitude than for the case of hapten inhibitions,[15] and they vary with change in experimental conditions, particularly the *p*H, by what seems to be an unreasonably great amount.

It is, of course, entirely possible that the reaction would proceed by more than one route or mechanism. If each of the mechanisms led independently to inactivation according to the simple first-order law, however, their sum would also follow the first-order law, as has been mentioned by Lauffer[17]; evidently the observed deviation is not to be accounted for in this manner.

A significantly different approach is suggested by the notions that an antibody globulin molecule may undergo denaturation in a number of different ways[18]; that some of these may involve an unfolding of the antibody region, with consequent inactivation, while others may not[18]; and that reactions of this second type can lead reversibly to a product which retains its activity (or regains it when the urea is dialyzed out) but is not susceptible to the inactivation by the first type of reaction. It turns out that the particular, comparatively very simple formulation of these notions

$$\mathrm{I} \xleftarrow{k_1} N \underset{k_3}{\overset{k_2}{\rightleftarrows}} P$$

is consistent with all our data. Here N represents the original, native antibody (or altered antibody not distinguishable from the native antibody in our experiments), I represents the inactivated antibody, and P stands for the postulated active, protected antibody. Transformations among these three molecular species by first-order reactions proceed according to the specific rate constants, k_1, k_2 and k_3, which, although constant in any one experiment, are dependent on the experimental conditions. It is easy to see how this mechanism leads to the correct general results including the straight-line tails of the log activity *vs.* time plots. At the beginning of the reaction the competing transformations of N into I and P predominate, and, although N disappears according to the first-order law, the total activity decidedly does not. Instead, it decays with a rapidly decreasing specific rate, corresponding to an incomplete limiting degree of inactivation. Gradually, however, the reverse action $P \xrightarrow{k_3} N$ becomes important (if $k_3 \neq 0$) and, by providing a continuing source of N such that ultimately a constant fraction of the active material is present as N in steady-state equilibrium with P, leads to ultimate complete inactivation of the antibody according to the first-order law.

It is not difficult to solve the differential equations

$$\begin{aligned} \mathrm{d}[N]/\mathrm{d}t &= -(k_1 + k_2)[N] + k_3[P] \\ \mathrm{d}[P]/\mathrm{d}t &= +k_2[N] - k_3[P] \end{aligned}$$

for this mechanism. The result is

$$\begin{aligned} [N] &= N_1e^{-\lambda_1 t} + N_2e^{-\lambda_2 t} \\ [P] &= P_1e^{-\lambda_1 t} + P_2e^{-\lambda_2 t} \end{aligned}$$

provided that λ_1 and λ_2, the roots (always positive, real numbers) of the determinantal equation

$$\begin{vmatrix} \lambda - k_1 - k_2 & +k_3 \\ +k_2 & \lambda - k_2 \end{vmatrix} = 0; \left\{\begin{matrix} \lambda_1 + \lambda_2 = k_1 + k_2 + k_3 \\ \lambda_1\lambda_2 = k_1k_3 \end{matrix}\right\}$$

are not equal. The constants N_1, N_2, P_1 and P_2 are determined by the general equations

$$\begin{aligned} N_1(\lambda_1 - k_1 - k_2) + P_1k_3 &= 0 \\ N_2(\lambda_2 - k_1 - k_2) + P_2k_3 &= 0 \end{aligned}$$

and the conditions for the initial amounts of N and P

$$N_{t=0} = N_0 = N_1 + N_2 \text{ and } P_{t=0} = P_0 = P_1 + P_2$$

In this way the constants $T_1 = N_1 + P_1$ and $T_2 = N_2 + P_2$ of the expression

$$[T] = [N] + [P] = T_1e^{-\lambda_1 t} + T_2e^{-\lambda_2 t} \qquad (1)$$

for the total activity are also determined

$$N_1 = \frac{(\lambda_1 - k_3)N_0 - k_3P_0}{\lambda_1 - \lambda_2} \quad N_2 = \frac{(\lambda_2 - k_3)N_0 - k_3P_0}{\lambda_2 - \lambda_1}$$

---

[16] L. Pauling, V. Schomaker and E. E. Hammond, Jr., to be published.

[17] M. A. Lauffer, *Arch. Biochem.*, **8**, 272 (1945).

[18] G. G. Wright and L. Pauling, *Science*, **99**, 198 (1944).

TABLE I

CONSTANTS OF THE EQUATION $T = T_1e^{-\lambda_1t} + T_2e^{-\lambda_2t}$ AS FITTED TO THE DATA OF FIGURES 1–8 ON THE INACTIVATION OF DIPHTHERIA ANTITOXIN BY UREA

T, °C.	Molar concn. of urea	pH	n[a]	T_1	T_2	λ_1[b]	$100\lambda_2$[b]
25	8	4.91	5	0.513 ± 0.042	0.487 ± 0.027	4.0 ± 1.6	0.31 ± 0.16
		5.38	6	.505 ± .038	.495 ± .023	2.92 ± 0.66	.34 ± .14
		6.25	6	.281 ± .043	.713 ± .037	0.59 ± .18	.17 ± .12
		7.82	6[c]	.381 ± .048	.618 ± .038	.45 ± .11	.25 ± .11
		8.85	7	.357 ± .044	.598 ± .039	.402 ± .080	.60 ± .10
		9.27	7	.328 ± .045	.649 ± .039	.67 ± .15	1.26 ± .18
		9.73	7	.282 ± .051	.701 ± .048	1.82 ± .48	4.11 ± .65
25	7	5.38	5	.504 ± .044	.490 ± .033	0.68 ± .18	0.32 ± .17
	6		10	.306 ± .038	.671 ± .033	.365 ± .086	.41 ± .11
25	7	9.26	5	.328 ± .057	.670 ± .051	.50 ± .14	1.42 ± .25
	6		7	.38 ± .13	.63 ± .13	.089 ± .032	0.82 ± .21
1.6	6	5.38	6	.291 ± .059	.692 ± .058	.194 ± .091	.24 ± .16
35			5	.375 ± .057	.618 ± .051	1.28 ± .34	2.79 ± .74
10	7	9.23	6	.130 ± .043	.870 ± .034	0.40 ± .26	0.292 ± .048
40			4			(>2.3)	(11.3)

[a] Number of experimental points. Altogether, fifty-six constants were determined from the eighty-eight experimental points of the fourteen curves which were fitted by least squares, leaving thirty-two degrees of freedom for the estimation of error. [b] In reciprocal hours. [c] Data previously reported,[2] not shown in the figures.

$$P_1 = \frac{k_2N_0 + (\lambda_2 - k_3)P_0}{\lambda_2 - \lambda_1} \quad P_2 = \frac{k_2N_0 + (\lambda_1 - k_3)P_0}{\lambda_1 - \lambda_2}$$

$$T_1 = \frac{(k_1 - \lambda_2)N_0 - \lambda_2P_0}{\lambda_1 - \lambda_2} \quad T_2 = \frac{(k_1 - \lambda_1)N_0 - \lambda_1P_0}{\lambda_2 - \lambda_1}$$

For our experiments the values of k_1, k_2 and k_3 were obtained by fitting equation (1) to the data, thereby fixing the values of λ_1, λ_2, T_1 and T_2, and applying the formulas

$$k_1 = \frac{\lambda_1T_1 + \lambda_2T_2}{T_1 + T_2} \quad k_3 = \lambda_1\lambda_2/k_1$$
$$k_2 = \lambda_1 + \lambda_2 - k_1 - k_3 \qquad (2)$$

which may be derived from the above expressions on substituting our initial conditions, $P_0 = 0$ and $N_0 = T_0 = T_1 + T_2$. If the conditions $T_1 + T_2 \cong 1$ (T_1 and T_2 are both positive) and $\lambda_1T_1 >> \lambda_2$ are satisfied, as they are for many of our experiments, k_1, k_2 and k_3 are approximated by the much simpler relations $k_1 \cong T_1\lambda_1$, $k_2 \cong T_2\lambda_1$, $(k_1/k_2 \cong T_1/T_2)$ and $k_3 \cong \lambda_2/T_1$.

Equation (1) was fitted to the data (except for the 40°, 7 M urea, pH 9.23 experiment) by the method of least squares,[19] starting with approximate graphical fits. Equal weights were assigned to all the points of the curves including the initial points, which were not assumed to be necessarily correct inasmuch as the assays of undenatured antitoxin samples were conducted with no greater precision than were the assays of the partially denatured samples. It was assumed that the nominal times of reaction were not in error. The resulting theoretical curves (Figs. 1–8), corresponding to the constants given in Table I and Figs. 9–11, represent the data very well, the root-mean-square of the deviations ($T_{\text{obs.}} - T_{\text{calcd.}}$) for the 88 experimental points being only 0.019, or 1.9% of the initial activity. The corresponding error of the experimental points ($\epsilon = ([v^2]/s-m)^{1/2}$, with $(s-m)$ equal to 32; see ref. 19, p. 245), estimated by the theory of least squares on the assumption that equation (1) is indeed the correct equation for the representation of the data, is 0.031, in good agreement with the accuracy that might be expected from the assay method. This agreement and the generally satisfactory random nature of the deviations provide some additional evidence that equation (1) is an adequate representation of the data. It is true that the average value of $T_1 + T_2$, 0.990, represents a tendency for the curves to pass below the initial assay points, but the discrepancy is not great enough to be regarded as significant.

Although the agreement between the curves and the data is good, the uncertainty in the derived constants is often great because the reactions were not followed intimately enough, particularly at very short and very long times of denaturation, to avoid ambiguity arising from the possibility of approximately fitting data for the intermediate region with different curves having rather different constants. The estimates of standard error of these constants depend on the shape of the particular curves and on the number and distribution of the measured points as well as on the estimated standard error (0.031) of the observations. For T_1, T_2, λ_1 and λ_2 the estimated standard errors are given in the table; for k_1, k_2 and k_3 representative values are perhaps the following for 25° and 8 M urea: at pH 4.91—0.78, 0.87 and 0.0033, respectively; at pH 5.38—0.37, 0.30 and 0.0026; and at pH 9.73—0.09, 0.47 and 0.034. These values, which are so large that only the major trends exhibited by Figs. 9–11 need be regarded as significant, do not tell the whole story, however,

---

(19) E. T. Whittaker and G. Robinson, "The Calculus of Observations," Blackie and Son Limited, London, 1944, pp. 209–259.

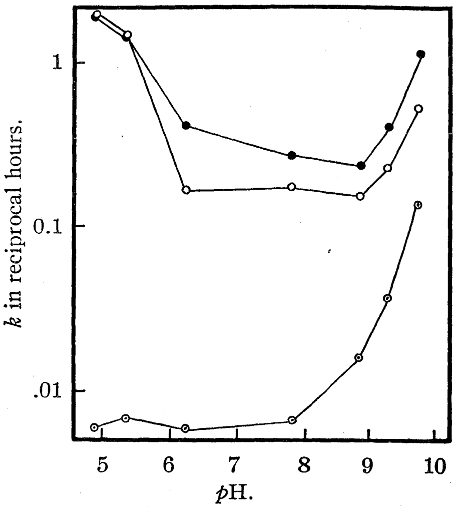


Fig. 9.—The variation of the rate constants discussed in the text with changes in *p*H; plots of log *k* *vs.* *p*H: open circles, k_1; filled circles, k_2; dotted circles, k_3.

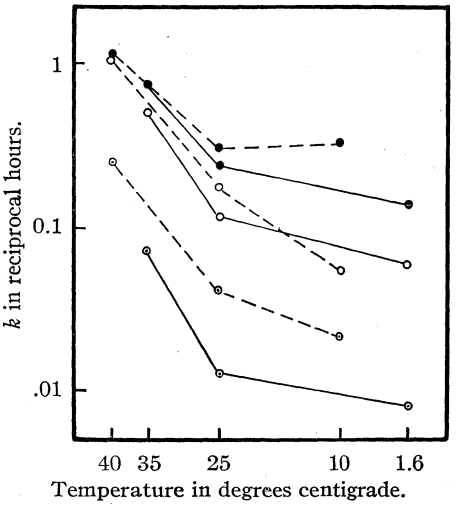


Fig. 10.—The variation of the rate constants with change in temperature; plots of log *k* against the reciprocal of the absolute temperature: open circles, k_1; filled circles, k_2; dotted circles, k_3. Solid lines connect points at *p*H 5.38 and 6 *M* urea; dotted lines, *p*H 9.23 and 7 *M* urea.

because various combinations of the constants may be more or less subject to error, particularly in accordance with their special dependence on the ambiguity just mentioned. This ambiguity is likely to lead to a set of errors such as, $\delta T_1 < 0$, $\delta T_2 > 0$, $(\delta(T_1 + T_2) \simeq 0)$, $\delta\lambda_1 > 0$ and $\delta k_1 > 0$ (increase in initial slope), and $\delta\lambda_2 > 0$, corresponding to $\delta k_2 > 0$, and $\delta k_3 > 0$ as well as $\delta(k_1/k_2) < 0$.

The notable features of the dependence of the *k*'s on *p*H (Fig. 9) are the almost parallel behavior of k_1 and k_2, which decrease with increasing *p*H to about *p*H 6.25 and then increase again beyond *p*H 9.0, and the strikingly different behavior of k_3—hence the great effect of *p*H on the shapes of the log activity *vs.* time curves—which is independent of *p*H below 8 but above *p*H 8 increases rapidly. If it is assumed that the effect of variation of *p*H on the rate is simply one of changing the equilibrium concentration of the critical reaction intermediate (the specific rates of transformation of the intermediate being unaffected by its ionization), these facts may be interpreted in terms of acidic (or basic) ionization constants which are different for the ordinary molecule and the intermediate. If there are *n* such groups, taken as acidic groups, with the same ionization constants *K* and *K** in the ordinary molecule and the intermediate, respectively, the specific rate constant turns out to be given by the expression

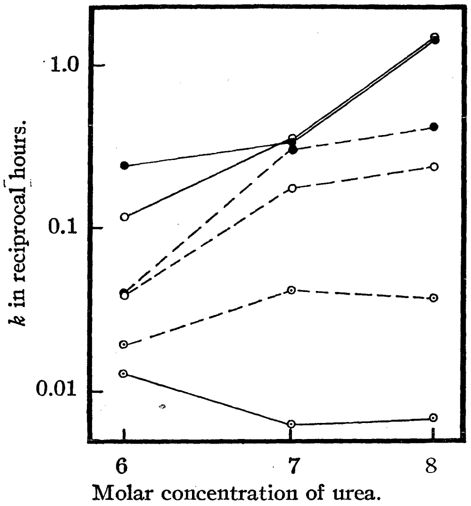


Fig. 11.—The variation of the rate constants with change in urea concentration at 25°; plots of log *k* *vs.* log urea concentration: open circles, k_1; filled circles, k_2; dotted circles, k_3. Solid lines connect points at *p*H 5.38; dotted lines, *p*H 9.26.

$$\log k = \log k_0 + \log([\mathrm{H}^+]^n + K^*) - \log([H^+]^n + K)$$

where k_0 is the specific rate constant at hydrogen ion concentrations so high that the groups are not ionized in either the ordinary molecule or the intermediate. A plot of this expression as a function of *p*H will be seen to consist essentially of two horizontal straight lines and, joining these with short intermediate curves, another straight line of slope $\pm n$. Also, the *p*H values at which the extended straight lines intersect are the values pK^* (*i. e.*, $-\log K^*$) and pK, pK being the greater of the two values if the intermediate line has sloped upward, and *vice versa*. Since the slopes of the steep sections of the curves of Fig. 9 are all essentially unity, one *p*H unit corresponding to a ten-fold change in the rate constant, it may be inferred that in effect only one group of a given kind is coupled with the denaturation reactions; the ionizations are one-step ionizations. It would appear also that only two such groups are strongly coupled with the reactions; regarded as acidic groups, one has $pK \simeq 6.2$ for *P* and the critical intermediates of the reactions $N \rightarrow I$ and $N \rightleftarrows P$ and $pK \geqslant 5$ for N, and the other has $pK \approx 8.8$ for the critical intermediates and $pK > 10$ for P and N. The reaction intermediates and P are accordingly all alike in regard to their reaction-coupled acidic properties in the low pH range (excepting the relatively slight difference that results in the change in the ratio of k_1 to k_2 on going from acidic to basic solutions), but are different at high pH, where P appears to resemble N. With change in temperature the over-all rate of inactivation varies greatly, although the shapes of the log activity *vs.* time curves (Figs. 7 and 8) are not much changed; the same observations are brought out by Fig. 10, which also emphasizes a rather sharp decrease (perhaps not significant) of the ratio k_1/k_2 at the lowest temperature at pH 9.23 and the suggestion, mentioned above, of a minimal over-all rate of reaction in the neighborhood of 0°. The most important point brought out by Fig. 11 is the relative independence of k_3 on urea concentration in contrast to the average eighth-order dependence of k_1 and k_2. In the light of the relatively great probability of errors of the same sign for the k's, particularly for k_2 and k_3, it seems likely that the deviations from these generalizations by the separate results for pH 5.23 and pH 9.26 may not be real.

The substance P is at present hypothetical, and as yet there is no independent evidence of its existence. In addition to the work presented in this paper we have evidence from viscosity studies of the antitoxin system during denaturation that seems to be compatible with the mechanism involving a substance P. Moreover, preliminary experiments in which the denaturation was interrupted by dialysis showed a tendency for the subsequent reaction (when urea was again added) to simulate the original course of reaction with its characteristic plot of log activity *vs.* time. This behavior to us seemed entirely incompatible with the heterogeneity hypothesis. It seems now to be also the sole experimental reason for choosing the scheme

$$\begin{tikzcd} N \arrow[r, shift left, "k_2"] \arrow[dr, "k_1"'] & P \arrow[l, shift left, "k_3"] \\ & I \end{tikzcd}$$

as the basis for our considerations of mechanism rather than the slightly more elaborate scheme

$$\begin{tikzcd} N \arrow[rr, shift left, "k_2"] \arrow[dr, "k_1"'] & & P \arrow[ll, shift left, "k_3"] \arrow[dl, "k_4"] \\ & I & \end{tikzcd}$$

or perhaps its other simplified form with $k_3 = 0$: if the sum of the concentrations of N and P are assumed always to be measured in the assays, the latter scheme gives the same results as the former for the dependence of remaining activity on time of denaturation provided that the rate constants are appropriately adjusted to fit the data. In fact, with $k_3 = 0$, and $\lambda_1 T_1 >> \lambda_2$, the same results are obtained for k_1 and k_2 as before, while for k_4 is found $k_4 = \lambda_2$, in close analogy to the corresponding approximate expression $k_3 = \lambda_2/T_1$ for the first scheme. It should be possible to measure k_3 independently of k_4 by carrying out the crucial interrupted experiment on a quantitative basis with the aid of more data on the denaturation reaction at lower urea concentrations to provide a sounder basis for estimating the rate of reconversion of P to N on dialysis. It should also be possible to gain information about the nature of P by performing interrupted experiments of other sorts, especially with abrupt changes of pH. If these experiments could be performed with enough precision, they, like the crucial dialysis experiment, would also serve to distinguish between our steps in k_3 and k_4, as considerations with the help of the constants shown in Table I and the equations for $k_4 = 0$ with general initial conditions will show.

It is interesting to speculate that from a general chemical point of view P is very similar to I, and that the reactions which form the two products are essentially identical except for the failure in the formation of P of the unfolding of the polypeptide chain to include those regions of the chain which constitute the combining sites[20] of the antibody. The similarity of dependence of k_1 and k_2 on pH, urea concentration, and temperature is in agreement with this view. The partially unfolded globulin molecule (it is known that the unfolding of serum globulin in urea stops far short of the point at which the polypeptide chain is completely extended[21]) may then be stabilized with respect to further unfolding or to refolding. Further processes of refolding and unfolding will no doubt occur, however, and we are particularly interested in the molecule P, which may need to refold into something like its native configuration in order that the antibody combining region may be exposed and thereby again be subjected to the possibility of unfolding and undergoing the detectable change of inactivation. The dependence of the rate constants on urea concentration suggests that the unfolding processes, being highly dependent on urea concentration, may be regarded tentatively as involving actual combination of the protein molecule with several urea molecules—the same number (about eight) for $N \rightarrow P$ as for $N \rightarrow I$—whereas the refolding processes, revealed in the case of $P \rightarrow N$ as independent of the urea concentration, involve dissociation of the protein molecule–urea complexes. According to this interpretation, which certainly cannot be regarded as strictly valid, P may be regarded as a complex formed between a globulin molecule and about eight urea molecules, as may I also if the thesis of general similarity of I and P is correct.

Further studies on the nature of the reactions are in progress. Preliminary experiments with a horse antitoxin against *Staphylococcus* α-hemolysin have indicated that the course of this reaction is closely similar to that of diphtheria antitoxin, and

---

(20) L. Pauling, THIS JOURNAL, **62**, 2643 (1940).

(21) H. Neurath, G. R. Cooper and J. O. Erickson, *J. Phys. Chem.*, **46**, 203 (1942).

the simpler technique of the *in vitro* assay for the antitoxin should make the system a favorable one for further kinetic investigations. It is possible that the mechanism proposed for the antitoxin inactivation may prove to be applicable to other denaturations which deviate in a similar way from first-order behavior.

This investigation was carried out with the aid of a grant from The Rockefeller Foundation. The authors are indebted to Professor Linus Pauling for suggestions and discussion, to J. Y. Chien for carrying out preliminary experiments on the effect of temperature, and to Sharp and Dohme, Glenolden, Pennsylvania, for supplying the antitoxin and toxin.

Summary

A study has been made of the influence of *p*H, urea concentration, temperature and certain other factors on the course of the inactivation of diphtheria antitoxin in urea solutions. The reaction is first-order with respect to initial antibody concentration but departs from typical first-order behavior in that the specific rate decreases as the reaction proceeds. The degree of this effect was found to vary greatly with the *p*H of the solution, and somewhat with the urea concentration. No negative temperature coefficient was observed in the temperature studies, although it was clear that the effect of change in temperature is not uniform over the region studied and possibly tends toward a minimum rate of inactivation at or below 0°. The interpretation of the experimental results has been discussed, and a simple kinetic mechanism which accounts for the observed behavior within the error of the measurements has been proposed. The proposed mechanism involves two competing reactions of the protein, one of which leads irreversibly to inactivation of the antibody and the other of which leads reversibly to an active product, more stable in urea solution than the original antibody and subject to inactivation only by way of slow reconversion to the original antibody or its kinetic equivalent.

PASADENA, CALIFORNIA RECEIVED JULY 2, 1947

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MARYLAND]

Tetratriacontanoic Acid and Related Compounds[1]

BY NATHAN L. DRAKE AND SIDNEY MELAMED[1a]

The present research was undertaken with the object of preparing certain aliphatic carboxylic acids and ethers in the C_{20}–C_{40} range. Francis, King and Willis[2] have prepared tetratriacontanoic acid with a yield of 14% from docosanoyl chloride and ethyl sodio-α-acetylbrassylate. More recently dotriacontanoic acid was obtained with a yield of 26% by the reaction of docosanyl zinc iodide and 9-carbethoxynonanoyl chloride.[3] The procedure employed in the present work gave greatly improved yields and is applicable to the preparation of relatively large amounts of material.

The reaction of a dialkyl cadmium with an ω-ester-acid chloride has been extensively studied by Cason.[4] The method has been applied in this work to the preparation of 10-ketohexacosanoic acid from 9-carbethoxynonanoyl chloride and dihexadecyl cadmium and of 18-ketotetratriacontanoic acid from 17-carbethoxyheptadecanoyl chloride and dihexadecyl cadmium; the yields obtained were of 32 and 79%, respectively. The reaction has been further applied to the condensation of an acid chloride and an ω-alkoxyalkyl cadmium compound. In this manner 1-cyclohexoxy-11-ketodotriacontane was obtained from di-(10-cyclohexoxydecyl)-cadmium and docosanoyl chloride and 1-cyclohexoxy-11-ketohexatriacontane was similarly prepared from hexacosanoyl chloride and the same dialkyl cadmium compound. The requisite 1-bromo-10-cyclohexoxydecane was obtained from 1,10-dibromodecane and sodium cyclohexoxide.[5]

The conversion of the keto-acids and keto-ethers to the desoxy acids and ethers, respectively, was accomplished in excellent yield by the application of a recently described modification of the Wolff–Kishner reaction.[6] The only adaptation required was the use of larger amounts of solvent. It is of interest that the method of Clemmensen proved less satisfactory.[7]

The use of the cadmium alkyl reaction for the preparation of these keto-acids is dependent upon the availability of long-chain acid esters. Ethyl hydrogen sebacate[8] is readily obtained by the partial esterification of sebacic acid and can be isolated by fractional distillation. In the preparation of ethyl hydrogen hexadecanedicarboxylate, distillation is not a practicable method of isolation. The partial saponification of the diester[9] leads to

---

[1] The work described in this paper was done under a contract between the University of Maryland and the Bureau of Aeronautics, Navy Department.

[1a] Present address: Rohm and Haas Company, Philadelphia, Pennsylvania.

[2] Francis, King and Willis, *J. Chem. Soc.*, 999 (1937).

[3] Schuette, *Oil & Soap*, **22**, 107 (1945).

[4] Cason, THIS JOURNAL, **68**, 2078 (1946), and previous papers.

[5] Drake, Anspon, Draper, Haywood, VanHook, Melamed, Peck, Sterling, Walton and Whiton, THIS JOURNAL, **68**, 1540 (1946).

[6] Huang-Minlon, *ibid.*, **68**, 2487 (1946).

[7] "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, Chap. 7.

[8] "Organic Syntheses," Coll. Vol. II, 276 (1943).

[9] The diethyl hexadecanedicarboxylate was prepared electrolytically from ethyl potassium sebacate by the procedure of Swann, Oehler and Pinkney, "Organic Syntheses," **21**, 48 (1941).

a mixture of the diacid, diester and half ester.[10,11] The diester was removed by extraction from the *dry* sodium salts by hot petroleum ether. The separation of the half-ester from the diacid was accomplished by extracting the mixture of free acids with petroleum ether (b. p. 30–60°), which selectively dissolved the half-ester.

The keto-esters obtained from the cadmium alkyl reaction were found difficult to purify and were therefore isolated as the keto-acids. Two main by-products were formed: the related dibasic acid and dotriacontane. Recrystallization of the crude product from petroleum ether readily removed the hydrocarbon which remained in solution. The separation of the keto-acid from the dibasic acid was accomplished by fractional extraction with sodium hydroxide dissolved in 60% aqueous ethanol.[12] The separation is dependent upon the greater acidity of the dibasic acid and the greater solubility of the sodium salt of the keto-acid in the organic phase.

Similarly in the preparation of the keto-ethers two by-products were formed: the related fatty acid and the diether, 1,20-dicyclohexoxycosane. Docosanoic acid was separated from the corresponding keto-ether by extraction with hot, alkaline 60% aqueous ethanol. In the case of hexacosanoic acid it was found that the sodium salt was completely soluble in hot, wet petroleum ether. The petroleum ether solution was therefore dried and the sodium hexacosanoate, which precipitated as a gel, was removed by filtration.

The dialkyl cadmium reaction is described in detail for the preparation of 18-ketotetratriacontanoic acid. The data for the other condensations are given in Table I. Similarly the modified Wolff–Kishner procedure employed is described for the preparation of tetratriacontanoic acid and the data for the other reductions are given in Table II.

Experimental

Ethyl Hydrogen Hexadecane-1,16-dicarboxylate.—A well-stirred solution of 370 g. (1 mole) of diethyl hexadecane-1,16-dicarboxylate[9] in 500 ml. of dry ethanol was treated dropwise with 400 ml. of dry ethanol containing one mole of sodium ethoxide and one mole of water and allowed to stand overnight. The solvent was removed by distillation and replaced with several liters of petroleum ether (90–100°). The mixture was heated and stirred to suspend the solid and extract the residual diester and finally cooled and filtered. The filtration may be facilitated by the use of a larger volume of petroleum ether or by the addition of ethyl methyl ketone or toluene to the petroleum ether. The sodium salts were extracted with several portions of petroleum ether or mixed solvent as described above and finally washed with ether and dried at 90° to give 271 g. of yellow, granular product; 98 g. of diester resulted from the evaporation of the petroleum ether filtrates.

The dried sodium salts were suspended in 4 liters of warm water (80–90°) and were converted to the free acids by the slow addition of 120 ml. of concentrated hydrochloric acid to the well-stirred suspension. The acids were liquid under these conditions and solidified to a cake when the solution was cooled. The solid cake could be readily separated from the water[13]; further separation of solution was effected by remelting and cooling. The product (252 g.) was powdered and employed in the next step.

The dry mixed acids were extracted in a Soxhlet extractor; 3–4 liters of petroleum ether (30–60°) was used as solvent.[14] The petroleum ether solution deposited 114 g. of ethyl hydrogen hexadecane-1,16-dicarboxylate, m. p. 67–70° (33%). *Anal.* Calcd. for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18; mol. wt., 342. Found: C, 70.45, 70.59; H, 11.32, 11.20; mol. wt. (saponification equivalent), 328.

The material insoluble in the petroleum ether (30–60°) amounted to 85 g.; it melted at 113–119° (27%), and was largely the diacid. A pure sample which melted at 124.5–125.3°, was obtained by recrystallization from methanol. *Anal.* Calcd. for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90. Found: C, 68.82, 68.56; H, 11.13, 10.94.

The petroleum ether filtrate from the crystallization of the half ester was concentrated to give an additional 35 g. of diester. The total quantity of diester recovered was 133 g. (36%); the total of products accounted for 96% of the starting material.

18-Ketotetratriacontanoic Acid.—A Grignard reagent was prepared from 14.9 g. (0.62 gram atom) of magnesium and 214 g. (0.7 mole) of cetyl bromide dissolved in 500 ml. of dry ether. The solution was cooled to 5° and 67.7 g. (0.37 mole) of dry cadmium chloride was added in one portion. The mixture was stirred and heated under reflux until a test for Grignard reagent was negative.[15] The bulk of the ether was removed by distillation and the solid was suspended in 1500 ml. of a mixture of benzene and toluene (2:1).

The acid chloride, 17-carbethoxyheptadecanoyl chloride, was prepared from 141 g. (0.412 mole) of ethyl hydrogen hexadecane-1,16-dicarboxylate by the addition of 85.8 g. (0.412 mole) of phosphorus pentachloride to the molten ester over a period of three to five minutes; the mixture was warmed on a steam-bath for ten to fifteen minutes to complete the reaction. The bulk of the phosphorus oxychloride formed was removed by distillation under diminished pressure; any traces remaining were removed by distilling 100 ml. of dry petroleum ether (60–80°) from the residue. After removal of the last of the petroleum ether, the acid chloride was dissolved in 400 ml. of hot toluene and used without further purification.

The solution of acid chloride in toluene was added over a period of thirty minutes to the well-stirred suspension of the dialkyl cadmium, and the mixture was heated under reflux for six hours and then allowed to stand overnight. A solution of 50 ml. of concentrated sulfuric acid in 1 liter of water was next added, and the mixture was heated to 70° and stirred for a time whereupon the layers were separated while hot. The toluene layer was washed with two 500-ml. portions of hot water and then concentrated to about 400 ml. by distillation. The residue was dissolved in 90% aqueous ethanol, 60 g. of potassium hydroxide was added, and the solution was heated under reflux for two hours to complete saponification of the ester. The well-stirred solution was diluted with 300 ml. of water and acidified with 150 ml. of concentrated hydrochloric acid while being heated under reflux. The hot slurry so formed was diluted with 500 ml. of hot water, cooled and filtered. The solid was melted, cooled and when solid again was removed as a cake from the water

---

(10) Ruzicka and Stoll, *Helv. Chim. Acta*, **10**, 692 (1927); **16**, 493 (1933).

(11) Drake, Carhart and Mozingo, This Journal, **63**, 617 (1941).

(12) Weitkamp, *ibid.*, **67**, 447 (1945), notes the value of 60% aqueous ethanol as a solvent for the sodium salts of fatty acids.

(13) Precipitation of the acids from a cold solution resulted in incomplete neutralization and the separation of a product which contained much solution after filtration.

(14) It was found important to use petroleum ether of the boiling range specified. Higher-boiling petroleum ether extracted hexadecane-1,16-dicarboxylic acid as well as the half ester.

(15) Gilman, "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 496.

TABLE I

COMPOUNDS PREPARED BY REACTIONS OF ALKYL CADMIUMS

Compound	M. p., °C.	Solvent for recrystallization	Analytical data Calcd. C	Calcd. H	Found C	Found H	Yield, %
10-Ketohexacosanoic acid[a]	94–96.5	Pet. ether	76.04	12.27	76.33	12.44	32
1-Cyclohexoxy-11-ketodotriacontane	96–97	Pet. ether	81.07	13.25	80.91 80.79	13.57 13.55	12[b]
1-Cyclohexoxy-11-ketohexatriacontane	93–95.5	Pet. ether or ethyl methyl ketone	81.48	13.35	80.65 80.31	13.45 13.47	15[c]

[a] Neutral equivalent: calcd. 410. Found: 414. [b] The yield based on the weight of recovered docosanoic acid is 32%. [c] The yield based on the weight of hexacosanoic acid recovered is 58%.

TABLE II

COMPOUNDS PREPARED BY MODIFIED WOLFF–KISHNER METHOD

Compound	M. p., °C.	Solvent for recrystn.	Analytical data, % Calcd. C	Calcd. H	Found C	Found H	Yield, %
Hexacosanoic acid (cerotic acid)	85.5–86.5[a]	Acetone	78.72	13.22	78.60 78.81	12.95 13.11	
1-Cyclohexoxydotriacontane	88–89	Pet. ether or acetone	83.13	13.95	83.11	14.43	76
1-Cyclohexoxyhexatriacontane	86.5–87.5	Ethyl methyl ketone	83.37	13.99	82.97 82.88	14.04 14.41	94

[a] Francis and Piper (ref. 17) have recorded the melting point as 87.7°. The cerotic acid obtained by the hydrolysis and oxidation of Chinese Insect Wax had a melting point of 78–80° (ref. 19).

which had separated. The keto-acid was recrystallized from 1 liter of petroleum ether (90–100°). After the acid had been dried at 90–100°, it melted at 98–103°; the yield was 170 g. (79%).

A 10-g. sample of the crude keto-acid was dissolved in 300 ml. of hot petroleum ether (90–100°) and heated and stirred with 200 ml. of 60% alcohol containing 0.004 mole of sodium hydroxide. The layers were separated hot, and the petroleum ether solution was concentrated and cooled; the crystals, after separation by filtration and drying, melted at 103–104°. A small sample, recrystallized twice from acetone for analysis, melted at 104–105°. *Anal.* Calcd. for $C_{34}H_{66}O_3$: C, 78.09; H, 12.72; mol. wt., 522.9. Found: C, 78.30; H, 12.75; mol. wt., (neut. equiv.) 508.

The petroleum ether filtrate from which the crude keto-acid had been isolated was heated and stirred with 700 ml. of 60% alcohol containing 30 g. of potassium hydroxide, the layers were separated, and the petroleum ether solution was washed with two 600-ml. portions of hot 60% alcohol. Acidification of the alkaline solution, filtration, and recrystallization of the solid from petroleum ether (90–100°) yielded 19 g. of impure hexadecane-1,16-dicarboxylic acid which melted at 110–120°. The petroleum ether solution was concentrated to small volume, and the solid which separated was recrystallized twice from absolute ethanol; 13 g. of white needles which melted at 68–70° was obtained. This product is probably dotriacontane. It can also be crystallized from ethyl methyl ketone. *Anal.* Calcd. for $C_{32}H_{66}$: C, 85.24; H, 14.76. Found: C, 84.06; H, 14.43.

1,20-Dicyclohexoxycosane.—The petroleum ether filtrate obtained from the recrystallization of the crude 1-cyclohexoxy-11-ketodotriacontane (see Table I) was concentrated to a small volume and cooled. The precipitate, 40 g. (from 0.2 mole of 1-bromo-10-cyclohexoxydecane), was recrystallized from 250 ml. of ethyl methyl ketone, and the solid so obtained was recrystallized twice from absolute ethanol; 5 g. of 1,20-dicyclohexoxycosane which melted at 54–56° was obtained. *Anal.* Calcd. for $C_{32}H_{62}O_2$: C, 80.26; H, 13.05. Found: C, 80.23; H, 13.28.

Docosanoic Acid (Behenic Acid).—Erucic acid[16] was hydrogenated in alcoholic solution in the presence of Raney nickel catalyst. Under 2000 p. s. i. of hydrogen and at a temperature of 75°, the hydrogenation proceeded rapidly and smoothly. The product, when recrystallized from petroleum ether (b. p. 90–100°), separated as white, shiny plates which melted at 79.5–80.5°. Francis and Piper[17] have recorded a melting point of 79.95° for this acid. *Anal.* Calcd. for $C_{22}H_{44}O_2$: mol. wt., 340. Found: mol. wt. (neut. equiv.), 355.

Tetratriacontanoic Acid.—A mixture of 85 g. of 18-ketotetratriacontanoic acid, 85 ml. of 85% hydrazine hydrate, 85 g. of sodium hydroxide and 3 liters of diethylene glycol was heated in a flask equipped with a stirrer, a thermometer, and an arrangement for the removal or return of refluxing liquid. When the temperature had reached 140–150°, the mixture began to foam, and it was necessary to apply heat less rapidly and to stir vigorously. Foaming stopped when the temperature passed 150°; solvent began to reflux at 175°, and the temperature was held at that point for one hour. Volatile material was then removed over a period of two hours, and the mixture was finally heated under reflux at 215° for an additional hour and a half. When the mixture had cooled to 160–180°, it was poured slowly into a warm (60°), well-stirred solution of 300 ml. of concentrated hydrochloric acid in 3 liters of water. The hot solution was extracted with 3 liters of hot toluene, and the toluene layer washed with hot water and finally with a dilute ethanolic solution of sodium hydroxide (60% aqueous ethanol). The toluene solution was then concentrated and cooled. Tetratriacontanoic acid, which melted at 92–93.5°, was obtained in 82% yield. The time of reaction was insufficient for the large quantities employed; the product contained unreduced keto-acid. Further treatment of the product by the procedure described gave purer material which melted at 95–96°. An analytical sample prepared by recrystallization from acetone melted at 95.5–96.4°.[18]

Anal. Calcd. for $C_{34}H_{68}O_2$: mol. wt., 508.9. Found: mol. wt. (neutral equivalent), 511.

Ethyl Tetratriacontanoate.—A solution of 5.0 g. of tetratriacontanoic acid in 150 ml. of dry alcohol, 250 ml. of benzene and 0.2 g. of *p*-toluenesulfonic acid were heated for two hours under an 18-inch helix-packed column. Distillate was then taken off slowly until 300 ml. had been collected. The residual solution was cooled, and the

---

(16) "Organic Syntheses," Coll. Vol. II, p. 258.

(17) Francis and Piper, THIS JOURNAL, **61**, 577 (1939).

(18) Francis, King and Willis, ref. 2, report a melting point of 98.2° for this acid obtained from distilled ethyl ester.

(19) Coover, Thesis, Cornell University, 1943.

precipitate was collected and recrystallized from petroleum ether (90–100°). The white, waxy crystals melted at 76–76.5°.[20] The ester also crystallized well from ethyl methyl ketone.

Anilide of Tetratriacontanoic Acid.—One gram of acid was mixed with 10 ml. of thionyl chloride, allowed to stand for thirty minutes and then heated under reflux for several minutes. Excess thionyl chloride was removed by distillation and the residue, dissolved in 60 ml. of petroleum ether, was added to 5 ml. of aniline. The mixture was stirred thoroughly and evaporated to dryness; the residue was triturated with cold, dilute hydrochloric acid and the crystals were separated by filtration. The product was recrystallized once from a small volume of ethyl methyl ketone and then twice from 100-ml. portions of petroleum ether (90–100°). The anilide, 1.05 g., melted at 110–110.5°. Francis[2] reported a melting point of 113–114°.

Acknowledgment.—We should like to acknowledge the continued interest and suggestions of Dr. Howard Gilbert of the Bureau of Aeronautics, Navy Department. Miss Eleanor Werble performed the microanalyses, and Mr. Herman Sanders aided in the preparation of certain intermediates.

Summary

1. The preparation of hexacosanoic acid and tetratriacontanoic acid is described.

2. The same method has been applied to the synthesis of 1-cyclohexoxydotriacontane and 1-cyclohexoxyhexatriacontane.

3. A convenient synthesis of ethyl hydrogen hexadecanedicarboxylate has been developed. The method depends upon the selective solvent action of petroleum ether which has been shown to be a solvent of useful specificity.

COLLEGE PARK, MD. RECEIVED JUNE 28, 1947

---

[20] Francis, King and Willis, ref. 2, have recorded the melting point of this ester as 75.4°.

[CONTRIBUTION FROM THE WOOD CONVERSION LABORATORY OF THE UNIVERSITY OF IDAHO]

The Constitution of Mesquite Gum. IV. 4-Methoxy-D-glucuronic Acid[1]

BY E. V. WHITE

A large number of the polysaccharides occurring in nature are known to contain uronic acid residues as an integral part of their molecular structure. The carboxyl group in such instances usually does not occur in the free state but rather is combined as a salt with metallic ions such as calcium, magnesium, and the like or as an ester with methyl alcohol. In general, the uronic acid possesses the glucose, mannose or galactose configuration and it has been considered to play an important role in the mechanism of plant synthesis. In a few instances polysaccharides have been reported to contain small percentages of ether type methoxyl and this grouping appears to be associated invariably with the uronic acid component. The observation is particularly interesting since it records the natural synthesis of an aliphatic ether linkage as contrasted with the usual aromatic, ester and acetal types. Unfortunately, however, the presence of this particular grouping[2] has been indicated hitherto only by analyses and no definite crystalline compounds or derivatives have been prepared to prove the actual existence of the group or to establish its exact location in any given polysaccharide.

The presence of ether methoxyl in mesquite gum was reported first by Anderson and co-workers[3a,b,c,d] who traced the group to the uronic acid component and, largely by a process of elimination, suggested the three position thereof as the most likely point of attachment. It has now been shown[4] that the uronic acid residues occupy terminal positions in the mesquite gum macromolecule and the present study was designed to locate definitely the position of the methyl ether linkage.

The well known reaction of polysaccharides with anhydrous acidic methyl alcohol solutions results in simultaneous esterification of the uronides and formation of the corresponding methyl glycosides and uronosides. In such reactions, whereas a single methyl group is substituted in the saccharides, two such groups are introduced into the uronic acid component. One of these is uronosidic or acetal in character while the second is of the ester type. In the present instance these two methyl groups together with the aliphatic ether group originally present furnish a trimethyl substituted uronic acid fission product which can be separated readily from the glycosidic fragments. Accordingly, mesquite gum which had been partially hydrolyzed to remove the labile arabinose fraction[5] was treated with methanolic hydrogen chloride and the resulting sirup extracted with anhydrous acetone. The extract was concentrated and then diluted with anhydrous ether to precipitate residual methyl galactoside. Evaporation of the mixed solvent and fractional

---

[1] Presented in part at the Fall Meeting of the Technical Association of the Pulp and Paper Industry, Appleton, Wisconsin, September 3–5, 1947.

[2] It should be noted that the aliphatic methyl ether grouping has been found in the carbohydrate component of certain cardiac glycosides, notably, cymarose and digitalose. A review of these compounds is given by Elderfield, "Recent Advances in Carbohydrate Chemistry," Vol. I, Academic Press, Inc., New York, N. Y., 1945, p. 147.

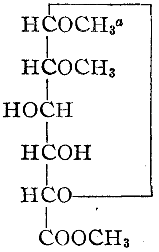
[3] (a) Anderson, Sands and Sturgis, *Am. J. Pharm.*, **97**, 589 (1925); (b) Anderson and Sands, *Ind. Eng. Chem.*, **17**, 1257 (1925); (c) Anderson and Sands, THIS JOURNAL, **48**, 3172 (1926); (d) Anderson and Otis, *ibid.*, **52**, 4461 (1930).

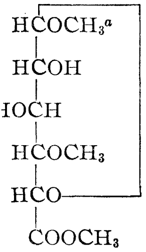
[4] White, *ibid.*, **68**, 272 (1946).

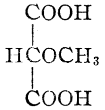
[5] White, *ibid*, **69**, 622 (1947).

vacuum distillation of the sirup furnished the methyl ester of monomethyl-methyl-glucuronoside.

The ether type methoxyl group of this compound must obviously be located at either the second, third or fourth carbon atom since the uronoside ester contains the normal pyranose ring structure.[4] A decision as to the correct position was provided by the selective action of periodic acid which reacts in stoichiometric proportion with the compound. Since such reaction necessitates vicinal hydroxyl groups in the reacting substance, the presence of an ether grouping at the third carbon atom is untenable and the uronoside ester must be represented either by Formula I or Formula II.

I


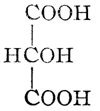
II


Ia


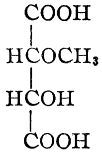
$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{HCOCH_3}\\ |\\ \mathrm{COOH}\end{array}$$

IIa


$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{COOH}\end{array}$$

Ib


$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{COOH}\end{array}$$

IIb


$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{HCOCH_3}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{COOH}\end{array}$$

[a] The alpha form is represented although both alpha and beta forms are present in the uronoside ester sirup.

In the first example (I) treatment of the compound with periodic acid followed by bromine oxidation, acetal hydrolysis and re-oxidation according to the splendid methods of Jackson and Hudson[6] should provide eventually methoxymalonic acid (Ia) and hydroxymalonic acid (Ib), both of which are optically inactive. On the other hand, a similar treatment of the compound represented by Formula II should furnish oxalic acid (IIa) and a methoxy-*meso*-tartaric acid (IIb), the latter being optically active.

With these possibilities in mind the compound in quesion was subjected to a series of reactions employing one molecular equivalent of periodic acid and followed by oxidation with bromine in the presence of strontium carbonate. The product was isolated as both a crystalline and an amorphous strontium salt with identical analyses but different optical activity. Further reaction of this compound after quantitative removal of strontium as sulfate involved hydrolysis of the acetal grouping and bromine oxidation of the aldehyde thus formed. The resulting reaction product now contained two dibasic organic acids which were separated and identified. One of these was found to be oxalic acid and identified as the dimethyl ester. The second acid proved to be an optically active methoxy-*meso*-tartaric acid which was also isolated as the dimethyl ester and from which a crystalline diamide was prepared. Complete methylation of this ester furnished crystalline dimethoxy-*i*-dimethyl-succinate which was identified further as the crystalline diamide.

The above experiments seem to provide convincing proof that the methyl ester of monomethyl-glucuronoside isolated from mesquite gum possesses the structure represented by Formula II. The methyl ether linkage in this particular polysaccharide is thus located at the fourth carbon atom of the uronic acid component and its synthesis by natural agencies seems well established. It is interesting to note also that the position of ether linkage is characteristically that involved in the glycosidic linkage of glucose in the polysaccharides. This property is, of course, shared to some extent with the terminal hydroxyl grouping, while the remaining groups appear to be inactive.

Experimental Part

Preparation of Monomethyl-methyl-glucuronoside Methyl Ester from Mesquite Gum.—Two hundred grams of crude mesquite gum was dissolved in one liter of distilled water and filtered to remove extraneous material. The solution was then made 0.15 *N* with sulfuric acid and heated at 92° on a water-bath for thirty-six hours.[5] The hydrolyzate was dialyzed against water for two days to remove acid, arabinose, etc., filtered and concentrated at 50° to a thin sirup by evaporation. The concentrate, diluted with an equal volume of methyl alcohol, was added slowly to rapidly stirred anhydrous methanol. The flocculent precipitate was settled, filtered, washed with fresh alcohol and ether, and finally dried at 40° under reduced pressure; yield 78 g.

The above product was suspended in 500 cc. of methanol containing 7% anhydrous hydrogen chloride and heated under reflux for eighteen hours. The polysaccharide under these conditions dissolves rapidly with frequent swirling during the first half hour. The concentration of hydrogen chloride decreased steadily during the heating period and residual acidity was finally removed with silver carbonate. After filtering off silver salts the solution was evaporated to a sirup, taken up in 100 cc. of fresh acetone and 400 cc. of anhydrous ether added slowly with swirling. After a few hours the clear solution was siphoned off and the residue re-extracted using one-third quantities of the same solvents. The combined extracts were evaporated to a sirup which was distilled, b. p. 130° (0.2 mm.), under high vacuum; yield 15.2 g.; specific rotation +95° (25°, *c* 10, water).

Anal. Calcd. for $C_9H_{16}O_7$: OCH_3, 39.4. Found: OCH_3, 39.3.

Treatment of a sample, 1.0 g., with methyl alcoholic ammonia in the usual manner furnished an amide, recrystallized from methanol–acetone, m. p. 218°.

Anal. Calcd. for $C_8H_{15}O_6N$: OCH_3, 28.0; N, 6.34. Found: OCH_3, 27.8; N, 6.3.

Preparation of the Strontium Salt of Oxidized Monomethyl-methyl-glucuronoside Methyl Ester.—The above ester, 16.7 g., was dissolved in 300 cc. of water, treated with norite and filtered. To the filtrate was added one molecular equivalent plus 5% excess of periodic acid dissolved in 200-cc. of water. The solution was allowed to stand at room temperature for sixteen hours when an excess of strontium carbonate was carefully added with stirring. The precipitate of strontium salts was then re-

---

(6) Jackson and Hudson, This Journal, **59**, 994 (1937).

moved and washed with 100 cc. of water. The filtrate, 600 cc., was added in 200-cc. portions to three flasks each containing 5 cc. of bromine dissolved in 500 cc. of water and 50 g. of strontium carbonate. After eighteen hours in the dark, with occasional swirling especially during the first two hours, excess bromine was removed by aeration. Silver carbonate was added to remove bromine ion and after filtering, silver ion was removed as sulfide. The colorless, combined filtrates were distilled at 30° under reduced pressure to a thin sirup which was diluted with two volumes of 95% ethanol. The crystalline strontium salt of the acid separated overnight and was removed, washed with cold 65% ethanol, ethanol and ether, and dried; yield 13.3 g.; specific rotation −24° (25°, *c* 5, water).

Anal. Calcd. for $C_9H_{12}O_9Sr$: OCH_3, 26.5; Sr, 24.9. Found: OCH_3, 25.4; Sr, 24.0.

The filtrates upon evaporation to dryness gave a residue which did not crystallize but gave the same analysis as above: yield, 7.8 g.; specific rotation +13° (25°, *c* 5, water).

The former compound, which has not yet been recrystallized in pure form, is thought to be derived from the alpha form of the uronoside, with the latter representing a mixture of the alpha and beta modifications.

Proof of Structure of the Strontium Salt of Oxidized Monomethyl-methyl-glucuronoside Methyl Ester.—Ten grams of either the crystalline or amorphous forms of the strontium salt was dissolved in 100 cc. of water and treated with the exact quantity of sulfuric acid dissolved in 100 cc. of ethanol to precipitate the strontium as sulfate. After several hours the precipitate was filtered off, washed with 50% ethanol and concentrated under reduced pressure (40–45° bath) to about 30 cc. The thin sirup was then diluted with ethanol, filtered free from residual strontium salt and re-evaporated. The sirup was diluted to 100 cc. with water and heated for two hours on a boiling water-bath to hydrolyze the acetal group. The hydrolyzate was then added to 500 cc. of distilled water containing 5 cc. of dissolved bromine. After forty-five hours in the dark excess bromine was removed by aeration and silver carbonate added to free the solution from bromine ion. Silver was then removed as sulfide and the clear solution evaporated to a thin sirup under reduced pressure. The sirup was extracted with ethanol, concentrated and re-extracted with ether to separate inorganic material. Excess solvent was then removed and the residue methylated by Purdie's method using methyl iodide and silver oxide. After complete methylation the silver residues were extracted with petroleum ether and upon removal of solvent the sirup was distilled fractionally under reduced pressure.

Fraction I, b. p. 62° (11 mm.), crystallized spontaneously and after recrystallization from light petroleum furnished dimethyl oxalate; m. p. 54°[7]; yield 2.4 g.

Anal. Calcd. for $C_4H_6O_4$: OCH_3, 52.5. Found: OCH_3, 52.1.

Fraction II, b. p. 78° (0.2 mm.), distilled as a colorless optically inactive liquid which crystallized completely upon standing, m. p. 68°[8] from ether; yield 4.6 g.

Anal. Calcd. for $C_8H_{14}O_6$: OCH_3, 60.2. Found: OCH_3, 60.2.

Treatment of a sample, 1.0 g., with methyl alcoholic ammonia in the usual manner furnished a crystalline compound upon removal of solvent. Recrystallization from methyl alcohol gave dimethoxy-*i*-succinic acid diamide; m. p. 256°.[9]

Anal. Calcd. for $C_6H_{12}O_4N_2$: OCH_3, 35.2. Found: OCH_3, 35.2.

Obviously, Fraction II must have been formed from a four-carbon dibasic acid in the above Purdie methylation. Accordingly, in a separate experiment a similar ether extract containing 4.0 g. dissolved material was treated with an excess of diazomethane in order to form the methyl esters of the dissolved organic acids. After removal of excess reactant and solvent the sirup was distilled under high vacuum. An optically active fraction was collected and redistilled, b. p. 87° (0.2 mm.); yield 2.2 g.; specific rotation +49° (25°, *c* 5, methanol).

Anal. Calcd. for $C_7H_{12}O_6$: OCH_3, 48.4. Found: OCH_3, 47.7.

Treatment of a sample, 0.5 g., with methyl alcoholic ammonia in the usual manner furnished the diamide of 3-hydroxy-2-methoxy-D-erythrosuccinic acid, recrystallized from acetone–methyl alcohol, m. p. 156°.

A similiar reaction using methyl alcoholic methylamine furnished 3-hydroxy-2-methoxy-D-erythrosuccinobismethyl amide; recrystallized from ethyl acetate, m. p. 135°[10]; specific rotation −10.5° (25°, *c*, 5, water).

Complete methylation of the ester by the Purdie method gave dimethoxy-*i*-dimethyl succinate which was identified as the above described diamide, m. p. 256°.[6]

Summary

1. The uronic acid component of mesquite gum has been isolated as the monomethyl-methyl-glucuronoside methyl ester.

2. The structure of this compound is shown to be that derived from 4-methoxy-D-glucuronic acid.

3. The methyl ester grouping in mesquite gum is located at the fourth carbon atom of the glucuronic acid component.

MOSCOW, IDAHO RECEIVED AUGUST 16, 1947

---

[7] Dumas and Peligot, *Ann. chim. phys.*, [2] **58**, 44 (1835).

[8] Patterson and Patterson, *J. Chem. Soc.*, **107**, 155 (1915).

[9] Haworth and Hirst, *ibid.*, **128**, 1965 (1926).

[10] Heslop, Salt and Smith, *ibid.*, 225, (1944).

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Preparation of Some Substituted β-Phenylisovaleric Acids

BY JOSEPH CORSE[1] AND EWALD ROHRMANN

β-Phenylisovaleric acid was prepared by Hoffman[2] by the haloform oxidation of 4-methyl-4-phenyl-2-pentanone, a substance readily prepared by the reaction of benzene and mesityl oxide with aluminum chloride as catalyst. The acid has also been prepared by the carbonation of neophylmagnesium chloride.[3]

We have carried out the synthesis of a number of substituted β-phenylisovaleric acids which were desired in connection with some antibiotic studies. These were prepared either from the corresponding substituted ketones by haloform oxidation or from the parent unsubstituted β-phenylisovaleric acid.

A number of substituted benzenes were subjected to reaction with mesityl oxide and aluminum chloride. The reaction was found to proceed well with benzene and with fluoro-, chloro- and bromobenzenes. We were unable to effect reaction with anisole and mesitylene, while complex mixtures resulted with toluene, *o*-xylene and tetralin. Eijkman[4] noted a similar failure of toluene to add to β,β-dimethylacrylic acid, in contrast to the behavior of benzene. Reaction of thiophene with mesityl oxide could not be satisfactorily effected with either aluminum chloride or stannic chloride.

Both Eijkman[4] and Hoffman[2] reported the preparation of the nitro derivative of β-phenylisovaleric acid by direct nitration of the acid. We have reduced this nitro acid catalytically to β-(*p*-aminophenyl)-isovaleric acid, which was diazotized and treated in the usual ways to give the *p*-arsono, *p*-arsenoso, *p*-bromo and *p*-hydroxy substituted phenylisovaleric acids. The bromo acid prepared by the Sandmeyer reaction from the amine was identical with that derived from 4-methyl-4-*p*-bromophenyl-2-pentanone and sodium hypochlorite. This indicates that the nitration of phenylisovaleric acid occurs largely in the para position, as one might expect.

β-(*p*-Iodophenyl)-isovaleric acid was made by the direct iodination of β-phenylisovaleric acid.[5]

We wish to thank Mr. W. L. Brown and Mr. H. L. Hunter of these Laboratories for the analyses.

Experimental

4-(*p*-Halophenyl)-4-methyl-2-pentanones.[2]—These were prepared by the aluminum chloride catalyst condensation of the *p*-halobenzene and mesityl oxide in carbon disulfide solution, essentially as described by Hoffman[2] for benzene. The organic layer was separated, dried and distilled *in vacuo*.

4-*p*-Fluorophenyl-4-methyl-2-pentanone.—B. p. 66° (0.1 mm.); $n^{28}\mathrm{D}$ 1.4911; yield, 38.0 g. (70%).

Anal. Calcd. for $C_{12}H_{15}OF$: C, 74.19; H, 7.78. Found: C, 74.33; H, 8.03.

4-*p*-Chlorophenyl-4-methyl-2-pentanone.—B. p. 169–171° (16 mm.); $n^{24.5}\mathrm{D}$ 1.5228; yield, 102.5 g. (95%).

Anal. Calcd. for $C_{12}H_{15}OCl$: C, 68.40; H, 7.17. Found: C, 68.35; H, 7.58.

4-*p*-Bromophenyl-4-methyl-2-pentanone.—B. p. 128–130° (0.6 mm.); $n^{28}\mathrm{D}$ 1.5392; yield, 52 g. (41%).

Anal. Calcd. for $C_{12}H_{15}OBr$: C, 56.48; H, 5.92. Found: C, 56.38; H, 5.85.

Haloform Oxidation of 4(*p*-Halophenyl)-4-methyl-2-pentanones.—The haloform reactions were run with sodium hypochlorite according to the directions of Newman and Holmes[6] to yield the corresponding β-substituted phenylisovaleric acids. The yields varied from 51 to 74% of theoretical.

β-(*p*-Fluorophenyl)-isovaleric acid.—M. p. 60–62°.

Anal. Calcd. for $C_{11}H_{13}O_2F$: C, 67.23; H, 6.67. Found: C, 66.76; H, 6.45.

β-(*p*-Chlorophenyl)-isovaleric acid.—M. p. 65–67°.

Anal. Calcd. for $C_{11}H_{13}O_2Cl$: C, 62.11; H, 6.16. Found: C, 62.24; H, 5.68.

β-(*p*-Bromophenyl)-isovaleric acid.—M. p. 60–61°.

Anal. Calcd. for $C_{11}H_{13}O_2Br$: C, 51.38; H, 5.09. Found: C, 51.66; H, 4.77.

β-(*p*-Iodophenyl)-isovaleric acid.—This acid was prepared by the method of Plati, *et al.* (*cf.* ref. 5(b)). The crude acid was purified by conversion to the ethyl ester which was fractionally distilled. That portion boiling at 145–146° (0.9 mm.) proved to be the desired ester; yield, 34.6 g. (53%), $n^{28}\mathrm{D}$ 1.5501.

Anal. Calcd. for $C_{13}H_{17}O_2I$: C, 46.99; H, 5.16. Found: C, 46.51; H, 4.80.

The acid was prepared by saponification with potassium hydroxide; m. p. 76–78°.

Anal. Calcd. for $C_{11}H_{13}O_2I$: C, 43.43; H, 4.31. Found: C, 43.32; H, 4.49.

β-(*p*-Nitrophenyl)-isovaleric Acid.—One hundred and forty grams of β-phenylisovaleric acid was added with stirring, over a period of one hour, to 250 ml. of fuming nitric acid cooled to −30° in a Dry Ice-bath. The temperature was then allowed to rise during another hour to +5°, and stirring was maintained an additional two hours at 0 to 5°. The solution was poured onto cracked ice and the product was collected on a filter and washed well with water. The product was recrystallized from alcohol–benzene; m. p. 172–175°.

Anal. Calcd. for $C_{11}H_{13}O_4N$: N, 6.28. Found: N, 6.63.

β-(*p*-Aminophenyl)-isovaleric acid.—Catalytic reduction of the above nitro acid in methanol solution on the Adams machine, using Raney nickel catalyst or platinum oxide at 3 atmospheres pressure, gave the *p*-amino substituted acid in almost quantitative yield. After being twice recrystallized from methanol–ether the melting point was 135°.

Anal. Calcd. for $C_{11}H_{15}O_2N$: N, 7.24. Found: N, 7.31.

---

(1) Present address: University of California at Los Angeles, California.

(2) Hoffman, THIS JOURNAL, **51**, 2542 (1929).

(3) Whitmore, *et al.*, *ibid.*, **65**, 1469 (1943).

(4) Eijkman, *Chem. Weekblad.*, **5**, 655 (1909); *C. A.*, **3**, 779 (1909); *Chem. Zentr.*, **79**, II, 1100 (1908).

(5) (a) Varma and Panickar, *J. Indian Chem. Soc.*, **7**, 503 (1930); *C. A.*, **24**, 5740 (1930); (b) Plati, Strain and Warren, THIS JOURNAL, **65**, 1273 (1943).

(6) "Organic Syntheses," Collective Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 428.

β-(*p*-Arsonophenyl)-isovaleric acid.—This acid was prepared from β-(*p*-aminophenyl)-isovaleric acid by the diazonium salt replacement reaction with arsenic trioxide. The crude acid was purified by recrystallization from hot water; yield, 56 g. (75%).

Anal. Calcd. for $C_{11}H_{15}O_5As$: As, 24.85. Found: As, 24.38, 24.35.

β-(*p*-Arsenosophenyl)-isovaleric acid.—Forty grams of the above arsono acid was dissolved in a solution of 100 ml. of concentrated hydrochloric acid and 100 ml. of water. A small crystal of potassium iodide was added, and sulfur dioxide was passed through the solution for four and one-half hours. The solid which formed was collected and dissolved in sodium bicarbonate solution. Careful acidification with 10% hydrochloric acid precipitated the acid, which was collected and washed several times with cold water; yield, 9.2 g. The material was hygroscopic and analyzed for the hydrate.

Anal. Calcd. for $C_{11}H_{15}O_4As$: As, 26.14. Found: As, 26.83, 26.81.

β-(*p*-Hydroxyphenyl)-isovaleric Acid.—This acid was prepared from β-(*p*-aminophenyl)-isovaleric acid by the diazonium salt replacement reaction. Purification was best done by esterifying the crude acid with ethanol and sulfuric acid and taking advantage of the alkali solubility of the ester. Subsequent saponification and recrystallization of the acid from ethanol–ether–petroleum ether gave a white crystalline product melting at 146–148°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.04; H, 7.08.

Summary

The Friedel–Crafts addition of three halogenated benzenes to mesityl oxide to give 4-methyl-4-halogen substituted phenyl-2-pentanones is described.

A number of β-(*p*-substituted phenyl)-isovaleric acids are described.

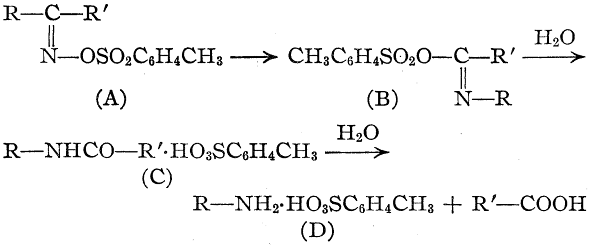
INDIANAPOLIS, INDIANA RECEIVED JULY 21, 1947

[CONTRIBUTION FROM THE ORGANIC CHEMICAL INSTITUTE OF THE HUNGARIAN UNIVERSITY "BOLYAI"]

Studies on Furan Compounds. I. Conversion of 2-Acetofuran to Hexen-2-dion-4,5-acetal-1 and Pyrocatechol

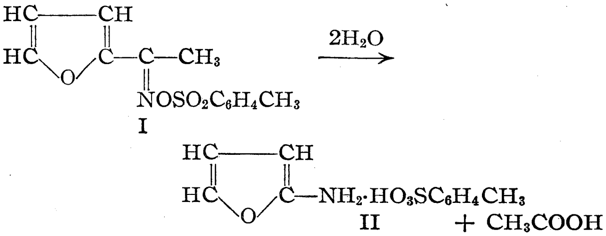
BY L. VARGHA, J. RAMONCZAI AND P. BITE

Several workers have already tried to synthesize 2-aminofuran. However, hydrolysis experiments on furan-2-ethylurethan[1] and on 2-benzyl- and 2-propionylaminofuran[2] have only resulted in the formation of ammonia and tar-like products, probably because 2-aminofuran decomposes very rapidly. We have thought that a milder procedure, such as the reaction discovered by Neber and v. Friedolfsheim[3] on the *p*-toluenesulfonyl derivatives of certain aromatic ketoximes (A) might lead to the desired goal. According to this process a compound like (A) when shaken with ethanol at room temperature, undergoes first a Beckmann rearrangement, then the intermediate (B) suffers hydrolytic cleavage (C) under the influence of traces of water with the eventual formation of an amine (D).[3,4]



$$\underset{(A)}{R{-}\underset{\overset{\|}{N}{-}OSO_2C_6H_4CH_3}{C}{-}R'} \longrightarrow \underset{(B)}{CH_3C_6H_4SO_2O{-}\underset{\overset{\|}{N}{-}R}{C}{-}R'} \xrightarrow{H_2O} \underset{(C)}{R{-}NHCO{-}R'\cdot HO_3SC_6H_4CH_3} \xrightarrow{H_2O} \underset{(D)}{R{-}NH_2\cdot HO_3SC_6H_4CH_3 + R'{-}COOH}$$

However, on shaking *p*-toluenesulfonyl 2-acetofuran oxime (I) with ethanol, not the expected toluenesulfonic acidic salt of 2-aminofuran (II) was obtained. Rather, we isolated, in addition to ammonium *p*-toluenesulfonate, a yellowish-green, strongly reducing liquid, which was free of nitrogen. Although very sensitive to heat, the liquid can be distilled *in vacuo* at constant temperature without being decomposed. The analysis and determination of molecular weight gave the elementary formula $C_{10}H_{16}O_4$ (III). Methanol, instead of ethanol, gave rise to a very similar substance with the formula $C_8H_{12}O_4$ (IV). These substances were found to represent *cis*-hexen-2-dion-4,5-diethylacetal-1 (III), and -dimethylacetal-1 (IV), respectively, as the end-products of the over-all reaction



$$CH_3COCOCH{=}CHCH(OR)_2$$
$$\text{III, } R = {-}C_2H_5$$
$$\text{IV, } R = {-}CH_3$$
$$CH_3COCOCH_2CH_2CH(OR)_2$$
$$\text{V, } R = {-}C_2H_5$$
$$\text{VI, } R = {-}CH_3$$

$$\underset{(I)}{C_6H_6O{-}NOSO_2C_6H_4CH_3} + H_2O + 2ROH = CH_3C_6H_4SO_3(NH_4) + \text{III or IV}$$

Proof of the structures of III and IV rests on the following experimental facts.

With maleic anhydride no adduct originated[5] from III; therefore, the latter could not possess the furan nucleus. On catalytic hydrogenation

---

[1] Leimbach, *J. prakt. Chem.*, [2], **65**, 20 (1902).

[2] Singleton and Edwards, THIS JOURNAL, **60**, 540 (1938).

[3] Neber and v. Friedolfsheim, *Ann.*, **449**, 109 (1926).

[4] Neber and Huh, *ibid.*, **515**, 292 (1935).

[5] Alder and Schmidt, *Ber.*, **76**, 18 (1943).

in the presence of palladium catalyst III and IV took up only one mole of hydrogen giving rise to two liquids with the elementary formulas of $C_{10}H_{18}O_4$ (V) and $C_8H_{14}O_4$ (VI), respectively, whereas a furan compound would have required two moles of hydrogen at least. These experiments, therefore, indicated that the furan ring opened up during the reaction of I with alcohol, and that the substances (III, IV) so formed must be regarded as unsaturated aliphatic compounds.

In spite of the strong reduction shown toward ammoniacal silver nitrate or cold Fehling solution, substances III to VI could not contain free aldehyde groups because they gave positive test with fuchsin–sulfurous acid solution only after acid-catalyzed hydrolysis. Since the latter operation, beside one mole of acetic acid, yielded ethyl or methyl alcohol, it was concluded that each compound from III to VI contained an acetal grouping, which accounted for two atoms of oxygen in the empirical formulas. This conclusion was confirmed by the reactions of III and IV with aqueous hydroxylamine hydrochloride which gave rise to an identical oxime with the formula $C_6H_6O_2({=}NOH)$. The fact that the latter substance was a true oxime was proved by benzoylation which produced the expected benzoyl ester, $C_6H_6O_2({=}NOCOC_6H_5)$.

The remaining two oxygen atoms in III and IV were assumed to belong to two carbonyl groups, for no active hydrogen could be found in equivalent quantity according to Zerewitinow's method. The presence of one of these carbonyl groups could be demonstrated experimentally by the reaction of either III or IV with phenylhydrazine which led, under loss of two moles of alcohol, to an identical bisphenylhydrazone, $C_6H_6O({=}NNHC_6H_5)_2$. The presence of the second carbonyl group could not be demonstrated in this reaction, because the substance suffered decomposition on prolonged heating with the carbonyl reagent.

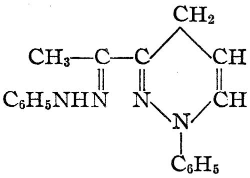
Final evidence of the correctness of structures III and IV was derived from the results of the oxidative degradations of these compounds. Thus it was found that, on treatment with ozone, compound IV gave rise to glyoxal which was isolated in form of its phenylosazone. This experiment proved that compound IV was essentially an unsaturated aldehyde, which contained its double bond between carbon atoms 2 and 3. Since oxidation of IV by potassium permanganate led to the formation of acetic acid and oxalic acid, the presence of an CH_3CO— group in the molecule was indicated. This conclusion was in accord with the result of the acid-catalyzed hydrolysis of IV, which, instead of giving the expected unsaturated diketo-aldehyde, $CH_3COCOCH{=}CHCHO$, decomposed with formation of acetic acid and methyl alcohol. The correctness of structural formulas III to VI was also confirmed by other degradation reactions. Hollemann[6] and Böeseken[7] have shown that the oxidation of 1,2-diketones by hydrogen peroxide results in the corresponding acids, according to the reaction

$$R{-}COCO{-}R' + H_2O_2 = R{-}COOH + R'{-}COOH$$

By the application of this reaction in glacial acetic acid to IV, we obtained maleic acid, in consequence of the simultaneous hydrolysis of the acetal grouping and further oxidation of the free aldehyde to the acid

$$CH_3COCOCH{=}CH{-}CH(OCH_3)_2 \longrightarrow$$
$$2CH_3OH + CH_3COOH +$$
$$[HOOC{-}CH{=}CH{-}CHO] \longrightarrow$$
$$HOOC{-}CH{=}CH{-}COOH$$

These results confirmed not only the correctness of the established structural formulas for III to VI, but they also proved, because of the formation of maleic acid, the *cis*-configuration of III and IV, which could exist in two geometrical isomeric forms. The oxidation of the saturated compound VI by silver oxide in aqueous solution resulted in succinic acid, in accordance with the result obtained on the corresponding unsaturated compounds III and IV. The 1,4-relationship between the acetal group and one of the two carbonyl groups in compounds III to VI follows from the behavior of the saturated diketo-acetal VI toward phenylhydrazine. It is known from the literature[8] that 1,4-dicarbonyl compounds usually give rise to pyridazine derivatives. Accordingly, we have obtained from V or VI, on treatment with phenylhydrazine, a light-yellowish, crystalline powder which, on the basis of analysis, represents the phenylhydrazone of the 1-phenyl-3-acetodihydropyridazine (VII).



VII

In the course of our further work, we wished to study the free aldehydes, corresponding with the acetals III to VI. However, the unsaturated diketo-aldehyde, $CH_3COCOCH{=}CHCHO$, could not be produced by hydrolysis of III or IV, because, as already mentioned, the carbon-chain between the adjacent carbonyl groups split up with formation of acetic acid, even in cold aqueous solution. We attribute this easy cleavage of the carbon to carbon linkage in the dicarbonyl grouping to a loosening effect of the double bond which occupies an α,β-position.

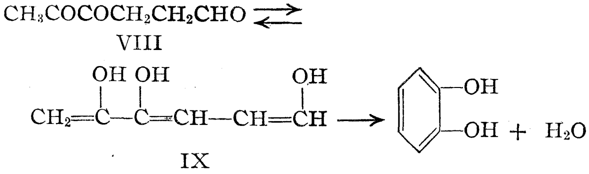
The hydrolysis of the saturated acetals V and VI also led to a surprising result; because instead of the expected diketo-aldehyde (VIII), $CH_3COCOCH_2CH_2CHO$, there was produced pyrocatechol. The formation of the latter, however, can easily be explained through the trienol form (IX)

---

(6) Hollemann, *Rec. trav. chim.*, **23**, 169 (1904).

(7) Böeseken, *ibid.*, **30**, 142 (1911).

(8) Smith, *Ann.*, 289, 310 (1896); *Ber.*, **35**, 2169 (1902).



VIII

IX

Since pyrocatechol and its derivatives are very common in nature, it is perhaps of interest to point out a possible way by which they can eventually be formed from carbohydrates through furan derivatives.

At present no definitive explanation can be offered as to the mechanism of the conversion of I into III or IV. It is very probable that the reaction does not proceed according to Neber's formulas through 2-aminofuran, because by such a process the formation of a six-membered carbon-chain cannot be explained. On the other hand, it is known that the furan ring may open up even under mild experimental conditions as illustrated by the formation of levulinic aldehyde dimethylacetal[9] from 2-methylfuran in methyl alcoholic hydrogen chloride solution.

Experimental

2-Acetofuranoxime.—A solution of 2-acetofuran[10] (40 g.), hydroxylamine hydrochloride (30 g.) and anhydrous sodium acetate[11] (40 g.) in 200 cc. of ethyl alcohol was refluxed for five hours. The hot solution was filtered from the precipitated sodium chloride, the filtrate concentrated *in vacuo*, and ice water was added to the residue. The substance first separated as an oil but soon became crystalline on stirring. It was recrystallized from methyl alcohol; yield, 90%, m. p. 104°.

***p*-Toluenesulfonyl 2-Acetofuranoxime** (I).—Fifty grams of powdered *p*-toluenesulfonyl chloride was added gradually to a solution of 2-acetofuran oxime (30 g.) in 140 cc. of pyridine at −10° with stirring. After standing at 0° for two hours the reaction mixture was poured into ice water. The crystalline precipitate was filtered, washed with water, dried *in vacuo* and recrystallized from benzene by addition of petroleum ether; yield, almost quantitative, m. p. 80° with decomposition. The colorless needles were soluble in ether, benzene and acetone, sparingly soluble in alcohol, practically insoluble in water and petroleum ether.

Anal. Calcd. for $C_{13}H_{13}O_4NS$: C, 55.90; H, 4.69. Found: C, 55.95; H, 4.61.

Hexen-2-dion-4,5-diethylacetal-1 (III).—A solution of fifty grams of the *p*-toluenesulfonyl ester (I) in 250 cc. of 95% ethyl alcohol was shaken for five days at room temperature on the machine. Then the ammonium *p*-toluenesulfonate precipitate was filtered off, the filtrate was concentrated *in vacuo* at 30–35° bath-temperature to a small volume, to which 250 cc. of ether was added. After removal by filtration of a small quantity of the ammonium salt, the ether solution was stirred with a little water, dried with anhydrous sodium sulfate and the solvent distilled off first under atmospheric pressure, finally *in vacuo*. The remaining liquid distilled at 75–90° (3 mm.). The bath temperature must not rise above 130° because the resinous residue on overheating decomposes with explosion-like violence. On rectification most of the substance distilled at 65–68° (1 mm.); yield, 80%. The acetal had a yellowish-green color, it was readily soluble in water and in the common organic solvents. It reduced Fehling solution and ammoniacal silver nitrate solution in the cold. Its freshly prepared aqueous solution was neutral to litmus and did not react with Schiff reagent. On standing, the solution became acidic because of decomposition with the production of acetic acid.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.96; H, 8.06; mol wt., 200.2. Found: C, 59.64; H, 8.25; mol. wt., 198, by freezing point depression in benzene.

For the attempted preparation of an adduct from III with maleic anhydride an ether solution of the equivalent quantities of the components was kept for two days in the ice-chest. After distillation of the solvent the starting materials were recovered unchanged almost quantitatively.

Hexen-2-dion-4,5-dimethylacetal-1 (IV).—The preparation of the dimethylacetal was carried out in the same manner as that of the diethylacetal (III), but methanol was applied instead of ethanol. The resulting yellowish-green liquid showed the same chemical behavior as III; yield, 80–90%, b. p. 80.5–81.5° (3 mm.).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.78; H, 7.03; mol. wt., 172.2. Found: C, 55.93; H, 7.11; mol. wt., 171.6, by freezing point depression in benzene.

Hexan-dion-4,5-diethylacetal-1 (V).—A 20.2-g. quantity of hexen-2-dion-4,5-diethylacetal-1 (III) in 100 cc. of ethyl alcohol was hydrogenated in the presence of 3 g. of palladium–charcoal (10% Pd) at room temperature and at atmospheric pressure. The substance took up 1 mole of hydrogen during a few hours, then the rate of the reaction decreased. At this point the hydrogenation was interrupted, the filtered solution evaporated *in vacuo*, and the remaining liquid distilled at 73–75° (3 mm.); yield, 80%. The almost colorless substance reduced ammoniacal silver nitrate solution in the cold; it was readily soluble in water and in the common organic solvents. According to Zerewitinow's method the substance contained about 0.3 atom of active hydrogen.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.41; H, 8.91; mol. wt., 202.2. Found: C, 59.45; H, 9.19; mol. wt., 200.5, by freezing point depression in benzene.

Hexandion-4,5-dimethylacetal (VI).—This substance was prepared from the unsaturated dimethylacetal (IV) as V from III, b. p. 78–82° (2 mm.). Both of the saturated acetals V and VI showed very similar properties. According to Zerewitinow's method the substance contained about 0.2 atom of active hydrogen.

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.14; H, 8.10. Found: C, 54.64; H, 8.21.

Hydrolysis of the Hexen-2-dion-4,5-diemthylacetal-1 (IV).—A solution of 5 g. of the acetal in 50 cc. of 2% sulfuric acid was refluxed for thirty minutes. The solution first became yellow, then brown and finally some resinous product precipitated. The filtered solution was evaporated *in vacuo*, the distillate exactly neutralized with 0.1 *N* sodium hydroxide solution, and then about two-thirds of its volume was distilled. In this distillate the presence of methyl alcohol could be demonstrated by Denigès' reaction. The residue was evaporated to dryness and mixed with a saturated silver nitrate solution. The crystalline precipitate was filtered off, washed with a little cold water and dried *in vacuo;* it proved to be silver acetate.

Anal. Calcd. for $C_2H_3O_2Ag$: Ag, 64.64. Found: Ag, 64.18.

Hexen-2-dion-4,5-aldoxime and its Benzoyl Derivative.—To 0.5 g. of either unsaturated acetal III or IV in 10 cc. of water there was added a concentrated aqueous solution of 0.5 g. of hydroxylamine hydrochloride. The oxime soon precipitated in needles which were recrystallized from hot water; m. p. 236° with decomposition. It was soluble in alkalies, sparingly soluble in cold water and alcohol, and almost insoluble in the other usual solvents. Its aqueous solution showed a red coloration with ferric chloride.

Anal. Calcd. for $C_6H_7O_3N$: C, 51.03; H, 4.96; N, 9.92. Found: C, 51.26; H, 5.18; N, 9.99.

---

[9] Harries, *Ber.*, **31**, 37 (1898).

[10] Sandolin, *ibid.*, **33**, 492, 1176 (1900); Torrey and Zanetti, *Chem. Zentr.*, **82**, I, 81 (1911).

[11] Sandolin (ref. 10) applied sodium carbonate instead of sodium acetate, and the yield was only 50%.

For benzoylation 0.1 g. of the oxime, dissolved in 15 cc. of 2 *N* sodium hydroxide solution, was shaken with 0.5 g. of benzoyl chloride for fifteen minutes. The ester was filtered, washed with water and recrystallized from alcohol; colorless needles, m. p. 168°.

Anal. Calcd. for $C_{13}H_{11}O_4N$: N, 5.71. Found: N, 5.77.

bis-Phenylhydrazone of Hexen-2-dion-4,5-al-1.—One gram of the acetal III or IV, dissolved in 30 cc. of water, was mixed with a solution of 3 g. of phenylhydrazine hydrochloride in 15 cc. of water. The bis-phenylhydrazone precipitated as an oil which soon changed into crystals. It was filtered, washed with water, and recrystallized from alcohol with activated carbon; orange-red crystals, m. p. 209° with decomposition.

Anal. Calcd. for $C_{18}H_{18}ON_4$: C, 70.55; H, 5.92; N, 18.29. Found: C, 70.48; H, 5.94; N, 18.19.

Oxidation of Hexen-2-dion-4,5-dimethylacetal-1 (IV): (a) **Oxidation by Ozone.**—Into a solution of the acetal (6 g.) in anhydrous chloroform (30 cc.) 1.1 mole of ozone was introduced. Then the solvent was distilled off *in vacuo* and the oily residue was boiled with 60 cc. of water under reflux until clear solution was obtained (two hours). Addition of phenylhydrazine in acetic acid solution caused the precipitation of glyoxal-bisphenylhydrazone which was recrystallized from alcohol; m. p. and mixed m. p. with an authentic sample, 169°.

(b) **Oxidation with Potassium Permanganate.**—To 6.8 g. of IV in 50 cc. of water which was made slightly alkaline by addition of a few drops of potassium hydroxide solution, there was added at 5 to 10° 28 g. of potassium permanganate in 500 cc. of water, in small portion during twelve hours with stirring. After completed oxidation the solution, filtered from the precipitated manganese dioxide, was concentrated *in vacuo* to 100 cc., then acidified with dilute sulfuric acid to congo paper, and distilled. About 70 cc. of the distillate, after neutralization with 0.1 *N* alkali, was evaporated to dryness on the steam-bath. For decomposition of the sodium formate which formed part of the residue, the latter was treated with concentrated sulfuric acid, then diluted with water and the solution was distilled. From this distillate the acetic acid, produced by the oxidation, was isolated in form of its silver salt.

Anal. Calcd. for $C_2H_3O_2Ag$: Ag, 64.64. Found: Ag, 64.12.

From the residue of the first distillation, by addition of an acetic acid solution of phenylhydrazine, the phenylhydrazine salt of oxalic acid was obtained in colorless plates; m. p. and mixed m. p. with an authentic sample, 182°.

(c) **Oxidation with Hydrogen Peroxide.**—One g. of IV in 10 cc. of glacial acetic acid was refluxed with 10 cc. of a 15% hydrogen peroxide solution for four hours. The colorless substance, obtained after evaporation of the solution *in vacuo* and recrystallization of the solid residue from water, was identified as maleic acid; m. p. and mixed m. p. with an authentic sample, 132°.

Oxidation of Hexandion-4,5-dimethylacetal-1 (VI) with Silver Oxide.—Four grams of the saturated acetal (VI) in 100 cc. of water was refluxed for one hour with 4 g. of freshly prepared silver oxide. The hot, filtered solution was then saturated with hydrogen sulfide, filtered from the precipitated silver sulfide and evaporated to dryness on the steam-bath. The solid residue was recrystallized from absolute alcohol. The colorless substance proved to be succinic acid; m. p. and mixed m. p. with an authentic sample, 183°.

1-Phenyl-3-acetodihydropyridazine Phenylhydrazone (VII).—About 0.5 g. of the saturated acetal V or VI was heated on the steam-bath for ten minutes with 1 g. of phenylhydrazine in 5 cc. of glacial acetic acid. After the precipitate was filtered and washed with water and alcohol, it had the appearance of a pale-yellow crystalline powder, which was practically insoluble in water and the other usual solvents. The substance did not melt up to 280°.

Anal. Calcd. for $C_{18}H_{18}N$: C, 74.41; H, 6.24; N, 19.34. Found: C, 74.51; H, 6.44; N, 19.12.

Formation of Pyrocatechol on Hydrolysis of Hexandion-4,5-dimethylacetal-1 (VI).—A solution of the acetal (2.5 g.) in 2% sulfuric acid (60 cc.) was refluxed for one hour. After cooling the faintly brown solution was saturated with sodium bicarbonate and extracted with ether. The ether extract was dried with anhydrous sodium sulfate, evaporated, and the residue distilled *in vacuo;* b. p. 111–112° (3 mm.). The distillate crystallized from ligroin in colorless plates which showed all the characteristic properties of pyrocatechol; m. p. and mixed m. p. with authentic sample, 104°. The aqueous solution of the substance gave an emerald-green coloration with ferric chloride.

Anal. Calcd. for $C_6H_6O_2$: C, 65.45; H, 5.45. Found: C, 65.78; H, 5.59.

Summary

On shaking *p*-toluenesulfonyl 2-acetofuranoxime (I) with ethanol or methanol, not the expected 2-aminofuran was formed, but unsaturated aliphatic compounds, represented by the formulas $C_{10}H_{16}O_4$ (III) and $C_8H_{12}O_4$ (IV), respectively. The constitution and configuration of these substances were determined by various methods which definitely established their identities as being *cis*-hexen-2-dion-4,5-diethylacetal-1 and -dimethylacetal-1, respectively.

The corresponding aldehydes could not be produced because the carbon-chain between the carbonyl groups 4 and 5 split up with formation of acetic acid, even in cold aqueous solution.

The hydrolysis of the saturated acetals also led to a surprising result; because instead of the expected hexandion-4,5-al-1, there was obtained pyrocatechol.

It is suggested that natural pyrocatechol derivatives might be formed in a similar manner from carbohydrates through furan derivatives.

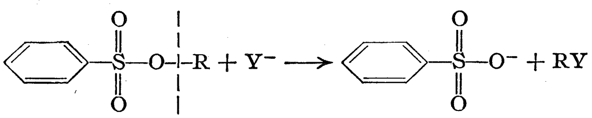
CLUJ-KOLOZSVÁR, RUMANIA RECEIVED JANUARY 31, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE]

A Kinetic Study of Alkylation by Ethyl Arylsulfonates

BY MARCUS S. MORGAN AND LEONARD H. CRETCHER

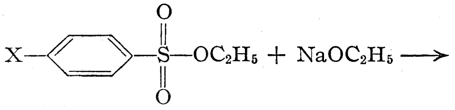
Alkyl esters of aromatic sulfonic acids function as strong alkylating agents[1] toward various types of organic compounds, this reaction occurring by alkyl-oxygen fission[2] according to the general scheme

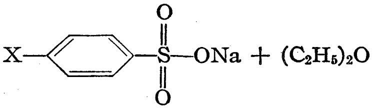


where R = alkyl group; Y^- = a nucleophilic reagent, *e. g.*, EtO^-, PhO^-, RS^-, I^-, etc.

Although various types of substituted benzenesulfonates are known and might conceivably be used, the vast majority of experimental alkylations have been carried out with the alkyl *p*-toluenesulfonates. Whereas the effect of nuclear substituents on the reactions of alkyl benzoates has been investigated extensively,[3] no such study has been made of the effect of nuclear substituents on the reactivity of alkyl esters of arylsulfonates. To do so seemed of considerable theoretical as well as potentially practical interest.[4] Such studies as have been made deal primarily with the hydrolysis of these compounds. It has been noted that with increasing nuclear halogen substitution, the ester is more readily saponified by alcohol.[5,6] The rate of the solvolytic reaction of ethyl toluenesulfonate and the rates of displacement of toluenesulfonate ion by chloride, bromide, iodide and hydroxyl ions has been studied kinetically.[7] Demeny's study[8] of the effect of a substituent in the aromatic nucleus upon the rate at which an alkyl sulfonate *hydrolyzes* demonstrated that a nitro group has a powerful accelerating influence while a *para* methyl reduces the reaction rate.

In this paper we present the results of a study of the influence of the *para* substituent on the reactivity of ethyl benzenesulfonate with sodium ethoxide in absolute ethanol solution.





where X = CH_3O, CH_3, H, Br and NO_2

The progress of this irreversible reaction was followed by titration of the unreacted sodium ethoxide at suitable time intervals with 0.05 *N* hydrochloric acid. Apparently the strong nucleophilic character of the ethoxide ion causes this reaction to take place readily at moderate temperature without observable side-effects. All of the rate constants reported in this study are based on an approximately equal initial concentration (0.05 molar) of each of the reactants. By trial, it was found that 35° was a suitable temperature at which to measure the relative reaction rates over a major part of the reaction. The measurements were repeated at a 10° interval to permit an approximate calculation of the energies of activation. The particular group of substituents selected represents a wide range of electronic character, varying from the electron-repulsion of the methoxy group to the electron attraction of the nitro-group, as exhibited in the benzene series.

p-Methoxybenzenesulfonyl chloride was prepared in 66% yield by the direct chlorosulfonation of anisole. High yields of the ethyl esters were obtained by reacting the corresponding sulfonyl chloride with an equimolar quantity of sodium ethoxide in alcohol or alcohol–ether solution under mild conditions.

Experimental

Aryl Sulfonyl Chlorides.—*p*-Toluenesulfonyl chloride, benzenesulfonyl chloride, *p*-bromobenzenesulfonyl chloride and *p*-nitrobenzenesulfonyl chloride were purchased from the Eastman Kodak Company.

***p*-Methoxybenzenesulfonyl Chloride.**—The literature on the preparation of this compound was very incomplete and in one case quite erroneous. This substance apparently was first synthesized by Moody[9] by sulfonation of anisole followed by treating the salt with phosphorus pentachloride. Although Huntress and Carten[10] prepared a small quantity of the compound by the action of chlorosulfonic acid on anisole, they did not isolate it, but immediately converted it into the sulfonamide in 53% yield. Gebauer-Fülnegg and Meissner[11] in a study of the action of chlorosulfonic acid on anisole made the statement, "An anisole monosulfonyl chloride could not be prepared in spite of extensive variations in reaction conditions."

Anisole (40 g., 0.37 mole) was dissolved in 150 ml. of chloroform and the solution cooled in an ice–salt-bath to −8°. Chlorosulfonic acid (86.2 g., 2 equiv., 0.74 mole) was added dropwise, as rapidly as possible while maintaining the internal temperature at 0°. Addition time was twenty minutes. The ice-bath was removed and the temperature allowed to approach room temperature during thirty minutes with continuous stirring. The solution

---

[1] (a) For a review of this field see Connor's chapter in Gilman, "Organic Chemistry," 2nd ed., Vol. I, John Wiley and Sons, New York, N. Y., 1943, p. 895; (b) Suter, "Organic Chemistry of Sulfur," John Wiley and Sons, New York, N. Y., 1944, pp. 514–539.

[2] Ferns and Lapworth, *J. Chem. Soc.*, **101**, 273 (1912).

[3] (a) Watson, "Modern Theories of Organic Chemistry," 2nd ed., Oxford University Press, 1942; (b) Hammett and Pfluger, THIS JOURNAL, **55**, 4079 (1933).

[4] Suter, ref. 1b, p. 527, mentions the desirability of a comparative study of these esters.

[5] Kastle and Murrill, *Am. Chem. J.*, **17**, 290 (1895).

[6] Boyle, *J. Chem. Soc.*, **97**, 211 (1910).

[7] McCleary and Hammett, THIS JOURNAL, **63**, 2254 (1941).

[8] Demeny, *Rec. trav. chim.*, **50**, 60 (1931).

[9] Moody, *Ber.*, **26**, ref. 606 (1893).

[10] Huntress and Carten, THIS JOURNAL, **62**, 603 (1940).

[11] Gebauer-Fülnegg and Meissner, *Monatsh.*, **50**, 55 (1928).

was poured onto chopped ice and the mixture transferred to a separatory funnel with an additional 200 ml. of chloroform. The chloroform extract was washed with three small portions of ice-water, dried with anhydrous sodium sulfate, filtered and redried with Drierite. On evaporating the chloroform solution under reduced pressure there remained a pale yellow liquid which crystallized on cooling and scratching. Yield was 54.7 g. (72%) of crude sulfonyl chloride. The product may be purified by recrystallization from boiling hexane (10 volumes) to give colorless crystals, m. p., 40–42° in 52% yield.

It was found that purification may be accomplished more efficiently by vacuum distillation. *p*-Methoxybenzenesulfonyl chloride boiled at 103–105° at 0.25 mm. (bath temp., 120–135°) to give a colorless distillate in 66% yield. The product had a m. p. of 41–42°, which is in agreement with values recorded in the literature.[12]

Anal.[13] Calcd. for $C_7H_7ClO_3S$: Cl, 17.16; S, 15.52. Found: Cl, 16.89; S, 15.38.

Ethyl Arylsulfonates—General Procedure.—The sulfonyl chloride (0.1 mole) was dissolved in 100 ml. of absolute ethanol in a 250-ml. three-necked flask fitted with a mercury-sealed stirrer, reflux condenser, dropping funnel and thermometer. In those cases where the sulfonyl chloride is not very soluble in ethanol (*e. g.*, *p*-nitro- and *p*-bromobenzenesulfonyl chloride) 75 ml. of ether was used. The flask was surrounded by a cold water-bath to maintain an internal temperature of 20°. A solution of 0.1 mole of sodium ethoxide in 100 ml. of ethanol (prepared by dissolving sodium in ethanol and standardizing the solution against standard hydrochloric acid) was added dropwise with continuous stirring. The reaction time varied somewhat with the reactivity of the sulfonyl chloride but was generally run until a test portion (10 drops) was no longer alkaline to phenolphthalein. The *p*-methoxy compound required forty-five minutes whereas the *p*-nitro was run for 145 minutes.

The suspension was poured into 300 to 500 cc. of water (sufficient to dissolve the precipitated sodium chloride) and the mixture thoroughly extracted with 200 ml. of chloroform. (Where ether was used as a solvent, the reaction mixture was first evaporated at reduced pressure to remove all of the ether.) The aqueous layer was extracted with two additional portions (100 ml.) of chloroform and the combined extract washed successively with 50 ml. of water, 150 ml. of saturated sodium bicarbonate and two 60-ml. portions of water.

The chloroform solution was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness at reduced pressure. With the exception of the *p*-nitro ester, the crude esters thus obtained were all purified by fractional vacuum distillation, the intermediate constant-boiling fraction being retained for kinetic study.

Ethyl *p*-Nitrobenzenesulfonate.—The crude, pale-yellow ester obtained in 81% yield (m. p., 91–91.5°) was recrystallized from absolute ether to give practically colorless crystals; m. p. 92–92.5°, in 70% yield. Demeny[8] reported m. p. as 92°.

Anal. Calcd. for $C_8H_9NO_5S$: N, 6.06; S, 13.87. Found: N, 6.01; S, 13.88.

Ethyl *p*-Methoxybenzenesulfonate.—The pure ester was obtained as a colorless liquid in 83% yield after fractional vacuum distillation, b. p., 137–139° at 0.3 mm. (bath temp., 164–169°), n^{20}_D 1.5230.

Anal. Calcd. for $C_9H_{12}O_4S$: C, 49.98; H, 5.60; S, 14.83. Found: C, 49.84; H, 5.53; S, 14.88.

This compound was recently reported by Carr and Brown[12b] who prepared it in a different manner.

Ethyl *p*-Bromobenzenesulfonate.—The pure ester (obtained in 74% yield) distilled at 111–113° at 0.15 mm. (bath temp., 132–135°), f. p., 39.0–39.1°. Krafft and Roos[14] reported the m. p. as 39.5°.

Ethyl *p*-Toluenesulfonate.—The pure ester distilled at 108–109° at 0.35 mm.; bath temp., 121–123°. The freezing point was 32.2° which is in agreement with the value reported by McCleary and Hammett,[7] m. p., 32.2–32.3°.

Ethyl Benzenesulfonate.—Although this ester can be prepared by the general procedure given above, it was prepared by the pyridine method[15] which is useful for esters which cannot be made from the sodium alkoxide. Benzenesulfonyl chloride (Eastman Kodak Co. 32, 36 g., 0.2 mole) was dissolved in 100 ml. of dry pyridine and the solution cooled to −8°. Absolute ethanol (11.7 ml., 0.2 mole) was now added from a pipet and the temperature kept between −8 and −5°. Crystallization of pyridine hydrochloride commenced after several minutes and the mixture was kept at −5° for a total of twenty-two minutes. Sulfuric acid (250 ml. of 5 *N*, pre-cooled to 3°) was now added rapidly, with cooling, thereby liberating a colorless oil which settled to the bottom of the flask. The oil was extracted with chloroform and this solution was treated in the described manner. The pure ester (obtained in 75% yield) distilled at 96–98° at 0.3 mm. (bath temp., 109–113°), n^{20}_D 1.5092.

Kinetic Technique.—The apparatus consisted essentially of a thermostatically controlled (±0.04°) water-bath fitted with clamps to hold a series (usually 7) of stoppered test-tubes and several 100-ml. volumetric flasks. Since it was not deemed desirable to mix a standardized solution of the ethyl arylsulfonate in ethanol with a standard solution of sodium ethoxide in ethanol (both solutions equilibrated to constant temperature) because of possible ester alcoholysis prior to mixing, a weighed amount of the ester (0.005 mole) in a small, thin glass vial (11 × 40 mm.) was added directly to an ethanol solution of sodium ethoxide already equilibrated to temperature. This was done in the following manner. The reaction vessel was a 100-ml. volumetric flask calibrated to correct for the thermal expansion of ethanol at the specific reaction temperature plus the volume-displacement of the glass vial. A solution of sodium ethoxide in ethanol, as close to 0.1 molar as expedient, was prepared in a 100-ml. volumetric flask and standardized against 0.05 *N* hydrochloric acid. A 50-ml. aliquot (0.005 mole) was then added to the calibrated flask and sufficient ethanol added to bring the volume to a point such that the addition of the ester-containing vial (after temperature equilibration) would bring the final volume close to the calibration mark. The final volume adjustment was thus made immediately after the addition of ester. The flask containing the ethoxide solution (representing about 99+% of the mass) could thus be accurately adjusted to the reaction temperature and the vial containing the ester only approximately adjusted in a separate tube. In all cases except the *p*-nitro, dissolution of the liquid ester was sufficiently rapid so that zero time was essentially that of the moment of mixing. The solid nitro-ester, which has the lowest alcohol solubility, was finely powdered; zero time being taken as of one-half time of solution. Owing to the graphic method of determining the rate, this factor had no bearing on the determination of the value of *k*.

As soon as the ester was completely dissolved, the homogeneous solution was aliquoted in seven, 10-ml. portions to the equilibrated, stoppered test-tubes. This was necessitated by the low alcohol-solubility and consequent crystallization of the sodium salts of the arylsulfonic acids. The pipet used in making these transfers was also calibrated for the thermal expansion of ethanol. At suitable time intervals, an aliquot-containing tube was removed from the water-bath and plunged into a Dry Ice–acetone mixture to stop the reaction. The cold mixture was then carefully diluted with 100 ml. of carbon dioxide-free water and titrated with 0.05 *N* hydrochloric acid using phenolphthalein as the indicator. Each run thus gave seven points with which to plot a graph.

---

[12] (a) Fichter and Tamm, *Ber.*, **43**, 3036 (1910); m. p. 42–43°; (b) Carr and Brown, THIS JOURNAL, **69**, 1170 (1947), m. p., 41.0°.

[13] The microanalyses were performed by G. L. Stragand of the University of Pittsburgh.

[14] Krafft and Roos, *Ber.*, **25**, 2257 (1892).

[15] Patterson and Frew, *J. Chem. Soc.*, **89**, 332 (1906); Tipson, *J. Org. Chem.*, **9**, 235 (1944).

Rate Calculations.—Since we were dealing with a nucleophilic displacement we postulated second-order kinetics and determined the rate constant, k, from the simplified equation for second-order reactions in which initial concentrations of reactants are equal; $k_2 = x/ta(a - x)$, where a = initial concentration of sodium ethoxide in moles/liter and x = moles per liter which have reacted in time t. The reported values of k (expressed in min.$^{-1}$ moles^{-1} liter) were determined graphically by plotting the function $x/(a - x)$ against t which resulted in a straight line with a slope equal to ak. This value was checked by plotting $1/(a - x)$ against t, the slope of the resulting line being directly equal to k. The excellent straight line relationship which we observed in every case, the graphs having been plotted over a major part of the course of each reaction, substantiated our assumption of second-order kinetics.

In Table I, we present a typical experimental record for the determination of the value of k in a specific reaction. The figures of column 5 and the inverse of the figures in column 3 were plotted against t to give a value of $k_2 = 0.235$. By using the equation[16] $k(t_2 - t_1)a = [x_2/(a - x_2) - x_1/(a - x_1)]$ or $\Delta(x/a - x)$ (column 6), the interval values of k_2 (column 7) may be obtained.

TABLE I

REACTION OF ETHYL BENZENESULFONATE WITH SODIUM ETHOXIDE AT 45°

Concn. of ester = 0.0489 molar
Concn. of ethoxide = 0.0504 molar

Time, min.	Acid titer*	$a - x$ m./l.	x m./l.	$x/(a - x)$	$\Delta[x/(a - x)]$	k_2
0	9.78	0.0489				
20	8.05	.0402	0.0086	0.215	0.215	0.220
40	6.74	.0337	.0152	.451	.236	.241
60	5.90	.0295	.0194	.658	.207	.211
90	4.85	.0242	.0246	1.017	.359	.245
120	4.17	.0208	.0280	1.345	.328	.224
150	3.59	.0179	.0309	1.724	.379	.258
180	3.17	.0158	.0330	2.085	.361	.246

* = ml. of 0.05 N hydrochloric acid used in titration of aliquot.

Since the rate constant for each ester was determined at two temperatures only, the energy of activation, E, was evaluated from the integrated expression[17]

$$E = \frac{2.303RT_2T_1}{(T_2 - T_1)} \log \frac{k_2}{k_1}$$

Results and Discussion

The rate constants, obtained at two temperatures, for the reaction of *para*-substituted ethyl benzenesulfonates with sodium ethoxide in ethanol solution are given in Table II. The substituents are listed in ascending order of ester reactivity which is also the order of relative electron-recession from the seat of the reaction, *i. e.*, the alkyl–oxygen bond in the ester.

TABLE II

Substituent X	Rate constant t, °C.	k_2	Relative reactivity at 35°	Energy of activation cal.	log PZ
p-CH_3O	35	0.0321	0.42	21,670	12.12
	45	.0977			
p-CH_3	35	.0484	.63	20,820	11.69
	45	.141			
p-H	35	.0769	1.00	21,750	12.56
	45	.235			
p-Br	35	.172	2.24	22,240	13.25
	45	.539			
p-NO_2	35	.901	11.8	24,040	15.25
	25	.241			

A comparison of the relative reactivity of these esters at 35° indicates a twenty-eight fold variation in the relative velocity constants, indicating the desirability of investigating the alkylating efficacy of arylsulfonic esters other than those of p-toluenesulfonic acid.

Due largely to the work of Hammett,[18] linear relationships have been found to apply between

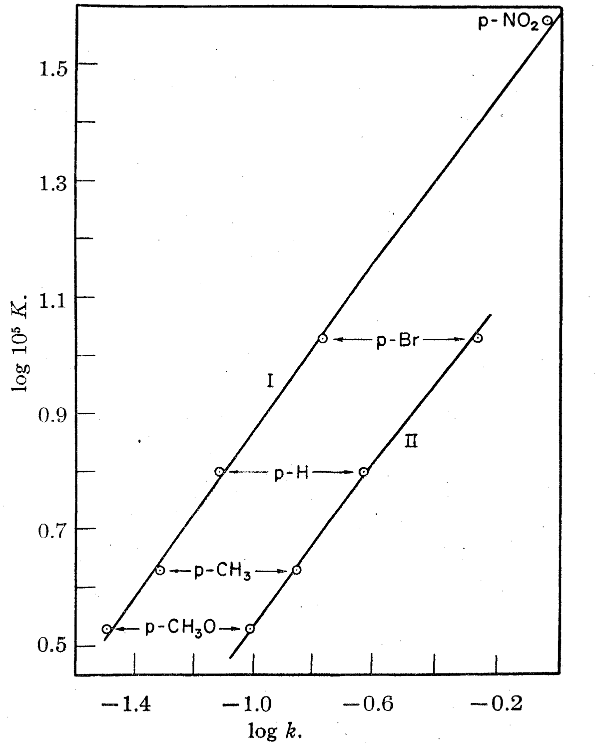


Fig. 1.—Relationship of log 10^5 K and log k, where K = dissociation constant of substituted benzoic acid; k = rate constant for reaction of substituted ethyl benzenesulfonate with sodium ethoxide in ethanol at (I) 35° and at (II) 45°.

---

[16] Rice, "The Mechanism of Homogeneous Organic Reactions," Chemical Catalog Co., New York, N. Y., 1928, p. 24.

[17] Moelwyn-Hughes, "Kinetics of Reactions in Solution," Oxford University Press, Oxford, 1933, p. 30.

[18] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York. N. Y., 1940, p. 184.

the rate and the equilibrium constants of practically all side chain reactions of benzene derivatives substituted in the *meta* or *para* positions. In accordance with this relationship we have plotted in Fig. 1, as ordinates the logarithms of the dissociation constants of several substituted benzoic acids[19] and as abscissas the logarithms of the rate constants (Table II, column 3) for the reaction of similarly substituted ethyl benzenesulfonates with ethoxide ion. In view of the satisfactory linear relationship resulting, the present example can be added to the list of reactions tabulated by Hammett.

Since in the Arrhenius equation, $k = PZe^{-E/RT}$, the collision frequency Z varies but little from one reaction to another, it is apparent that the influence of a polar substituent on the velocity constant may be due to an effect on the energy of activation, E, or on the probability factor P, or both. For most reactions of nuclear substituted benzene derivatives it is commonly observed that the influence of substituents is almost entirely upon changes in E.[20] In several instances, however, it has been observed that substituents cause appreciable changes in the PZ term of the equation, *e. g.*, the acid hydrolysis of ethyl benzoates,[21] the alcoholysis of benzyl chlorides,[22] and the hydrolysis of arylsulfuric acids.[23] In the present investigation, since E has been estimated from values of k obtained at only two reaction temperatures, it probably is not to be considered accurate to more than ±1000 calories. From the results given in Table II it may be seen that although there is a slight trend to E, the individual values are grouped about the average of 22,100 calories almost within limits of the estimated experimental error.

Following Branch and Nixon,[22] the logarithm of the probability factors in the Arrhenius equation have been calculated from the relationship $\log PZ = \log k_{35} + E/2.3RT$ and are included in Table II. The values of $\log PZ$ listed are in the general region of those usually associated with reactions between ions and neutral molecules and belong to the class characterized by Moelwyn-Hughes as "normal" reactions. In view of the near-constancy of E, and the definite trend to the values of $\log PZ$, it would appear that we have here an additional example of a case in which the effect of polar substituents is mainly on the PZ term of the Arrhenius equation. It may be noted from Table II that although the effect of a *para*-methoxy substituent on the velocity constant is in accord with its electron-repulsive character, its effect on E and $\log PZ$ is anomalous.

Acknowledgment.—The authors wish to express appreciation to Dr. Warner W. Carlson of these laboratories for helpful discussion in the preparation of this manuscript.

Summary

Details have been worked out for the synthesis of *p*-methoxybenzenesulfonyl chloride by direct chlorosulfonation of anisole. The preparation and purification of five substituted ethyl benzenesulfonates are described.

The effect of a nuclear substituent on the alkylating efficacy of alkyl benzenesulfonates has been investigated by a study of the relative reaction rates of these esters with sodium ethoxide in ethanol. This reaction followed second-order kinetics.

The value of the rate-constants increased in the order *p*-CH_3O < *p*-CH_3 < *p*-H < *p*-Br < *p*-NO_2, which is in agreement with the electronic influence exhibited by these groups on the dissociation constants of substituted benzoic acids. Good quantitative accord was also observed with Hammett's relationship for the effect of structure on reactivity.

PITTSBURGH 13, PA. RECEIVED AUGUST 11, 1947

---

(19) Dippy, *Chem. Rev.*, **25**, 151 (1939).

(20) (a) Watson, ref. 3a, p. 78; (b) Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 207.

(21) Timm and Hinshelwood, *J. Chem. Soc.*, 862 (1938).

(22) Branch and Nixon, THIS JOURNAL, **58**, 2499 (1936).

(23) Burkhardt, Horrex and Jenkins, *J. Chem. Soc.*, 1649 (1936).

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES, UNIVERSAL OIL PRODUCTS COMPANY]

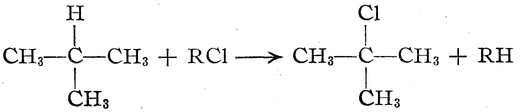
Condensation of Saturated Hydrocarbons with Haloöefins. II. The Reaction of Isobutane with *cis*- and *trans*-Dichloroethylene

BY LOUIS SCHMERLING

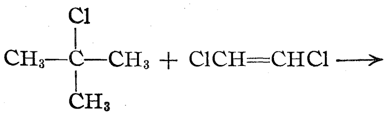
It was shown previously[1] that the condensation of isobutane with allyl chloride and vinyl chloride in the presence of aluminum chloride at −10° apparently proceeds via the conversion of the isoparaffin to *t*-butyl chloride which then adds to the chloroölefin to yield, respectively, 1,2-dichloro-4,4-dimethylpentane and 1,1-dichloro-3,3-dimethylbutane. The greater part of the former reacts with isobutane, producing 1-chloro-3,4-dimethylpentane as the major product. On the other hand, the 1,1-dichloro-3,3-dimethylbutane undergoes little conversion to monochloride and is, therefore, isolated as the principal chlorine-containing product.

The condensation of isobutane with a dichloroolefin, namely, 1,2-dichloroethylene, has now been investigated. It was found that the chief product is 1,1,2-trichloro-3,3-dimethylbutane, the same trichlorohexane which is obtained by the addition of *t*-butyl chloride to the dichloroethylene.[2] The intermediate conversion of the isobutane to *t*-butyl chloride is again indicated. Furthermore, since no dichlorohexane was isolated, it may be concluded that the trichloride is quite stable toward further reaction with the isobutane; that portion which does react is eventually reduced to paraffin (*i. e.*, all three chlorine atoms are successively replaced by hydrogen) by means of the hydrogen–chlorine exchange reaction with isobutane.[3] The trichloride is relatively unreactive because two of the chlorine atoms are attached to a primary carbon atom and the third to a secondary carbon atom which is in a neopentyl group. The intermediate di- and mono-chlorohexanes are comparatively unstable because tertiary carbon atoms are formed during the hydrogen–chlorine exchange; for example, the trichloride is probably converted to 1,1-dichloro-2,3-dimethylbutane which then isomerizes to reactive 1,2-dichloro-2,3-dimethylbutane.

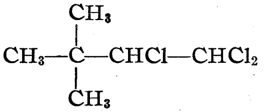
The mechanism of the condensation may be written as



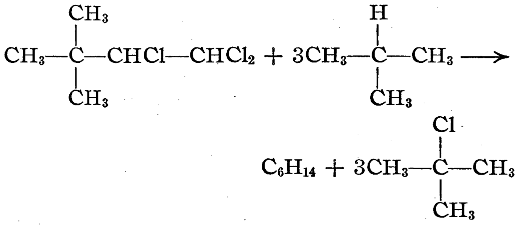
$$CH_3-\underset{CH_3}{\overset{H}{C}}-CH_3 + RCl \longrightarrow CH_3-\underset{CH_3}{\overset{Cl}{C}}-CH_3 + RH \quad (1)$$



$$CH_3-\underset{CH_3}{\overset{Cl}{C}}-CH_3 + ClCH{=}CHCl \longrightarrow$$



$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CHCl-CHCl_2 \quad (2)$$



$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CHCl-CHCl_2 + 3CH_3-\underset{CH_3}{\overset{H}{C}}-CH_3 \longrightarrow$$

$$C_6H_{14} + 3CH_3-\underset{CH_3}{\overset{Cl}{C}}-CH_3 \quad (3)$$

t-Butyl chloride formed as in equation 3 (actually the sum of three successive reactions) reacts with dichloroethylene as in equation 2. Since the reaction of equation 1 is a chain initiating step only, the nature of RCl (which might be dichloroethylene, trichloroethane, complex of catalyst with dichloroethylene, etc.) is unimportant. It is apparent that the highest possible yield of trichlorohexane is two-thirds of a mole per mole of dichloroethylene.

There is a very marked difference in reactivity between the *cis* and *trans* isomers of 1,2-dichloroethylene. The trichloride was obtained in 35% yield[4] by the reaction of isobutane with the *cis* compound at room temperature and in less than 5% yield by reaction with the *trans* isomer under the same conditions. A similar difference was found[2] for the condensation of the two isomers with isopropyl chloride or *t*-butyl chloride. Steric effects are presumably involved.

The structure of the trichloride was proved by converting it to a chlorohexene by reaction with zinc and alcohol; that the chlorohexene was 1-chloro-3,3-dimethyl-1-butene was shown by the facts that it yielded trimethylacetic acid on oxidation and that it was identical with the product obtained by the dehydrochlorination of 1,1-dichloro-3,3-dimethylbutane (obtained by the condensation of *t*-butyl chloride with vinyl chloride[5]).

It seems worth while at this time to discuss further[6] the significance which the reaction of isobutane with chloroölefins bears on the mechanism of the alkylation of isoparaffins with olefins. Gorin, Kuhn and Miles[7] have recently proposed an alkylation mechanism which is similar to those of Caesar and Francis[8] and of McAllister, Anderson,

---

(1) L. Schmerling, THIS JOURNAL, **67**, 1438 (1945).

(2) L. Schmerling, *ibid.*, **68**, 1655 (1946).

(3) P. D. Bartlett, F. E. Condon and A. Schneider, *ibid.*, **66**, 1531 (1944).

(4) Based on the dichloroethylene charge, assuming that the limiting, over-all reaction may be represented by $3C_4H_{10} + 3C_2H_2Cl_2 \rightarrow C_6H_{14} + 2C_6H_{11}Cl_3$.

(5) L. Schmerling, THIS JOURNAL, **68**, 1650 (1946).

(6) *Cf.* L. Schmerling, *ibid.*, **67**, 1778 (1945).

(7) M. H. Gorin, C. S. Kuhn, Jr., and C. B. Miles, *Ind. Eng. Chem.*, **38**, 795 (1946).

(8) P. D. Caesar and A. W. Francis, *ibid.*, **33**, 1426 (1941).

Ballard and Ross[9] in that all three postulate that the isoparaffin undergoes carbon to carbon cleavage to yield two alkyl fragments (isopropyl and methyl in the case of isobutane). By assuming that the fragments (behaving as if positively and negatively charged) add to a complex formed between catalyst and olefin and by setting up rules governing the structure of the complex, Gorin, *et al.*, make it possible for this type of mechanism to explain why some isomers are formed and others are not. They state "The assumption that carbon–carbon fission occurs in the isobutane molecule . . . was recently rejected by Schmerling[6] in a criticism of the alkylation mechanisms proposed by these investigators [Caesar and Francis,[8] and McAllister, *et al.*[9]]. In the opinion of the writers, however, such a rupture of the isobutane molecule is scarcely less likely, *a priori*, than the similar α–β shift of a methyl group embodied in the mechanism of Schmerling or required, for that matter, to account for isomerization of alkanes. There seems to be little to choose between the two proposals on the basis of information now available."

Even without entering into a discussion of the vast literature on intramolecular rearrangements which involve shifting of methyl groups,[10] it is possible to furnish information which permits making a choice between the two proposals. This information consists in the results obtained in the condensation of isobutane with chloroölefins (*i. e.*, with olefins which have been "tagged"). The Gorin, *et al.*, mechanism can explain the formation of 1-chloro-3,4-dimethylbutane by the reaction of isobutane with allyl chloride; on the other hand, it cannot explain the formation of 1,2-dichloro-4,4-dimethylpentane as by-product of this reaction. Furthermore, it does not account for the principal chlorinated product of the reaction of isobutane with vinyl chloride (namely, 1,1-dichloro-3,3-dimethylbutane) or with 1,2-dichloroethylene (namely, 1,1,2-trichloro-3,5-dimethylbutane). In contrast to this, the mechanism proposed by the present writer for the alkylation of isoparaffins with olefins readily explains the formation of these polychloroalkanes; indeed, they are the inherent products of the second step of the mechanism (*cf.* equation 2). As has already been indicated, these compounds are comparatively unreactive and more or less of each will therefore be isolated as such. The analogous product of the alkylation of an isoparaffin with an olefin is an alkyl chloride (or other alkyl ester if catalyst other than aluminum chloride is used) which is usually not isolated because it readily undergoes the third step of the mechanism (*cf.* equation 3).

Experimental[11]

Procedure.—The dichloroethylene, isobutane and aluminum chloride were weighed into a glass liner (cooled in a bath at −78°) for an Ipatieff-type rotating autoclave of 850-cc. capacity. The liner was sealed into the autoclave which was then rotated at room temperature for four hours, after which it was allowed to stand overnight. The gaseous products were discharged through a soda lime tower to absorb hydrogen chloride and thence into a trap immersed in Dry Ice–acetone. The liquid product in the liner was decanted from the catalyst layer, washed, dried and distilled.

Reaction of *cis*-Dichloroethylene with Isobutane.—The reaction of 50 g. (0.52 mole) of *cis*-dichloroethylene (prepared by the isomerization[12] of *trans*-dichloroethylene) and 122 g. (2.1 mole) of isobutane in the presence of 10 g. of aluminum chloride yielded 11 g. (0.30 mole) of hydrogen chloride, 28 g. of red-brown, fluid catalyst layer, and a liquid product, distillation of which yielded 13 g. of product, b. p. 39–100°, $n^{20}\text{D}$ 1.3680–1.3842; 9 g., b. p. 100–106°, $n^{20}\text{D}$ 1.4056–1.4508; 23.5 g. (0.12 mole, 35% yield) of trichlorohexane, b. p. 196–200°, m. p. −16 to −17°, $n^{20}\text{D}$ 1.4755; and residue, 2.5.g.

Similar results were obtained in the presence of added hydrogen chloride. The reaction of 60 g. (0.62 mole) of *cis*-dichloroethylene and 125 g. (2.2 mole) of isobutane in the presence of 10 g. of aluminum chloride and 12 g. of anhydrous hydrogen chloride yielded 18 g. of liquid product, b. p. 45–190°; 28 g. (0.15 mole, 36% yield) of the trichlorohexane, b. p. 68–70° (6 mm.) or 198–200°

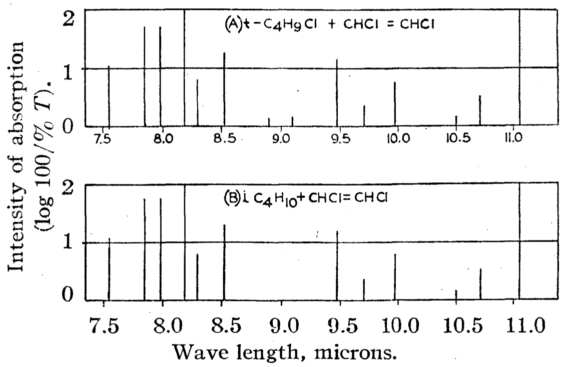


Fig. 1.—The infrared absorption spectra of the trichlorohexane formed by the reaction of *cis*-dichloroethylene with (A) *t*-butyl chloride and (B) isobutane.

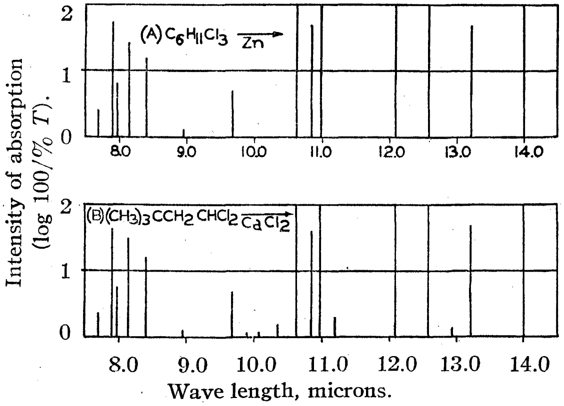


Fig. 2.—The infrared absorption spectra of the chlorohexene obtained by the reaction of (A) the trichlorohexane with zinc and (B) 1,1-dichloro-3,3-dimethylbutane over calcium chloride.

---

(9) S. H. McAllister, J. Anderson, S. A. Ballard and W. E. Ross, *J. Org. Chem.*, **6**, 647 (1941).

(10) That the postulated migrations of methyl groups do occur when the particular alkylation intermediates are converted to paraffins was proved experimentally.[6]

(11) Microanalyses by Dr. T. S. Ma, University of Chicago.

(12) G. Chavanne, *C. A.*, **7**, 1180 (1913); **9**, 2898 (1915).

(760 mm.), m. p. −13 to −12°, $n^{20}D$ 1.4760; d^{20}_4 1.2078; and residue, 2.5 g. The catalyst was converted to 30 g. of red-brown viscous liquid; 14 g. of hydrogen chloride was recovered.

Anal. Calcd. for $C_6H_{11}Cl_3$: C, 38.00; H, 5.85; Cl, 56.15. Found: C, 38.10; H, 5.71; Cl, 56.42.

The presence of *t*-butyl chloride in the lower-boiling liquid (b. p. 45–60°) was proved by adding about 0.1 g. of aluminum chloride to a solution of 1 cc. of the liquid in 1 cc. of benzene. Hydrogen chloride was evolved and the catalyst was converted to a clear yellow liquid. The upper layer was decanted and the excess benzene was permitted to evaporate spontaneously (overnight). Crystals of *p*-di-*t*-butylbenzene (m. p. 76°) were deposited.

The trichlorohexane (m. p. −13 to −12°) was shown to be substantially the same as the product (m. p. −14 to −13°) obtained by the addition of *t*-butyl chloride to *cis*-dichloroethylene[2] in the presence of aluminum chloride. A mixture of the two products melted at −13.5 to −13°. Comparison of the infrared spectra[13] (see Fig. 1) confirmed their identity.

Reaction of *trans*-Dichloroethylene with Isobutane.—Comparatively little reaction occurred when a mixture of 30 g. of *trans*-dichloroethylene (purchased from Eimer and Amend), 55 g. of isobutane and 6 g. of aluminum chloride was rotated in the autoclave at room temperature. The liquid product consisted chiefly of unreacted dichloroethylene; about 6 g. of intermediate material and 2 g. of trichlorohexane fraction (b. p. 190–200°) were obtained.

Reaction of 1,1,2-Trichloro-3,3-dimethylbutane with Zinc.—A solution of 30 g. of the trichlorohexane in 100 g. of *n*-propyl alcohol was refluxed over 10 g. of zinc dust for sixteen hours. The product was distilled until addition of water to the distillate no longer yielded an appreciable amount of water-insoluble material. There was obtained 15.5 g. of reaction product, $n^{20}D$ 1.4272. Redistillation yielded 14 g. (75% yield) of chlorohexene (b. p. 102–103°; $n^{20}D$ 1.4260; d^{20}_4 0.8815; *MR* calcd., 34.26; *MR* obs. 34.42) and 1.5 g. of residue ($n^{20}D$ 1.4320).

Anal. Calcd. for $C_6H_{11}Cl$: C, 60.74; H, 9.35; Cl, 29.91. Found: C, 60.54; H, 8.85; Cl, 30.34.

The infrared spectrum[13] of the chlorohexene was compared with that of product (b. p. 102–104°, $n^{20}D$ 1.4262) obtained by the dehydrochlorination of 1,1-dichloro-3,3-dimethylbutane[5] over calcium chloride at 450°. The materials were found to be substantially the same (see Fig. 2).

Oxidation of 1-Chloro-3,3-dimethyl-1-butene.—A mixture of 6.5 g. of the chlorohexene and a solution of 16 g. of potassium permanganate in 500 cc. of water was stirred at ice-bath temperature for eight hours and then at 2–10° for an additional eight hours. All of the permanganate reacted. The product was filtered and the filtrate was evaporated to 30 cc. and acidified with dilute sulfuric acid. Steam distillation of the acidified solution yielded 3 cc. of organic material which was taken up in ether. Removal of the ether yielded 2.5 g. of trimethylacetic acid, b. p. 161–162°, m. p. 30–31°, characterized as the *p*-bromophenacyl ester, m. p. 76°.

Acknowledgment.—The continued interest of Professor V. N. Ipatieff is gratefully acknowledged.

Summary

A trichloride, 1,1,2-trichloro-3,3-dimethylbutane, is the principal product of the reaction of isobutane with 1,2-dichloroethylene in the presence of aluminum chloride at room temperature. It is obtained in 35% yield when *cis*-dichloroethylene is used, and in less than 5% yield when *trans*-dichloroethylene is used.

The probable mechanism of the reaction is presented.

It is shown that the reaction serves as a means of evaluating recently proposed mechanisms for the alkylation of isoparaffins with olefins.

RIVERSIDE, ILLINOIS RECEIVED MAY 28, 1947

---

[13] The writer is indebted to Dr. W. S. Gallaway of the Physics Division, Universal Oil Products Co. for the infrared analyses and the figures; for a description of the procedure used, see THIS JOURNAL, **69**, 1124 (1947).

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

Sulfur as a Promoter for a Nickel Catalyst in Dehydrogenation

BY HOMER ADKINS, DOROTHY S. RAE,[1] JAMES W. DAVIS,[2] GLENN F. HAGER[3] AND KATHRYN HOYLE[1]

The method of aromatizing a hydroaromatic compound by oxidizing it with benzene has given excellent results.[4] However, uniformly good yields were not obtained in attempting to duplicate results and extend the method. For example, in testing catalysts in the conversion of dicyclohexyl to diphenyl, *i.e.*

$$C_6H_{11}C_6H_{11} + 2C_6H_5 \xrightarrow[350°]{Ni} C_6H_5C_6H_5 + 2C_6H_{12}$$

the yield of diphenyl after reaction for two hours varied from 1 to 90%.

The variability in yields was found to depend upon the quality of the benzene used. Fractionation of a sample of benzene which gave good results showed that the lower boiling fractions were better than the higher boiling ones. A number of false leads were followed which, however, led to the discovery that the addition of 25 mg. of tetramethyl tin or of carbon tetrachloride to 20 ml. of benzene and 2 g. of catalyst improved the yield of diphenyl so that the conversion was approximately 80%. The fruitful observation was made that the more thoroughly the benzene was purified from thiophene the poorer were the yields of diphenyl obtained. It was then found that the addition of a suitable amount of thiophene to pure benzene gave excellent yields of diphenyl. For example, the per cent. conversions of dicyclohexyl to diphenyl were with varying amounts of thiophene

---

[1] Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

[2] Allied Chemical and Dye Corporation Fellow 1941–1942.

[3] Monsanto Chemical Company Fellow 1942–1943.

[4] Adkins, Richards and Davis, THIS JOURNAL, **63**, 1320 (1941).

as follows: 0 mg., 1%; 1 mg., 32%; 2 mg., 61%; 3 mg., 79%; 5 mg., 79%; 20 mg., 89% and 40 mg., 4%. These results were with 5 g. of dicyclohexyl in 20 ml. of thiophene-free benzene and 2 g. of reduced nickel chromite catalyst for two hours at 350° in a 270 ml. (void) steel reaction vessel. When the amount of catalyst was reduced to 1 g. the optimum amount of thiophene was 10 mg., the conversion being the same as with 20 mg. of thiophene and 2 g. of catalyst. The use of larger ratios than 10 mg. of thiophene per gram of catalyst gave lower conversions of dicyclohexyl. Thiophene-free benzene was obtained by boiling commercial benzene with Raney nickel and distilling.

Diphenyl sulfide was found to be even more satisfactory than thiophene as a promoter for the nickel catalyst. Some of the data are summarized in Table I. It may be noted that the ratio of diphenyl sulfide to catalyst for the optimum results is about twice as large as for thiophene, as might be expected from the sulfur content of the two compounds.

TABLE I

DEHYDROGENATION OF DICYCLOHEXYL (5 g.) WITH DIPHENYL SULFIDE AS A PROMOTER WITH A NICKEL CATALYST (2 g.) AT 350° FOR TWO HOURS

Diphenyl sulfide, mg.	Benzene, ml.	Diphenyl,[a] % Conversion	Solid
0	20	1	0
6	20	82	57
12	20	91	66
24	20	93	71
48	20	98	94
96	20	13	0
30	40	96	88
30	30	95	82
30	15	93	81
30	10	91	62

[a] The "% solid" indicates the amount of diphenyl actually isolated. The "% conversion" given in this table and earlier is based upon refraction indices of the liquid product which may have also contained phenylcyclohexane as well as dicyclohexyl.

The effect of the addition of various amounts of thiophene, in promoting the formation of 4,5-benzohydrindene from 1-methyl-1,2-cyclopentanodecalin was also determined.[5] The reaction was carried out at 350° for eight hours on 4 g. of the hydroaromatic compound in 20 ml. of pure benzene with 2 g. of catalyst. The optimum ratio of thiophene to catalyst was found to be approximately 10 mg. per gram of catalyst just as in the aromatization of dicyclohexyl. The yields of 4,5-benzohydrindene varied from 5 to 27 to 39 to 44 to 33 to 20 to 15 as the thiophene was increased from 0 to 5 to 10 to 20 to 30 to 40 to 50 mg. for 2 g. of catalyst.

The catalyst used in the dehydrogenations described above was prepared by the reduction of "nickel chromite" as previously described.[4] The amount of nickel in the catalyst before reduction is from 25 to 30%. The lower value corresponds to the analysis for $NiCr_2O_4$, *i.e.*, nickel chromite. After reduction all catalysts analyzed contained about 11% nickel in the metallic state.[6] Thus it may be calculated that the optimum ratio is of the order to 1 part of sulfur to about 30 parts of reduced nickel. It appears that the catalyst is deactivated if the ratio of sulfur to reduced nickel is as much as 1 to 20.

The addition of thiophene to a Raney nickel catalyst did not render it active for the dehydrogenation of dicyclohexyl in the process. Neither thiophene nor diphenyl sulfide had any effect either in promoting or poisoning the activity of platinum or palladium catalysts for the aromatization of dicyclohexyl. The addition of small amounts of sulfur or of nickel sulfide to the nickel catalyst increased the formation of diphenyl from dicyclohexyl in benzene solution, but the effect was not nearly so marked as with thiophene or diphenyl sulfide. Carbon bisulfide did not promote the activity of the nickel catalyst.

Summary

Thiophene-free benzene is not effective with a nickel catalyst at 350° in the oxidation (dehydrogenation) of dicyclohexyl to diphenyl. However, benzene containing thiophene or diphenyl sulfide in a suitable proportion to the weight of catalyst present brings about an almost quantitative conversion of dicyclohexyl to diphenyl.

MADISON, WISCONSIN RECEIVED AUGUST 25, 1947

---

[5] Experimental details on the preparation and properties of these compounds will be given in a subsequent paper on the synthesis and dehydrogenation of polynuclear compounds.

[6] Covert, Connor and Adkins, THIS JOURNAL, **54**, 1652 (1932).

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

Preparation of Aldehydes from Alkenes by the Addition of Carbon Monoxide and Hydrogen with Cobalt Carbonyls as Intermediates

BY HOMER ADKINS AND GEORGE KRSEK

A U. S. patent issued to Otto Roelen[1] discloses a most interesting and rather surprising reaction, *i.e.*

$$RCH{=}CH_2 + CO + H_2 \xrightarrow[125\text{–}200\text{ atm.}]{90\text{–}200^\circ} RCH_2CH_2CHO$$

In the examples given in the patent the reaction is applied to ethylene, to oil of turpentine and to a lubricating oil. The catalysts specified contained cobalt, thorium oxide, kieselguhr and sometimes copper. The liquid product from ethylene was reported as made up of "40% propionaldehyde, 20% diethyl ketone and 40% higher boiling aldehydes and ketones or other oxygenated products." The results of inquiries made in Germany in 1945–1946 indicated the practicality of this so called "oxo process," particularly for the preparation of primary alcohols from alkenes through the reduction of the aldehydes first formed.

Apart from the merits of the process for commercial utilization, the Roelen reaction is obviously of considerable potential value in organic syntheses. We were interested in working out the best conditions for carrying out the reaction in standard steel equipment in the laboratory, and in ascertaining the yields of aldehyde from various unsaturated compounds. There are limitations to the reaction as, for example, two aldehydes might be obtained by the addition of carbon monoxide and hydrogen to an alkene $RCH{=}CH_2$, *i.e.*, RCH_2CH_2CHO and $RCH(CH_3)CHO$ as well as ketones where two molecules of the alkene and one of carbon monoxide reacted. Other reactions which may occur under the conditions used are the reduction of the alkene or the reduction or condensation of the carbonyl compounds.

In view of the well-known variation in the reactivity of alkenes, depending upon their structure, it seemed improbable that all compounds containing a carbon to carbon double bond would add carbon monoxide and hydrogen. However, it has been possible to produce aldehydes in the indicated yield from unsaturated compounds having as diverse structures as pentene-2 (75%), styrene (30%), methyl undecylenate (75%), ethyl crotonate (36%), diethyl fumarate (51%), allyl alcohol (18%) and allyl acetate (70%).

The range of conditions specified in the Roelen patent are, as might be expected, rather wide. However, after a considerable number of experiments, conditions were found under which the reaction has proceeded well with several unsaturated compounds. For example, 25 g. of commercial pentene-2 in 60 ml. of ether, with 0.6 g. of a reduced cobalt on kieselguhr catalyst, was placed in a steel reaction vessel having a 270-ml. void. The vessel was charged with carbon monoxide to a pressure of 2400 p.s.i. and hydrogen was added until the total pressure was 3600 p.s.i. The bomb was then shaken and heated to 150° when the pressure was 4300 p.s.i. During three hours the pressure dropped to 2200 p.s.i. The pressure drop was 96% of that required for the absorption of one mole of carbon monoxide and one mole of hydrogen per mole of pentene. The bomb was allowed to cool to room temperature, opened and the catalyst separated by centrifugation. The ether was removed by distillation and the product distilled under reduced pressure. The yield of aldehydes amounted to 75% of the theoretical. The boiling range of the product indicated that the aldehydes were those which would be produced by the alternate possible adducts of pentene-2, *i.e.*, $CH_3CH_2CH_2CH(CH_3)CHO$ and $CH_3CH_2CH(C_2H_5)CHO$.

Another representative synthesis was with 21.5 g. of methyl undecylenate in 80 ml. of ether under the same condition of temperature, pressure and catalyst as given for pentene-2. There was an incubation period of about twenty minutes after the reaction mixture reached 150°. However, 100% of the theoretical amount of carbon monoxide and hydrogen was then taken up within 140 minutes. Methyl 11-aldehydo-undecanoate was obtained in yield of 75% of the theoretical by distillation under reduced pressure.

While carrying out experiments of the type described above we began to suspect that we were not primarily concerned with a reaction in heterogenous catalysis where the reaction occurs at the surface of a solid, as in catalytic hydrogenation. The reaction mixture in successful syntheses was always colored, whereas in the failures it was colorless. In order to test the hypothesis that the catalyst was soluble in ether, the reactions were carried out in two stages. In the first stage an ether soluble cobalt compound, dicobalt octacarbonyl, was prepared by reaction of cobalt and carbon monoxide. The ether solution so obtained was used as the catalyst for the reaction of an alkene with carbon monoxide and hydrogen. The reaction, in the presence of the preformed dicobalt octacarbonyl, proceeded to completion within a few minutes at a temperature 25° lower than was necessary where a soluble cobalt compound was not used.

It appears that the synthesis may be considered to involve at least four reactions which may be outlined as

---

[1] Otto Roelen, U. S. Patent 2,327,066 (1943). The patent was vested in the Alien Property Custodian.

$$2Co + 8CO \xrightleftharpoons[150^\circ]{} [Co(CO)_4]_2 \qquad (1)$$

$$[Co(CO)_4]_2 \xrightleftharpoons[125^\circ]{H_2} 2Co(CO)_3COH \qquad (2)$$

$$4Co(CO)_3COH + 4CH_2{=}CH_2 \xrightarrow[125^\circ]{H_2} 4CH_3CH_2CHO + [Co(CO)_3]_4 \qquad (3)$$

$$[Co(CO)_3]_4 + 4CO \xrightleftharpoons[125^\circ]{} 2[Co(CO)_4]_2 \qquad (4)$$

In the first stage metallic cobalt is converted to dicobalt octacarbonyl (as in 1), a reaction which requires a higher temperature than the subsequent steps and even so goes more slowly. Dicobalt octacarbonyl is then reduced to cobalt tetracarbonyl hydride as indicated in (2). We suggest that a hydride is the reagent effective in the synthesis as shown in 3. The tetracobalt dodecacarbonyl $[Co(CO)_3]_4$, postulated as formed in 3, would be converted to dicobaltoctacarbonyl $[Co(CO)_4]_2$ by reaction with carbon monoxide as indicated in 4. The transformations involved are perhaps more clearly seen if the brackets in the formulas, indicating polymeric forms, are disregarded. The chemistry of the cobalt carbonyls, except that suggested in reaction 3, is covered in recent publications.[2,3]

The direct preparation of dicobalt octacarbonyl[4] from cobalt and carbon monoxide was carried out as follows: Raney cobalt (4 to 8 g.) was placed with 145 ml. of ether under carbon monoxide at 3200 p.s.i. and heated with shaking for five or six hours at 150°, after which the reaction vessel was allowed to cool. The pressure during the period of heating dropped from 4900 to 4300 p.s.i. and then to 2200 p.s.i. when the bomb was cooled to room temperature. The insoluble portion of the reaction mixture was removed by centrifugation. The dark reddish brown clear solution of 160 ml., including ether used in the transfers, contained 8.9 g. of dicobalt octacarbonyl. This compound was found to be soluble in ether to the extent of approximately 7.5 g. per 100 ml. of solution. The Raney cobalt has been specified above but the metal obtained by reduction of the Harshaw cobalt on kieselguhr catalyst, "Co-100 powder," has also been used.

Our practice has been to place the ether solution of dicobalt octacarbonyl as obtained from the reaction of cobalt and carbon monoxide in a 250 ml. Pyrex centrifuge bottle held in a wire guard, such as is used in hydrogenation at 2 or 3 atm. pressure. The bottle was provided with a rubber stopper held in place by a clamp. One leg of an inverted glass U tube extended through the stopper to the bottom of the flask. The other leg of the tube carried a stopcock. The container was kept in a refrigerator until a quantity of the catalyst solution was needed. The bottle was then allowed to warm up to room temperature or a little higher. Sufficient pressure was thus developed in the bottle so that the ether solution would flow through the U tube into a graduate when the stopcock was opened. The pressure developed over the solution at 30° was less than 0.5 atmosphere and was largely due to the vapor pressure of the ether.

The synthesis was carried out by placing 50 g. of allyl acetate, 40 ml. of the ether solution containing 2.2 g. of dicobalt octacarbonyl and 40 ml. of ether in a steel reaction vessel. Carbon monoxide was introduced to a pressure of 3200 p.s.i. and hydrogen added to a pressure of 4800 p.s.i. The pressure dropped to 4250 p.s.i. when the mixture was shaken and then rose to a maximum of 5050 p.s.i. when it was heated up to 115°. The bomb was then heated more slowly so that the temperature did not exceed 125°, by which time the pressure had already fallen to 4000 p.s.i. Within less than nine minutes the pressure had fallen to 3100 p.s.i. and the reaction was considered complete. The pressure in the bomb, when it had cooled to room temperature, was 2000 p.s.i. The drop in pressure during the reaction corresponded to the absorption of approximately 1 mole of each gas per mole of allyl acetate. When the product was worked up in the usual way γ-acetoxybutyraldehyde was obtained in 69% yield.

Hazards

The use of carbon monoxide under pressure with the highly poisonous cobalt carbonyls is not without danger. The ill effect of breathing carbon monoxide is sufficiently well known so that a warning is perhaps not necessary. According to Gilmont and Blanchard[2] "the odor of cobalt tetracarbonyl hydride is so intolerable that the danger from inhaling it is much less than from nickel tetracarbonyl. However, it is probably equally poisonous, and the same precautions should be taken as with nickel tetracarbonyl." The hydride decomposes even at room temperature, so that it will disappear rapidly from reaction mixtures held at atmospheric pressure, with the formation of dicobalt octacarbonyl. Fortunately this latter compound has a low vapor pressure and so may be handled with much less hazard than nickel tetracarbonyl. The dicobalt octacarbonyl also decomposes slowly in an open vessel to give carbon monoxide at room temperature. However, in an ether solution in a closed Pyrex bottle there is no development of pressure or appreciable decomposition at room temperature.

---

(2) For a brief summary and references see Gilmont and Blanchard, "Inorganic Syntheses," Vol. 2, McGraw-Hill Book Co., New York, N. Y., 1946, p. 238.

(3) Hieber, Schulten and Marin, *Z. anorg. allgem. Chem.*, **240**, 261–272 (1939).

(4) Apparently the preferred procedure for preparing dicobalt octacarbonyl has been that described by Gilmont and Blanchard.[2] Their procedure involves a series of reactions from cobalt nitrate to a potassium cobaltocyanide, to a potassium salt of cobalt tetracarbonyl hydride, to the hydride and then to the desired product. The process seems rather long and laborious, and while the weight of product is not stated it is apparently of the order of 2 g. The availability of steel reaction vessels and carbon monoxide under pressure makes the preparation of dicobalt octacarbonyl an easy and simple process.

First class steel equipment in good condition and in the hands of a competent operator are essential if accidents are to be avoided. There should be no leaks of any kind in the equipment. All transfers of material and washing of the reaction vessel should be carried out in a hood with rapid ventilation. The residual gas from the reaction vessel, which contains carbon monoxide and probably volatile cobalt compounds, should be burned in a Bunsen burner or slowly vented in the hood. The exit gas from all distillations or filtrations should be taken care of by large quantities of running water. Residues after distillation should be similarly disposed of, *all* operations being carried out under a hood.

It is said that the presence of traces of volatile cobalt or nickel compounds in the air may be detected by the color of the flame of a burner. The U. S. Bureau of Standards has developed a tube with a filler which we have found useful in detecting carbon monoxide in air. In some laboratories canaries are used as detectors for carbon monoxide.

Pressures higher than necessary probably were used. This was done so that a quantity of carbon monoxide and hydrogen, sufficient to react with the desired quantity of alkene, could be placed in the bomb. The ratio of carbon monoxide to hydrogen was probably higher than necessary. Incidentally it may be noted that successful hydrogenations, with nickel or copper chromium oxide, usually cannot be carried out for some time after a bomb has been used with carbon monoxide.

Experimental Details

Cobalt Catalysts.—The cobalt on kieselguhr catalyst was "Co-100 powder" as supplied by the Harshaw Chemical Co. of Cleveland, Ohio. According to the supplier the "Co-100 powder" would give 50% of its weight of cobalt when reduced. In our experience the reduced catalyst contained 12 to 15% metallic cobalt after treatment with hydrogen at 425° for four hours. Raney cobalt was made from the Raney 40% cobalt–60% aluminum alloy, by the procedure used for preparing Raney nickel.[5]

Isolation and Characterization of Products.—The products (27 g.) from pentene-2 (25 g.) distilled at 40–50° (12 mm.) A titration by the hydroxylamine method[6] with methyl orange as the indicator, showed that the aldehyde content, calculated for $C_5H_{13}CHO$, was 88%. Fractional distillation gave a fraction, b.p. 28–29° (10 mm.), $n^{25}\text{D}$ 1.4009, which was 95% aldehyde. The 2,4-dinitrophenylhydrazones melted over the range 90–120°. The boiling points of the two aldehydes[7,8] which would be produced from pentene-2 are too close together to make their separation feasible.

Styrene (18 g.) reacted as did the other unsaturated compounds giving a product (9.3 g.) boiling 78–120° (10 mm.) which analyzed[6] for 80% aldehyde. After fractionation hydrotropaldehyde, b.p. 76–77° (0.08 mm.), $n^{25}\text{D}$ 1.5148, was obtained 95% pure.[9] It gave a semicarbazone,[10] m.p. 153–154°.

Diethyl fumarate (17.2 g.) reacted with carbon monoxide and hydrogen as did methyl undecenylate. The product (14.3 g.) distilled at 85-120° (1 mm.) and was 70% pure by titration.[6] After fractionation the diethyl α-formyl-succinate[11] had a b.p. 104–105° (0.04 mm.), $n^{25}\text{D}$ 1.4486, and was 95% pure. It gave a semicarbazone, m.p. 124–125°, and a *p*-nitrophenylhydrazone, m.p. 100–101°.

The product (18 g.) from methyl undecylenate (21.5 g.) distilled at 125–150° at less than 1 mm. pressure, was 90% methyl 11-aldehydo-undecanoate according to hydroxylamine titration.[6] After fractionation the aldehyde, b.p. 144–147° (0.1 mm.), $n^{25}\text{D}$ 1.4432, was 97% pure.[12] The 2,4-dinitrophenylhydrazone had the m.p. 69–70°. Oxidation with air at 60° followed by saponification to dodecanedioic acid $(CH_2)_{10}(CO_2H)_2$, m.p. 122–124°, showed the aldehyde to be methyl 11-aldehydo-undecanoate,[13] $CHO(CH_2)_{10}CO_2CH_3$.

Allyl alcohol (29 g.) in ether reacted with carbon monoxide and hydrogen in the presence of 2.2 g. of dicobalt octacarbonyl, as has been described for allyl acetate. The product (16 g.) distilled at 80–100° (28 mm.) and was found to be 55% pure. After fractionation γ-hydroxybutyraldehyde, 96% pure, b.p. 98–99° (35 mm.), $n^{25}\text{D}$ 1.4384, gave a 2,4-dinitrophenyl-hydrazone, m.p. 178–179°. The aldehyde was oxidized with air at 60° and lactonized to give an 80% yield of butyrolactone,[14] b.p. 90–91° (25 mm.), $n^{25}\text{D}$ 1.4345, having a saponification equivalent of 85.

The product (46 g.) from the reaction as described above of allyl acetate (50 g.) distilled at 60–90° (10 mm.) and was 92% pure by titration. After fractionation the γ-acetoxybutyraldehyde, b.p. 59–60° (1 mm.), $n^{25}\text{D}$ 1.4245, was 94% pure and gave a 2,4-dinitrophenylhydrazone, m.p. 180–181°. The aldehyde was oxidized with air at 60° in 97% yield to give γ-acetoxybutyric acid, b.p. 112–113° (1 mm.), $n^{25}\text{D}$ 1.4343, which was by titration 99% pure. The acid was hydrolyzed and lactonized to butyrolactone. *Anal.* Calcd. for γ-acetoxybutyraldehyde $C_6H_{10}O_3$: C, 55.4; H, 7.8, Found: C, 55.4; H, 8.0. *Anal.* Calcd. for γ-acetoxybutyric acid $C_6H_{10}O_4$: C, 49.3; H, 6.7. Found: C, 49.3; H, 7.1.

Ethyl crotonate (29 g.) in ether reacted with carbon monoxide and hydrogen in the presence of dicobalt octacarbonyl (2.2 g.) as described for allyl acetate. The product (19.1 g.), b.p. 96–100° (35 mm.), was 96% pure by titration. The ethyl β-formylbutyrate distilled at 58–59° (0.01 mm.), had $n^{25}\text{D}$ 1.4236 and gave a 2,4-dinitrophenylhydrazone, m.p. 87–88°.

Anal. Calcd. for $C_7H_{11}O_3$: C, 58.3; H, 8.4. Found: C, 58.5; H, 8.5.

Summary

Several aldehydes, *i.e.*, hexaldehydes, hydratropaldehyde, diethyl α-formylsuccinate, methyl 11-aldehydoundecanoate, γ-hydroxybutyraldehyde, γ-acetoxybutyraldehyde and ethyl β-formylbutyrate, have been prepared in an average yield of 50% by the addition of carbon monoxide and hydrogen to the alkene linkage in pentene-2, styrene, diethyl fumarate, methyl undecylenate, allyl alcohol, allyl acetate or ethyl crotonate.[15]

The first step in the catalysis of the reaction appears to be the formation of an ether-soluble cobalt compound, dicobalt octacarbonyl. While the conversion of the alkene to the aldehyde may be brought about at 150° in the presence of cobalt

---

[5] Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946).

[6] Alexander Halasz, *Ann. Chim.*, **14**, 336 (1940).

[7] Stoermer, *Ber.*, **39**, 2297 (1906).

[8] Skita, *ibid.*, **48**, 1491 (1915).

[9] Wooten, *J. Chem. Soc.*, **97**, 409 (1910).

[10] Claisen, *Ber.*, **38**, 705 (1905).

[11] Schtschukena and Preobrashenski, *Ber.*, **68B**, 1991 (1935).

[12] Adams, THIS JOURNAL, **49**, 522 (1927).

[13] Noerdlinger, *Ber.*, **23**, 2357 (1890).

[14] Sircar, *J. Chem. Soc.*, 898 (1928).

[15] Succindialdehyde-1,1-diacetate and γ-carbethoxypropionaldehyde were prepared in 74–75% yields from 50 g. of allylidene diacetate and of ethyl acrylate, respectively, with 0.6 g. of dicobalt octacarbonyl as a catalyst in benzene at 125° and 1200 to 4000 p. s. i. (Added in proof, January 5, 1948.)

on a support, it appears advantageous to use preformed dicobalt octacarbonyl in ether or other solvent for the catalysis of the synthetic reaction. The dicobalt octacarbonyl is readily made at 150° by the direct reaction of cobalt and carbon monoxide, and may be kept in ether for use as needed as a catalyst. The addition of carbon monoxide and hydrogen to an alkene goes very rapidly at 125° or lower in the presence of dicobalt octacarbonyl. The reactions may be carried out at 100 to 300 atm. pressure in the steel reaction vessels ordinarily used for hydrogenation.

The poisonous properties of carbon monoxide and of the cobalt carbonyls suggest that considerable care be exercised in carrying out the syntheses of aldehydes for alkenes by the method outlined.

MADISON, WISCONSIN RECEIVED SEPTEMBER 6, 1947

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

Some Quinoline Derivatives of 2-Amino-*p*-cymene[1]

BY ALVIN SAWYER WHEELER AND JOSEPH NISBET LECONTE

Introduction

This paper records a study of several methyl homologs of 5-isopropylquinoline. The 8-methyl derivative was prepared by the method of Cohn and Gustavson,[2] and the 2,4,8-trimethyl compound was obtained by cyclizing, according to Bulow and Issler,[3] the compound I obtained by condensing 2-amino-*p*-cymene with acetylacetone.

The 8-methyl derivative and the 2,8-dimethyl compound of Phillips and Goss[4] on reduction with sodium and absolute ethanol yielded py-tetrahydroquinolines.

Experimental

Temperatures are in °C., uncorrected.

5-Isopropyl-8-methylquinoline.—2-Amino-*p*-cymene (59.6 g.), 2-nitro-*p*-cymene (35.8 g.), 80% acetic acid (60 cc.), 95% sulfuric acid (54 cc.) and glycerol (100 g.) were treated in the manner of Cohn and Gustavson[2] to yield 20 g. (27%) of the quinoline which is a pale yellow oil with the characteristic quinoline-like odor; b. p. 175° (35 mm.); $d^{26.2}_{4}$ 1.0287; n^{27}_{D} 1.5798. *Anal.* Calcd. for $C_{13}H_{15}N$: N, 7.56. Found: N, 7.43. Chloroplatinate, m. p. 212° (shrinks at 160°). *Anal.* Calcd. for $C_{13}H_{17}NCl_6Pt$: Pt, 24.82. Found: Pt, 24.90. Picrate, m. p. 166–168°. *Anal.* Calcd. for $C_{19}H_{18}N_4O_7$: N, 13.52. Found: N, 13.44.

Reduction of this quinoline with sodium and absolute ethanol yielded py-tetrahydro-5-isopropyl-8-methylquinoline, b. p. 165–167° (27 mm.). *Anal.* Calcd. for $C_{13}H_{19}N$: N, 7.40. Found: N, 7.39. Chloroplatinate, m. p. 198°. *Anal.* Calcd. for $C_{13}H_{21}NCl_6Pt$: Pt, 24.22. Found: Pt, 24.37.

2,8-Dimethyl-5-isopropylquinoline was prepared in the manner formerly employed by Phillips and Goss.[4] Chloroplatinate, m. p. 226° (shrinks 212°). *Anal.* Calcd. for $C_{14}H_{19}NCl_6Pt$: Pt, 23.62. Found: Pt, 23.80. Picrate, m. p. 142°. *Anal.* Calcd. for $C_{20}H_{20}N_4O_7$: N, 14.52. Found: N, 14.60.

Reduction of this quinoline with sodium and absolute ethanol yielded py-tetrahydro-2,8-dimethyl-5-isopropylquinoline, m. p. 65°. *Anal.* Calcd. for $C_{14}H_{21}N$: N, 6.89. Found: N, 6.78. Chloroplatinate, m. p. 202° (shrinks 199°). *Anal.* Calcd. for $C_{14}H_{23}NCl_6Pt$: Pt, 23.39. Found: Pt, 23.80.

Compound I.—A mixture of 2-amino-*p*-cymene (15.05 g.) and acetylacetone (10 g.) was refluxed on a steam-bath for three hours, during which water appeared in the mixture and the mixture became dark red in color. Distillation of the mixture under reduced pressure yielded 11.8 g. of a pale yellow oil, b. p. 184–185° (22 mm.), $d^{27.5}$ 0.9827, insoluble in water, easily soluble in alcohol and ether, blood-red color with ferric chloride, and no reaction with the Hinsberg reagent. *Anal.* Calcd. for $C_{15}H_{21}ON$: N, 6.06. Found: N, 5.89. Chloroplatinate, m. p. 177°. *Anal.* Calcd. for $C_{15}H_{23}ONCl_6Pt$: Pt, 21.93. Found: Pt, 22.04.

2,4,8-Trimethyl-5-isopropylquinoline.—Ninety-five per cent. sulfuric acid (60 cc.) was cooled to 0° and 19.5 g. of compound I was cautiously added. The mixture was allowed to stand ten minutes, heated on a steam-bath for one hour, poured into a mixture of ice (100 g.) and water (60 cc.), made basic with ammonium hydroxide, saturated with sodium chloride and extracted with ether. Distillation of the dried ether solution under reduced pressure yielded 5 g. of a pale yellow oil, b. p. 170–178° (22 mm.) (boiling mostly at 177–178°). *Anal.* Calcd. for $C_{15}H_{19}N$: N, 6.57. Found: N, 6.70. Chloroplatinate, m. p. 213–216°. *Anal.* Calcd. for $C_{15}H_{21}NCl_6Pt$: Pt, 22.85. Found: Pt, 22.89. Picrate, m. p. 181–183°. *Anal.* Calcd. for $C_{21}H_{22}N_4O_7$: N, 12.67. Found: N, 12.58.

Summary

1. Some methyl homologs of 5-isopropylquinoline have been prepared.

2. 8-Methyl and 2,8-dimethyl-5-isopropylquinolines were reduced to their corresponding py-tetrahydroquinolines.

UNIVERSITY OF GEORGIA
ATHENS, GEORGIA
RECEIVED SEPTEMBER 11, 1947

---

[1] This paper is a portion of a thesis submitted by Joseph N. LeConte in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry, University of North Carolina. Doctor Wheeler is now deceased.

[2] Cohn and Gustavson, THIS JOURNAL, **50**, 2709 (1928).

[3] Bulow and Isler, *Ber.*, **36**, 2448 (1903); **36**, 4013 (1903).

[4] Phillips and Goss, THIS JOURNAL, **48**, 823 (1926).

[CONTRIBUTED FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

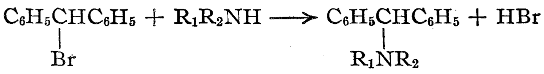
N-Substituted Benzohydrylamines

BY NORMAN H. CROMWELL AND W. E. FITZGIBBON

Numerous investigators[1] have reported the preparation of benzohydrylamines.

Sommelet[1a] found that when such compounds are prepared by condensing benzohydryl bromide with various amines the medium should not be a reactive one such as an alcohol because it is possible for the benzohydryl ether to form instead of the desired benzohydryl amine, especially at elevated temperatures.

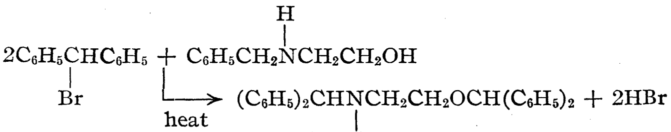
N-Methyl-*p*-methoxybenzylamine, N-methylethanolamine and N-benzylethanolamine each was condensed with benzohydryl bromide in benzene solution using essentially the conditions reported previously[1j] to give good yields of the desired N-substituted benzohydryl amines, (I), (II) and (III). The latter two compounds were isolated as their hydrochlorides.



$$C_6H_5\underset{\underset{Br}{|}}{C}HC_6H_5 + R_1R_2NH \longrightarrow C_6H_5\underset{\underset{R_1NR_2}{|}}{C}HC_6H_5 + HBr$$

(I), $R_1 = CH_3$; $R_2 = p\text{-}CH_3OC_6H_4$
(II), $R_1 = CH_3$; $R_2 = CH_2CH_2OH$
(III), $R_1 = C_6H_5CH_2$; $R_2 = CH_2CH_2OH$

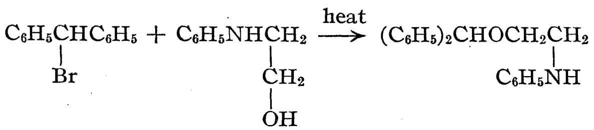
In one experiment N-benzylethanolamine was heated with benzohydryl bromide to the boiling point of the toluene solution. From this reaction mixture only the amino ether (IV) was isolated, resulting from reaction of the bromide with both the amino group and the hydroxyl group of the N-benzylethanolamine.



$$2C_6H_5\underset{\underset{Br}{|}}{C}HC_6H_5 + C_6H_5CH_2\overset{\overset{H}{|}}{N}CH_2CH_2OH \xrightarrow{\text{heat}} (C_6H_5)_2CH\underset{\underset{C_6H_5CH_2}{|}}{N}CH_2CH_2OCH(C_6H_5)_2 + 2HBr$$

(IV)

N-Phenylethanolamine proved to be too nonreactive to condense with benzohydryl bromide under the usual conditions. Moreover, at elevated temperatures the reaction proceeded in such a manner as to give the amino ether (V), resulting from reaction of the benzohydryl bromide with only the hydroxyl group of the N-phenylethanolamine.

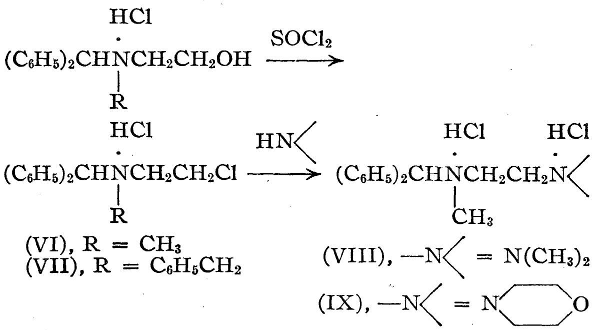


$$C_6H_5\underset{\underset{Br}{|}}{C}HC_6H_5 + C_6H_5NH\underset{\underset{\underset{OH}{|}}{CH_2}}{\underset{|}{C}}H_2 \xrightarrow{\text{heat}} (C_6H_5)_2CHOCH_2\underset{\underset{C_6H_5NH}{|}}{C}H_2$$

(V)

When this condensation was attempted in aqueous alcohol in the presence of potassium carbonate the benzohydryl bromide was slowly converted to benzohydrol. Using absolute alcohol and anhydrous potassium carbonate at reflux temperature for four hours, the benzohydryl bromide apparently reacted only with the ethyl alcohol to give benzohydryl ethyl ether. When (V) was treated with thionyl chloride only the hydrochloride of (V) resulted, indicating the absence of the alcohol group.

The low reactivity of the amino group in N-phenylethanolamine with the benzohydryl bromide would seem to be the result of the reduced electron density at the nitrogen, combined with the steric difficulties involved in the approach of the benzohydryl group toward this nitrogen that is attached to both a phenyl and an ethanol group.



$$(C_6H_5)_2CH\underset{\underset{R}{|}}{\overset{\overset{HCl}{\cdot}}{N}}CH_2CH_2OH \xrightarrow{SOCl_2} (C_6H_5)_2CH\underset{\underset{R}{|}}{\overset{\overset{HCl}{\cdot}}{N}}CH_2CH_2Cl \xrightarrow{HN\langle} (C_6H_5)_2CH\underset{\underset{CH_3}{|}}{\overset{\overset{HCl}{\cdot}}{N}}CH_2CH_2\overset{\overset{HCl}{\cdot}}{N}\langle$$

(VI), $R = CH_3$
(VII), $R = C_6H_5CH_2$
(VIII), $-N\langle = N(CH_3)_2$
(IX), $-N\langle = N\qquad O$

The hydrochlorides of the N-benzohydrylethanolamines (II) and (III) were each readily converted to the β-chloroethylamine hydrochlorides (VI) and (VII) by reaction with thionyl chloride in chloroform solution.

The β-chloroethylamine hydrochloride (VI) was condensed with dimethylamine and with morpholine, respectively, to give the substituted ethylenediamines (VIII) and (IX), isolated as their dihydrochlorides.

The various N-substituted benzohydrylamines resulting from this investigation have been submitted for pharmacological screen testing, the results of which will be reported elsewhere.

Experimental

Benzohydryl Bromide.—The benzohydryl bromide used in these condensations was prepared from benzohydrol in 90% yields by the method given by Courtot,[2] and purified

---

[1] For examples see: (a) Sommelet, *Compt. rend.*, **175**, 1149 (1922); (b) Gilman and Hoyle, THIS JOURNAL, **44**, 2621 (1922); (c) Valette, *Bull. soc. chim.*, (4) **47**, 289 (1930); (d) Bonnard and Meyer-Oulif, *ibid.*, (4) **49**, 1303 (1931); (e) Hughes and Ingold, *J. Chem. Soc.*, 69 (1933); (f) Maxim and Mavrodineanu, *Bull. soc. chim.*, (5) **3**, 1084 (1936); (g) Ogata and Shinnobu, *J. Pharm. Soc. Japan*, **56**, 497 (1936); (h) Grammaticakis, *Compt. rend.*, **207**, 1224 (1938); (i) Grammaticakis, *ibid.*, **210**, 716 (1940); (j) Cromwell, THIS JOURNAL, **69**, 1859 (1947).

[2] Courtot, *Ann. chim.*, [9] **5**, 80 (1916).

TABLE I

PHYSICAL AND ANALYTICAL DATA

Benzohydrylamines	No.	M. p., °C.	Yield, %	Formula	Chlorine, %[a] Calcd.	Chlorine, %[a] Found
N-Methyl-N-(*p*-methoxybenzyl)-benzohydrylamine	(I)[b]	62	83	$C_{22}H_{23}NO$		
N-Benzohydrylethanolamine hydrochlorides						
N-Methyl	(II)	159	62	$C_{16}H_{20}ClNO$	12.76	12.72
N-Benzyl	(III)	179	75	$C_{22}H_{24}ClNO$	10.02	9.94
β-Aminoethylbenzohydryl ethers						
N-Benzohydryl-N-benzyl[c]	(IV)	109	10	$C_{35}H_{33}NO$		
N-Phenyl[d]	(V)	100	17	$C_{21}H_{21}NO$		
Hydrochloride		210	90	$C_{21}H_{22}ClNO$	10.43	10.40
N-Benzohydryl-β-chloroethylamine hydrochlorides						
N-Methyl	(VI)	191	90	$C_{16}H_{19}Cl_2N$	23.93	23.93
N-Benzyl	(VII)	171	63	$C_{22}H_{23}Cl_2N$	19.05	19.01
N-Benzohydryl-N-methylethylamine dihydrochlorides						
β-Dimethylamino	(VIII)	227	67	$C_{18}H_{26}Cl_2N_2$	20.78	20.47
β-Morpholino	(IX)	236	70	$C_{20}H_{28}Cl_2N_2O$	18.50	18.46

[a] We are indebted to Dr. H. Armin Pagel of the University of Nebraska for advice in carrying out the total chlorine analyses of the β-chloroethyl amine hydrochlorides by the hydrogen jet method, reported by Winter, *Ind. Eng. Chem., Anal. Ed.*, **15**, 571 (1943). [b] Calcd.: C, 83.25; H, 7.30. Found: C, 82.93; H, 7.49. [c] Calcd.: C, 86.91; H, 6.87; N, 2.90. Found: C, 86.86; H, 7.01; N, 2.99. [d] Calcd.: C, 83.32; H, 6.98. Found: C, 83.53; H, 6.84.

to a colorless crystalline product by vacuum distillation, b. p. 176–180° (17 mm.).

N-Methyl-N-(*p*-methoxylbenzyl)-benzohydrylamine (I).—This compound was prepared by the method given previously[1j] for the preparation of N-benzohydrylmorpholine, by condensing benzohydryl bromide with N-methyl-*p*-methoxybenzylamine[3] (see Table I).

N-Benzohydrylethanolamine Hydrochlorides (II) and (III).—Pure benzohydryl bromide (24.7 g., 0.10 mole) was mixed with 14.8 g. (0.21 mole) of N-methylethanolamine[4] and with 31.7 g. (0.21 mole) of N-benzylethanolamine,[5] respectively, in 30 ml. of dry benzene. After standing for twelve hours at room temperature the solutions were diluted with 300 ml. of dry ether to complete the precipitation of the by-product hydrobromides of the starting ethanol amines. The ether–benzene solutions of the products were decanted from the oily by-product and washed with ten 10-ml. portions of water and dried for twelve hours over anhydrous calcium sulfate.

The hydrochlorides (II) and (III) were precipitated by passing dry hydrogen chloride gas into the solutions. These crude products were recrystallized twice from mixtures of absolute alcohol and dry ether to give colorless granular products, (II) and (III).

N-Benzohydryl-N-benzyl-β-aminoethyl Benzohydryl Ether, (IV).—Pure benzohydryl bromide (16.05 g., 0.065 mole) was mixed with 20.8 g. (0.137 mole) of N-benzylethanolamine in 16 ml. of toluene and refluxed for one hour. After standing at room temperature for twelve hours 100 ml. of dry ether was added to complete the precipitation of the by-product hydrobromide. The ether–toluene layer was decanted from the oily hydrobromide and washed with water. Evaporation of the solvent left an oil which was dissolved in alcohol. Addition of water to this solution and cooling caused an oily solid to form (3.6 g.). Recrystallization of this product first from boiling absolute alcohol and then from boiling petroleum ether (b. p. 60–70°) gave a colorless granular product (IV).

N-Phenyl-β-aminoethyl Benzohydryl Ether, (V).—When 10 g. of benzohydryl bromide was mixed with 11.1 g. (2.1 equiv.) of N-phenylethanolamine in 25 ml. of dry benzene and refluxed for two hours no precipitate of an amine hydrobromide appeared. The benzene was removed by distillation and the residual dark oil heated on an oil-bath for two hours at 130–140°. Dry ether and benzene were added to the cooled, dark mass to cause precipitation of a grey powder which was removed by filtration (10.8 g. as compared with the expected theoretical weight of 8.9 g. of N-phenylethanolamine hydrobromide). The filtrate was washed with water, dried and evaporated to leave a brown oil. Crystallization from benzene and petroleum ether followed by recrystallization from alcohol and water gave a colorless, flaky product (V).

When a sample of (V) was treated with thionyl chloride according to the procedure given below for the preparation of β-chloroethylamines only the hydrochloride of (V) resulted, identical with a sample prepared by treating (V) with dry hydrogen chloride gas in dry ether. When a sample of (V) was treated with a solution of nitrous acid in an alcohol–water mixture a pale yellow oil precipitated which could not be crystallized, but which gave the Liebermann test[6] for a nitrosamine.

N-Benzohydryl-β-chloroethylamine Hydrochlorides (VI) and (VII).—Cold solutions of the N-benzohydrylethanolamines (II) and (III) (0.10 mole) in 100 ml. of chloroform were treated dropwise over a period of one-half hour with an ice-cold solution of 0.20 mole of thionyl chloride in 15 ml. of chloroform. The solutions were allowed to come to room temperature and then refluxed for two hours. The solvent and excess thionyl chloride were removed under reduced pressure on a steam-bath. The resulting white powders were recrystallized three times from absolute alcohol and ether to give colorless granular products (VI) and (VII).

N-Benzohydryl-N-methyl-β-dimethylaminoethylamine Dihydrochloride, (VIII).—Anhydrous dimethylamine (5.41 g., 0.12 mole) was added to a solution of 8.9 g. (0.030 mole) of (VI) in 100 ml. of absolute alcohol at room temperature and allowed to stand in a tightly stoppered flask for ninety-six hours. The solution was refluxed for an hour and the solvent removed by distillation. The solid residue was extracted with four 20-ml. portions of ether but this extract left no residue on evaporation.

The ether-insoluble residue was mixed with 10 ml. of 6 *N* sodium hydroxide and the resulting oil extracted with

---

(3) Cromwell and Hoeksema, THIS JOURNAL, **67**, 1658 (1945).

(4) Supplied by the Carbide and Carbon Chemicals Corporation, New York, N. Y.

(5) N-Benzylethanolamine for this experiment was prepared by condensing benzaldehyde with ethanolamine in absolute alcohol solution, followed by reduction of the crude imine with hydrogen under 40 lb. pressure in the presence of platinum oxide catalyst; b. p. 153° (14.5 mm.); yield, 69%. See Schotte, Priewe and Roescheisen, *Z. physiol. Chem.*, **174**, 119 (1928); Rumpf and Kwass, *Bull. soc. chim.*, **10**, 342 (1943); West, *J. Soc. Chem. Ind.*, **61**, 158 (1942).

(6) S. M. McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1946, p. 120.

ether. The ether extract was washed with four 10-ml. portions of 6 *N* sodium hydroxide. The ether solution was dried and evaporated to leave a yellow oil which was dissolved in 15 ml. of absolute alcohol and treated with dry hydrogen chloride gas. Addition of dry ether precipitated a colorless solid which was recrystallized from absolute alcohol and dry ether to give (VIII).

N-Benzohydryl-N-methyl-β-morpholinoethylamine Dihydrochloride (IX).—A solution of 7.0 g. (0.08 mole) of morpholine and 7.41 g. (0.025 mole) of (VI) in 25 ml. of 70% ethyl alcohol was placed in a closed flask and allowed to stand at room temperature for twenty-four hours. The solvent was removed by distillation from a steam-bath under reduced pressure. The residue was extracted with dry ether and the ether solution washed with water, dried and evaporated to leave a colorless oil that could not be crystallized from petroleum ether or alcohol–water mixtures. The oily product was dissolved in 30 ml. of absolute alcohol and dry hydrogen chloride gas added. After addition of 200 ml. of dry ether a colorless crystalline precipitate formed which was recrystallized from absolute alcohol and dry ether to give (IX).

Summary

1. The synthesis of certain N-benzohydrylethanolamines by reaction of benzohydryl bromide with ethanolamines of the type $RNHCH_2CH_2OH$ has been studied. When R was methyl or benzyl the desired N-benzohydrylethanolamines were obtained, but when R was phenyl only ether formation resulted.

2. The N-benzohydrylethanolamines were converted to N-benzohydryl-β-chloroethylamines, one of which was condensed with dimethylamine and morpholine, respectively, to give substituted ethylenediamines.

LINCOLN, NEBRASKA RECEIVED SEPTEMBER 12, 1947

[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

Isomeric Unsaturated Esters. II. The Dehydration of Ethyl 3-Hydroxy-2-ethyl-3-methylbutanoate

BY RALPH C. HUSTON, GORDON L. GOERNER AND HANS H. GYÖRGY

In a previous communication[1] the dehydration of ethyl 3-hydroxy-2,3-dimethylbutanoate was shown to yield a mixture of α,β and β,γ unsaturated esters which were readily separated because of their large difference in boiling points. The β,γ unsaturated ester, contrary to the report in the literature, was found to possess the lower boiling point. It appeared that other unsaturated esters might be recorded erroneously.

Blaise and Maire[2] dehydrated ethyl 3-hydroxy-2-ethyl-3-methylbutanoate (I) and obtained an unsaturated ester boiling at 167°. To this they assigned formula III. They also obtained a small quantity of an ester boiling at 175°.

$$\underset{\text{I}}{(CH_3)_2C(OH)CH(C_2H_5)COOC_2H_5} \longrightarrow$$

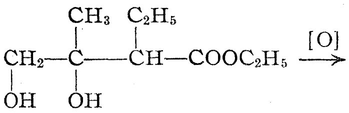
$$\underset{\text{II}}{CH_2{=}C(CH_3)CH(C_2H_5)COOC_2H_5}, \text{ and}$$

$$\underset{\text{III}}{(CH_3)_2C{=}C(C_2H_5)COOC_2H_5}$$

This was assumed to be an isomer of the low boiling ester. Hydrolysis of the ester boiling at 167° yielded an acid distilling at 100° (10 mm.). If esters II and III are analogous to those obtained by Huston and Goerner,[1] ester II should boil at 167° and ester III at the higher temperature. Further evidence that Blaise and Maire had probably assigned the incorrect formula to their low boiling ester was found in the fact that Crossley and LeSueur[3] report a boiling point of 175–180° (748 mm.) for a mixture of ester III and ethyl 2-(1-methylethyl)-2-butenoate obtained by dehydrobromination of ethyl 2-bromo-2-ethyl-3-methylbutanoate by diethylaniline.

Ester I was prepared from propanone and ethyl 2-bromobutanoate by the Reformatsky reaction. It proved to be more stable than expected. An attempt to dehydrate it with dry hydrogen chloride[4] was unsuccessful. Phosphorus pentoxide[2,5] in benzene gave the unsaturated esters in good yield. Esters II and III could be separated readily in approximately equal quantities by fractionation under diminished pressure.

The proof of structure consisted of hydroxylating the esters to the glycols[6] IV and VI and splitting these into aldehydes and ketones by means of "ceric perchlorate"[1,7] or by thermal decomposition. The low boiling ester gave glycol IV. This was split into methanal (which is oxidized to carbon dioxide and water) and ethyl 3-keto-2-ethylbutanoate (V). The solution containing compound V gave 2-pentanone upon alkaline hydrolysis. The high boiling ester gave glycol VI. On distillation this decomposed into propanone and 2-ketobutanoic acid.



$$CH_2(OH){-}C(CH_3)(OH){-}CH(C_2H_5){-}COOC_2H_5 \xrightarrow{[O]}$$

IV

$$HCHO + \underset{\text{V}}{CH_3COCH(C_2H_5)COOC_2H_5}$$

---

[1] Huston and Goerner, THIS JOURNAL, **68**, 2504 (1946).

[2] Blaise and Maire, *Ann. chim.*, [8] **15**, 573 (1908).

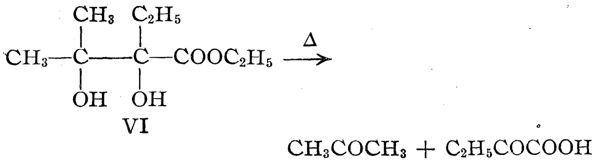
[3] Crossley and LeSueur, *J. Chem. Soc.*, **77**, 95 (1900).

[4] Natelson and Gottfried, THIS JOURNAL, **61**, 970 (1939).

[5] Kon and Nargund, *J. Chem. Soc.*, 2461 (1932).

[6] Milas and Sussman, THIS JOURNAL, **58**, 1302 (1936).

[7] Smith and Duke, *Ind. Eng. Chem., Anal. Ed.*, **13**, 558 (1941); **15**, 120 (1943).



VI

$$CH_3-\underset{OH}{\overset{CH_3}{C}}-\underset{OH}{\overset{C_2H_5}{C}}-COOC_2H_5 \xrightarrow{\Delta} CH_3COCH_3 + C_2H_5COCOOH$$

The ketones were identified through the 2,4-dinitrophenylhydrazones. Catalytic hydrogenation of both unsaturated esters yielded ethyl 2-ethyl-3-methylbutanoate.[8] Here again[1] the reduction of the β,γ ester was found to proceed much more easily than the reduction of the α,β isomer.

Hydrolysis of the esters yielded the corresponding unsaturated acids. The acid obtained from the high boiling ester III appears to be identical with the β,β-dimethyl-α-ethylacrylic acid of Kon, Smith and Thorpe[9] which melted at 49.5°. The acid obtained from the low boiling ester appears to be identical with the acid obtained by Blaise and Maire.[2]

Experimental

All melting points and micro boiling points are corrected.

Ethyl 3-Hydroxy-2-ethyl-3-methylbutanoate (I) was prepared by the Reformatsky reaction, using 1.5 moles of propanone per mole of ethyl 2-bromobutanoate and excess zinc, as suggested by Perkin and Thorpe.[10] The propanone was dried over anhydrous potassium carbonate and the benzene over sodium. Ethyl 2-bromobutanoate was prepared by the bromination of butanoic acid[11] followed by its subsequent esterification.[12] Ten-mesh zinc was cleaned and dried by the method of Fieser and Johnson.[13]

A solution of 15 g. of acetone and 15 g. of ethyl 2-bromobutanoate in 75 ml. of benzene was added to 245 g. (3.75 moles) of zinc. The reaction was initiated by the addition of a small crystal of iodine and slight heating. When vigorous reflux had begun, a solution of the rest of the reactants was added at a rate rapid enough to maintain reflux. Using 585 g. (3 moles) of ethyl 2-bromobutanoate and 261 g. (4.5 moles) of propanone in 750 ml. of benzene, a reaction time of one hour was required with a maximum reaction temperature of 75°.

After refluxing for one and one-half hours the reaction mixture was cooled and poured into 1800 ml. of cold 10% (volume) sulfuric acid. After forty-five minutes the clear benzene layer was removed and the acid layer washed with benzene. The combined benzene extracts were washed with 250 ml. of 5% (volume) sulfuric acid, 250 ml. of 10% (weight) sodium carbonate, and 400 ml. of water. These were then dried over anhydrous sodium sulfate.

Separation of I was attained by the removal of the benzene under reduced pressure and the fractionation of the ester through a 60-cm. Fenske-type column packed with 3/32-inch glass helices. (This column was used for all subsequent fractionations.) The yield of ethyl 3-hydroxy-2-ethyl-3-methylbutanoate was 163 g. (31%) distilling at 76 to 77° (3 mm.), $n^{20}{}_D$ 1.4310, $d^{20}{}_4$ 0.9668, γ_{20} 27.8 (du Noüy, cor.[14]).

Dehydration of Ethyl 3-Hydroxy-2-ethyl-3-methylbutanoate.—One hundred seventy-four grams (1 mole) of ester I was refluxed for two hours with 177 g. of phosphorus pentoxide in three volumes (555 ml.) of benzene.[2,5] The supernatant liquid was decanted and fractionated under reduced pressure. The yield of ethyl 2-ethyl-3-methyl-3-butenoate (II) boiling at 57° (13 mm.) was 49 g., (31%, based on hydroxy ester); micro b.p. 167° (741 mm.), $n^{20}{}_D$ 1.4250, $d^{20}{}_4$ 0.9005, γ_{20} 20.61 (drop-weight, cor.[15]).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.25; H, 10.30.

Fifty-one grams (33%, based on hydroxy ester) of III was obtained boiling at 67° (13 mm.); micro b.p. 180° (741 mm.), $n^{20}{}_D$ 1.4430, $d^{20}{}_4$ 0.9492, γ_{20} 24.05 (drop-weight, cor.[15]).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.27; H, 10.25.

The total yield of the unsaturated esters was 20%, based on the bromo ester. By dehydrating the crude reaction mixture without isolating the hydroxy ester, a yield of 25% was obtained.

Reduction of the Unsaturated Esters.—One-tenth mole of the ester, 150 ml. of ethanol, 0.1 g. of the platinic oxide catalyst,[16] and 50 lb. of hydrogen pressure were used. The low boiling ester (II) was completely reduced in thirty minutes. In the case of the high-boiling ester (III), four hours were necessary for complete reduction. Ethyl 2-ethyl-3-methylbutanoate, micro b.p. 167° (744 mm.), was recovered upon fractionation,[8] $n^{20}{}_D$ 1.4100; $d^{20}{}_4$ 0.8686; γ_{20} 22.30 (drop-weight, cor.[15]).

Degradation of Ethyl 2-Ethyl-3-methyl-3-butenoate (II).—Seven and eight-tenths grams (0.05 mole) of the ester was dissolved in a 7% solution of hydrogen peroxide (0.05 mole) in 2-methyl-2-propanol. Two milliliters of osmium tetroxide solution was added according to the procedure of Milas and Sussman.[6] After fifteen minutes the 2-methyl-2-propanol was removed under reduced pressure and the glycol treated with "ceric perchlorate."[1,7] When the "ceric perchlorate" no longer gave a red color, the solution was made alkaline with potassium hydroxide and was refluxed for four hours. Air was bubbled through the warmed reaction mixture and then into a 5% solution of 2,4-dinitrophenylhydrazine in 20% perchloric acid. The precipitate obtained was crystallized twice from ethanol, m.p. 142–144°. A mixed melting point with a known sample of 2-pentanone-2,4-dinitrophenylhydrazone (m.p. 143–144°) gave no depression.

Degradation of Ethyl 2-Ethyl-3-methyl-2-butenoate (III).—The glycol of this ester was synthesized as described above. It proved to be thermally unstable, yielding propanone and 2-ketobutanoic acid. On distillation from a Claisen flask at 15 mm. pressure, the 2-ketobutanoic acid was collected as distillate. The 2,4-dinitrophenylhydrazone of propanone was recovered by placing a trap containing a 5% solution of 2,4-dinitrophenylhydrazine in 20% perchloric acid in the vacuum line. The formation of propanal by decarboxylation of the keto acid caused some difficulty in the isolation of the propanone-2,4-dinitrophenylhydrazone.

The 2,4-dinitrophenylhydrazone of the propanone obtained by the degradation melted at 124–126°; a mixed melting point with an authentic sample of propanone-2,4-dinitrophenylhydrazone (m.p. 126°) gave no depression.

The 2,4-dinitrophenylhydrazone of the 2-ketobutanoic acid melted at 139–141°. The method described by Tschelinzeff and Schmidt[17] was used for the preparation of 2-ketobutanoic acid. Its 2,4-dinitrophenylhydrazone was prepared in perchloric acid solution and melted at 139–141°. A mixed melting point with the above degradation product gave no depression. No melting point is recorded in the literature for this derivative. *Anal.* Calcd. for $C_{10}H_{10}N_4O_6$: N, 19.86. Found: N, 19.65.

Hydrolysis of the Unsaturated Esters.—Both esters proved difficult to hydrolyze. Hydrolysis was carried out

---

(8) (a) Ref. 3, p. 93; (b) Roland and McElvain, THIS JOURNAL, **59**, 134 (1937); (c) Hudson and Hauser, *ibid.*, **62**, 2459 (1940); **63**, 3161 (1941).

(9) Kon, Smith and Thorpe, *J. Chem. Soc.*, **127**, 572 (1925).

(10) Perkin and Thorpe, *ibid.*, **69**, 1482 (1896).

(11) "Organic Syntheses," Vol. 20, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 106.

(12) *Ibid.*, Vol. 23, 1943, p. 38.

(13) Fieser and Johnson, THIS JOURNAL, **62**, 576 (1940).

(14) Harkins and Jordan, *ibid.*, **52**, 1751 (1930).

(15) (a) Harkins and Brown, *ibid.*, **41**, 499 (1919); (b) "I. C. T.," Vol. IV, 1928, p. 435.

(16) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 463.

(17) Tschelinzeff and Schmidt, *Ber.*, **62**, 2210 (1929).

by refluxing in alcoholic potassium hydroxide solution and subsequently neutralizing with hydrochloric acid.

Ethyl 2-ethyl-3-methyl-3-butenoate (II) yielded an acid, b.p. 85° at 4 mm.; $n^{20}D$ 1.4400; neutralization equivalent calcd. 128, found 130. This acid was isolated with difficulty due to the general tendency of β,γ-unsaturated acids to rearrange to the conjugated α,β-acids in the presence of base.[18] Hydrolysis of (III) yielded a white solid which, on recrystallization from water–ethanol, gave plates melting at 47–48°; b.p. 85° (2 mm.); micro b.p. 218° (741 mm.) with decomposition; neutralization equivalent calcd. 128, found 129.

---

[18] Gilman, "Organic Chemistry, An Advanced Treatise," second edition, Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 684.

Summary

Ethyl 3-hydroxy-2-ethyl-3-methylbutanoate has been dehydrated to ethyl 2-ethyl-3-methyl-2-butenoate and ethyl 2-ethyl-3-methyl-3-butenoate. These have been isolated and their physical constants determined.

The structure of these unsaturated esters has been assigned on the basis of the ketones to which they have been degraded.

These unsaturated esters have been hydrolyzed and the corresponding acids isolated.

EAST LANSING, MICHIGAN RECEIVED SEPTEMBER 12, 1947

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Some Derivatives of 2-Acylthiophenes[1]

BY E. CAMPAIGNE AND JAMES LOREN DIEDRICH[2]

Several acylthiophenes ranging in side-chain length from two to eighteen carbon atoms[3] have been prepared, usually by some modification of the procedure described by Johnson and May[4] for the preparation of 2-acetylthiophene. The capric acid derivative was prepared by Schleicher,[5] but the homologous 2-hexanoyl, 2-octanoyl, and 2-nonanoylthiophenes have not been synthesized previously.[5a]

The acylthiophenes provide convenient intermediates for the preparation of the corresponding alcohols and alkylthiophenes. The thienyl ketones were readily reduced to the corresponding secondary alcohols by using aluminum isopropoxide in isopropyl alcohol as described by Mowry, Renoll and Huber[6] for 2-acetylthiophene; however, the yields were somewhat lower with the higher molecular weight ketones. The alkylthiophenes were prepared from the ketones by a slight modification of the Clemmensen method described by Fieser and Kennelly.[7]

In addition to the ketones, alcohols and alkylthiophenes, the characteristics of which are summarized in Table I, the oximes, semicarbazones and 2,4-dinitrophenylhydrazones of the ketones, and the 5-chloromercuri derivatives of the alkylthiophenes were prepared and characterized.

An attempt was made to prepare suitable urethans or esters of the secondary alcohols as solid derivatives but the hydroxy group is relatively inactive, apparently due to hindrance of the α-carbon in 2-substituted thiophenes,[8] and no derivatives were isolated.

Experimental

Acylthiophenes.—The procedure used for the ketone preparations was essentially that of Johnson and May[4] for the preparation of acetylthiophene. The thiophene, obtained from the Socony–Vacuum Oil Company, was distilled through a column and the fraction boiling from 82–84° was collected and stored in brown bottles until used. In each acylation freshly distilled stannic chloride was employed. The best yields of the ketones were obtained under the following conditions: 0.5 mole of thiophene and 0.5 mole of the required acid chloride were dissolved in 500 ml. of benzene in a 3-necked flask equipped with a mechanical stirrer, thermometer and dropping funnel, and the mixture was cooled to 0° with stirring. Stannic chloride (0.5 mole) was then added dropwise over a period of one and one-half hours, maintaining the temperature at 0°. When all of the stannic chloride had been added, the cooling bath was removed and stirring was continued for one hour longer. Dilute hydrochloric acid was then added and the benzene layer was separated, washed and dried. The ketone was isolated and purified by distillation.

2-Alkylthiophenes.—The preparation of 2-octylthiophene is typical. A mixture of 125 g. of amalgamated zinc, 225 ml. of 1:1 hydrochloric acid and 26.2 g. (0.125 mole) of 2-octanoylthiophene was allowed to stand in a water-bath at 22° for three and one-half days. To complete the reaction the mixture was refluxed gently for twenty minutes. It was then cooled, extracted several times with ether and the combined ether extracts dried. The ether was removed and the residue distilled at reduced pressure. The yield of colorless oil, b.p. 106–108° at 1 mm., was 13.5 g. (55%).

1-(2-Thienyl)-alkanols.—The preparation of 1-(2-thienyl)-nonanol is typical. In a 125-ml. three-necked flask equipped with stirrer, distilling column and nitrogen-inlet tube was mixed 5.6 g. (0.025 mole) of 2-nonanoylthiophene and three times the calculated quantity of pure freshly distilled aluminum isopropoxide (5 g., 0.025 mole) in 30 ml. of dry isopropyl alcohol. The mixture was heated under an atmosphere of nitrogen to 100–110°, and acetone and isopropyl alcohol were allowed to distill from the mixture. When 12–13 ml. of distillate had been collected an additional 10 ml. of dry isopropyl alcohol was

---

[1] Taken from a thesis submitted by James Loren Diedrich to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Master of Arts, in the Department of Chemistry, Indiana University, June, 1947.

[2] The Ohio Oil Company Fellow in Chemistry.

[3] Ralston and Christensen, *Ind. Eng. Chem.*, **29**, 194 (1937).

[4] Johnson and May, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 8.

[5] Schleicher, *Ber.*, **19**, 660 (1886).

[5a] Since this paper was accepted, Cagniant and Deluzarche (*Compt. rend.*, **225**, 455 (1947)) report the preparation of a series of acylthiophenes, including those described here.

[6] Mowry, Renoll and Huber, THIS JOURNAL, **68**, 1105 (1946).

[7] Fieser and Kennelly, *ibid.*, **57**, 1615 (1935).

[8] Chabrier and Tchoubar, *Compt. rend.*, **220**, 284 (1945).

TABLE I

2-SUBSTITUTED THIOPHENES AND DERIVATIVES[a]

	Yield, %	B. p., °C. (1 mm.)	d^{20}_4[b]	n^{20}_D	Formula	Sulfur, % Calcd.	Sulfur, % Found	Oximes M. p., °C.	Oximes Sulfur, % Calcd.	Oximes Sulfur, % Found
2-Hexanoylthiophene[c]	78	117–119	1.065	1.5301	$C_{10}H_{14}OS$	17.59	17.73	53–54[d]	16.25	16.58
2-Octanoylthiophene[e]	78	140–143	1.005	1.5214	$C_{12}H_{18}OS$	15.24	14.88	56–57[f]	14.23	14.30
2-Nonanoylthiophene[g]	80	155–157	0.970	1.4917	$C_{13}H_{20}OS$	14.29	13.85	(Oil)[h]		
1-(2-thienyl)-hexanol	60	110–112	1.055	1.5155	$C_{10}H_{16}OS$	17.40	17.48			
1-(2-thienyl)-octanol	41	133–135	0.973	1.5203	$C_{12}H_{20}OS$	15.10	15.37		5-Chloromercuri- Mercury, %	
1-(2-thienyl)-nonanol	47	149–152	.938	1.4902	$C_{13}H_{22}OS$	13.45	13.71		Calcd.	Found
2-Hexylthiophene	44	79–82	.946	1.4970	$C_{10}H_{16}S$	19.05	19.02	140–141[i]	49.8	49.3
2-Octylthiophene[j]	55	106–108	.920	1.4824	$C_{12}H_{20}S$	16.33	15.94	136–137[i]	46.5	46.3
2-Nonylthiophene	38	128–131	.906	1.4763	$C_{13}H_{22}S$	15.24	15.11	135–136[i]	45.0	44.6

[a] All boiling and melting points uncorrected. [b] All density measurements made with a Fisher–Davidson Gravitometer. [c] Semicarbazone, m. p. 133–134°; % S, calcd.,13.40; found, 13.59. 2,4-DNP (2,4-dinitrophenylhydrazone), m. p. 152–153°; % S, calcd., 8.85; found, 9.10. [d] Yield, 83% on 0.1 mole run. [e] Semicarbazone, m. p. 127–129°; % S, calcd., 11.99; found, 12.27. 2,4-DNP, m. p. 123–125; % S, calcd., 8.21; found, 8.40. [f] Mixed m. p. with 2-hexanoylthiophene oxime, 48–51°. [g] Semicarbazone, m. p. 134–135 (mixed m. p. with 2-hexanoylthiophene semicarbazone, 103–109°). % S, calcd., 11.40; found, 11.50. 2,4-DNP, m. p. 108–109°. % S, calcd., 7.93; found, 7.73. [h] An intractable oil, not isolated. [i] Mixture of all possible pairs of these three derivatives melted about 40° lower and over a 20° range, *i. e.*, about 95–120°. [j] Prepared by Schweinitz (*Ber.*, 19, 644 (1886)) by a Wurtz–Fittig reaction, b. p. 257–259°.

added to the reaction mixture and distillation continued until 25 ml. of distillate had been collected. The residue was decomposed with dilute acid, extracted with ether and the ether extracts washed and dried over potassium carbonate. Distillation of the ether-free residue yielded 2.8 g. (47%) of 1-(2-thienyl)-nonanol, b.p. 150–156° at 2 mm.

Acknowledgment.—We are deeply indebted to the Ohio Oil Company for the financial support of this research.

Summary

A number of thiophenes having alkyl, 1-alkanol and acyl groups substituted in the 2-position have been synthesized and characterized. Some solid derivatives of these compounds have also been made.

BLOOMINGTON, INDIANA RECEIVED AUGUST 15, 1947

[CONTRIBUTION FROM THE DIVISION OF FUEL TECHNOLOGY, THE PENNSYLVANIA STATE COLLEGE]

The Distribution of Nitrogen in the Oxidation Products of Coals and Selected Nitrogen Compounds[1]

BY C. R. KINNEY, J. W. ECKERD, PAULINE REXFORD AND H. B. CHARMBURY

The chemical nature of the nitrogen occurring in coals is little understood, although it is agreed that its source is the proteins of the plants, animals, and microörganisms that inhabited the coal-swamps. In a peat, as much as 78.5% of the nitrogen can be extracted by dilute acid[2] but the percentage of the nitrogen extracted from coals rapidly falls with increasing rank; lignite, 21.8%; bituminous coal, 5.4%; anthracite, 2.6%. The nitrogen compounds which are extracted are largely amino acids among which present-day acids have been identified. The decrease in extractability of nitrogen compounds from the higher rank fuels indicates that the proteins or the amino acids present in the original starting material have undergone condensation reactions, possibly of the type suggested by Maillard.[3]

A knowledge of the chemical nature of the nitrogen in coal might be of particular value in the coking industry because of the possibility of making changes in the yields of nitrogen products and it might also be of importance in the hydrogenation of coal because of the amines which may be obtained. When coal is coked, 50% or more of the nitrogen remains in the coke,[4,5] about 15–20% is evolved as ammonia and 25–30% as free nitrogen. The formation of a variety of nitrogen-containing products strongly suggests that more than one nitrogen structure occurs in coal.

On the hydrogenolysis of coal[6] a considerable part of the nitrogen is evolved as ammonia. At moderate temperatures, less than 500°, the maxi-

---

[1] Presented before the Division of Gas and Fuels, Atlantic City Meeting of the American Chemical Society, April 17, 1947.

[2] Shacklock and Drakely, *J. Soc. Chem. Ind.*, **46**, 478–81T (1927).

[3] Maillard, *Ann. chim.*, **7**, 113–152 (1917); for a discussion of this work see "Chemistry of Coal Utilization," H. H. Lowry, Editor, John Wiley and Sons, Inc., New York, N. Y., 1945, chapter 13, W. R. Kirner, page 452.

[4] In the older literature low nitrogen analyses of cokes were reported because the ordinary Kjeldahl procedure failed to obtain all of the nitrogen from cokes and to obtain a material balance the difference was often ascribed to a larger yield of gaseous nitrogen.

[5] Lowry, Landan and Naugle, *Trans. A. I. M. E.*, **149**, 297–330 (1942), have published average percentages of nitrogen distributed among the carbonization products of a number of coals. Using these data it can be calculated that the average per cent. of the nitrogen remaining in 1000°-coke is 56.6%.

[6] Storch, Hirst, Fisher and Sprunk, *U. S. Bur. Mines Tech. Paper* **622**, 53, Table 24 (1941).

TABLE I

PERCENTAGE DISTRIBUTION OF NITROGEN IN THE OXIDATION PRODUCTS OF COAL[a]

Coals	N in coal, Kjeldahl	Total N, oxid.	Difference in Kjeldahl and oxidation N	N from coal as NH_3	N from coal as NO_3^-	Proportion of N	
						as NH_3	as NO_3^-
Lignite, Velva, No. Dakota	0.85	0.74	−0.11	0.46	0.28	61.6	38.4
Sub-bituminous, Monarch, Wyoming	1.51	1.31	.20	.80	.51	61.3	38.7
Bituminous, high-volatile A							
Upper Freeport, Pennsylvania	1.38	1.34	.04	.88	.46	65.9	34.1
Pittsburgh, Pennsylvania	1.66	1.35	.31	.88	.47	65.2	34.8
No. 2, Washington,	2.11	1.92	.19	1.34	.58	69.9	30.1
Medium-volatile Sewell, West Virginia,	1.68	1.32	.36	0.86	.46	65.4	34.6
Low-volatile Pocahontas No. 3, West Virginia	1.24	1.04	.20	.66	.38	63.7	36.3
Anthracite, high-volatile, Williamstown, Pa.	0.95	1.02	+ .07	.67	.35	65.3	34.7
Low-volatile, Highland, Pa.	.82	0.77	− .05	.42	.35	54.8	45.2
Coke, metallurgical, from							
Pittsburgh Bed Coal above	1.12	.36	.76	.13	.23	36.1	63.9
Breeze from same	0.77	.58	.22	.34	.24	58.7	41.3

[a] As received basis. All samples were minus 60 mesh. Metallurgical coke 95% minus 150 mesh; coke breeze 90% minus 100 mesh.

mum amount of ammonia appears to be about 30–35%. The remainder of the nitrogen is converted to nitrogen containing oils, which are probably amines. This also suggests that coals contain more than one kind of nitrogen structure. On the other hand Fisher and Eisner[7] have shown that the rate of removal of nitrogen during hydrogenolysis of coal is constant although quite slow, at least over the temperature range of 385–415° and up to twelve hours time. This may be due to the presence of only one form of nitrogen in coal but it seems more reasonable to assume that the constant rate of nitrogen removal is dependent upon another reaction which is relatively slow.

In view of these differences in the behavior of nitrogen in coals, an investigation of the distribution of the nitrogen in the products of the oxidation of coals and of a variety of pure organic compounds has been made. As the oxidizing reagent for this purpose, alkaline permanganate was selected.

Experimental

Oxidation Procedure.—Oxidations were carried out in iron kettles of 3 liters capacity, equipped with condensers of one meter length and with an opening for admitting air. Samples of 3 g. were used with 60 g. of potassium permanganate and 50 g. of potassium hydroxide dissolved in a liter of water. The mixture was refluxed and any ammonia that was formed was carried out by a slow stream of air entering the kettle, passing out through the condenser and into a beaker containing standard acid. A plug of glass wool was inserted in the top of the condenser to prevent any spray from being carried into the acid. The oxidation was continued until only traces of ammonia (less than 0.01% nitrogen) were obtained in an eight hour period of refluxing. The residue was then tested quantitatively for nitrate ion.

The Determination of Ammonia.—The ammonia formed during the oxidation was trapped in 400-ml. tall-form beakers containing 25 ml. of 0.1 *N* sulfuric acid diluted to 200 ml. With most of the samples used several days of refluxing were required to complete the liberation of ammonia and in these cases a fresh lot of acid was used daily. The amount of ammonia was determined by back titration with 0.1 *N* base using methyl red indicator. When the ammonia titration fell below 0.01% nitrogen in the sample on two successive days, the liberation of ammonia was considered to be complete.

Since ammonia might be oxidized by alkaline permanganate, test runs were made with samples of ammonium chloride. The per cent. nitrogen obtained was 26.22 and 26.32% which compared with the theory of 26.17% shows that ammonia is not readily oxidized by alkaline permanganate.

The Determination of Nitrate Nitrogen.—After the ammonia had been completely removed, the excess permanganate was destroyed with formic acid. The manganese dioxide was filtered out and washed thoroughly. The filtrate and washings were returned to the kettle together with 50 g. of potassium hydroxide and 20 g. of Devarda alloy. The condenser and air inlet were arranged as before to collect the ammonia formed by the reduction of the nitrate ion. When all of the alloy had reacted, the ammonia was distilled out and titrated in the usual manner.

The results of these determinations, calculated as per cent. of nitrogen in the sample, are arranged in Tables I and II.

Discussion

Table I gives the data obtained from the various coals and cokes oxidized. The total quantity of nitrogen recovered during the oxidation approached that obtained by the Kjeldahl procedure. The difference between the two results varied between −0.36 and ±0.07% nitrogen in the sample. Similar differences between the theory and the total recovered nitrogen from the pure compounds (Table II) were observed and it seems likely that certain nitrogen structures are not quantitatively partitioned into ammonia and nitrate. Possibly, in these cases, a part of the nitrogen is converted into free nitrogen since it escapes detection.

Also in Table I are compared the percentages of nitrogen converted to ammonia and nitrate ion and the relative percentages of ammonia and nitrate based on the total of these products. It will be observed that about two-thirds of the nitrogen is liberated as ammonia from the coal samples,

---

(7) Fisher and Eisner, *Ind. Eng. Chem.*, **29**, 1371 (1937).

Table II

Percentage Distribution of Nitrogen in the Oxidation Products of Certain Organic Substances

Substance	Oxid. hours	Total N	N as NH_3	N as NO_3^-	Proportion of N as NH_3	as NO_3^-
Glycine[a]	75	99.8	99.8	..	100.0	0.0
Nicotinic acid[a]	76	95.8	95.8[b]	..	95.8	..
p-Aminobenzoic acid[a]	43	72.0	54.7	17.3	76.0	24.0
p-Benzalaminophenol	75	98.0	71.7	26.3	73.2	26.8
β-Naphthylamine	107	87.7	56.3	31.4	64.2	35.8
Diethanolamine	63	85.4	52.7	32.7	61.7	38.3
Carbazole	255	87.4	50.6	36.8	57.9	42.1
Diphenylamine	120	81.0	42.9	38.1	53.0	47.0
Edestin	107	96.7	57.9	38.8	59.8	40.2
Gluten (wheat)	117	91.0	50.8	40.2	55.8	44.2
Benzalaniline	79	94.9	39.7	55.2	41.8	58.2
p-Nitrobenzoic acid[a]	28	93.1	3.3	89.8	3.5	96.5

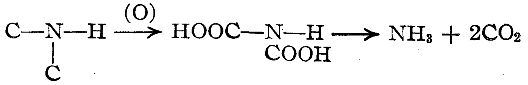
[a] Glass apparatus used. [b] Flask destroyed by the alkali at this point.

with the exception of the low-volatile anthracite, and about one-third as nitrate. With the low-volatile anthracite and the coke samples, a larger yield of nitrate was obtained and less ammonia.

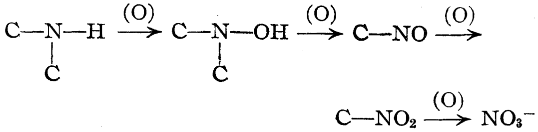
These results most closely approximate the yields of ammonia and nitrate ion obtained from β-naphthylamine (Table II). The secondary amine structure in diethanolamine, carbazole and diphenylamine also appears to be a possibility, particularly if other structures are present to offset the somewhat low yield of ammonia. The imino grouping in *p*-benzalaminophenol and benzalaniline gave more widely separated results, but apparently this structure is also a possibility depending upon the character of other groups in combination with it.

The results obtained with the plant proteins, edestin and wheat gluten, suggest that, while proteins are not present in coal, the basic nitrogen structures in the proteins have not been greatly altered by the process of coalification. Because of the almost quantitative yields of ammonia from glycine and nicotinic acid, structures such as these would be expected to be present in coal in relatively small quantities. For the same reason the nitro group which is oxidized in high yield to nitrate would not be expected in coal.

The mechanism of the oxidation of nitrogen-containing carbon compounds with the liberation of nitrogen as ammonia seems most likely to be the result of reaction (1) while the oxidation of nitrogen to nitrate ion may be accounted for by reaction (2).

(1)


$$\underset{\textstyle C}{C{-}\underset{|}{N}{-}H} \xrightarrow{(O)} HOOC{-}\underset{COOH}{N}{-}H \longrightarrow NH_3 + 2CO_2$$

(2)


$$\underset{\textstyle C}{C{-}\underset{|}{N}{-}H} \xrightarrow{(O)} \underset{\textstyle C}{C{-}\underset{|}{N}{-}OH} \xrightarrow{(O)} C{-}NO \xrightarrow{(O)} C{-}NO_2 \xrightarrow{(O)} NO_3^-$$

From the results in Table II it would appear that the two reactions are competitive, but that in those compounds in which a higher oxidation potential is required to oxidize the carbon radical a greater proportion of the nitrogen is oxidized to nitrate.[8]

While alkaline permanganate does not differentiate sharply between all of the various nitrogen structures, the surprising constancy of the quantities of ammonia and nitrate obtained from the various ranks of coal, considering the wide variations in yields from pure compounds, indicate that coals of different rank and from different localities contain the same kind of nitrogen linkages, that these similar nitrogen structures were produced in all coals by means of similar chemical reactions acting on similar proteins which were present in the peats from which the coals were made and that on oxidation these structures gave about the same yields of ammonia and nitrate ion. These condensed structures, formed during coalification, may possibly be aromatic amino or imino derivatives related to those in Table II, although an essentially carbon structure in which the carbon atoms are interspersed with nitrogen atoms appears likely for the cokes and possibly to a limited extent in anthracites and the fusain and opaque attritus of the lower rank coals as well. Such a structure would be, so far as the nitrogen is concerned, that of a tertiary amine. This conclusion is suggested by the higher yield of nitrate ion obtained from cokes and low volatile anthracite.

Summary

The oxidation of coals with alkaline permanganate liberates the nitrogen in two forms, ammonia and nitrate ion. A comparison of the relative amounts with similar data obtained from pure nitrogen compounds has been made.

State College, Pennsylvania

Received August 1, 1947

---

[8] In this connection, a less vigorous oxidizing reagent than alkaline permanganate might better differentiate between certain nitrogen structures.

[CONTRIBUTION FROM THE CENTRAL EXPERIMENT STATION, U. S. BUREAU OF MINES]

Pyrolysis of Methane Flowing Through a Porcelain Tube in the Region 1000°[1]

BY ALVIN S. GORDON[2]

The reaction between methane and steam at temperatures between 1000 and 1100° has been investigated,[3] using a porcelain reaction vessel in a flowing system. It was found that steam does not attack methane directly, but rather the carbon or highly carbonaceous material which results from the decomposition of methane. It seemed worth while to investigate the decomposition of methane at the same temperature and pressure conditions and in the absence of steam. Kassel[4] made an exhaustive study of methane decomposition in the range between 700 and 800° and sub-atmospheric pressure, using a static system of quartz. He also used a sillimanite vessel and did not report appreciable difference in decomposition rate. Kassel found that the first portion of the reaction was first order and homogeneous, with hydrogen depressing the rate. There was an induction period of indeterminate origin. Wheeler and Wood[5] used a static system and found that quartz chips gave an initial decomposition-rate increase at 700° and sub-atmospheric pressure. In a flowing system, increase in quartz surface had no effect. The same authors reported in another paper[6] that, in a flowing system up to 1050°, no appreciable difference in rate of decomposition was observed with quartz and porcelain tubes. Holliday and Excell[7] found that hydrogen was somewhat soluble in quartz, the solubility increasing with temperature. They also reported that hydrogen slowed the velocity of decomposition of methane.

Apparatus, Materials and Procedure

The essential parts of the apparatus have previously been described[8]: a platinum-rhodium furnace 24″ long surrounded a McDaniel porcelain combustion tube, 1″ o. d. × 3/4″ i. d. × 30″ long, the porcelain tubing extending beyond the furnace about 3 inches at each end. A 2-mm. Pyrex capillary was sealed to the small-diameter end and a 29/42 Pyrex ground-glass joint to the other. Two closely fitting porcelain tubes, faced with porcelain discs at the ends, were inserted into the combustion tube; the space between these inserts determined the volume of the reaction cell. The temperature was measured by two platinum–platinum-rhodium thermocouples, one cemented at each end of the reaction cell to the outer porcelain surface.

Purification of methane from a cylinder involved removal of ethane and higher hydrocarbons by passage through an activated charcoal trap at Dry-Ice temperature and of hydrogen, through a cupric oxide tube at about 300°. This gas was dried and passed through a flowmeter into the furnace. From the furnace the gases were led into a collection bottle filled with nearly saturated sodium chloride solution, constructed so that the gases discharged at atmospheric pressure. The rate of displacement of the salt solution was measured to determine the exit velocity of the gases.

During the investigation it was noted that the products of decomposition which covered the surface slowed down the reaction; after run 257 these products were burned off with oxygen after every few experiments. The rate was reproducible within 5–10% by this method; *e. g.*, runs 318 and 319 are reproduced to about 8%.

The gas analyses for each experiment were made by a mass spectrometer (under the supervision of Dr. R. A. Friedel). Most of the analyses were done in duplicate; percentages of hydrocarbons present in tenths of a per cent. could be reproduced within ten per cent., whereas methane could be reproduced within one-tenth per cent. Nitrogen reproducibility was quite erratic. These analyses were used to determine the methane percentage decomposed on an original volume basis. To obtain this value, hydrocarbon products with a molecular weight higher than benzene were calculated as carbon. Since naphthalene, anthracene, phenanthrene and pyrene were identified by their ultraviolet spectra, this assumption introduced an error. Benzene was present in very small percentage, so that these products, presumably formed from benzene, will probably be present in small percentage. From the percentages of hydrocarbons in the exit gas, the percentage of methane decomposed on an original volume basis was calculated.

Benton's[9] equation for reaction in a flowing system with change in volume was used in treating these data. It is assumed, in deriving this equation, that the diffusion was small compared to the linear velocity. For small percentage of decomposition, even a large diffusion effect will not give a large error in using the above equation.

The rate of decomposition was assumed to be first order, and the specific rate constant was calculated from the equation

$$k = \frac{V_o}{V_b}\left(g \ln \frac{1}{1 - F} - (g - 1)\, F\right)$$

---

[1] Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior.

[2] Physical Chemist, Bureau of Mines, Central Experiment Station, Pittsburgh, Pennsylvania.

[3] A. S. Gordon, unpublished results.

[4] Kassel, THIS JOURNAL, **54**, 3949 (1932).

[5] Wheeler and Wood, *Fuel*, **9**, 567 (1930).

[6] Wheeler and Wood, *ibid.*, **7**, 535 (1928).

[7] Holliday and Excell, *J. Chem. Soc.*, 1066 (1929).

[8] Gordon, *Ind. Eng. Chem.*, **38**, 718 (1946).

[9] Benton, THIS JOURNAL, **53**, 2984 (1931).

TABLE I

KINETIC DATA AT 1007° THROUGH 1075° OF METHANE DECOMPOSITION IN A PORCELAIN TUBE

Pressure = 1 atm., $S:V$ = 2.47

Run	Methane decom- posed, %	$\bar{t}$,[a] sec.	T, °C.	"k"[b]	Products of methane decomposition, per cent. exit volume C_2H_4	C_2H_2	C_2H_6	C_3H_6	$CH_3—C\equiv CH$	H_2	C_6H_6
191	1.27	0.288	1007	0.044	0.11	0.04	0.09	0.02	0.02	1.91	0.00
190	1.54	.364	1007	.043	.13	.05	.09	.02	.02	2.36	.00
189	2.40	.533	1007	.046	.22	.09	.09	.03	.04	3.74	.00
188	3.69	.724	1007	.052	.34	.16	.11	.05	.06	5.69	.01
187	7.36	1.130	1007	.068	.65	.36	.12	.06	.07	11.41	.03
186	8.70	1.329	1007	.069	.80	.40	.11	.07	.07	13.51	.02
185	9.82	1.454	1007	.071	.91	.41	.09	.06	.07	15.28	.01
180	10.54	1.499	1007	.074	.87	.39	.10	.07	.05	16.56	.01
193	1.27	0.219	1033	.058	.13	.05	.09	.02	.03	1.87	.00
194	1.74	.299	1033	.059	.18	.07	.10	.02	.04	2.59	.00
195	2.39	.347	1033	.069	.26	.12	.12	.04	.05	3.50	.00
196	3.10	.402	1033	.078	.37	.18	.11	.04	.07	4.53	.00
197	6.28	.632	1033	.103	.72	.37	.12	.07	.09	9.44	.00
198	7.42	.671	1033	.115	.81	.45	.11	.07	.11	11.10	.02
200	10.88	.893	1033	.107	1.08	.62	.10	.08	.10	16.35	.04
211	14.39	1.293	1033	.120	1.27	.65	.10	.08	.08	21.53	.08
212	16.91	1.516	1033	.122	1.36	.68	.11	.09	.06	25.32	.04
215	2.29	0.184	1053	.125	0.31	.08	.12	.03	.07	3.15	.02
216	2.37	.202	1053	.118	.32	.09	.13	.03	.06	3.28	.01
218	2.74	.232	1053	.119	.37	.14	.12	.04	.06	3.85	.01
219	3.72	.255	1053	.129	.49	.22	.13	.05	.12	5.22	.02
221	4.30	.334	1053	.131	.55	.27	.13	.06	.12	6.07	.03
222	5.68	.399	1053	.146	.69	.37	.12	.07	.12	8.25	.03
256	6.61	.431	1053	.158	.75	.34	.14	.05	.11	9.89	.03
255	8.22	.495	1053	.173	.88	.42	.13	.06	.11	12.32	.05
223	9.66	.571	1053	.177	.98	.65	.14	.08	.14	14.25	.07
224	3.96	.162	1075	.250	.49	.25	.15	.03	.11	5.67	.02
225	4.15	.166	1075	.254	.51	.26	.14	.02	.11	6.02	.02
226	4.80	.190	1075	.259	.60	.30	.12	.05	.12	7.00	.02

[a] $\bar{t}$ = average time of contact of methane in reaction cell. [b] "k" = first-order constant (sec.$^{-1}$).

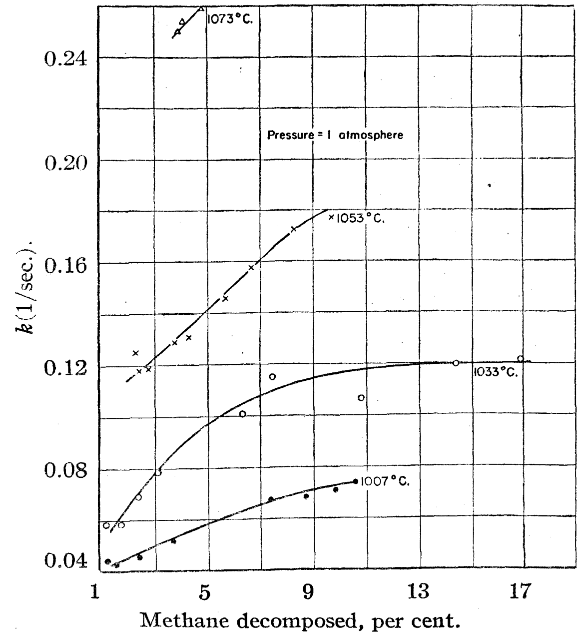


Fig. 1.—First-order constants against percentage of methane decomposed at various temperatures.

where

k = first-order specific rate constant (1/second)
V_0 = velocity (cc./second) of the gases entering the reaction cell
V_b = volume of the reaction cell (cc.)
$g = \dfrac{\text{gaseous moles formed from methane decomposed}}{\text{moles methane decomposed}}$
F = fraction of methane decomposed

Results and Discussion

Effect of Product Gases on the Pyrolysis

Referring to the data in Table I, which have been plotted in Fig. 1, it may be seen that the first-order constant always tended to increase with increasing decomposition of methane at each of the temperatures studied. It may be shown[9a] that increase of first-order constants with time indicates a less-than-first-order reaction or an autocatalytic reaction. To test the latter hypothesis, small percentages of the product gases were added to the methane entering the reaction vessel. When 0.72%

(9a) If k_T is the true constant and k_1 is the first-order constant

$$-\frac{d(CH_4)}{dt} = k_1(CH_4) = k_T(CH_4)^T$$

$$k_T = k_1\ (CH_4)^{1-T}$$

since k_1 increases with time, T must be less than 1 so that $(CH_4)^{1-T}$ will decrease correspondingly with time in order to keep k_T constant.

TABLE II

EFFECT OF SMALL PERCENTAGES OF PRODUCT GASES ON THE DECOMPOSITION OF METHANE AT 1007°

Pressure = 1 atm., *S*:*V* ratio = 2.47.

Run	Methane decomposed, %	$\bar{t}$,[a] sec.	"*k*"[b]	Product gases, per cent. exit volume						
				C_2H_4	C_2H_2	C_2H_6	C_3H_6	$CH_3—C{\equiv}CH$	H_2	C_6H_6
0.72% of Acetylene										
265	3.11	0.281	0.115	0.52	0.24	0.12	0.06	0.10	4.67	0.02
266	3.45	.281	.124	.52	.25	.12	.06	.12	5.20	.04
267	5.50	.476	.122	.74	.30	.12	.07	.10	8.47	.07
268	5.82	.482	.129	.80	.34	.12	.08	.11	8.95	.05
269	8.37	.707	.131	1.01	.41	.12	.08	.10	12.95	.09
270	8.42	.723	.130	1.03	.42	.13	.08	.09	12.99	.09
301	2.49	.160	.159	0.40	.29	.13	.03	.10	3.82	.01
1.00% of Ethylene										
303	3.41	0.290	0.121	0.86	0.28	0.14	0.08	0.12	5.88	0.02
309	3.25	.291	.116	.85	.31	.12	.08	.11	5.99	.03
304	4.95	.434	.119	.98	.37	.13	.09	.12	8.40	.02
306	6.64	.547	.128	1.06	.44	.12	.09	.09	11.17	.04
307	6.72	.556	.127	0.99	.44	.13	.08	.10	11.54	.05
2.08% of Hydrogen										
314	1.64	0.275	0.063	0.33	0.10	0.11	0.04	0.06	4.54	0.00
315	3.09	.467	.070	.49	.18	.11	.06	.08	6.87	.02
316	5.24	.731	.740	.68	.28	.08	.05	.09	10.45	.03
Decomposition of Pure Methane at 1007°										
318	1.39	0.279	0.050	0.08	0.02	0.10	0.02	0.03	2.15	0.00
319	1.51	.279	.054	.12	.02	.07	.01	.01	2.49	.00
320	2.57	.473	.055	.23	.06	.08	.02	.04	4.17	.00
321	4.41	.738	.061	.40	.14	.10	.05	.07	6.95	.03

[a] $\bar{t}$ = average time of contact of methane in the reaction cell. [b] "*k*" = first-order constant (sec.$^{-1}$).

of acetylene was in the entering gas, as the results in Table II show, 2 to 2.5 times as much methane decomposed in the same time as when no acetylene was present, even after as much as 8.5% of methane had been decomposed. With the smallest contact time (0.16 second) only 0.29% of acetylene appears in the exit gas when 0.72% of acetylene was in the in-gas, and the temperature was 1007°. After a short time in the reaction cell, even though the percentage of acetylene was quite small, it had a large catalytic effect on the decomposition rate of methane. Because the percentage of ethylene in the exit gas in the study with acetylene in the in-gas was increased somewhat over the percentage observed for pure methane, the decomposition was studied with about 1% of ethylene in the in-gas. As may be seen in Table II, the ethylene in the exit gas was never less than 0.85%. For about the same contact time, the percentages of methane decomposed were in the same range, whether acetylene or ethylene was added to the in-gas. If the shorter of the comparable contact times was examined, it was seen that, with acetylene in the in-gas (average of runs 265 and 266), 0.52% of ethylene and 0.25% of acetylene appeared in the exit gas; when the contact time was 0.281 second, 3.28% of methane was decomposed. On the other hand, with ethylene in the in-gas (average of runs 303 and 309), 0.86% of ethylene and 0.30% of acetylene were in the exit gas when the contact time was 0.291 second; 3.33% of methane was decomposed in these experiments. These data showed that increasing the percentage of ethylene has little, if any, effect on the rate of decomposition. For longer contact times, comparisons between ethylene and acetylene in the in-gas were not possible because the percentages of ethylene and acetylene in the exit gas were so nearly the same.

It may be noted that the percentage of acetylene in the exit gas increased with increasing percentage of methane decomposed; since acetylene was a catalyst for the decomposition of methane, the reaction was autocatalytic.

It was of some interest to examine the possible reactions of acetylene as a catalyst in this reaction. If the primary products of methane pyrolysis were methyl radicals and hydrogen atoms, these atoms of hydrogen probably formed hydrogen molecules by reaction with methane molecules before any appreciable reverse reaction with methyl radicals occurred. On the other hand, the primary products may have been methylene radicals and hydrogen molecules, as suggested by Kassel,[4] so that the reverse reaction would be with hydrogen molecules. For both mechanisms, the concentration of hydrogen molecules would determine the reverse-reaction velocity. In the early stages of the reaction, acetylene could react with hydrogen, preventing the reverse reaction to reform methane, and a percentage of methane equal to the acetylene percentage could be decomposed, which is not enough to account for the large observed effect. If acetylene should react with the free radicals, not enough methane would be decomposed to account for the large observed effect. It was thought possible that acetylene attacked methane directly, yielding ethylene and a methylene radical. The methylene reacted with methane to form ethane, which decomposed to ethylene and then acetylene, setting up a chain reaction. Another possibility was that only one hydrogen atom was removed from the methane by acetylene, forming a C_2H_3 and CH_3 radical, the C_2H_3 reacting with another methane molecule to form ethylene and a second CH_3 radical. The above mechanism required the percentage of ethylene to be increased over the normal percentage in the exit gas. This increase of ethylene percentage was noted.

Kassel[4] studied the effect of the addition of hydrogen on the velocity of decomposition at 760° in a static system and found that 10% or more of hydrogen greatly retarded the reaction. The effect of hydrogen was studied in the present investigation at 1007° by adding 2.01% hydrogen to the reactant gas. As seen in Table II, there was a 20 to 30% increase in reaction rate over that of the untreated gas when between 1.64 to 3.09% of methane was decomposed. More ethylene and acetylene appeared in the exit gas for the same percentage of methane decomposed in these experiments than when there was no hydrogen in the reactant gas. Thus there was a greater catalysis of the decomposition.

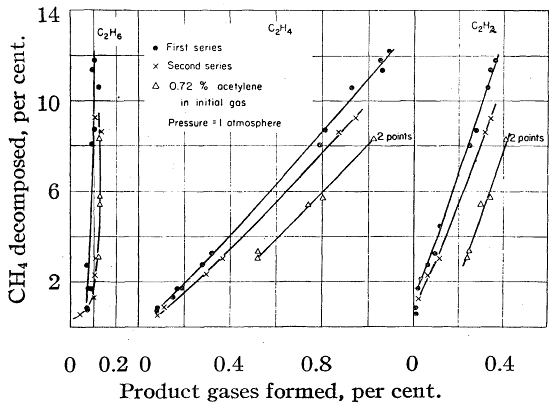


Fig. 2.—Gases formed from methane decomposed at 1007°.

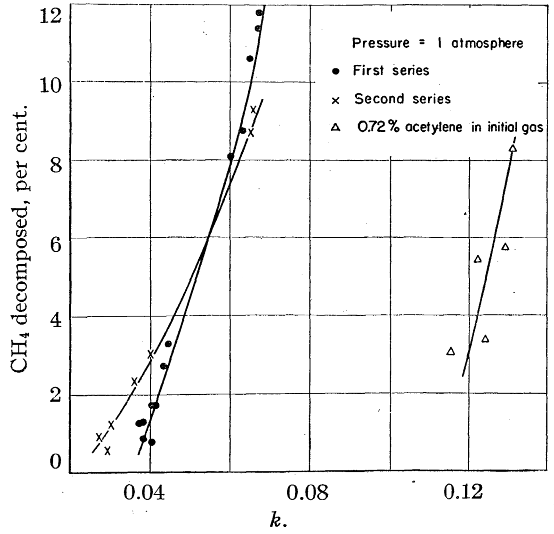


Fig. 3.—The first-order constants at various percentages of methane decomposed at 1007°.

It was hard to account for the difference in the effect of hydrogen in Kassel's paper and the present work, because the experimental conditions were different. The increase in acetylene catalysis when hydrogen was in the entering gas could more than compensate for a hydrogen retardation effect.

Effect of Surface on the Pyrolysis

If a series of runs with successively greater decomposition of methane at 1007° was followed, without any cleansing of the reaction vessel, by a similar series of successively greater decomposition, the first-order constants were smaller in the second series for the same percentage of methane decomposed. At the same time, the percentages of ethylene and acetylene were greater in the second series. These data are plotted in Figs. 2 and 3. Since the catalytic effect of acetylene was greater in the second series, the higher reaction constants must be viewed as the larger effect of surface, the surface being partly poisoned in the second series by decomposition products. Results obtained when the porcelain tube was cleansed with oxygen, *e. g.*, runs 318–321, Table II, show that the velocity of methane decomposition was greatest in this case. To compare the effect of surface and product gases at an equally active surface, the surface was cleansed with oxygen after every few runs.

The effect of increased surface : volume ratio was studied by inserting three porcelain tubes $^3/_8$-inch o. d. by 2 inches length by $^1/_{32}$-inch wall thickness (to get a large surface increase with small volume decrease) into the reaction cell. The results of experiments at 1007 and 1033° are reported in Table III. Results of experiments without any additional surface are included for comparison. It was seen that, at comparable times of contact, between two and three times as much methane was decomposed in the same time when the extra surface was present as in the normal decomposition of methane. From the results in Table III, it was seen that the concentration of ethylene or acetylene or both (since the concentration of one always influences the other) was relatively increased by increases $S : V$ ratio at very low concentrations of these gases, and relatively decreased with increased $S : V$ ratio when a small concentration of ethylene and acetylene had been built up. Thus the surface catalyzes the decomposition of ethylene and acetylene.

The effect of surface was not quantitative be-

TABLE III

EFFECT OF SURFACE:VOLUME RATIO ON THE DECOMPOSITION OF METHANE

Pressure = 1 atm.

Run	Methane decomposed, %	$\bar{t}$,[a] sec.	$S:V$,[b] cm.$^{-1}$	T, °C.	Product gases, per cent. exit volume						
					C_2H_4	C_2H_2	C_2H_6	C_3H_6	$CH_3—C\equiv CH$	H_2	C_6H_6
277	3.62	0.235	9.52	1007	0.22	0.03	0.10	0.02	0.01	6.15	0.00
278	3.62	.236	9.52	1007	.23	.03	.08	.03	.01	6.19	.00
279	3.78	.273	9.52	1007	.29	.04	.11	.04	.02	6.24	.00
280	3.85	.276	9.52	1007	.30	.03	.08	.04	.02	6.44	.00
281	5.97	.462	9.52	1007	.40	.06	.05	.07	.02	10.09	.00
282	6.02	.480	9.52	1007	.36	.06	.08	.04	.02	10.22	.00
283	8.07	.693	9.52	1007	.39	.08	.07	.04	.02	13.79	.00
284	8.14	.694	9.52	1007	.41	.07	.05	.04	.03	13.93	.00
318	1.39	.279	2.47	1007	.08	.02	.10	.02	.03	2.15	.00
319	1.51	.279	2.47	1007	.12	.02	.07	.01	.01	2.49	.00
320	2.57	.473	2.47	1007	.23	.06	.08	.02	.04	4.17	.00
321	4.41	.738	2.47	1007	.40	.14	.10	.05	.07	6.95	.03
358	4.32	.208	9.52	1033	.42	.09	.12	.05	.05	6.76	.01
359	4.39	.209	9.52	1033	.43	.08	.10	.05	.04	7.01	.00
344	3.10	.154	9.52	1033	.36	.07	.12	.04	.04	4.73	.01
322	1.42	.210	2.47	1033	.15	.03	.07	.02	.02	2.17	.02
323	1.52	.211	2.47	1033	.15	.03	.08	.02	.02	2.37	.00
324	3.27	.383	2.47	1033	.37	.13	.11	.05	.08	4.89	.02
325	3.99	.438	2.47	1033	.51	.16	.10	.06	.10	5.81	.02
0.72% of Acetylene in the Reactant Gas											
285	4.81	0.268	9.52	1007	0.51	0.22	0.10	0.06	0.08	8.20	0.01
286	5.06	.266	9.52	1007	.50	.21	.10	.05	.08	8.44	.02
287	8.58	.495	9.52	1007	.61	.20	.07	.05	.05	14.53	.03
288	8.66	.486	9.52	1007	.60	.20	.07	.06	.05	14.73	.02
289	11.37	.722	9.52	1007	.64	.21	.07	.05	.03	19.21	.02

[a] $\bar{t}$ = average time of contact of methane in reaction cell. [b] $S:V$ = surface:volume ratio in reaction cell.

cause, in the effort to make the porcelain wall thickness as small as possible to get a large increase in area with a small increase in volume, a much more porous structure results than is present in the porcelain of the reaction cell. Thus these reported values err on the high side for the effect of macro-measured surface.

The effect of surface probably was quite high, and there was therefore a large but indeterminate effect of the large $S:V$ ratio (67.5) in the annular entrance and exit spaces, since the temperature varies; the effects compared at constant contact time are not affected by this correction.

The results of increased $S:V$ ratio on the rate of decomposition of methane containing 0.72% of acetylene, keeping contact time as near constant as possible, may be compared in Tables II and III. They show that the larger $S:V$ ratio increases the decomposition velocity, the effect decreasing with increasing contact time. The acetylene content of the exit gases built up faster with time for the smaller $S:V$ ratio; its effect counterbalanced the $S:V$ ratio effect, and the difference in per cent. of methane decomposed between the larger and smaller $S:V$ ratios became smaller.

At the shortest contact time studied, the acetylene in the exit gas was about the same for the two different $S:V$ ratios. Since the acetylene in the in-gas was also the same, it seemed reasonable to assume that the acetylene contents were not too different at any point in the reaction vessel. The effect of acetylene alone, $S:V$ ratio alone, and the two acting simultaneously was obtained by subtracting the normal methane decomposed at the same contact time from the value of methane decomposed when one or both of the above effects were present in addition. Using the average values of the duplicate experiments reported in Tables II and III, the following resulted:

Methane Decomposed, Per cent.

Acetylene + $S:V$	Acetylene	$S:V$
4.94	3.28	3.82

subtracting the average of the normal methane decomposition (1.45) from each of these values

3.49	1.83	2.37

Adding the effect of acetylene and $S:V$ and comparing with acetylene plus $S:V$, it was seen that the sum of the separate values was 0.71 per cent. *greater* than the effect of the two combined. This was evidence for no interaction of surface and acetylene, which pointed to a homogeneous catalysis by acetylene. For the longer contact times the above procedure could not be employed because the acetylene percentage in exit gases was quite different for the two $S:V$ ratios.

The products of reaction besides those mentioned include propene, methyleneacetylene, benzene, naphthalene, pyrene and anthracene. There

TABLE IV

EFFECT OF NITROGEN AND STEAM ON THE DECOMPOSITION OF METHANE AT 1007° AND $S:V = 2.47$

Pressure = 1 atm.

Run	Methane decomposed, %	$\bar{t}$,[a] sec.	N_2 in inlet gas, %	H_2O in inlet gas %	Product gases, per cent. exit volume C_2H_4	C_2H_2	C_2H_6	C_3H_6	$CH_3—C{\equiv}CH$	H_2	C_6H_6
318	1.39	0.279	..	..	0.08	0.02	0.10	0.02	0.03	2.15	0.00
319	1.51	.279	..	..	.12	.02	.07	.01	.01	2.49	.00
320	2.57	.473	..	..	.23	.06	.08	.02	.04	4.17	.00
321	4.41	.738	..	..	.40	.14	.10	.05	.07	6.95	.03
310[b]	2.12	.406	52.6	..	.08	.05	.05	.02	.03	1.53	.02
311[b]	2.77	.543	52.6	..	.16	.05	.03	.00	.02	2.27	.00
312[b]	3.43	.648	52.6	..	.19	.09	.05	.02	.04	2.62	.00
380	1.17	.246	..	50	.10	.02	.11	.03	.01	2.11	.01
381	1.16	.245	..	50	.12	.01	.08	.02	.01	2.22	.00

[a] $\bar{t}$ = average time of contact of methane in reaction cell. [b] There is 0.05% ethane in the inlet gas.

was always less than 0.01% of propane, or butadiene, contrary to the experience of Hague and Wheeler,[10] who found butadiene in the products from the decomposition of methane in a flowing system at 950° in quartz, from which they concluded that benzene was formed with butadiene as an intermediate. The results in this research indicated no stable 4-carbon intermediate. If the naphthalene is formed from benzene, it is presumably made in a two-step reaction with acetylene or ethylene, or both.

Propene and methylacetylene were observed as products in the decomposition of methane. These compounds could form by the reaction of free methylene radicals and ethylene to give propene, which dehydrogenates to methylacetylene, or alternatively acetylene could react with methylene to give methylacetylene. The question of whether methylene, methyl or both are the primary radicals of methane decomposition has not been definitely answered. Barrow, Pearson and Purcell[11] reviewed the question and concluded that both may be present. Eltenton[12] used a mass spectrometer to detect the free radicals from methane decomposition and reported that only methyl radicals were detected.

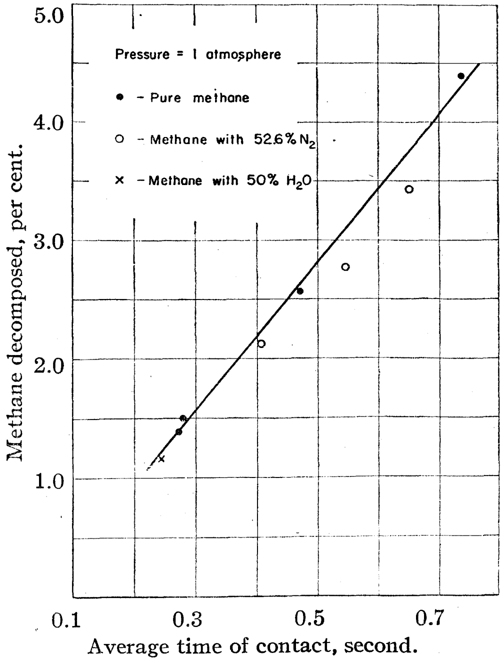


Fig. 4.—Percentage of methane decomposed *vs.* average time of contact at 1007° and $s/v = 2.47$.

Three tubes of quartz were added to the reaction cell with quartz surface:volume of reaction cell = 10.24. At 1007°, there was only an increase from 1.45% of methane decomposed, with no extra surface, to 1.97% of methane decomposed for the added quartz surface at about the same average time of contact. Part of the above increase may be explained by the increased time spent in the entrance and exit annular spacing, since the volume of these tubes necessitated about a 30% decrease in velocity through the reaction cell to keep the contact time stationary. Thus quartz surface had a minor effect on the reaction velocity.

The effect of porcelain surface when 30% of methane was decomposed was investigated at 1033°. For the same contact time, the decomposition of methane when the $S:V$ ratio = 6.94 was *less* than the decomposition of methane when the $S:V$ ratio = 2.47. Thus, surface had a large effect on the decomposition velocity only in the early stages of the decomposition, and this may account for the small effect of porcelain over quartz surface previously reported.

The average time of contact here was over four seconds. About 1% of carbon monoxide was found in the exit gas, owing to the slow reaction between methyl or some intermediate and porcelain. A similar result with much larger carbon monoxide was reported previously by Bone and Coward.[13]

The result of percentages of the methane decomposed in passage through the furnace, with

---

(10 Hague and Wheeler, *J. Chem. Soc.*, **363** (1929).

(11) Barrow, Pearson, and Purcell, *Trans. Faraday Soc.*, **35**, 880 (1939).

(12) Eltenton, *J. Chem. Phys.*, **10**, 403 (1942).

(13) Bone and Coward, *J. Chem. Soc.*, **93**, 1197 (1908).

pure methane and with methane diluted about 1:1 with nitrogen and with steam, were shown in Table IV and plotted in Fig. 4. A straight line was drawn through the four points for pure methane decomposition; the three points with nitrogen fell reasonably close to this line and the two almost identical points with steam fell on the line. Since the first-order "constants" for pure methane over this range of contact times increased some 36%, these plotted results were quite interesting because they indicated a first-order decomposition. It may be noted in Table IV that the percentages of acetylene in the exit gas for the same percentage of methane decomposed were not very different for these various cases. One possible way the observed results may be explained was by assuming that, in the rate of decomposition of methane, the effect of surface and of acetylene depended on the concentration of methane to the first power; the acetylene and surface may be to any power. Kassel[4] has already shown the homogeneous decomposition to be first order at somewhat lower temperatures.

Acknowledgments.—I should especially like to thank Dr. R. A. Friedel and his group, including Mr. A. G. Sharkey, Jr., Mr. C. R. Humbert, Mrs. G. Bloom, and Miss H. R. Borgman, for their kindness in analyzing the off-gas from each run with the mass spectrometer. I should like to express my appreciation to Dr. Helmut Pichler for illuminating discussions of the results, and to Dr. H. H. Storch, chief of the synthetic liquid fuels research program, for his encouragement during this research. Mrs. Norma Golumbic read the manuscript critically and made many valuable suggestions.

Summary

The decomposition of methane has been studied in a porcelain tube at temperatures between 1007 and 1075°. The following observations were made:

1. Within this range the first-order reaction constants increased with increasing decomposition.
2. There was a catalytic effect of acetylene, probably homogeneous, which accounts for (1), since the percentage of acetylene increased with increasing percentage of decomposition.
3. There was probably no effect of ethylene on the decomposition of methane.
4. There was a large catalytic effect of surface in the early stages of the reaction which disappeared by the time 30% of the methane was decomposed.
5. No induction period was found.
6. In the early stages of the decomposition, 50% nitrogen or steam in the entering gas resulted in about the same percentage of decomposition of the methane for equal contact time.

PITTSBURGH, PENNSYLVANIA RECEIVED APRIL 11, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Effect of Activator Concentration on the Infrared-Sensitive Phosphor, Strontium Sulfide–Samarium, Europium[1]

BY KENNETH F. STRIPP AND ROLAND WARD

The recognition by Urbach[2] that the double activator principle permits long storage of energy in infrared-sensitive phosphors at room temperatures led to the development of his Standard VI phosphor. This material was originally prepared by heating a mixture containing approximately 70% strontium sulfide, 25% strontium sulfate and 5% calcium fluoride to which samarium and europium salts had been added. It has been shown[3] that the strontium sulfate and calcium fluoride constitute the flux for this phosphor and that the sulfate may cause some oxidation to occur.

In attempts to simplify the composition of these phosphors, it was found that satisfactory fluxing could be obtained with strontium chloride. The only complication which this flux may cause is the introduction of chloride ions. The lattice constants from pure strontium sulfide and from strontium sulfide fluxed with strontium chloride were the same within experimental error, indicating a very limited solubility of the chloride in the sulfide. The luminescent characteristics of phosphors prepared in this way appeared to be much more consistent than those obtained by the Lenard procedure so that it was thought worthwhile to undertake a more critical determination of the optimum concentrations of the activators.

Experimental

(a) The Preparation and Measurement of Samples.—Pure strontium sulfate obtained by precipitation from purified strontium nitrate solution[4] was reduced to the sulfide by heating in silica glass boats to constant weight in a stream of dry hydrogen or hydrogen sulfide. The products were white powders which showed neither fluorescence nor phosphorescence on exposure to ultraviolet radiation.

Strontium chloride solution was purified by a procedure

---

[1] This work was carried out at the Polytechnic Institute of Brooklyn under Contract NObs 28370 with the Bureau of Ships.

[2] F. Urbach, D. Pearlman and H. Hemmendinger, *J. Optical Soc. Am.*, **36**, 372 (1946).

[3] W. Primak, R. K. Osterheld and R. Ward, THIS JOURNAL, **69**, 1283 (1947).

[4] A. L. Smith, R. D. Rosenstein and R. Ward, *ibid.*, **69**, 1725 (1947).

similar to that described for strontium nitrate.[4] The strontium chloride hexahydrate was crystallized from this solution and dried at 200° to give the anhydrous salt. The most satisfactory weight proportion of base and flux for our purpose was found to be 100 strontium sulfide to 12 strontium chloride. The samples were prepared as previously described for the selenide phosphor.[4] When the fired samples were split open it was observed that a thin layer at the surface which had been exposed during the fluxing operation was noticeably different in optical properties from the fracture surface. This was shown later to be due to oxidation at the surface of the sample which might be attributable to the effect of traces of moisture adsorbed on the sample during its preparation, or to oxygen in the nitrogen stream. Since neither of these factors could conveniently be brought under strict control it was decided to split the fired sample and measure the brightness of the fracture surface. With some practice it is possible to obtain reasonably plane fracture surfaces and in most cases both halves of the sample were measured. Preliminary experiments indicated that after heating for one and one-half hours at 1050° very little change occurred in the brightness of the fracture surfaces and that during this period the variable outer layer did not penetrate deeply into the sample.

The apparatus used to measure the brightness of the phosphors under constant I. R. stimulation is shown in Fig. 1. The stimulating light source (L) is a 6 volt, 3 c. p. lamp run from a 6-volt constant voltage transformer. The light passes through a ground glass (G) and through a Corning 2540 infrared filter (F) to be reflected by a mirror (M) to the surface of the phosphor sample (P). The light emitted by the phosphor is measured by the phototube multiplier (T). A calibrating light (a 6 volt, 3 c. p. tungsten lamp) was run off the same transformer as the stimulating light (L). It was placed directly above the aperture for the phosphor in a box in which a small pinhole covered with opalescent glass permitted the light to fall on the phototube multiplier. To take a calibrating reading the phosphor was replaced by a piece of ground glass which was illuminated by the light from the pinhole. To make sure that readings on different samples were strictly relative, this was done at the beginning and end of every set of readings. It was fairly easy to obtain brightness measurements on duplicate samples which agreed within 5%. Two minutes of exposure to the filtered light of a 60-watt tungsten lamp at a distance of 8 inches was the standard excitation given all phosphor samples. The filters were Corning Aklo and Blue-Green each about 5 mm. thick. The phosphorescence was measured up to five minutes after excitation at which time the phosphor was stimulated by infrared. The increment in emission was taken as the Brightness. At five minutes after excitation the phosphorescence (Background) of most samples was usually less than 10% of the Brightness except for those with low samarium concentrations in which it rose as high as 40%. The Brightness is given in galvanometer divisions.

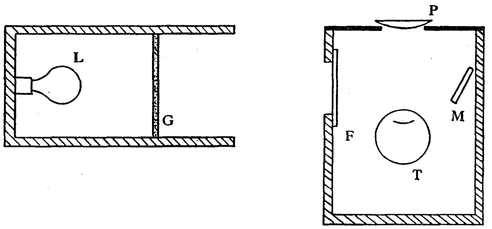


Fig. 1.—Apparatus for measuring the brightness of infrared-sensitive phosphors under constant infrared stimulation.

(b) The Effect of Addition of Oxide upon the Brightness of the SrS(Sm,Eu) Phosphor.—The first experiments were carried out using lithium fluoride as flux. Samples of composition 100SrS + xSrO(0.017 Eu, 0.02 Sm)9 LiF were prepared as described above. The numbers refer to parts by weight. The amount of strontium oxide (x) consciously added to the mixture ranged from 0 to 10. The stimulated brightness of these samples as a function of added oxide is shown in curve 1, Fig. 2. It can be seen that maximum brightness is reached at 3% added oxide and the further increase in oxide concentration leads to a decline in brightness. This is similar to the results reported for the strontium selenide phosphor.[4]

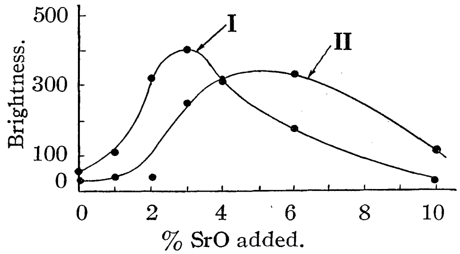


Fig. 2.—The effect of addition of oxide upon brightness: I, SrS(0.2 Sm, 0.017 Eu) 9 LiF, X SrO; II, 90 SrS:10 CaS(0.02 Sm, 0.017 Eu) 9 LiF, XSrO.

When similar experiments were tried using strontium chloride as flux, it was found that in general the addition of 1% strontium oxide led to a decrease in brightness and that with 2% oxide the brightness was reduced to a very low value. By using smaller increments of added oxide, however, a measurable maximum in brightness was usually obtained.

Several typical brightness *vs.* oxide plots are shown in

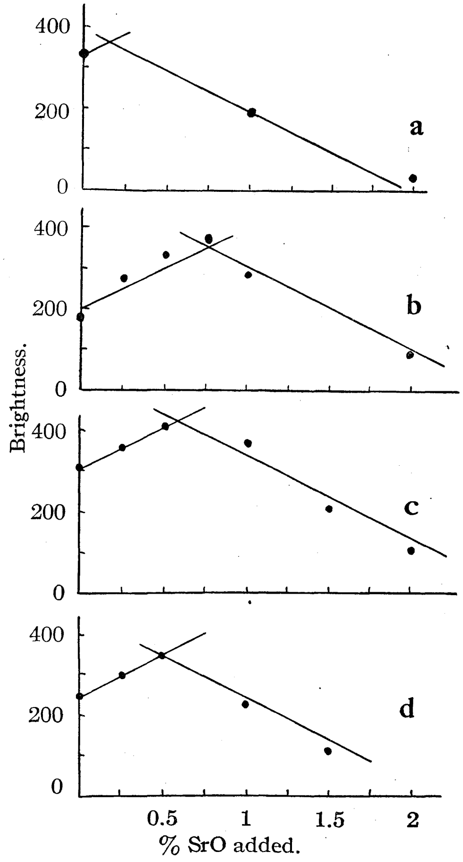


Fig. 3.—The effect of addition of oxide upon brightness: 100 SrS(0.02 Sm, 0.017 Eu) 12 $SrCl_2$, XSrO.

Fig. 3. The strontium sulfide represented in Fig. 3(a) is the same as that used with the lithium fluoride flux (Fig. 2). It was prepared by reduction of strontium sulfate with hydrogen. Fig. 3(b) represents another batch of strontium sulfide prepared by the same procedure while Fig. 3(c) was obtained by use of a sample of strontium sulfide prepared by heating the sulfate in hydrogen sulfide. Straight lines with the same slopes have been drawn rather arbitrarily through the experimental points. The point of intersection of these lines lies within 10 Brightness units of 380, which is about the maximum value obtained with lithium fluoride.

It appeared reasonable to suppose that the relative position of the maxima is indicative of the relative amount of oxide in different samples of strontium sulfide. Thus, Fig. 3(a) represents a sulfide which contains about 0.75% more oxide than represented by Fib. 3(b).

Many attempts were made to prepare a sample of strontium sulfide completely free from oxide. One of these involves the reaction between anhydrous strontium chloride and dry hydrogen sulfide. Under suitable conditions this reaction can be carried essentially to completion and the only impurity which should be present is strontium chloride. The oxide–brightness curve for strontium sulfide prepared in this way is shown in Fig. 3(d). It differs very little from the others.

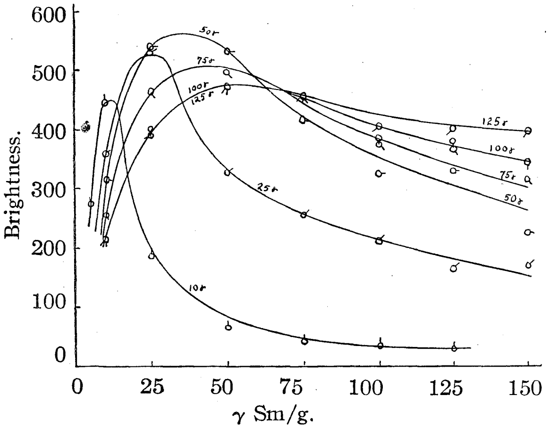


Fig. 4.—Variation of brightness with samarium concentration, SrS(XSm, Eu) 12% SrCl$_2$: ό, 10γEu; σ', 25γEu; o-, 50γ Eu; ɑ, 75γEu; ♀, 100γEu; ρ, 125γEu.

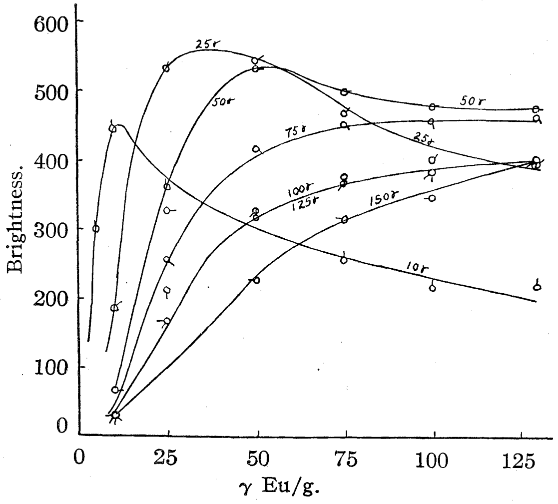


Fig. 5.—Variation of brightness with europium concentration, SrS(Sm, XEu) 12% SrCl$_2$: ό, 10γSm; σ', 25γ Sm; o-, 50γSm; ɑ, 75γSm; ♀, 100γSm; ρ, 125γSm; -o, 150γSm.

A mixture of 90 parts of strontium sulfide to 10 parts calcium sulfide was tested in this way using lithium fluoride as flux. The results shown in Curve II, Fig. 2, indicate that much more oxide can be tolerated in this mixture. The maximum brightness is obtained with 5 to 6% oxide. With 0 to 2% oxide, phosphors of very low stimulability are formed. The lower value for the maximum brightness is probably to be attributed to the shift in emission color toward the red caused by the introduction of calcium.

(c) **The Effect of Varying Concentrations of Samarium and Europium upon the Brightness of the Strontium Sulfide Phosphor using Strontium Chloride as the Flux.**—Strontium chloride was chosen as the flux for this investigation. Strontium sulfide was prepared by reduction of the sulfate with hydrogen. Several batches were intimately mixed to give a sufficient quantity so that the entire investigation could be carried out with the same base material. No addition of oxide was made to the material to be used in the activator concentration experiments. A sample of the sulfide, however, was found to give a maximum in brightness upon the addition of about $^1/_3$ per cent. oxide.

Samples of composition 100SrS(xSm,0.001Eu)12SrCl$_2$ were prepared where x varied from 0 to 125 γ per g. of strontium sulfide. The brightness under infrared stimulation of these samples was plotted as a function of the samarium concentration. This gave a curve which may be called a constant europium profile. Similar series of constant europium samples were prepared with 25, 50, 75, 100 and 125 γ of europium per gram of strontium sulfide. The results are shown in Fig. 4. Constant samarium profiles were also determined for the concentrations 10, 25, 50, 75, 100, 125 and 150 γ of samarium per gram of strontium sulfide.

From Fig. 4 we see that at 10 γ europium concentration the addition of samarium causes a very rapid rise in infrared sensitivity to a maximum value at about 10 γ samarium. Further addition of samarium causes a rapid decline in sensitivity. At progressively higher europium concentrations the maxima become broader and the sensitivity does not fall off so rapidly at higher samarium concentrations. There is also a shift in the position of the maxima toward higher samarium concentrations as the europium concentration increases. The brightness represented by the peaks of the profiles passes through a maximum in the 50 γ europium profile but appears to level off at the 100 γ europium profile.

In Fig. 5 which gives the constant samarium profiles it is shown that similar shifts in the maxima are obtained.

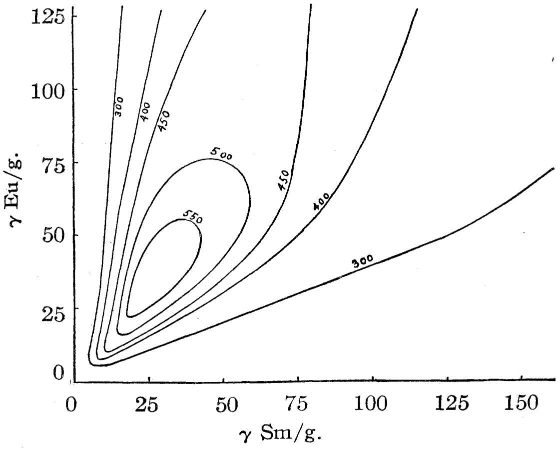


Fig. 6.—Brightness as a function of samarium and europium concentration: SrS(XSm, YEu)12% SrCl$_2$.

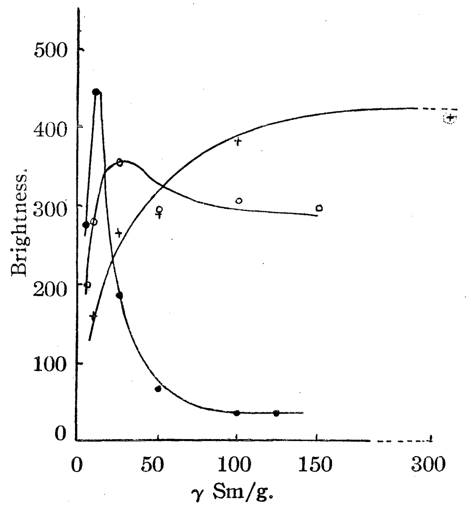


Fig. 7.—The influence of oxide upon the brightness of phosphors with varying samarium concentration, SrS-(XSm, 10Eu) 12% $SrCl_2$: ●, no SrO added; ○, 0.5%; +, 1%.

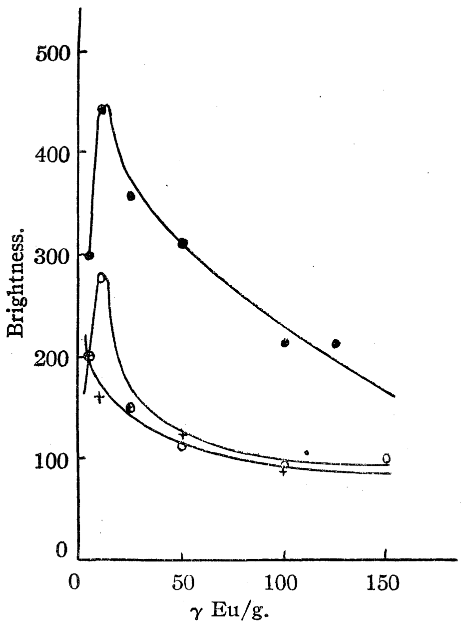


Fig. 9.—The influence of oxide upon the brightness of phosphors with varying europium concentration, SrS-(10Sm, XEu) 12% $SrCl_2$: ●, no SrO added; ○, 0.5%; +, 1%.

At the higher samarium concentrations no maxima were observed within the limits of europium concentrations used.

From Figs. 4 and 5 a contour plot was made of the brightness as a function of the samarium and europium concentrations. This is shown in Fig. 6 which indicates that at low concentrations of activators the optimum ratio of europium to samarium concentrations is about unity. Above 15 parts per million, however, this ratio increases and the brightest phosphors are those in which the europium concentration falls between 22 and 55 γ and the samarium concentration between 17 and 42 γ. If we were to assume that all of the activators entered the base material lattice and were uniformly distributed, the linear separation of activator ions in the maximum brightness region would be about 15 to 18 cation–cation distances. This must represent the minimum separation of the activator ions. The distribution coefficients of the activators between the flux and the strontium sulfide, however, are not at present known and an investigation of this problem is now being made. The increase of the europium to samarium ratio above unity at higher activator concentrations may be in

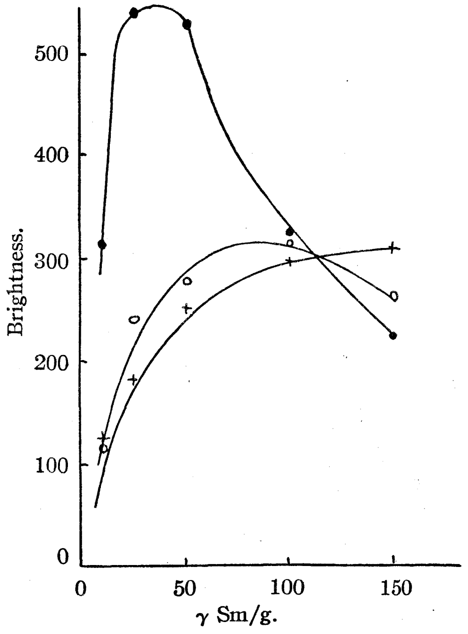


Fig. 8.—The influence of oxide upon the brightness of phosphors with varying samarium concentration, SrS-(XSm, 50Eu) 12% $SrCl_2$: ●, no SrO added; ○, 0.5%; +, 1%.

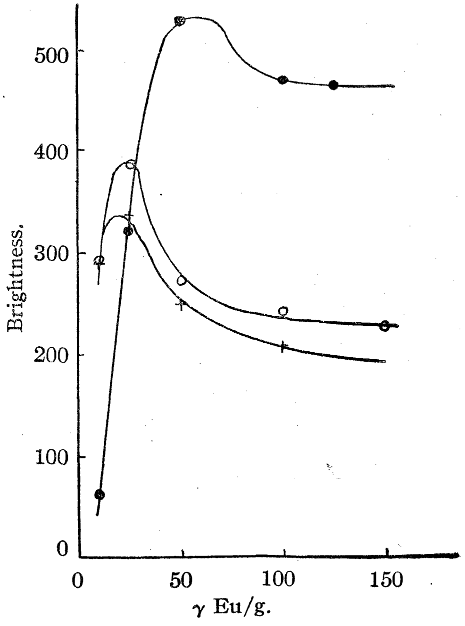


Fig. 10.—The influence of oxide upon the brightness of phosphors with varying europium concentration, SrS-(50 Sm, XEu) 12% $SrCl_2$: ●, no SrO added; ○, 0.5%; +, 1%.

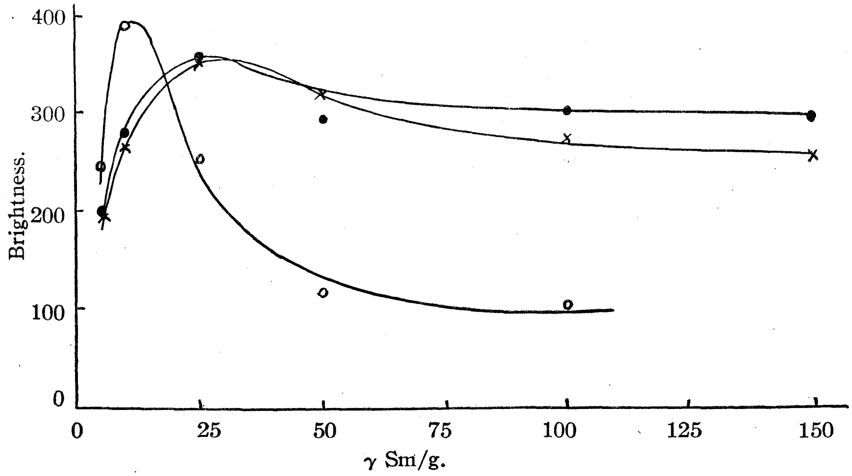


Fig. 11.—Brightness *vs.* samarium concentration for the surfaces of phosphor samples containing no oxide and for the fracture surfaces of samples containing oxide: O, inside and ×, outside, no SrO added; ●, inside 0.5% SrO added.

part due to a difference in distribution coefficients of the two activators.

It should be noted that the measurement of brightness made here is the stimulated emission of the fully excited phosphor after the normal phosphorescence (or background) has decreased to a negligible value. The phosphors with low activator concentration showed a time lag in stimulation. The maximum brightness in these cases was recorded.

From the work of Urbach[2] it would seem likely that the samarium ion (auxiliary activator) provides the trapping states which lead to long storage of energy while the europium ion (the dominant activator) supplies the excited electrons. The stimulation involves the transfer of the trapped electrons to the conduction band whence they may return to the dominant activator ion with the emission of light or may return to a trap without the emission of visible radiation. From this model we would expect an increase in brightness with increasing samarium concentration up to the point at which the re-trapping of excited electrons predominates. This point appears to be reached at 40 to 50 γ of samarium or at a minimum lattice separation of 36 cation distances.

The effect of increasing the europium concentration beyond that required for maximum brightness is not so pronounced. With low samarium concentrations, however, it causes a definite decrease in brightness. This also would be predicted from the mechanism suggested above. Upon excitation of the phosphor the electrons from the europium are transferred to the conduction band. They may subsequently be trapped by the samarium or return to the europium, the latter giving rise to phosphorescence. Qualitatively, it would seem reasonable to suppose that fewer electrons would be trapped by the samarium when europium concentration is relatively high.

(d) **The Effect of Addition of Oxide to Samples with Varying Samarium and Europium Concentrations.**—Three series of samples containing 10 γ of europium per gram of strontium sulfide were prepared with zero, one-half and one per cent. added oxide. In each series the samarium concentration ranged from 5 to over 100 γ. The stimulated brightness of these series as a function of samarium concentration is shown in Fig. 7. The results for a similar set of samples containing 50 γ of europium are presented in Fig. 8. These data show that at low samarium concentrations the addition of oxide causes a marked decrease in brightness while the reverse is true at higher samarium concentrations. The maximum in brightness, shown by the series containing no added oxide, is not so well marked in the series containing 0.5% oxide and does not appear when 1% oxide is added.

The influence of oxide additions upon the constant samarium profiles was also determined at 10 and 50 γ of samarium. The results given in Figs. 9 and 10 show that the addition of oxide causes increase in brightness only at low concentrations of europium with 50 γ of samarium. At high europium concentrations the addition of oxide causes a lowering of the brightness.

It should be noted that the most sensitive phosphor was produced without the addition of oxide. The effect of oxide in general appears to be most noticeable at high samarium and low europium concentrations.

An interesting observation was made by the comparison of the brightness values of the fracture surfaces of a series of constant europium phosphors to which 0.5% oxide had been added with the brightness values of the outside surfaces of a similar series to which no oxide had been added. The curves are shown in Fig. 11. The close correspondence between the 0.5% oxide series and the outside surfaces of the phosphors to which no oxide was added is a strong indication that the change occurring at the surface of the samples in heating is the introduction of a small amount of oxide.

(e) **The Effect of Oxide upon the Phosphorescence of Strontium Sulfide Activated with Europium.**—The light emission from the singly activated phosphor 100SrS-(xEu)12SrCl$_2$ was measured as a function of europium concentration. The results shown in Fig. 12 indicate that there is a maximum at about 10 γ/g. of europium.

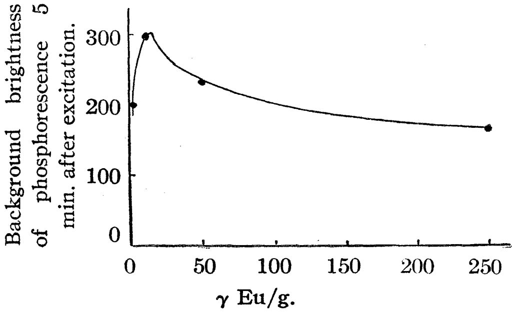


Fig. 12.—Phosphorescence of 100 SrS(Eu) 12SrCl$_2$ as a function of europium concentration.

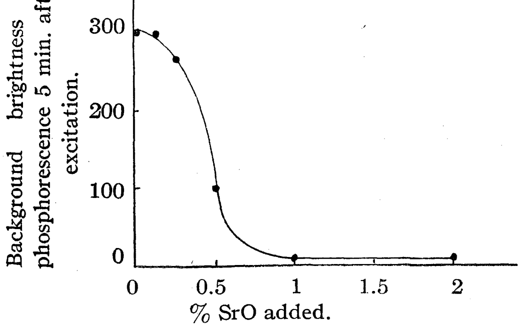


Fig. 13.—Phosphorescence of 100SrS(0.001Eu)12SrCl$_2$, XSrO as a function of oxide concentration.

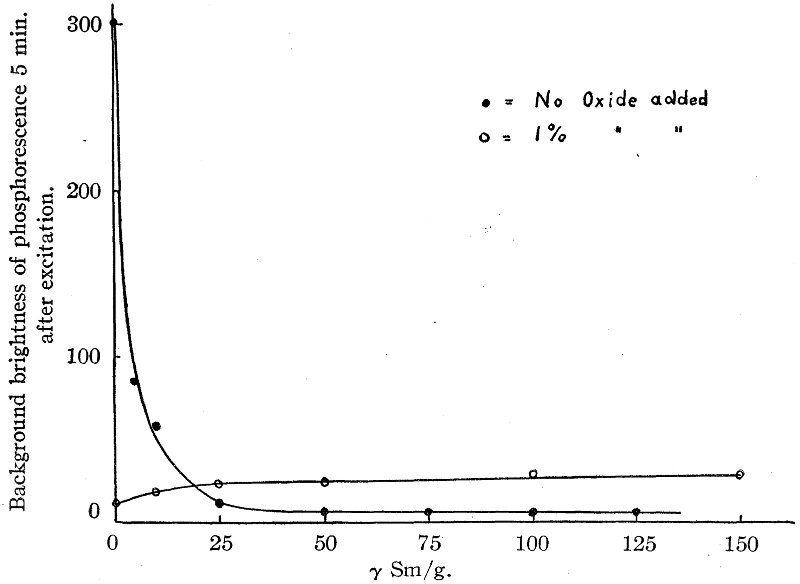


Fig. 14.—The phosphorescence of 100 SrS(0.001Eu, XSm) with and without the addition of oxide.

The phosphorescence was measured at one minute intervals after the phosphor had been fully excited. The data given represent the brightness at five minutes. From these results it would appear that the number of electrons which remain in the excited state is decreased by the addition of europium beyond 10 γ.

Samples of composition $100SrS(0.001Eu)12SrCl_2,xSrO$ where x varied from 0 to 2 were prepared and the phosphorescence measured as described above. The results, given in Fig. 13, show that the phosphorescence is lowered by a factor of one-third upon the addition of 0.5% strontium oxide and becomes practically zero at 1%.

The effect of the addition of samarium upon the phosphorescence of the europium phosphors $100SrS(xSm,0.001Eu)12SrCl_2$ and $100SrS(xSm,0.001Eu)12SrCl_2 \cdot 1SrO$ is shown in Fig. 14.

Unfortunately we have no theoretical interpretation of the peculiar influence of oxide upon the luminescent characteristics of the strontium sulfide phosphors. The measurement of brightness under infrared stimulation is obviously rather superficial. More fundamental information should be forthcoming from the measurement of light sum, quantum efficiency, photoconductivity, etc. Some preliminary investigations of these have been made.

The facts presented here, however, show clearly that impurities other than heavy metals may have profound effects on the behavior of these phosphors and that great care must be exercised in the preparation of samples.

Acknowledgments.—The authors wish to thank R. T. Ellickson and W. L. Parker for the construction of apparatus used in measuring the brightness of the phosphors.

Summary

A method is described by which reproducible measurements of the brightness of infrared sensitive phosphors can be made. The strontium sulfide–samarium, europium phosphor fluxed with lithium fluoride and with strontium chloride was shown to be affected by the addition of small quantities of strontium oxide. The presence of lithium fluoride or of calcium ions increases the tolerance of the phosphor toward oxide.

The dependence of the brightness of the phosphor upon the concentrations of samarium and europium, using strontium chloride as flux, was determined. It was shown that, at activator concentrations from 0 to 15 (γ) parts per million, the brightest phosphors are obtained with about equal concentrations of the two activators. At higher activator concentrations an excess of europium seems to be best. The brightest phosphors contain between 22 and 55 γ of europium and 17 and 42 γ of samarium per gram of strontium sulfide.

BROOKLYN, N. Y. RECEIVED JUNE 24, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Preparation of Optically Active Hydrocarbons by the Wurtz Reaction

BY R. L. LETSINGER

Of the attempts to prepare optically active hydrocarbons by the Wurtz reaction with secondary halides,[1,2] the only successful cases which have been reported are (a) the preparation of (+)2,3-diphenylbutane by the reaction of sodium with (−)1-chloro-1-phenylethane[3] and (b) the preparation of (−)3-methylnonane by the condensation of ethylsodium with (−)2-bromoöctane.[2] Even in these cases the yields were so low and the products so extensively racemized that the reactions are of little synthetic interest.

In the present paper it is shown that benzylsodium condenses with optically active 2-bromoöctane and 2-bromobutane to give good yields of the corresponding hydrocarbons and, furthermore, that in the reaction with 2-bromobutane a major portion of the optical activity is retained and an inversion of configuration probably occurs.

Hydrocarbon Preparation.—Data on the hydrocarbon syntheses are presented in Tables I and II. For comparative purposes, the reaction

---

[1] Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 386.

[2] Brink, Lane and Wallis, THIS JOURNAL, **65**, 943 (1943).

[3] Ott, *Ber.*, **61**, 2124 (1928).

TABLE I

REAGENTS FOR CONDENSATION OF ORGANOSODIUM COMPOUNDS WITH 2-BROMOALKANES[a]

Reaction	Sodium, g. atom	Alkyl, chloride, m.	Toluene, m.	Sodium reagent	Secondary bromide,		
						m.	$[\alpha]^{25}D$
1	0.50	0.25[b]	1.0	$C_6H_5CH_2Na$	2-BrC_4H_9[d]	0.037	0
2	.25	.125[b]	0.5	$C_6H_5CH_2Na$	2-BrC_4H_9	.035	+6.84
3	.25	.10[c]	1.0	$C_6H_5CH_2Na$	2-BrC_8H_{17}	.049	+28.8
4	.25	.10[c]	1.0	$C_6H_5CH_2Na$	2-BrC_8H_{17}	.050	−32.5
5	.50	.25[b]	...	C_4H_9Na	2-BrC_8H_{17}[e]	.050	0
6	.50	.25[b]	...	C_4H_9Na	2-BrC_8H_{17}	.050	−32.5

[a] Petroleum ether (b. p. 30–60°) was used as solvent. The quantities were: 70 cc. in Reaction 2 which was carried out in a 250-cc. flask, and 200 cc. in the other reactions which were carried out in a 500-cc. flask. [b] *n*-Butyl chloride. [c] *n*-Amyl chloride. [d] Eastman Kodak Co. *s*-butyl bromide was used. [e] The *d,l*-2-bromoöctane was prepared from *d,l*-2-octanol in the same manner as the optically active 2-bromoöctane.

TABLE II

PRODUCTS FROM CONDENSATIONS OF ORGANOSODIUM COMPOUNDS WITH 2-BROMOALKANES

Reaction	Hydrocarbon	Yield,[a] %	$[\alpha]^{25}D$	d^{25}_4	$n^{25}D$	B. p. °C.	Mm.
1	$C_7H_7CH(CH_3)C_2H_5$	64	....	0.8570	1.4856	86–87	20
2	$C_7H_7CH(CH_3)C_2H_5$	69	−2.25	.8572	1.4856	95	30
3	$C_7H_7CH(CH_3)C_6H_{13}$	80	+4.53	.8552	1.4828	135–136	15
4	$C_7H_7CH(CH_3)C_6H_{13}$	81	−5.20	.8534	1.4823	128–129	10
5	$C_4H_9CH(CH_3)C_6H_{13}$	36	....	.7512	1.4205	96–98	20
6	$C_4H_9CH(CH_3)C_6H_{13}$	35	0.00	.7510	1.4200	98–99	20

[a] Calculated on the basis of the 2-bromoalkane.

of an alkylsodium compound, butylsodium, is also included. The complete racemization observed in the butylsodium reaction and the extensive racemization reported for ethylsodium[2] suggest that a practical preparation of optically active hydrocarbons by this procedure may be limited to the use of organosodium compounds which do not appreciably exceed benzylsodium in activity. This point will be investigated further.

Extent of Racemization.—In order to determine the extent of racemization in the condensation step, it is necessary to know the maximum rotation for both the hydrocarbon formed and the alkyl bromide employed. An estimation of these rotations for optically active 1-phenyl-2-methylbutane and 2-bromobutane follows. The remaining discussion is limited to a consideration of the 1-phenyl-2-methylbutane synthesis since an independent value for the rotation of 1-phenyl-2-methyloctane is not available.

A sample of 1-phenyl-2-methylbutane which was prepared by the reaction of phenylsodium with optically active 2-methyl-1-bromobutane ($[\alpha]^{25}D + 3.84°$) had a rotation $[\alpha]^{25}D + 10.73°$. On the basis of Braun's value[4] for the maximum rotation of 2-methyl-1-bromobutane, the bromide employed in this reaction contained 95% optically active amyl bromide and 5% inactive material. The inactive material may have been either isoamyl bromide or *t*-amyl bromide. In order to estimate the amount of amylbenzene which would form from the impurity, therefore, the reactions of these two bromides with phenylsodium were investigated. Isoamyl bromide gave approximately one and a half times as great a yield of amylbenzene as did the active amyl bromide, whereas *t*-amyl bromide yielded no isolatable coupling product with phenylsodium. Therefore, since the 1-phenyl-2-methylbutane sample may have contained from zero to 7.5% of an inactive isomer (depending upon the relative amounts of isoamyl and *t*-amyl bromide which had been present), the maximum rotation for the pure hydrocarbon should lie between $[\alpha]^{25}D + 10.7°$ and 11.6°[5,6]

The rotation of optically pure 2-bromobutane is not known. Different methods for preparing the bromide lead to different degrees of racemization.[7] The best case observed in this Laboratory was the conversion of 2-butanol, $[\alpha]^{25}D + 7.25°$, to 2-bromobutane with a rotation $[\alpha]^{25}D - 13.66°$. From this information and the maximum rotation of 2-butanol,[8] it is apparent that the rotation of a pure enantiomorph of 2-bromobutane would be at least $[\alpha]^{25}D$ 26.1°.

The extent of racemization in the reaction of benzylsodium with (+)2-bromobutane, which can be calculated from these rotations (11.6° for the hydrocarbon and 26.1° for the bromide) and the data in Tables I and II, is 26%. Since the values for the maximum rotations are only limiting values, however, the actual racemization is probably considerably less.

---

[4] Braun, *J. Research Natl. Bur. Standards*, **18**, 315 (1937).

(5) These limits correspond to $[M]^{25}D$ +15.8° and 17.1°. Therefore, the approximate value, $[M]^{25}D \pm 9.5°$, set by Levene and Rothen, *J. Org. Chem.*, **1**, 85 (1936), was too low.

(6) These rotations are based on the assumption that no racemization occurred during the Wurtz step. This assumption is valid since the reaction is not at the asymmetric carbon atom, and Whitmore and Olewine, THIS JOURNAL, **60**, 2570 (1938), reported a series of reactions which involved conversion of optically active amyl alcohol to the Grignard, and back to the alcohol, with less than 10% racemization.

(7) (a) Kenyon, Phillips and Pittman, *J. Chem. Soc.*, 1072 (1935); (b) Levene and Marker, *J. Biol. Chem.*, **91**, 412 (1931); (c) Sprung and Wallis, THIS JOURNAL, **56**, 1717 (1934).

(8) Pickard and Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

Configuration.—(+)1-Phenyl-2-methylbutane corresponds to (−)2-methyl-1-butanol,[9] and (+)2-bromobutane corresponds to (+)2-butanol.[10] The determination of the configurational change in the benzylsodium condensation, therefore, depends upon a knowledge of the relationship of 2-methyl-1-butanol and 2-butanol. Unfortunately, this relationship has not been unequivocally established; however, a considerable body of evidence[7a,11] indicates that (−)2-methyl-1-butanol corresponds to (+)2-butanol. On this basis, the reaction of benzylsodium with 2-bromobutane (reaction 2) took place with an inversion of configuration.

A survey of related reactions revealed at least six other cases for which it is possible to relate the configuration of the reactant to (+)2-butanol and that of the product to (−)2-methyl-1-butanol. These reactions include the condensations of secondary bromides with methylmagnesium bromide,[12] ethylsodium,[2] and sodium malonic ester[7b,12] and the reactions of (+)*s*-butyl-*p*-toluenesulfonate[7a] with potassium cyanide and phenylmagnesium bromide. It is interesting that all of these reactions, and the benzylsodium condensation, are found to take place in the same stereochemical sense,[13] *i. e.*, either all take place with inversion or none of them do.

It has been demonstrated that a Walden inversion occurs in the reaction of sodium malonic ester with cyclopentene oxide.[14] Since this reaction probably takes place in the same manner as the condensation of sodium malonic ester with a secondary bromide,[14] this fact supports the view that all the reactions previously listed are accompanied by an inversion of configuration.

Experimental

2-Bromobutane.—Eastman Kodak Company white label 2-butanol was partially resolved by means of the brucine salt of the acid phthalate ester.[15] Physical constants for the optically active alcohols were: (−)2-butanol, b.p. 99–100°, $[\alpha]^{25}\mathrm{D}$ − 3.82°, d^{25}_4 0.806, $n^{25}\mathrm{D}$ 1.3931; (+)2-butanol, b.p. 99–100°, $[\alpha]^{25}\mathrm{D}$ + 7.25°, d^{25}_4 0.807, $n^{25}\mathrm{D}$ 1.3931.

The bromides were prepared by passing dry hydrogen bromide into solutions made up of equal parts of the alcohol and petroleum ether (b.p. 30–60°) at a temperature of 5–10°. The resulting mixtures were allowed to warm up slowly overnight, refluxed for four hours the following day, and worked up as described by Levene[7b]; yield, 50–59%. The bromide from (−)2-butanol boiled at 89–91°, $[\alpha]^{25}\mathrm{D}$ + 6.84°, d^{25}_4 1.256, $n^{26}\mathrm{D}$ 1.4330; that from (+)2-butanol boiled at 90–91°, $[\alpha]^{25}\mathrm{D}$ − 13.66°, d^{25}_4 1.254.

2-Bromoöctane.—Eastman Kodak Co. 2-octanol was resolved by the method of Ingersoll,[15] and converted to the bromide with phosphorus tribromide according to Hsueh and Marvel[16]; b.p. of (+)2-bromoöctane 76° (15 mm.), $[\alpha]^{25}\mathrm{D}$ + 28.8°, d^{24}_4 1.102, $n^{25}\mathrm{D}$ 1.4481; b.p. of (−)2-bromoöctane, 84° (22-mm.), $[\alpha]^{25}\mathrm{D}$ − 32.5°, d^{25}_4 1.101.

Amyl Bromides.—Optically active 2-methyl-1-butanol, obtained by fractionation of fusel oil, had the following constants:[17] $[\alpha]^{25}\mathrm{D}$ −5.74°, d^{25}_4 0.8186, $n^{25}\mathrm{D}$ 1.4077. It was converted to the bromide by the same procedure employed for the butyl bromides; b.p. of (+)2-methyl-1-bromobutane 120–120.5°, $[\alpha]^{25}\mathrm{D}$ + 3.84°, d^{25}_4 1.214, $n^{25}\mathrm{D}$ 1.4412.

Eastman Kodak Co. isoamyl bromide was used after distillation, b.p. 119–120°. *t*-Amyl bromide was prepared from Sharples refined *t*-amyl alcohol and hydrogen bromide at 0°; b.p. 44–45° (90 mm.).

Organosodium Reagents.—The preparation of the organosodium reagents and the condensation reactions were carried out in creased flasks with high speed stirring (5000 r.p.m.) in a nitrogen atmosphere. Petroleum ether (b.p. 30–60°) was used as solvent. Butylsodium, amylsodium[18a] and phenylsodium[18b] were prepared from the corresponding chlorides by the method of Morton and co-workers. Benzylsodium was prepared by the metalation of toluene[19]; amylsodium was used to metalate the toluene in the reaction in which 1-phenyl-2-methyloctane was prepared, and butylsodium was used as metalating agent in the preparation of 1-phenyl-2-methylbutane.

Condensations with 2-Bromoalkanes.—For the hydrocarbon synthesis the 2-bromoalkane, dissolved in an equal volume of petroleum ether (b.p. 30–60°), was added dropwise (fifteen-minute period) to the rapidly stirred suspension of organosodium reagent at a temperature of 20°. The resulting mixture was stirred for another hour, allowed to stand overnight and forced from the flask with nitrogen pressure onto Dry Ice the following morning. After the Dry Ice had disappeared, water was added (cautiously at first); the hydrocarbon layer was then separated by conventional methods and distilled at reduced pressure. Tests for unreacted halide were negative in all cases. Data on the quantities of reagents used in these experiments are given in Table I; data on the products are given in Table II.

Anal. (−)1-phenyl-2-methylbutane (Ex.2). Calcd. for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.99; H, 10.78. (−)1-phenyl-2-methyloctane (Ex.4). Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.01; H, 12.17.

Condensations with 2-Methyl-1-bromobutane.—Two reactions with phenylsodium were carried out. In the first case, (a), the major product was 3,6-dimethyloctane; in the second case, (b), the desired 1-phenyl-2-methylbutane was obtained in moderate yield. In both reactions the amyl bromide was added to the phenylsodium at 0° over a fifteen-minute period. After an hour of stirring at 0° and then another hour at 20–25° the mixture was forced with nitrogen pressure into a centrifuge bottle. Solid matter was separated by centrifugation, then recentrifuged with fresh petroleum ether. The combined hydrocarbon portions were distilled through a 6″ Vigreux column, and the solid phenylsodium was converted to sodium benzoate with Dry Ice. In both cases benzoic acid was isolated, and tests for halogen in the hydrocarbon portion were negative.

---

(9) (+)1-Phenyl-2-methylbutane has the same configuration as (−)2-methyl-1-butanol since there was no possibility for inversion in the reactions of hydrogen bromide with (−)2-methyl-1-butanol and of phenylsodium with (+)2-methyl-1-bromobutane. See also Levene, *J. Biol. Chem.*, **110**, 323 (1935).

(10) Cowdrey, Hughes, Ingold, Mastermann and Scott, *J. Chem. Soc.*, 1268 (1937).

(11) (a) Levene and Rothen, *J. Org. Chem.*, **1**, 76 (1936); (b) Levene and Rothen, *J. Biol. Chem.*, **116**, 209 (1936).

(12) Levene and Marker, *ibid.*, **97**, 563 (1932).

(13) The correlations of configurations can be made from the data of Levene and Rothen (note 11a) on the basis that secondary halides (note 10) and sulfonate esters (note 7a, also Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1940, p. 160) have the same configuration as the corresponding alcohols of the same sign of rotation.

(14) Grigsby, Hind, Chanley and Westheimer, THIS JOURNAL, **64**, 2606 (1942).

(15) Ingersoll, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 400–404.

(16) Hsueh and Marvel, THIS JOURNAL, **50**, 855 (1928).

(17) For reported values for these constants see Whitmore and Olewine, *ibid.*, **60**, 2569 (1938); Braun, note 4.

(18) (a) Morton, Paterson, Donovan and Little, *ibid.*, **68**, 93 (1946); (b) Morton and Letsinger, *ibid.*, **69**, 172 (1947).

(19) Morton, Little and Strong, *ibid.*, **65**, 1339 (1943).

(a) The reaction was carried out in a 500-cc. flask with 11.5 g. (0.50 m.) sodium, 25.5 cc. (0.25 m.) chlorobenzene and 15.1 g. (0.1 m.) active amyl bromide. Distillation of the hydrocarbon layer gave 3.8 g. material boiling at 65–75° (30 mm.) and only 0.2 g. boiling from 75–90° (30 mm.). Redistillation of the first fraction yielded 3.3 g. hydrocarbon, b.p. 65–70° (28 mm.), $[\alpha]^{25}\text{D} + 18.7$, d^{25}_4 0.731, $n^{25}\text{D}$ 1.4166. Literature values for 3,6-dimethyloctane: $[\alpha]^{27}\text{D} + 16.85$,[20] d^{27}_4 0.7269,[20] d^{15}_4 0.7402,[21] $n^{20}\text{D}$ 1.4145.[21]

Only a trace of 1-phenyl-2-methylbutane was obtained from this reaction. The principal product, apparently 3,6-dimethyloctane, was probably produced by a Wurtz reaction of the active amyl bromide with metallic sodium. To reduce the amount of sodium present during the condensation, therefore, excess chlorobenzene was employed in preparing the phenylsodium, and the effectiveness of the agitation was increased by carrying the reaction out in a smaller flask.

(b) A 250-cc. creased flask was employed with 5.75 g. (0.25 mole) of sodium, 15.5 cc. (0.152 mole) of chlorobenzene and 9.8 g. (0.065 mole) of amyl bromide.

The following fractions were obtained from the first distillation.

Fraction	B. p., °C. (30 mm.)	Wt., g.
1	60–75	1.4
2	75–94	0.2
3	94–103	3.8
4	Residue	1.2

Fraction 3 was redistilled twice to give 2.6 g. (27%) of 1-phenyl-2-methylbutane: b.p. 94° (28 mm.), $[\alpha]^{25}\text{D} + 10.73°$, d^{25}_4 0.854, n^{25}_4 1.4862; literature values:[22] d^{25}_4 0.8584, d^{25}_4 0.855; $n^{25}\text{D}$ 1.4873, $n^{25}\text{D}$ 1.4849, etc.

Anal. Calcd. for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.29, 89.34; H, 11.00, 11.11.

From redistillation of fraction 1, 0.8 g. hydrocarbon (3,6-dimethyloctane) was obtained, b.p. 65–70° (28 mm.), $n^{25}\text{D}$ 1.4171. (Compare values with those listed under experiment (a) for 3,6-dimethyloctane.)

Anal. Calcd. for $C_{10}H_{22}$: C, 84.43; H, 15.57. Found: C, 84.60; H, 15.66.

Condensations with Isoamyl Bromide and *t*-Amyl Bromide.—The procedure and quantities of reagents were the same as employed in the previous reaction (condensation of active amyl bromide and phenylsodium, b).

Distillation of the hydrocarbons from the isoamyl bromide reaction gave the fractions:

Fraction	B. p., °C. (31 mm.)	Wt., g.
1	42–85	0.7
2	85–98	0.2
3	98–107	4.5
4	residue	3.0

Isoamylbenzene (4.1 g. 43%) was obtained by distillation of fraction 3: b.p. 94–96° (28 mm.), $n^{24}\text{D}$ 1.4839, d^{25}_4 0.854.

No *t*-amylbenzene was isolated from the reaction of phenylsodium with *t*-amyl bromide. After the removal of petroleum ether from the hydrocarbon layer biphenyl (2.2 g.) crystallized out, and on distillation no hydrocarbon forerun was obtained before the biphenyl started passing over.

Diacetamido Derivatives of 1-Phenyl-2-methylbutane.—These derivatives were prepared by the method of Ipatieff and Schmerling.[23] The derivative of (+)1-phenyl-2-methylbutane (from (+)2-methyl-1-bromobutane) melted at 201–202° (taken with an Anschütz thermometer immersed in the sulfuric acid-bath); that of the less active (−)1-phenyl-2-methylbutane (from (+)2-bromobutane) melted at 198–199°. The mixed m.p. was 198–199°. Ipatieff and Schmerling report 198–199° cor. as the m.p. of the *d,l*-diacetamido derivative of 1-phenyl-2-methylbutane.

Acknowledgment.—The author is very grateful to Professor Robert L. Burwell, who kindly supplied the sample of optically active 2-methyl-1-butanol which was used in this work. The analyses were performed by Margaret M. Ledyard and Patricia Craig. Ruth Peterson assisted in the resolution of 2-butanol.

Summary

(−)1-Phenyl-2-methylbutane and (+)1-phenyl-2-methyloctane were prepared in good yields by the reaction of benzylsodium with (+)2-bromobutane and (+)2-bromoöctane, respectively.

(+)1-Phenyl-2-methylbutane was prepared by the condensation of phenylsodium with (+)2-methyl-1-bromobutane.

The extent of racemization in the reaction of benzylsodium and 2-bromobutane was estimated and the stereochemical relationships were discussed.

EVANSTON, ILLINOIS RECEIVED JUNE 9, 1947

---

[20] Hardin and Sikorsky, *J. chim. phys.*, **6**, 179 (1907).

[21] Dupont, *Compt. rend.*, **156**, 1623 (1913). These values were obtained on the *dl* compound.

[22] Egloff, "Physical Constants of Hydrocarbons," Vol. III, Reinhold Publishing Corp., New York, N. Y., 1946.

[23] Ipatieff and Schmerling, THIS JOURNAL, **60**, 1476 (1938).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, INDIANA UNIVERSITY]

Ionization Constants of Some Substituted 8-Hydroxyquinolines

BY JOHN P. PHILLIPS[1] AND LYNNE L. MERRITT, JR.

In the course of other work still in progress, values for the acidic and basic ionization constants of some methyl substituted 8-hydroxyquinolines and their sulfonic acid derivatives were needed. The optical method of Stenstrom and Goldsmith[2] was used to determine these constants.

Experimental

The methyl substituted 8-hydroxyquinolines and 8-methoxyquinaldine were prepared by modification of the Skraup reaction. 8-Hydroxyquinaldine, m.p. 73–73.5°, was made by the Doebner–v. Miller method[3]; 2,4-dimethyl-8-hydroxyquinoline, m.p. 64–64.5°, was prepared according to Bauer and Engler from *o*-aminophenol plus a mixture of paraldehyde and acetone saturated with dry hydrogen chloride[4]; 8-hydroxylepidine, m.p. 140–141°, and 3,4-dimethyl-8-hydroxyquinoline, m.p. 123–124°, were obtained by the analogous reactions of *o*-aminophenol with methylal plus acetone saturated with hydrogen chloride gas and with methylal plus methyl ethyl ketone saturated with hydrogen chloride gas, respectively; 8-methoxyquinaldine, m.p. 123°, was made from *o*-anisidine and crotonaldehyde by the type of procedure used by Campbell and Schaffner to make 4-methylquinolines.[5]

8-Methoxyquinoline,[6] m.p. 45.5–46°, was made from 8-hydroxyquinoline, m.p. 75°, by methylation with dimethyl sulfate.

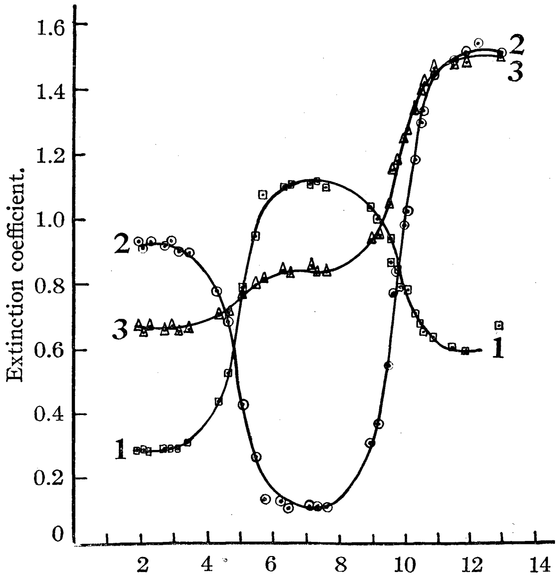


Fig. 1.—8-Hydroxyquinoline, 0.008% in aqueous solution: 1, at 280 mμ; 2, at 330 mμ; 3, at 355 mμ.

The sulfonic acid derivatives of these compounds were formed by direct sulfonation with fuming sulfuric acid at 0–10°.[7]

All compounds were recrystallized until the melting points agreed with those in the literature or, in the case of those compounds whose melting points are not recorded in the literature, until a constant melting point was obtained. The sulfonic acid derivatives melt above 300° and therefore their melting points were not accurately determined.

The ultraviolet absorption spectra of accurately prepared 0.008% aqueous solutions of these compounds (excepting 3,4-dimethyl-8-hydroxyquinoline which had to be run in 0.004% solution owing to its low solubility) at varying *p*H values were measured with a Beckman Model DU Quartz Spectrophotometer using 1.0-cm. cells and slit widths from 1.2 to 0.2 mm. as required. The *p*H was adjusted by additions of dilute sodium hydroxide or hydrochloric acid and was determined with a Beckman *p*H meter that had been standardized against a potassium acid phthalate buffer of *p*H 4.01 and also against five known sodium carbonate–hydrochloric acid buffers in the range of *p*H 10.17–11.36. *p*H above 11.36 was calculated approximately by adding known amounts of a standard sodium hydroxide solution.

From thirty to forty solutions of *p*H between 2 and 13 were measured for each compound, and extinction values at two different wave lengths (280 mμ and 355 mμ in most cases) were used in the calculations. A typical plot of extinction against *p*H at three wave length values for 8-hydroxyquinoline is shown in Fig. 1.

Results

The phenolic ionization constants were obtained by a graphical determination of the *p*H at which the extinction was halfway between its values in alkaline and in neutral solution. (The average values at two wave lengths were used; in no case did the *pKa* determined at one wave length differ by more than about 0.1 unit from the *pKa* at the other wave length.) According to Stenstrom and Goldsmith,[2] at the mid-point *p*H = *pKa*. By analogy, the graphical determination of the *p*OH at which the extinction was halfway between its neutral and acid values gave *pKb*.

For 8-methoxyquinoline and 8-methoxyquinaldine, the extinctions in neutral and basic solutions were the same since no acid ionization could occur.

The experimental results are listed in Table I and the constants *Ka* and *Kb* are given in Table II. By *Ka* is meant the dissociation constant for the phenolic group alone.

Discussion

The relative basicities of these compounds agree very well with what would be predicted from the electron-releasing tendencies of methyl groups substituted *o*, *m*, and *p* to the basic nitrogen; methyl groups in *ortho* or *para* position increase the basicity and decrease the acidity of the substituted

---

[1] Abstracted from a thesis to be presented to the faculty of the Graduate School of Indiana University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] W. Stenstrom and N. Goldsmith, *J. Phys. Chem.*, **30**, 1683 (1926).

[3] L. L. Merritt and J. K. Walker, *Ind. Eng. Chem., Anal. Ed.*, **16**, 387 (1944).

[4] C. Engler and A. Bauer, *Ber.*, **22**, 209 (1889).

[5] K. N. Campbell and I. J. Schaffner, THIS JOURNAL, **67**, 86 (1945).

[6] B. Vargolici and E. Rothlin, *Ber.*, **49**, 581 (1916).

[7] K. Matsumura, THIS JOURNAL, **49**, 810 (1927).

8-hydroxyquinoline; *meta* substitution exerts a relatively slight influence.

TABLE I

pKa AND *pKb* OF 8-HYDROXYQUINOLINE DERIVATIVES

Compound	Wave length mμ	*pKa*	*pKb*
8-Hydroxyquinoline	280	9.70	9.08
	330	9.70	9.10
	355	9.72	9.08
8-Hydroxylepidine	280	10.08	8.50
	330	9.90	..
	355	10.00	8.38
3,4-Dimethyl-8-hydroxyquinoline	280	10.10	8.20
	355	10.00	8.20
8-Hydroxyquinaldine	280	...	8.43
	330	10.33	8.48
	355	10.28	8.45
2,4-Dimethyl-8-hydroxyquinoline	330	10.60	7.77
	355	10.60	7.83
8-Methoxyquinoline	305	...	8.99
8-Methoxyquinaldine	350	...	8.30
8-Hydroxyquinoline-5-sulfonic acid	280	8.85	9.98
	355	8.87	9.87
8-Hydroxyquinaldine-5?-sulfonic acid	290	9.30	9.20
	355	9.30	9.20
8-Hydroxylepidine-7?-sulfonic acid	300	10.00	9.21
	340	10.01	9.24
2,4-Dimethyl-8-hydroxyquinoline-7?-sulfonic acid	340	10.17	8.80
	350	10.10	8.80

TABLE II

ACIDIC AND BASIC IONIZATION CONSTANTS OF 8-HYDROXYQUINOLINE DERIVATIVES

Substance	$Ka \times 10^{+10}$	$Kb \times 10^{+10}$
8-Hydroxyquinoline	1.95	8.32
8-Hydroxylepidine	1.00	36.4
3,4-Dimethyl-8-hydroxyquinoline	0.892	63.1
8-Hydroxyquinaldine	.490	35.5
2,4-Dimethyl-8-hydroxyquinoline	.252	159
8-Methoxyquinoline	....	10.2
8-Methoxyquinaldine	....	50.1
8-Hydroxyquinoline-5-sulfonic acid	13.8	1.20
8-Hydroxyquinaldine-5?-sulfonic acid	5.01	6.30
8-Hydroxylepidine-7?-sulfonic acid	0.976	6.04
2,4-Dimethyl-8-hydroxyquinoline-7?-sulfonic acid	.725	15.9

The fact that the basic dissociation constants of 8-methoxyquinoline and 8-methoxyquinaldine are only slightly larger than those of the corresponding 8-hydroxy compounds suggests that the hydroxyl group in the latter does not have much influence on the basic dissociation, and hence that the 8-hydroxyquinolines are not ampholytes.

It appears probable from its physical and spectral resemblance to 8-hydroxyquinoline-5-sulfonic acid that the sulfonation product of 8-hydroxyquinaldine has the sulfonic acid group in the 5 position. Owing to the physical differences between these two compounds and the sulfonation products of 8-hydroxylepidine and 2,4-dimethyl-8-hydroxyquinoline and also to the marked discrepancy in their phenolic ionization constants, it is likely that the latter compounds sulfonate in the 7-position rather than the 5-position.

Previous measurements of *Ka* for 8-hydroxyquinoline have been made by Fox[8] and by Stone and Friedman.[9] By hydrolysis measurements Fox obtained 0.368×10^{-10} and by solubility and spectroscopic measurements Stone and Friedman obtain the values 0.420×10^{-10} and 0.428×10^{-10}. Our measurements are not in too good agreement with these values, but we feel that the checks obtained by using different wave lengths for measurement and the care in determining *p*H at a large number of values justify this report. Furthermore the ionic strength was not considered in either case. Feldman and Powell[10] by colorimetric means obtain 80×10^{-10} and 0.8×10^{-10}, respectively, for *Ka* and *Kb* for 8-hydroxyquinoline-5-sulfonic acid. These values from visual comparisons are not as precise as spectrophotometric measurements but are of the same order of magnitude as our results.

Summary

The phenolic and basic ionization constants of some methyl substituted 8-hydroxyquinolines and their sulfonic acid derivatives have been determined spectrophotometrically, and have been found to be in good agreement with predictions based on the electron-releasing tendencies of methyl groups.

BLOOMINGTON, INDIANA RECEIVED AUGUST 26, 1947

---

[8] J. J. Fox, *J. Chem. Soc.*, **97**, 1119 (1910).

[9] K. G. Stone and L. Friedman, THIS JOURNAL, **69**, 209 (1947).

[10] H. B. Feldman and A. L. Powell, *ibid.*, **62**, 3107 (1940).

NOTES

Comparison of Nickel Catalysts in the Hydrogenation of β-Naphthol

By Homer Adkins and George Krsek

The partial hydrogenation of β-naphthol over nickel catalysts may give predominantly either the alcohol, 1,2,3,4-tetrahydro-2-naphthol or the phenol, 5,6,7,8-tetrahydro-2-naphthol. In this Laboratory Musser[1] obtained the alcohol in a 55% yield, while Schultz[2] prepared the phenol in 70% yield. Stork[3] obtained the phenol in 55% or the alcohol in 66% yield depending upon the alkalinity of the reaction mixture. With copper–chromium oxide as the catalyst the alcohol is produced to the exclusion of the phenol.[1]

Musser used Raney nickel (W-1) prepared by the Covert process.[4] Schultz and Stork used Raney nickel (W-2), prepared by the Mozingo procedure,[5] under a pressure of about 200 atmospheres. Schultz completed the reaction in less than thirty minutes at 120° while Stork did the hydrogenation in two to three hours at 85°. Musser used a lower pressure of about 100 atmospheres and somewhat more drastic conditions, *i. e.*, six hours at 140°, in forcing the hydrogenation to completion so that decalols and decalin were also produced.

It seemed worth while to test different nickel catalysts for activity in the hydrogenation of β-naphthol. There is recorded in Table I the temperature and time required for the addition of two moles of hydrogen per mole of β-naphthol over various catalysts and the yields of the alcohol and the phenol obtained. The hydrogenations were on 36 g. of β-naphthol in 50 ml. of ethanol with 1 g. of catalyst at 3600 to 4000 p. s. i. The results given are the average of two runs. The catalysts could not be compared at the same temperature because the activity of a Raney nickel catalyst is so dependent upon the procedure followed in preparing it from the nickel aluminum alloy. The catalyst W-4 gave a more rapid hydrogenation at 65° than did the W-1 catalyst at 140°. The data show that in the order of increasing activity the Raney nickel catalysts are: W-1 as prepared by the Covert process; commercial Raney nickel catalyst as supplied by the Gilman Paint and Varnish Co., Chattanooga, Tenn.; W-2 as prepared by the Mozingo procedures; and W-4 as prepared by the Pavlic procedure.[6] The W-6 Raney nickel, described in a paper submitted for publication, is even more active than W-4. Catalysts W-1 and W-2 were somewhat more active if the procedure for washing the catalyst described in the Pavlic process was used.

Table I

Comparison of Raney Nickel Catalysts in Hydrogenation of β-Naphthol

Catalyst	Temp., °C.	Time, minutes	Yield, % Alcohol	Yield, % Phenol
Commercial	90	260	7	86
Commercial	120	25	11	75
W-1[f]	140	160	8	83
W-1	140	240	9	72
W-2	65	245	6	81
W-2	90	180	6	84
W-2	140	15	7	82
W-4	65	120	9	87
U. O. P.	130	30	21	65
W-1[a]	140	240	48	31
W-4[b]	65	90	65	19
W-4[c]	65	90	23	61
W-4[d]	65	90	22	59
U. O. P.[e]	130	30	68	8
W-6[g]	65	30	18	73

[a] 0.02 g. sodium hydroxide. [b] 0.24 g. sodium hydroxide. [c] 0.02 g. sodium hydroxide. [d] 0.6 ml. triethylamine. [e] 0.24 g. sodium hydroxide. [f] Washed by Pavlic method. [g] test by Harry Billica with a Raney nickel W-6 catalyst described in a forthcoming paper.

All of the catalysts referred to above except W-6 gave 6 to 11% yields of the alcohol and yields of the order of 80% of the phenol. The addition of small amounts of sodium hydroxide or of triethylamine to the hydrogenation mixture changed the proportion of the products so that with the W-4 catalyst, for example, the yield of alcohol was increased almost eight-fold with a corresponding decrease in the yield of the phenol. In no case did the addition of sodium hydroxide, in the quantities used, decrease the rate of hydrogenation.

The nickel on kieselguhr catalyst sold by the Universal Oil Products Co. was also tested for the hydrogenation of β-naphthol. It was similar in rate of reaction to the commercial Raney nickel but gave a higher yield of alcohol and a lower yield of the phenol than did any of the Raney nickel catalysts. The U.O.P. catalyst, for a similar rate of hydrogenation, must be used at a temperature 50 or 60° higher than that required by a Raney nickel catalyst prepared by the preferred procedure. The addition of a small amount of sodium hydroxide to the U.O.P. catalyst had the same effect in shifting the course of the hydrogenation to the production of the alcohol as with Raney nickel catalysts.

Laboratory of Organic Chemistry
University of Wisconsin
Madison 5, Wisconsin

Received July 21, 1947

---

(1) Musser and Adkins, This Journal, **60**, 664 (1938).

(2) Harry Schultz, unpublished report (1943).

(3) Stork, This Journal, **69**, 576 (1947).

(4) Covert and Adkins, *ibid.*, **59**, 416 (1932).

(5) Mozingo, "Organic Syntheses," **21**, 14 (1941).

(6) Pavlic and Adkins, This Journal, **68**, 1471 (1946).

On the Fortification of Edible Fat with Vitamin A

By U. P. Basu and S. K. Sen Gupta

For making up the deficiency of vitamin A edible fat is fortified with some vitamin preparation; but on storage the preparation often loses its vitamin A potency, mainly due to oxidation. The addition of a suitable anti-oxidant retards this oxidation. Baxter and Robeson[1] have further shown that vitamin A in the form of its ester (vitamin A acetate) is less susceptible to oxidation. Accordingly, it has been of interest to see how an edible fat in which vitamin A acetate had been incorporated would behave on aeration in presence of some suitable anti-oxidant.

Cow's "ghee" (butter clarified by boiling) was fortified in one case with a vitamin A concentrate made by saponification containing 0.2 million I.U. per gram and in another with a crystalline vitamin A acetate, in presence of 0.05% ethyl gallate (*cf.* Lea,[2] and Bose and Banerjee[3]) and the initial potencies of vitamin A in both the preparations were measured in terms of Carr–Price blue value. Air free from moisture and carbon dioxide was passed through both the preparations under identical conditions at 40°. The relative fall in C.-P. blue values in the two preparations was noted from time to time and the results are being recorded in the table.

Table I

Loss of Vitamin A Potency on Aeration

Period of aeration, hours	Carr-Price value in preparations With concentrate	With acetate
0	19.2	17.4
20	18.2	17.2
60	15.3	17.0
100	9.8	17.0
150	6.4	16.0
200	3.2	15.3
250	nil	12.8

The preliminary investigations indicate that vitamin A acetate may preferentially be used in fortifying an edible fat. Details of the work will be published elsewhere.

---

(1) J. G. Baxter and C. D. Robeson, This Journal, **64**, 2411 (1942).

(2) C. H. Lea, *J. Soc. Chem. Ind.*, **63**, 107 (1941).

(3) S. M. Bose and B. N. Banerjee, *Ind. J. Med. Res.*, **33**, 303 (1945).

Bengal Immunity Research Laboratory,
Calcutta, India
Received June 5, 1947

Influence of Temperature on the Production of Glycerol during Alcoholic Fermentation

By M. C. Brockmann[1] and T. J. B. Stier

A small amount of glycerol is always produced during alcoholic fermentation. The intermediary processes leading to this formation of glycerol are included in the current theory for the mechanism of alcoholic fermentation (see Meyerhof).[2] This scheme, however, does not provide an insight into the way in which substrate is diverted into the series of reactions leading to glycerol formation. Inasmuch as the immediate origin of glycerol involves the hydrolysis of glycerol-1-phosphate, it follows that the phosphatase activity of yeast can be assumed to play a part in its production. While certain special conditions are known to enhance glycerol formation, the influence of common environmental factors—such as temperature, oxygen tension and concentration of ammonium salts—on the production of glycerol during alcoholic fermentation remains unsettled. This paper deals with the production of glycerol in the course of fermentations maintained at 30 and 37 or 40°. As a means of throwing further light on differences in glycerol formation at these temperatures, observations were made on the phosphatase activity of yeast recovered from fermentations maintained at different temperatures.

Experimental

Yeast Strain.—All experiments were performed with a distillery strain of *Saccharomyces cerevisiae.*

Medium.—The medium contained 10 g. of glucose, 0.7 g. of dehydrated yeast extract (Difco) and 0.5 g. of potassium dihydrogen phosphate per 100 ml. This medium was autoclaved at 120° for ten minutes.

Preparation of Inoculum and Management of Fermentation.—In the development of inoculum, yeast was transferred through the following steps at twenty-four-hour intervals: (A) from the stock slant to 10 ml. of medium; (B) 1 ml. from (A) to each of two tubes containing 10 ml. of medium apiece; (C) the contents of each tube from (B) were added to 150 ml. of medium in a centrifuge bottle. All cultures were incubated at 30°. At the time of inoculation, yeast was centrifuged from the cultures prepared in step (C), washed twice with potassium dihydrogen phosphate solution (0.5 g. per 100 ml.) and transferred to 1300 ml. of medium. After a thorough mixing, 600-ml. portions of the inoculated medium were transferred to 2 sterile, 1-liter Florence flasks which were plugged with cotton and suspended in water-baths maintained at 30, 37 or 40°. Both flasks were continuously agitated.

Analytical Operations.—Immediately after inoculation and at intervals throughout the twelve–fourteen hour observation period samples were withdrawn for evaluation of glucose and glycerol concentrations. Glycerol concentration was determined by the procedure of Amerine and Dietrich.[3] Because the yeast extract present in the medium contributes to the observed glycerol concentration, the apparent glycerol concentration of the medium immediately after inoculation was subtracted from the observed concentration of subsequent samples. This difference was recorded as "glycerol formed." At the end of the indicated observation period yeast cells were centrifuged from the culture, washed with water, and dried for forty hours in a vacuum desiccator over activated alumina. A known weight of dried cells was assayed for phosphatase activity at *p*H 4.1 using disodium glycerol phosphate (Eastman Kodak Co. #644) as substrate.

Results

In Fig. 1 glycerol formation during fermentation at 30, 37 and 40° is identified as a function of

---

(1) Seagram Research Associate at the Laboratory of Cell Physiology, Indiana University, 1944–1946, on special assignment from Joseph E. Seagram and Sons, Inc., Louisville, Kentucky.

(2) Otto Meyerhof, "A Symposium on Respiratory Enzymes," University of Wisconsin Press, Madison, Wis., 1942, pp. 3–15.

(3) Maynard A. Amerine and William C. Dietrich, *J. Assoc. Off. Agr. Chem.*, **26**, 408 (1943).

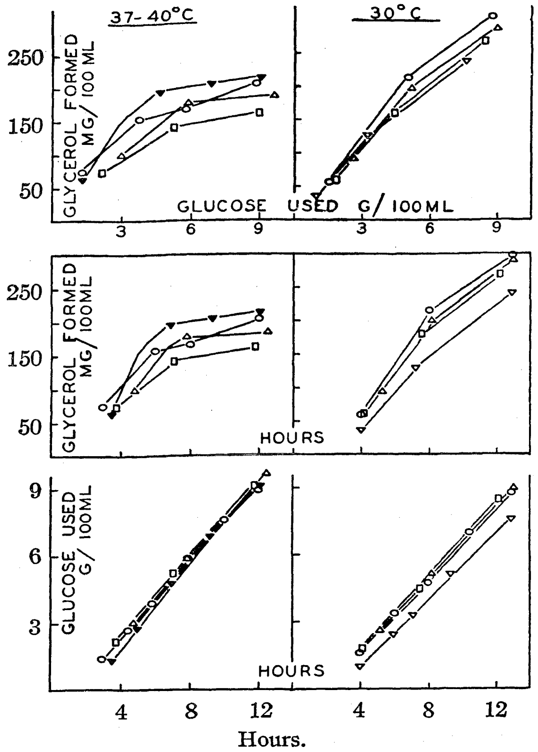


Fig. 1.—Glycerol formation and glucose utilization during four representative experiments conducted at 30° and 37 or 40° (closed triangle represents observations at 37°).

time as well as of the glucose metabolized. With fermentations maintained at 30°, the yield of glycerol after 40 to 50% of the initial sugar has been metabolized is from 3.7 to 4.2 g. per 100 g. of glucose utilized. Later, when 80 to 90% of the sugar has been metabolized, the glycerol yield is between 3.0 and 3.5 g. per 100 g. of sugar used. This represents a slight but consistent decrease in the yield of glycerol during the latter half of fermentation.

In fermentations held at 37 or 40° glycerol formation with respect to sugar utilization follows about the same pattern as at 30°, up to the point of the metabolism of 25 to 30% of the sugar initially present. When approximately half of the sugar has been metabolized, the yield of glycerol in fermentations held at 37 or 40° is 2.7 to 3.2 g per 100 g. of sugar used—a range definitely lower than that observed at a corresponding point of the fermentations maintained at 30°. By the time 85 to 90% of the sugar has been metabolized, the yield of glycerol in fermentations held at 37 to 40° amounts to only 1.8 to 2.3 g. per 100 g. of glucose utilized. Of the glycerol produced during the entire observation period, more than three-fourths was formed by the time one-half of the ultimate sugar utilization was attained.

As is evident from the glucose-used time relationships shown in Fig. 1, the rate of glucose utilization in the 30° fermentations was only slightly less than in those held at 40°. This, however, is an incomplete picture, because in fermentations held at 40°, the cell populations were only 40 to 50% of those observed at like periods in fermentations maintained at 30°. Thus, on a per cell basis, the rate of glucose utilization at 40° was always more than twice the rate at 30°.

From the observations summarized in Fig. 1, it is apparent, particularly in the fermentations conducted at 40°, that the production of glycerol was not constant throughout the observation period, although the rate of glucose utilization during the same period was nearly constant. It follows, therefore, that glycerol production must be controlled by some enzyme system not involved directly in the over-all utilization of substrate. These specifications appear to be met by the cell phosphatases capable of promoting the hydrolysis of glycerol-1-phosphate. To test this concept, yeast cells were recovered from fermentations at the end of a twelve–fourteen hour holding period and assayed for phosphatase activity. Representative results from essays are shown in Table I.

TABLE I

PHOSPHATASE ACTIVITY OF YEAST AND FERMENTATION MEDIUM AFTER TWELVE–FOURTEEN HOURS OF FERMENTATION AT DIFFERENT TEMPERATURES

Phosphatase activity[a]			
30° fermentation		37 or 40° fermentation	
For 5 mg. dry yeast	For 1 ml. medium	For 5 mg. dry yeast	For 1 ml. medium
155	205	60[b]	55
122	239	25	32
110	136	52	73
100	148	30	29

[a] Micrograms of phosphorus liberated from disodium glycerol phosphate by either 5 mg. of dry yeast or yeast present in 1 ml. of fermentation medium during ninety minutes at 30°. [b] 37°.

While the results shown in Table I indicate a considerable variation in the phosphatase activity observed in yeast cultures of comparable history, there can be little question that yeast held at 37 or 40° has far less phosphatase activity than yeast maintained at 30° over corresponding periods of time. Because the procedure employed for the assay of cell phosphatase activity is not specific for those enzymes which hydrolyze *l*-glycerol-1-phosphate to glycerol, it cannot be stated conclusively that the reduction in the amount of glycerol formed in fermentations maintained at 37 or 40° is related to a deterioration of cell phosphatase activity. However, if glycerol formation parallels the combined activities of the cell phosphatases capable of hydrolyzing the isomers of glycerol phosphate, this relationship suggests that the phosphatase activity of yeast is a significant factor in the control of glycerol formation during normal alcoholic fermentation.

DEPARTMENT OF PHYSIOLOGY
INDIANA UNIVERSITY
BLOOMINGTON, INDIANA

RECEIVED JUNE 27, 1947

A Simplified Synthesis of α-Phenylcinnamic Acid and α-Phenyl-*p*-nitrocinnamic Acid[1]

BY ROBERT E. BUCKLES AND EUGENE A. HAUSMAN

Benzaldehyde or *p*-nitrobenzaldehyde can be condensed with phenylacetic acid in the presence of tertiary amines with about the same yields as the Perkin reaction.[2] The advantage of this synthesis is that it does not require the anhydrous sodium salt, nor is it carried out at the high temperature of the Perkin reaction. The method is an application of one used by Bakunin and Peccerillo[3] for the synthesis of α-phenyl-*o*-nitrocinnamic acid.

A comparison of triethylamine, tri-*n*-propylamine and tri-*n*-butylamine as catalysts in the preparation of α-phenyl-*p*-nitrocinnamic acid was made. The yields in three identical experiments except for catalyst were: triethylamine, 52%; tripropylamine, 56%; tributylamine, 33%.

When the reactions were carried out with *p*-nitrophenylacetic acid in place of phenylacetic acid a successful condensation was obtained only with benzaldehyde.

Experimental

α-Phenylcinnamic Acid.[1]—Twelve cc. of benzaldehyde, 11 g. of phenylacetic acid, 23 cc. of acetic anhydride and 8 cc. of tripropylamine[4] were heated together on a steam-bath for ten hours. The reaction mixture was then poured into a dilute (10%) hydrochloric acid solution. The solid which precipitated was dissolved in benzene (125 cc.). This solution was extracted three times with 100-cc. portions of 5% sodium hydroxide. The aqueous solution was acidified with hydrochloric acid to precipitate the crude product. Two recrystallizations from a mixture of equal volumes of benzene and ligroin yielded 9.0 g. (50%) of phenylcinnamic acid, m. p. 172°.

α-Phenyl-*p*-nitrocinnamic Acid.[5]—A mixture of 3.0 g. of *p*-nitrobenzaldehyde,[6] 2.7 g. of phenylacetic acid, 5.7 cc. of acetic anhydride and 2.8 cc. of triethylamine was heated on a steam-bath for four hours. The resulting solution was made basic with sodium carbonate solution and then filtered while warm. The filtrate was acidified with hydrochloric acid. The precipitate was removed by filtration and recrystallized from ethyl alcohol. A yield of 3.6 g. (66%) of product, m. p. 208°, was obtained. A second recrystallization gave a 3.3 g. (61%) of α-phenyl-*p*-nitrocinnamic acid of m. p. 213°.

Smaller amounts were used in similar experiments to determine the relative merits of triethylamine, tripropylamine[4] and tributylamine[4] as catalysts.

When 3.6 g. of *p*-nitrophenylacetic acid (Eastman Kodak Co.) was used instead of phenylacetic acid in the above procedure, a negligible precipitate was obtained on acidification.

α-*p*-Nitrophenylcinnamic Acid.[7]—A mixture of 3.0 cc. of benzaldehyde, 3.6 g. of *p*-nitrophenylacetic acid, 5.7 cc. of acetic anhydride and 2.8 cc. of triethylamine was heated for ten hours. The red solution was poured into a 10% hydrochloric acid solution. The resinous mass obtained in this manner was extracted with ether. The yellow crystals not soluble in ether were recrystallized from ethyl alcohol. A yield of 0.7 g. (13%) of α-*p*-nitrophenylcinnamic acid, m. p. 224° was obtained.

DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA

RECEIVED AUGUST 12, 1947

---

[1] Part of the M.S. thesis of Eugene A. Hausman, August, 1947.

[2] Johnson, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 252.

[3] Bakunin and Peccerillo, *Gazz. chim. ital.*, **65**, 1145 (1935).

[4] Supplied through the courtesy of Sharples Chemicals, Inc.

[5] Bakunin, *Gazz. chim. ital.*, **25**, I, 146 (1895).

[6] Liebermann and Connor, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 441.

[7] Borsche, *Ber.*, **42**, 3597 (1909).

Chlorination of Thiophenes with Sulfuryl Chloride

BY E. CAMPAIGNE AND WILLIAM M. LESUER

In an attempted preparation of 3-thenyl chloride from 3-methylthiophene it was found that sulfuryl chloride did not react with alkyl thiophenes as it does with alkyl benzenes. Kharasch and Brown[1] reported a high yield of benzyl or benzal chloride, depending on the mole ratio of reactants, on treatment of toluene with sulfuryl chloride in the presence of small amounts of benzoyl peroxide. No nuclear substitution occurred. The reactive thiophene nucleus yielded only nuclear substitution products in high yield on chlorination of 2- and 3-methylthiophene by this procedure. Thiophene was also readily chlorinated by this method. The chlorinations were effected in similarly high yields in the absence of the peroxide catalyst. The chlorination of thiophene has been reported previously using sulfuryl chloride in the presence of aluminum chloride.[2]

Experimental

Chlorination of 3-Methylthiophene.—To a solution of 98 g. (1.0 mole) of 3-methylthiophene was added 140 g. (1.03 mole) of sulfuryl chloride. Spontaneous refluxing commenced during the addition and continued throughout the addition, about one-half hour being required. The solution was then heated to reflux for one additional hour. Fractionation of the product yielded 104 g. (79%) of 2-chloro-3-methylthiophene, b. p. 153–155° (754 mm.). Vacuum distillation yielded a product with an odor of chlorotoluene, b. p. 154–155° (742 mm.), 54° (19 mm.); $n^{20}{}_D$ 1.5408, $d^{25}{}_4$ 1.2281. The physical constants are in accordance with those previously reported.[3]

Chlorination of Thiophene and 2-Methylthiophene.—These compounds were chlorinated by the same procedure as described above. The yield of 2-methyl-5(?)-chlorothiophene from 2-methylthiophene was 77% theory, b p. 154–155° (742 mm.), 55° (19 mm.); $n^{20}{}_D$ 1.5372, $d^{25}{}_4$ 1.2147. This is the same compound obtained by Opolski[4] on direct chlorination of 2-methylthiophene.

Three moles of thiophene on treatment with three moles of sulfuryl chloride yielded on distillation 0.8 mole of unchanged thiophene, 1.3 moles of 2-chlorothiophene (43%), and 0.3 mole of 2,5-dichlorothiophene (10%). Higher chlorination products were not identified.

2-Chlorothiophene.—B. p. 127–129° (742 mm.), 56° (56 mm.); $n^{20}{}_D$ 1.5490, $d^{26}{}_4$ 1.2923.

2,5-Dichlorothiophene.—B. p. 160–162° (742 mm.), 64.5° (25 mm.); $n^{20}{}_D$ 1.5627, $d^{27}{}_4$ 1.4486.

The physical constants for the mono- and dichlorothiophenes are in agreement with those previously reported.[5]

Acknowledgment.—The authors wish to thank Dr. George A. Harrington and Dr. Darwin E.

---

[1] Kharasch and Brown, THIS JOURNAL, **61**, 2142 (1939).

[2] Tohl and Eberhard, *Ber.*, **26**, 2947 (1893).

[3] Opolski, *Anz. Akad. Wiss. Krakau*, 548 (1905); *Chem. Zentr.*, **76**, II, 1796 (1905).

[4] Opolski, *Anz. Akad. Wiss. Krakau*, 730 (1904); *Chem. Zentr.*, **76**, I, 1255 (1905).

[5] "Thiophene Chemicals," Socony-Vacuum Oil Co., Inc., New York, N. Y., 1946.

Badertscher, of the Socony Vacuum Laboratories, for the generous gifts of thiophene, 2-methylthiophene and 3-methylthiophene used in this work.

CHEMISTRY DEPARTMENT
INDIANA UNIVERSITY
BLOOMINGTON, INDIANA

RECEIVED JULY 9, 1947

Some N-Basically Substituted Derivatives of *o*-Nitroaniline

BY ALFRED BURGER AND JAMES M. FREDERICKSEN

Some syntheses designed by us to lead to 9-(dialkylaminoalkyl)-isoalloxazine derivatives as potential metabolite antagonists to natural flavines were interrupted by the war four years ago, and the appearance of several recent articles based on similar thoughts[1,2,3,4] made resumption of this work inadvisable. We wish to report the syntheses and properties of some of the intermediates prepared in these studies.

TABLE I

Deriv. of chlorobenzene	Amine	Product	Yield, %	M. p., °C.	B. p., °C. (mm.)	Formula	% Composition		
								Calcd.	Found
2-Nitro-5-methoxy[a]	N-β-Aminoethylmorpholine	3-(2-Morpholinoethyl)amino-4-nitroanisole	63[b]	85–86[c]	235–245 (9–10)[d]	$C_{13}H_{19}N_3O_4$	N,	14.94	15.03
Same	1-Diethylamino-4-aminopentane	3-(1-Methyl-4-diethylaminobutyl)-amino-4-nitroanisole	51[e]		193[f] (4–5)	$C_{28}H_{33}N_9O_{17}$[g]	N,	16.43	16.83
Same	Cyclohexylamine	3-Cyclohexylamino-4-nitroanisole	36	76–77[h]	195–205 (2–3)	$C_{13}H_{18}N_2O_3$	N, OCH_3,	11.19 12.40	10.75 12.02
Same	Piperazine	1,4-Bis-(2-nitro-5-methoxyphenyl)-piperazine	29	240–242[i]		$C_{18}H_{20}N_4O_6$	N, OCH_3,	14.43 15.98	14.55 15.98
2-Nitro-	N-β-Aminoethylmorpholine	2-(2-Morpholinoethyl) aminonitrobenzene[j]	47	44–45[k]	190–195 (2)	$C_{12}H_{17}N_3O_3$	N,	16.72	16.69
2-Nitro-	2-Amino-2-methylpropanol	2-(1,1-Dimethyl-2-hydroxyethyl)-aminonitrobenzene	8		150–160[l] (1–2)	$C_{12}H_{16}N_2O_4$[m]	N,	11.11	11.33

[a] Prepared by the method of Hodgson and Handley, *J. Chem. Soc.*, **128**, 543 (1926). [b] 20% of unchanged chloronitroanisole was recovered by steam distillation. [c] Yellow crystals from ethanol or benzene–ligroin. [d] Distilled at 150° (2 mm.), and collected crystalline on a cold surface. [e] 16% of unchanged chloronitroanisole recovered. [f] Yellow oil. [g] Dipicrate m. p. 112–113°. [h] Red crystals from ligroin. [i] The insoluble orange solid was washed with ether and sublimed at 1 mm. [j] Dipicrate m. p. 210–212° (dec.); $C_{24}H_{23}N_9O_{17}$: % N calcd., 17.76; found, 17.56. [k] Red crystals from dilute ethanol. [l] Red oil. [m] O-Acetyl derivative prepared with acetic anhydride in pyridine at 100°, *cf.* Karrer and Naef, *Helv. Chim. Acta*, **19**, 1029 (1936), yellow crystals m. p. 64–65° from ethanol.

Experimental

Alkylaminonitrobenzenes.—Approximately equivalent amounts of 2-nitrochlorobenzene or its 5-methoxy derivative and the amine were refluxed for several hours in two equivalents of dry pyridine, 0.5 mole of the 2-nitrochlorobenzene and 0.01 to 0.05 mole of the 5-methoxy derivative being taken. Four to five hours of reaction time was used for runs of one-twentieth mole or less; eight hours for those of one-half mole. In some cases, unreacted chloronitroanisole was then removed by steam distillation. The residue was extracted with several portions of ether, and the reaction product obtained by evaporation of the solvent. Data as to the percentage composition and the physical properties of the substances prepared from the derivatives of chlorobenzene are given in Table I.

2-(2-Morpholinoethyl)-aminoaniline.—When a solution of 7.5 g. of 2-(2-morpholinoethyl)-aminonitrobenzene in 150 cc. of hot 50% ethanol was treated with a freshly prepared solution of 20.7 g. of sodium hydrosulfite dihydrate in 100 cc. of hot water, the red color soon changed to green. After brief boiling, the mixture was acidified with 80 cc. of 10% hydrochloric acid, the solution was cleared with norite, and evaporated to dryness under reduced pressure. The residue was washed with ether, and then decomposed with a cold 20% sodium hydroxide solution under ether. The aniline derivative was extracted into ether and worked up, yielding 5.3 g. (80%) of a red oil. Its *tripicrate* crystallized from ethanol, m. p. 201–203° (dec.).

Anal. Calcd. for $C_{30}H_{28}N_{12}O_{22}$: N, 18.50. Found: 18.33, 18.75.

1,4-bis-(2-Nitro-ethylaminophenyl)-piperazine.—A mixture of 3.0 g. of *o*-(β-chloroethyl)-aminonitrobenzene, 2.8 g. of piperazine and 0.05 g. of sodium iodide reacted exothermically, and was then refluxed for six hours. It was poured into water, the small amount of precipitated solid was filtered from much red oil, and washed with water. The oil from the filtrate was treated with alcohol and deposited another crop of the same orange crystals. Recrystallization from ethanol raised the melting point to 140–141°. The yield was 0.9 g.

Anal. Calcd. for $C_{20}H_{26}N_6O_4$: N, 20.28. Found: N, 20.27.

CHARLOTTESVILLE, VIRGINIA

RECEIVED MAY 22, 1947

---

[1] Hall and Turner, *J. Chem. Soc.*, 699 (1945).

[2] Neeman, *ibid.*, 812 (1946).

[3] Adams, Weisel and Mosher, THIS JOURNAL, **68**, 883 (1946).

[4] Kipnis, Weiner and Spoerri, *ibid.*, **69**, 799 (1947).

Preparation of 2- and 4-Benzylpyridine

BY KENNETH E. CROOK

Several investigators have reported the preparation of 2- and 4-benzylpyridines by heating a mixture of benzyl chloride, pyridine and a copper catalyst.[1]

Reported yields of the mixed benzylpyridines are 40 to 50%. The isomers have usually been separated as the picrates. Yields of the pure isomers are seldom given. The article of von Braun and Pinkernelle[1b] reporting a 50% yield of the 2-isomer, is not explicit as to whether this yield is based on the starting material or on the mixture of isomers.

Need for rather large quantities of 2- and 4-benzylpyridine prompted a search for conditions giving better yields. It was found possible to obtain 75% yields of a mixture of 2- and 4-benzylpyridines, 90% of which was separated into the two isomers by fractional distillation.

Experimental

Solvent.—By using pyridine hydrochloride as a solvent, the yields of the mixed benzylpyridines were nearly double and the violence of the initial exothermal reaction between benzyl chloride and pyridine was greatly reduced. At the conclusion of the rearrangement, the pyridine hydrochloride was recovered by distillation and used for succeeding runs without purification or replenishment.

Catalyst.—Copper metal (or cuprous chloride into which the copper is assumed to be converted) has been used as the catalyst for the rearrangement of the pyridinium salt. Copper (or cuprous chloride) has been reported to cause the conversion of benzyl chloride into dibenzyl and products of unknown composition.[2] This reaction may account for most of the tarry material produced when a mixture of copper, benzyl chloride and pyridine is heated. If benzylpyridinium chloride (no catalyst) is distilled, the vapors which pass over at about 190° (liquid temperature) consist of a mixture of benzyl chloride and pyridine. Rearrangement of benzylpyridinium chloride (catalyst present) is negligible at 190°. By dissolving the catalyst in the hot pyridine–pyridine hydrochloride mixture *prior* to the addition of benzyl chloride, the amount of tar formation is negligible. Copper, equivalent quantities of copper and cupric chloride, or cupric chloride alone, may be used.

Procedure

The procedure employed was a modification of that originally used by Tschitschibabin[1a] as modified by LaForge[1a] and by Crook and McElvain.[1c] The procedure finally adopted is given in some detail since it was found to be advantageous to modify most of the steps in previously recorded procedures.

Four moles (462 g.) of pyridine hydrochloride was distilled into a one-liter flask and allowed to solidify while the flask lay on its side. This flask was fitted with a Claisen adapter carrying a dropping funnel and a water reflux condenser bearing a tube containing calcium chloride, 5 g. of anhydrous cupric chloride and 80 cc. (1 mole) of pyridine were added, and the flask heated until all the pyridine hydrochloride had melted and the cupric chloride dissolved. Heating was discontinued and 115 cc. (1 mole) of benzyl chloride (b. p. 90–91° at 40 mm.) was added during ten–fifteen minutes while the flask was shaken continuously. The mixture was then refluxed gently for twelve hours. The pyridine hydrochloride was distilled off through a 45-cm. Vigreux column at 90 mm. pressure. Distillation was stopped when the vapor temperature reached 195°. This pyridine hydrochloride was used without purification for the next run. There was a slight gain in quantity of pyridine hydrochloride with succeeding runs.

The black residue was cooled, 200 cc. of water and 15 cc. of hydrochloric acid (sp. gr. 1.2) added, and the mixture warmed until it appeared homogeneous. The brown to black liquid was made basic with ammonium hydroxide, 100 cc. of a 1–1 mixture of benzene and ligroin added and the organic layer washed with 100-cc. portions of 1–10 ammonium hydroxide until the aqueous layer ceased to acquire a blue color (2–4 times), then washed once with water.

The organic layer was dried by placing it, together with stock potassium hydroxide, in a separatory funnel and withdrawing the aqueous layer periodically until no more formed.

After removing the solvent at atmospheric pressure, the residue was distilled through a 45-cm. Vigreux column and gave 123.5–128.5 g. of a mixture of 2- and 4-benzylpyridines boiling at 175–190° (40 mm.) and a higher boiling residue of 16–20 g.

By using 0, 1 and 2 moles of pyridine hydrochloride as the solvent, the quantities of benzylpyridines and of higher boiling material were 60 and 56 g., 88 and 30 g., and 103 and 28 g., respectively. Decreasing the time of heating to six hours gave erratic results. Other modifications which did not increase yields were: heating for twenty-four hours, heating in a carbon dioxide atmosphere, stirring, continuous addition of cupric chloride during the heating period, and the use of equivalent amounts of copper and cupric chloride as the catalyst.

The isomers were separated by fractional distillation through a 1.2 × 115-cm. column packed with 0.32-cm. glass helices. In order to minimize losses of the less abundant 4-isomer, as much as possible of the 2-isomer was removed at 276.5–277° and two intermediate fractions of 277–280.5 and 280.5–289° were collected. The residue in the still was then set aside while the intermediate fractions were put through the column a second time. All material boiling at 289° and above was then returned to the still and the fraction boiling at 289–289.5° collected as 4-benzylpyridine. From 1 kg. lots, 640–680 g. of 2-benzylpyridine (b. p. 276.5–277° cor. (730 mm.)) and 245–255 g. of 4-benzylpyridine (b. p. 289–289.5° cor. (730 mm.)) were obtained.

As an indication of purity the 2- and 4-isomer gave picrates which melted without purification at 139.5–140° and 138.5–139°, respectively. Reported melting points of the picrates of the 2- and 4-isomer are 140° and 136–138°.[1a]

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF OKLAHOMA
NORMAN, OKLAHOMA

RECEIVED AUGUST 11, 1947

---

[1] (a) Maier-Bode u. Altpeter, "Pyridin u. Seine Derivate in Wissenschaft u. technik," Edwards Brothers, Ann Arbor, Michigan, 1943; (b) J. von Braun and W. Pinkernelle, *Ber.*, **64**, 1871 (1931); (c) J. Overhoff and J. P. Wibaut, *Rec. chim.*, **50**, 957 (1931); K. E. Crook and S. M. McElvain, THIS JOURNAL, **52**, 4006 (1931); P. C. Teague, *ibid.*, **69**, 714 (1947).

[2] A. Onufrowies, *Ber.*, **17**, 836 (1884); T. Zincke, *ibid.*, **2**, 739 (1869).

Brominations with Pyridine Hydrobromide Perbromide

BY CARL DJERASSI AND CAESAR R. SCHOLZ

In connection with another problem, we had occasion to investigate the action of pyridine hydrobromide perbromide on some steroid ketones. Although pyridine and quinoline hydrobromide perbromides have been used occasionally as brominating agents, particularly with phenols and for the addition of bromine to double bonds,[1] no examples of the bromination of ketones with these reagents seem to have been recorded.

---

[1] *Cf.* Rosenmund, Kuhnhenn and Lesch, *Ber.*, **56**, 1262, 2042 (1923).

Pyridine hydrobromide perbromide[2] is a crystalline and stable salt, which is quite useful for brominations of ketones on a micro or semimicro scale, since it can be weighed very accurately in small quantities in contrast to bromine. Representative examples of monobromination and dibromination of steroid ketones are given in the experimental section. The reactions were carried out by warming equimolar quantities of the salt and ketone in glacial acetic acid or ethanol and the yields were comparable to those obtained by using bromine.

Aliphatic and alicyclic ketones, such as acetone or cyclohexanone, also readily decolorize the reagent, and details of the small scale bromination of an amino ketone are given in the experimental section. It is very likely that this reagent could be used in most brominations which are successful with bromine, with particular application to small scale experiments.

Attempts to employ pyridine perbromide,[3] a reagent which should bind any hydrogen bromide liberated, proved disappointing.

Experimental

Pyridine Hydrobromide Perbromide ($C_5H_5N\cdot HBr\cdot Br_2$).—The reagent was prepared in 85% yield by adding one mole of bromine to one mole of pyridine in 48% hydrobromic acid solution and recrystallizing the product from acetic acid; red prismatic crystals, m. p. 134° (dec.) with previous softening; lit.,[2] m. p. 132–134°. We are indebted to Dr. A. C. Shabica of our development department for a supply of this salt.

Monobromination of 3-Ketosteroids

Allo Series.—To a warm solution (40–60°) of 38 mg. of cholestanone in 1 cc. of glacial acetic acid was added 31 mg. of pyridine hydrobromide perbromide. Hydrogen bromide was evolved, the solution turned colorless and crystals of 2-bromocholestanone appeared within one minute. On cooling and filtering the crystals, 37 mg. (81%) of 2-bromocholestanone of m. p. 168–169°, $[\alpha]^{23}\mathrm{D}$ +38.1° (chloroform) was obtained, which gave no depression in melting point on admixture with an authentic sample.[4] By the same procedure, but using methyl 3-keto*allo*etiocholanate, there was obtained 75% of the corresponding 2-bromo derivative[5] of m. p. 184–188°. Glacial acetic acid could be replaced by ethanol or a mixture of ethanol and chloroform as solvent for the bromination.

Normal Series.—A mixture of 110 mg. of methyl 3-keto-12-acetoxycholanate and 75 mg. of the hydrobromide perbromide was warmed to *ca.* 40° for one minute in 5 cc. of glacial acetic acid and diluted with a few drops of water to yield 80 mg. (61%) of the 4-bromo derivative of m. p. 165–167°, $[\alpha]^{23}\mathrm{D}$ +91.5° (chloroform), identical (rotation and mixed m. p.) with an authentic sample prepared by the method of Burckhardt and Reichstein.[6] Similarly, coprostanone gave the 4-bromo compound[4] of m. p. 104–107°, $[\alpha]^{23}\mathrm{D}$ +40.5° (chloroform).

Monobromination of a 12-Ketosteroid.—A mixture of 195 mg. of methyl 3(α)-acetoxy-12-ketoetiocholanate and 155 mg. of pyridine hydrobromide perbromide in 1.2 cc. of glacial acetic acid was warmed until complete solution resulted, allowed to stand at room temperature for two and one-half hours and diluted with ether. The ether solution was washed well with water, evaporated to dryness and the residue was saponified and rearranged as described by Gallagher.[7] The crude yield of 3(α),12-dihydroxy-11-ketoetiocholanic acid of m. p. 248–257° was 130 mg. (74%); one recrystallization from ethanol gave colorless prisms of the acid melting at 274–278° (uncor.), with foaming at 282°. This material gave no depression in m. p. when mixed with an authentic sample (kindly furnished by Dr. H. B. MacPhillamy of our laboratories).

Dibromination of Cholestanone.—Treatment of 380 mg. of cholestanone with 640 mg. of the reagent in the usual manner gave after ten minutes 390 mg. (73%) of 2,4-dibromocholestanone[8] of m. p. 193–194° (dec.)

Bromination of an Aminoketone.—A solution of 65 mg. of 4-piperidino-2-butanone in 1 cc. of acetic acid containing 41% of hydrogen bromide was warmed with 135 mg. of pyridine hydrobromide perbromide for *ca.* thirty seconds until all the reagent had dissolved. Excess isopropyl ether was added which precipitated a pale yellow oil, which in turn was washed several times by decantation with isopropyl ether and crystallized from isopropyl alcohol. The yield of colorless, long needles of **1-bromo-4-piperidino-2-butanone hydrobromide** of m. p. 157–158° (dec.) was 77 mg. (55%). The product gave no depression in m. p. on admixture with a colorless sample prepared by the method of Land and co-workers[9] who reported a 44% yield of brown material of m. p. 157–158°.

Brominations with Pyridine Perbromide ($C_5H_5N\cdot Br_2$).—Pyridine perbromide (m. p. 62–63.5°) was prepared freshly for each reaction by the method of Williams,[3] since it decomposed within a few hours. The bromination of cholestanone and coprostanone was carried out in acetic acid as described above for the hydrobromide perbromide and required three to five days for completion. Warming caused polymerization of the reagent,[10] but exposure to ultraviolet light shortened the reaction time to about twenty-four hours. No hydrogen bromide was evolved, but for substances sensitive to hydrogen bromide, N-bromosuccinimide[11] should be preferred, since the latter reagent is stable and reaction is complete after a few minutes.

RESEARCH DEPARTMENT
DIVISION OF CHEMISTRY
CIBA PHARMACEUTICAL PRODUCTS, INC.
SUMMIT, N. J.

RECEIVED SEPTEMBER 4, 1947

---

[2] Englert and McElvain, THIS JOURNAL, **51**, 863 (1929).

[3] Williams, *J. Chem. Soc.*, 2783 (1931).

[4] Butenandt and Wolff, *Ber.*, **68**, 2091 (1935).

[5] Djerassi and Scholz, THIS JOURNAL, **69**, 2404 (1947).

[6] Burckhardt and Reichstein, *Helv. Chim. Acta*, **25**, 829 (1942).

[7] Gallagher, *J. Biol. Chem.*, **165**, 211 (1946).

[8] Wilds and Djerassi, THIS JOURNAL, **68**, 1712 (1946).

[9] Land, Ziegler and Sprague, *ibid.*, **69**, 125 (1947).

[10] *Cf.* McElvain and Goese, *ibid.*, **65**, 2227 (1943).

[11] Djerassi and Scholz, *Experientia*, **3**, 107 (1947).

The Stobbe Condensation with Sodium Hydride

BY GUIDO H. DAUB AND WILLIAM S. JOHNSON

In previous communications[1] it was shown that in the Stobbe condensation of a ketone with succinic ester, the use of potassium *t*-butoxide as the catalyst generally gave higher yields and purer products during shorter reaction periods than were obtained by the classical procedure with sodium ethoxide. Since sodium hydride has been employed with considerable success in place of alkoxides in certain ester condensations,[2] it seemed worth while to investigate its possible

---

[1] (a) Johnson, Goldman and Schneider, THIS JOURNAL, **67**, 1357 (1945); (b) W. S. Johnson, H. C. E. Johnson and Petersen, *ibid.*, **67**, 1360 (1945); (c) Johnson and Petersen, *ibid.*, **67**, 1366 (1945); (d) Johnson, Petersen and Schneider, *ibid.*, **69**, 74 (1947).

[2] See the review article of Hansley and Carlisle, *Chem. Eng. News*, **23**, 1332 (1945).

use in the Stobbe condensation. The preliminary results of our study were so promising that we are announcing them herewith. The new procedure appears to afford some advantage over the *t*-butoxide method in that it is considerably simplified, while the yields with two representative ketones, acetophenone and benzophenone, are at least as good. In a future communication we expect to report on a more extensive study of this new modification as well as on the mechanism of the condensation.

Experimental[3]

Stobbe Condensation with Acetophenone.—A mixture of 6.00 g. (0.05 mole) of the ketone, 26.13 g. (0.15 mole) of diethyl succinate and 2.4 g. (0.1 mole) of sodium hydride[4] was stirred for three and three-quarters hours at room temperature, care being taken to exclude all moisture from reagents and apparatus. The rate of evolution of hydrogen which was very slow at first gradually increased until after two hours it became quite rapid, slackening off toward the end of the reaction period. After three hours, 10 ml. of anhydrous benzene was added to facilitate stirring. The mixture was acidified with acetic acid, and extracted with ether. The ether solution was extracted with 5% sodium bicarbonate solution which on acidification gave 11.59 g. (93.5% yield) of pale yellow semi-solid acid undoubtedly consisting of a mixture of isomeric half-esters of Stobbe condensation product (neut. equiv., calcd., 248; found, 261). Crystallization from petroleum ether (b. p. 60–68°) rendered about one-third of the material crystalline; m. p. 111–112° after recrystallization from benzene–petrolum ether. This is probably identical with the half-ester of γ-methyl-γ-phenylisoitaconic acid, described by Stobbe[5] as melting at 110–112°. Saponification of the 112° half-ester with barium hydroxide afforded the crystalline dibasic acid, m. p. 180–182° with dec. (reported,[5] 178–179° and 183–185° with dec.).

Extraction of the ether solution, remaining after removal of the bicarbonate-soluble fraction, with 5% potassium hydroxide solution gave 1.23 g. of crude diethyl 1,4-diketocyclohexane-2,5-dicarboxylate, m. p. 117–123.5°, arising from the self-condensation of diethyl succinate. Recrystallization from alcohol raised the melting point to 126–127.5°, undepressed on admixture with an authentic specimen. This product gave a deep cherry-red color with alcoholic ferric chloride solution.

With Benzophenone.—When 9.11 g. (0.05 mole) of benzophenone and 26.13 g. (0.15 mole) of diethyl succinate were treated with 2.4 g. (0.1 mole) of sodium hydride as described above, no appreciable reaction took place even at steam-bath temperature. The addition of 10 drops of ethanol, however, initiated the reaction which proceeded readily at room temperature. The rate of hydrogen evolution increased as the reaction progressed until the sodium hydride was consumed (about eight hours). After about five hours 25 ml. of dry ether was added to facilitate the stirring of the mixture, which had become quite thick. The bicarbonate-soluble material, isolated as described above, amounted to 15.05 g. (a 97% yield) of almost colorless crystals, m. p. 124.5–125.5°, undepressed on admixture with an authentic specimen of β-carbethoxy-γ,γ-diphenylvinylacetic acid (m. p. 125–126°).[1c]

The 1,4-diketocyclohexane-2,5-dicarboxylate isolated by extraction with potassium hydroxide amounted to 1.58 g., m. p. 119–123.5°.

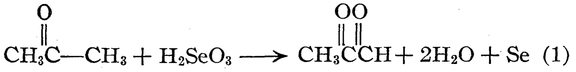
LABORATORY OF ORGANIC CHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN

RECEIVED SEPTEMBER 4, 1947

Kinetics of the Oxidation of Acetone by Selenious Acid

BY FREDERICK R. DUKE

The discovery of intermediates in appreciable concentration during the glycol-splitting type of specific oxidation[1] prompted this investigation of the selenious acid–acetone reaction. The stoichiometry is represented by the equation[2]



$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}—CH_3 + H_2SeO_3 \longrightarrow CH_3\overset{\overset{\displaystyle O}{\|}}{C}\overset{\overset{\displaystyle O}{\|}}{C}H + 2H_2O + Se \quad (1)$$

The reaction was studied extensively by Mel'nikov and Rokitskaya.[3] They found that the common alkyl esters of selenious acid decomposed at high temperatures to yield the corresponding aldehyde or ketone and selenium, and from this concluded that the oxidation of aldehydes and ketones proceeded through the enol ester intermediate. Data on the ease of oxidation of a series of aldehydes and ketones was used by these investigators to arrange the compounds in order of ease of enolization.

In the present investigation, the effects of high hydrogen ion and acetone concentrations on the rate of the reaction were studied in an attempt to demonstrate kinetically the presence of an intermediate. The data obtained clearly show that no appreciable amount of intermediate accumulates; however, certain conclusions may be drawn from the results and these are presented below.

Experimental

C. P. reagents were used. The specific gravity of the acetone was 0.7890 (25°/4°), fixing the water content at less than 1.5%.[4] Fifty-ml. volumetric flasks were used as reaction vessels; in Experiments I the appropriate amount of 5 *M* perchloric acid, 5 *M* sodium perchlorate, pure water and acetone and 2.0 ml. of 0.1 *M* selenious acid were pipetted into the flasks; then the latter were filled to the mark with *t*-butanol. After fifteen minutes in the constant temperature bath, sampling was begun with a 5-ml. pipet. The samples were quenched in acidified 5% KI solution, and the iodine titrated with 0.01 *N* thiosulfate. *t*-Butanol was used to maintain the reaction mixture at approximately constant dielectric as the acetone concentration was varied; the alcohol possesses the additional desirable property of low reactivity in esterification and aldol formation.

Experiments II were run in the same manner as Experiments I, except that the reacting mixture was prepared from 2 *M* acetone and 2 *M* perchloric acid. The acetone concentration was kept sufficiently low that the solutions in all cases may be considered truly aqueous. Sodium perchlorate was added where necessary to maintain constant ionic strength.

Experiments III were identical with the low-temperature runs of Experiment I except that the water concentration was varied and the acetone kept constant.

The constant temperature-bath was water maintained to ±0.1°.

Results.—In each of the experiments, the concentrations of reactants were chosen such that

---

(3) All melting points are corrected.

(4) Procured from Electrochemicals Department, E. I. du Pont de Nemours and Company.

(5) Stobbe, *Ann.*, **308**, 114 (1899).

(1) Duke, THIS JOURNAL, **69**, 2885 (1947); **69**, 3054 (1947).

(2) Riley, Morley and Friend, *J. Chem. Soc.*, 1875–1883 (1932).

(3) Mel'nikov and Rokitskaya, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 1532–1538, 2738–2746 (1937); **8**, 1369–1380 (1938); **9**, 1158–1161, 1808–1812 (1939); **10**, 1439–1441, 1713–1716 (1940).

(4) Hughes and Hartley, *Phil. Mag.*, [7] **15**, 61 (1933).

essentially only the selenious acid concentration changed. Plots of log $[H_2SeO_3]$ *vs.* time yielded straight lines, the slopes being the first order (in oxidant) pseudoconstants.

The results of Experiments I are listed in Table I. It is evident that the reaction is first-order in acetone over a wide range of concentration. Experiments II (Table II) run at relatively low acetone concentrations and in aqueous solution to ensure incontrovertible meaning for $[H^+]$, demonstrate that equation I holds over a wide range of acidity

$$-d[H_2SeO_3]/dt = k\,[\text{acetone}][H_2SeO_3][H^+] \quad \text{(I)}$$

No acidities lower than 0.04 *N* were studied because at higher *p*H values the loss of selenious acid from solution would invalidate the assumption that $[H^+]$ remains constant throughout a given run.

TABLE I

PSEUDO-CONSTANTS (1/MIN.) IN WATER–*t*-BUTANOL MIXTURES

$[H_2O] = 22.2$, $[H^+] = 0.50$, concentrations in m./l.

	T 43.1°		*T* 24.0°	
[acetone]	$k' \times 10^3$	$k' \times 10^3$/[acetone]	$k' \times 10^3$	$k' \times 10^3$/[acetone]
1.34	1.64	1.22	0.192	0.143
2.01	2.56	1.27	.290	.144
2.68	3.333	1.24	...	...
3.35	..	..	.488	.146
4.69	5.55	1.18	.680	.145
6.70	7.41	1.11	1.03	.154

TABLE II

PSEUDO-CONSTANTS (1/MIN.) IN AQUEOUS SOLUTION

Concentrations in m./l., *T* 47.1°

$[H^+] = 0.10$			[Acetone] = 0.30		
[acetone]	$k' \times 10^5$	$k' \times 10^5$/[acetone]	$[H^+]$	$k' \times 10^5$	$k' \times 10^5/[H^+]$
0.04	0.83	20.8	0.04	2.40	60
.10	2.08	20.8	.10	7.04	70
.20	4.00	20.0	.20	13.0	65
.30	7.04	23.5	.30	20.0	67
.50	12.5	25.0	.50	31.3	63

TABLE III

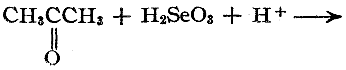
PSEUDO-CONSTANTS (1/MIN.) IN WATER–*t*-BUTANOL MIXTURES

$[H^+] = 0.50$, [acetone] = 4.69, *T* 24.0, concentrations in m./l.

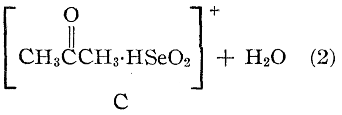
$[H_2O]$	$k' \times 10^3$	$k' \times 10^3 \times [H_2O]$
11.1	0.80	8.9
16.6	.74	11.9
22.2	.68	15.1
33.3	.63	21.0

Experiments III indicate that an increase in the concentration of water results in a lowered reaction rate. These results are discussed below.

Discussion.—Since the stoichiometry of reaction (1), contrary to the kinetics data, requires no hydrogen ion, the logical conclusion is that an intermediate, C, is formed



$$CH_3\underset{\underset{O}{\|}}{C}CH_3 + H_2SeO_3 + H^+ \longrightarrow$$



$$\underset{C}{\left[CH_3\overset{\overset{O}{\|}}{C}CH_3{\cdot}HSeO_2\right]^+} + H_2O \quad (2)$$

(C, as written, is not intended to include an implication of structure.) Reaction (2) presents two alternative possibilities: that the rate of formation of C is the measurable reaction, equation I correctly designating the kinetics; or that reaction (2) is an equilibrium reaction with $K = [C][H_2O]/[\text{acetone}][H_2SeO_3][H^+]$. In the latter case, the correct kinetics expression is $-d[H_2SeO_3]/dt = kK[\text{acetone}][H_2SeO_3][H^+]/[H_2O]$, since the data demonstrate that no detectable concentration of C is present. The variation in rate with water concentration (Table III) is in the right direction for this equation but is as reasonably explained by changes in activities of reactants with change of solvent. Thus, although no definite conclusion may be reached concerning these possibilities, it seems likely that equation I correctly expresses the kinetics. On this basis, the activation energy for reaction (2) may be calculated to be 18 kcal. per mole.

The Nature of the Intermediate.—One possible structure for C, postulated by Mel'nikov and Rokitskaya[2] is the enol ester. However, Olivier and Berge[5] have shown that for acids similar to selenious, the rate of esterification is not proportional to $[H^+]$. In addition, the oxidation proceeds at a negligible rate in alkaline solution (experiment not reported) under conditions favoring both enolization and esterification. Further, Michaelis and Landmann[6] have demonstrated that diethyl selenite is easily decomposed by pure water, a characteristic of esters whose rates of formation and hydrolysis are relatively independent of acidity.

Consideration of a second structure is dictated by the reaction under similar conditions of sulfurous acid, the closest analog of selenious acid. The preponderance of evidence[7] indicates that acetone and sulfurous acid react to yield an α-hydroxysulfonic acid, the analog being an α-hydroxyselenonic acid. Since, however, no compounds of the type $RSeO_3H$ have ever been prepared directly from selenious acid in spite of repeated attempts to do so,[8] and since the reaction rate of sulfurous acid with carbonyl compounds is inverse to $[H^+]$,[9] it does not seem that the selenonic acid structure deserves further consideration.

The demonstrated basicity of acetone toward selenium dioxide[10] is the basis for a third possibil-

[5] Olivier and Berge, *Rec. trav. chim.*, **41**, 637 (1922); **46**, 861 (1927).

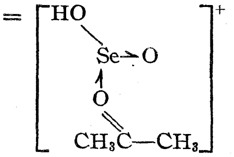
[6] Michaelis and Landmann, *Ann.*, **241**, 150 (1887).

[7] Raschig and Prahl, *Ber.*, **61B**, 179–189 (1928); Stelling, *Cellulosechemie*, **9**, 100–102 (1928); Lauer and Langkammerer, THIS JOURNAL, **57**, 2360–2362 (1935).

[8] Strecker and Daniel, *Ann.*, **462**, 186 (1928).

[9] Stewart and Donnally, THIS JOURNAL, **54**, 3555 (1932).

[10] F. Feigl and E. Feigl, *Z. anorg. allgem. Chem.*, **203**, 60 (1932).

ity =  where the acetone has displaced a hydroxyl ion from the selenium. In favor of this structure, one may cite the complete agreement with the kinetic evidence; but also, the subsequent disproportionation of the intermediate to pyruvaldehyde and selenium is most reasonable. The coördination of the acetone through its oxygen necessarily results in a redistribution of charge within the acetone molecule which would result in enhanced reactivity of the α-hydrogens; and it is not unlikely that the bond distances and angles in the complex are such that the selenium oxygens are placed in a favorable steric position for reaction with α-carbon.

KEDZIE CHEMICAL LABORATORY
MICHIGAN STATE COLLEGE
EAST LANSING, MICHIGAN
RECEIVED AUGUST 1, 1947

Iodometric Analysis of *o*-Nitrobenzeneseleninic Acid

BY OLAV FOSS

o-Nitrobenzeneseleninic acid has been found to react with thiosulfuric acid as follows

$$o\text{-}O_2NC_6H_4Se(O)OH + 3S_2O_3^{--} + 3H^+ = o\text{-}O_2NC_6H_4SeS_2O_3^- + S_4O_6^{--} + 2H_2O$$

The reaction is rapid and quantitative. The reaction product, *o*-nitrobenzeneselenenyl thiosulfate, has previously been isolated as a potassium salt by the reaction of *o*-nitrobenzeneselenenyl bromide with potassium thiosulfate,[1] and is also formed in reactions of various *o*-nitrobenzeneselenenyl sulfur compounds with thiosulfate.[1] It forms yellowish green, stable solutions. In neutral and acid solutions it is indifferent to iodine and does not interfere with iodine–thiosulfate titrations carried out in the same solutions. Hence the above reaction may be utilized for the iodometric analysis of *o*-nitrobenzeneseleninic acid, excess of thiosulfate being back-titrated with iodine. The following procedure may be employed.

To 12–20 mg. of *o*-nitrobenzeneseleninic acid dissolved in 25 ml. of water are added 5 ml. of 0.1 *N* sulfuric acid and then 20–30 ml. of 0.01 *N* sodium thiosulfate (5 ml. excess). After standing for two to three minutes at room temperature, starch is added, and the excess of thiosulfate is back-titrated with 0.01 *N* iodine.

Notice may be made to the analogous method of Norris and Fay[2] for the iodometric analysis of selenious acid, by means of the change

$$SeO_2 + 4S_2O_3^{--} + 4H^+ = Se(S_2O_3)_2^{--} + S_4O_6^{--} + 2H_2O$$

Experimental

The *o*-nitrobenzeneseleninic acid employed was prepared from the trichloride by hydrolysis,[3] and recrystallized from water until colorless.

0.1589 g. of the acid was dissolved to 250 ml. in water in a volumetric flask. Twenty-five ml. was pipetted out and 5 ml. 0.1 *N* sulfuric acid and then 25 ml. 0.01 *N* sodium thiosulfate (consuming 24.79 ml. of 0.01078 *N* iodine) were added. The time of standing was 2, 2, 5, 5, 8, 8 minutes. Amounts of 0.01078 *N* iodine then consumed: 5.95, 5.92, 5.92, 5.93, 5.92, 5.93 ml., respectively. Average: 5.93 ml., which gives 0.1585 g. of *o*-nitrobenzeneseleninic acid, *i.e.*, 99.7%.

Indifference of *o*-nitrobenzeneselenenyl thiosulfate to iodine. To 25 ml. of 0.01 *N* sodium thiosulfate were added 5 ml. 10% acetic acid, 5 ml. of starch solution, and (a) 20 ml. of water, (b) 20 ml. of 0.01 *M* potassium *o*-nitrobenzeneselenenyl thiosulfate. The solutions were then titrated with 0.01 *N* iodine. Amounts consumed: (a) 24.49, 24.50 ml. (b) 24.50, 24.50, 24.49 ml.

---

[1] Foss, THIS JOURNAL, **69**, 2236 (1947).

[2] Norris and Fay, *Am. Chem. J.*, **18**, 703 (1896); **23**, 119 (1900).

[3] Behaghel and Seibert, *Ber.*, **66**, 708 (1933).

INSTITUTT FOR UORGANISK KJEMI
NORGES TEKNISKE HÖGSKOLE
TRONDHEIM, NORWAY
RECEIVED AUGUST 22, 1947

Mixed Crystal Formation in Linear Copolyesters

BY C. S. FULLER

Slagle and Ott[1] showed that solidified mixes of normal aliphatic acids frequently exhibit a single X-ray spacing along the direction of the molecule axes in the mixed crystal. The purpose of this note is to point out that an analogous behavior occurs in copolymers in which the constituents are ethylene glycol dibasic acid residues of different chain lengths and, presumably, are randomly distributed along the long chain molecules.

A copolyester capable of being cold drawn into strong fibers was prepared by treating equal molar quantities of pure 10-, 11- and 12-membered aliphatic dicarboxylic acids with ethylene glycol. The X-ray fiber diagram of the copolymer (Fig. 1 (a)) is similar to that exhibited by many simple linear polyesters.[2] A mixed crystal is therefore indicated.

The average fiber period for the copolyester measures 17.83 Å. This value was obtained from the three strongest layer-line reflections (17.78, 18.00, 17.70). The fiber periods of the constituent ethylene polyesters prepared from the individual pure dibasic acids according to the same procedure are as follows ·

Ethylene decane 1-10 polyester	16.86 Å.
Ethylene undecane 1-11 polyester	36.32 (18.16 Å.)
Ethylene dodecane 1-12 polyester	19.40 Å.

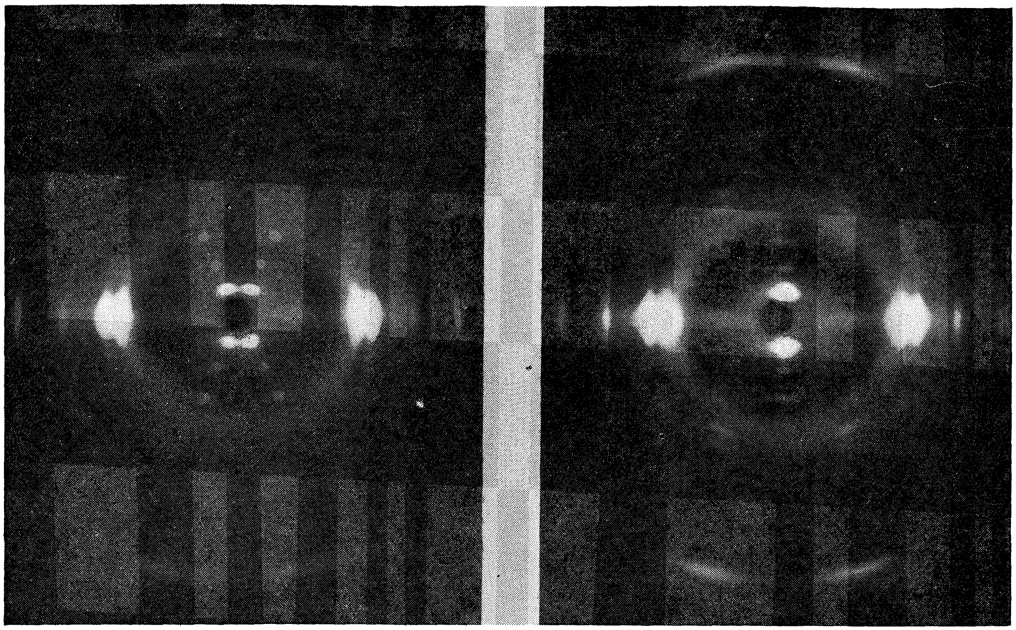
The odd number of chain atoms in the 1-11 polyester causes a doubling of the fiber period. In addition, as the fiber pattern of Fig. 1b shows, the polar layers are perpendicular to the fiber axis unlike the even polyesters in which these planes are inclined to the axis.[3] It is noteworthy that (insofar as we can speak of polar layers in the copolymer) the pattern of the copolyester exhibits

---

[1] Slagle and Ott, THIS JOURNAL, **55**, 4396 (1933).

[2] Carothers and Hill, *ibid.*, **54**, 1579 (1932).

[3] Fuller and Frosch, *J. Phys. Chem.*, **43**, 323 (1939).



(a) Ethylene 10,11,12 copolyester. (b) Ethylene 11 polyester.

Fig. 1.—X-Ray fiber patterns of ethylene 10,11,12 dibasic acids copolyester (a) and ethylene 11 dibasic acid polyester (b). Fiber axes vertical. Photographs have been retouched to assist reproduction.

layer-line reflections corresponding to *inclined* polar layers.

The fiber period of 17.83 Å. observed for the copolyester is somewhat lower than the value (18.03) obtained by averaging the three repeating lengths of the pure polyesters (19.40, 18.16, 16.84). However, it seems unlikely that an accuracy of greater than ±0.15 Å. can be expected in these measurements. Consequently, for the purposes of the present work the observed fiber period of the copolyester may be considered to be the same as the average of the lengths of the units which have been put into the copolymer.

The presence of pyramidal rather than meridian reflections in the copolyester indicates a preponderance of the staggered over the horizontal type of packing of the polar groups of adjacent chains. This might be anticipated from the fact that there are two "even" type units in the chain molecules to every one of the "odd" type. Strong meridian reflections must occur at the Bragg spacings corresponding to the approximate C–C component distance (1.25) along the fiber axis, but this is only observable with electron rays.[4]

We conclude from these results that a fiber pattern showing discrete reflections can be obtained from random copolymers composed of units which are able to crystallize together such as those comprising chain hydrocarbon spacers and small side polar groups. When equal numbers of units are present, the fiber period observed under such circumstances is given by the averages of those of the units present, but it bears no real relation to the structure present. There is evidence, however, that the longitudinal adjustment of adjacent chains is not random but is determined by the dipole interactions in such a way as to provide a minimum free energy for the entire structure. Recently Bunn and Peiser[5] reported a similar instance to that described here for a copolymer consisting of ethylene and hydroxyl substituted ethylene units. Bunn gives no information however about the kind of polar packing exhibited, so a full comparison with the results here reported is not possible.

Experimental

The polyesters were prepared by passing dry hydrogen through mixtures of the reactants at 200° until the degree of condensation was sufficient to allow fibers to be cold-drawn from solidified filaments. The dibasic acids all melted sharply and agreed with literature values for the respective compounds. The sebacic acid (m. p. 133°) was distilled from the commercial product. The 11- and 12-member acids (m. p.'s 110 and 124°) were prepared from 11-hydroxyundecylic acid and ω-bromoundecylic acid, respectively. From ultimate analysis the 11 member acid was estimated to be 97% pure. The ethylene glycol was redistilled from the C. P. laboratory product. About 5% excess of the equivalent amount of glycol needed for reaction was added and the mixture pre-condensed at about 120° until most of the water was removed. The condensation was then continued at 200° in bubbling hydrogen until the cold-drawing stage was reached.

The X-ray diagrams were taken on individual uniaxially oriented specimens. Filtered copper radiation was employed. Sodium chloride was dusted on the specimens as a reference standard. The fiber periods were calculated from the best reflections on several photographs. Five photographs were used to obtain the fiber period of the 14-membered polyester (16.84), four for the 15-

---

[4] K. H. Storks, This Journal, **60**, 1753 (1938).

[5] Bunn and Peiser, *Nature*, **159**, 161 (1947).

member (36.32) and three for the 16-member (19.40). The fiber period of the copolyester (17.83) was taken from one sharp fiber pattern obtained at 6 cm.

Acknowledgment.—The author is indebted to B. S. Biggs, W. S. Bishop and R. H. Erickson for the preparation of the intermediates and the polyesters and to N. R. Pape for taking and measuring the photographs.

BELL TELEPHONE LABORATORY
MURRAY HILL, NEW JERSEY
RECEIVED JULY 31, 1947

Some Halogenated Naphthoxyacetic Acids[1]—A Confirmation

BY C. ROBERT GEISER AND HOKE S. GREENE

The preparation of 2,4-dichloro-1-naphthoxyacetic acid, 1,6-dibromo-2-naphthoxyacetic acid, 4-chloro-1-naphthoxyacetic acid, and 2,4-dibromo-1-naphthoxyacetic acid reported by Haskelberg[2] has been independently confirmed by us using similar methods. Templeman and Sexton[3] had previously reported the melting point of 2,4-dichloro-1-naphthoxyacetic acid as 135° but we have found it to be 178° in agreement with Haskelberg.[2]

The aforementioned compounds showed selectivity as weed killers in 0.1% solution as a triethanolamine salt. However, at that concentration they were not as effective as 2,4-dichlorophenoxyacetic acid.

(1) From the M.S. thesis of C. Robert Geiser, University of Cincinnati, June, 1947.

(2) L. Haskelberg, *J. Org. Chem.*, **12**, 426 (1947).

(3) Templeton and Sexton, *Proc. Roy. Soc.* (*London*), **B133**, 300–313 (1946).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CINCINNATI
CINCINNATI, OHIO
RECEIVED JUNE 30, 1947

Separation of Tropic and Atropic Acids by Partition Chromatography

BY SIDNEY GOTTLIEB

In the course of a study on the hydrolysis of alkaloids of the atropine group, it became necessary to separate tropic from atropic acids in a large number of hydrolysates. Although the solubility characteristics of these two acids permit their separation from one another by several steps involving fractional crystallization, a much more rapid and convenient method was developed using partition chromatography.

This technique, originally developed by Martin and Synge,[1] consists essentially of passing one of a pair of immiscible solvents over a film of the other, the latter solvent being adsorbed onto an inert lattice. The substances dissolved in the mobile solvent will then partition themselves between the two phases according to their partition coefficients in such a way as to form distinct bands. Since tropic and atropic acids differ significantly in their partition coefficients between water and chloroform, this pair of solvents was used, with precipitated silicic acid as the supporting lattice. An acid–base indicator in the form of an azo dye was incorporated into the aqueous phase and, as the acids moved down the column, their positions were clearly indicated by dark blue bands against a red background.

In several parallel determinations, the identity of the first fraction to come through the column was established as atropic acid by evaporating the solvent and recrystallizing the residue once from hot water, which yielded monoclinic prisms, m. p. 106.0–106.5° (cor.). That the material comprising the upper band was tropic acid was proved by evaporating the solvent and recrystallizing the residue twice from boiling benzene to yield needes, m. p. 116.0–117.0° (cor.).

Experimental

A typical column was prepared by intimately mixing 10 cc. of a 0.1% aqueous solution of 3,6-disulfo-β-naphthaleneazo-N-phenyl-α-naphthylamine[2] with 20 g. of dry precipitated silicic acid. In this investigation Eimer and Amend C. P. silicic acid, batch #403320, was used. The mixing was done with a mortar and pestle until the mixture had uniformly taken on the red color of the dye, and no lumpiness remained. A slurry of this preparation was made with 50 cc. of chloroform and the slurry poured into a glass tube having a diameter of 24 mm., constricted and plugged with cotton at one end. When enough chloroform had run through the column so that the suspension acted like a stiff gel on shaking, a mixture of 5 mg. each of tropic and atropic acids dissolved in 3 cc. of chloroform was pipetted into the column. After this solution had just passed the top of the column, 5 cc. of chloroform was added to wash any acid remaining on the sides of the column into the narrow band. Then 50 cc. of chloroform was run through the column to separate and develop the bands. The atropic acid, being more soluble in chloroform, moved rapidly down in a sharp band, usually being completely washed out by 40 cc. of chloroform. The upper band, containing the slower-moving tropic acid, which had moved about one-fourth of the way down the column, was then washed through with a mixture of 10% butyl alcohol in chloroform. Titration of the residues with $N/50$ sodium hydroxide indicated essentially quantitative recovery and separation of the two acids.

---

(1) Martin and Synge, *Biochem. J.*, **35**, 1358 (1941).

(2) Liddel and Rydon, *Biochem. J.*, **38**, 68 (1944).

CHEMICAL SECTION, MEDICAL DIVISION
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D. C.
RECEIVED JULY 25, 1947

The Existence of Beta Cristobalite at Room Temperature

BY ALEXANDER GRENALL

Due to some unexplained circumstance, overheating of pelleted clay catalyst occurred in the regenerator kiln of a catalytic cracking unit to such a degree that some of the pellets were fused and glassy in appearance. On breaking open these pellets it was found that while the surfaces were glassy, the centers were not.

Independent X-ray diffraction examinations were made of the surface and center material. A complete analysis of the diffraction data from Debye–Scherrer photographs revealed, in addition to other phases, the presence of β-cristobalite in the glassy surface of the pellets and the existence of α-cristobalite in the centers. The identity of these substances was established by comparison of the data from this work with that for β- and α-cristobalite given by the A.S.T.M. index,[1] excellent agreement in line position and relative intensities being shown.

Sosman,[2] in his authoritative treatise on silica, states that the inversion of the high temperature form, β-cristobalite, to the low temperature form, α-cristobalite, is rapid and occurs promptly as soon as the inversion temperature range of 200 to 275° is reached. In order to substantiate our identification of the β-cristobalite pattern for the overheated catalyst, a literature search was made and two other reported instances in which β-cristobalite had been identified in room temperature samples were found: in opals[3,4] and in glassy matrices containing silica.[4] In the latter publication this phenomenon was attributed to the prevention of inversion by the glassy matrix in which the crystals of β-cristobalite existed. Sosman[2,5] has denied the possibility of maintaining the beta structure by quenching but[5] has kept open the possibility that in a glass this might occur and asked for further study.

Our results are of interest because the cristobalite in the glassy surface of the fused clay catalyst pellets was shown to be the beta form while in the non-glassy interior, complete inversion to the alpha form had taken place. This provides an excellent confirmation of Greig's[4] contentions that the high-low inversion of cristobalite may be restrained and the high temperature form, β-cristobalite, may exist indefinitely at room temperature when the crystals of cristobalite are formed in a glassy medium. At the same time the results on the non-glassy centers are in agreement with Sosman's contention that the transformation to the alpha form cannot be delayed by quenching, if now this statement is qualified to apply to the changes occurring in a non-enclosing solid medium. As demonstrated by Greig,[4] when adhesion between enclosing medium and cristobalite crystal is broken, then inversion to the low temperature form takes place readily. Furthermore, from his results, it appears that once the α form has been developed, cristobalite may be taken up and down through the high-low inversion point with rapid transformation into the phase expected in complete accord with Sosman's statement.

It may be of significance to researchers in the field of ceramics to note that the diffraction patterns of both α- and β-cristobalite showed practically the same extent of line broadening. From the information that line broadening is present, it is possible to fix an upper limit to the crystal size of the cristobalites at 10^{-5} cm. Since the lines are only moderately broadened by comparison with sharp diffraction lines of the other phases present it is estimated that the crystal size lies between 5×10^{-6} and 10^{-5} cm.

---

[1] First Supplement to the card file of X-ray diffraction data published by the American Society for Testing Materials, 1944.

[2] R. B. Sosman, "Properties of Silica," A. C. S. Monograph Series 37, Reinhold Publishing Corp., New York, N. Y., 1927, p. 126.

[3] I. Levin and E. Ott, THIS JOURNAL, **54**, 828 (1932).

[4] J. W. Greig, *ibid.*, **54**, 2846 (1932).

[5] R. B. Sosman, *ibid.*, **54**, 3015 (1932).

THE UNION OIL COMPANY OF CALIFORNIA
WILMINGTON, CALIFORNIA
RECEIVED JUNE 16, 1947

Crystallization of Triacetin

BY BERNARD HANCOCK, DONALD M. SYLVESTER AND SYLVAN E. FORMAN

Triacetin has been reported to form a glass at −78 and at −60°.[1] We have observed triacetin to crystallize at +3.2°.

A tank car of impure triacetin which had been shipped a long distance in cold weather was received with the contents partly solidified. Some of this slush was kept overnight in a refrigerator at +5°, but the solids had melted before morning.

The melt would not crystallize when cooled with dry ice or with an ice and salt mixture, but a portion diluted with an equal volume of absolute ethyl alcohol was crystallized readily by cooling to about −10 or −15°. Several such portions were crystallized on that day and some crystals were preserved in an ice and salt mixture.

On subsequent occasions, crystallizations of triacetin samples were induced by seeding. However, no crystals could be obtained without this aid.

A sample of triacetin was distilled at 130.5° (7 mm.). It had $n^{26}\mathrm{D}$ 1.4288 and gave saponification equivalents of 72.42 and 72.35 (theory 72.70). Five small portions were cooled to about −15° and the first one was seeded with triacetin. This tube was used to seed the second tube, the second to seed the third, and so forth. This procedure was carried out to prevent impurities from being transferred by the seed crystals. Finally about 10 ml. of pure triacetin in a shielded tube was cooled to about −15° and seeded from the fifth tube. The temperature rose to +3.2° (cor.) where it remained until all of the solid melted.

The triacetin was converted into glycerol and ethyl acetate with ethyl alcohol and a trace of sulfuric acid. The glycerol was vacuum steam distilled. It was 98.5% glycerol by acetylation and 1.3% water by Karl Fischer titration; $n^{25}\mathrm{D}$ 1.4698.

The ethyl acetate was purified by extraction with water followed by rectification. It distilled at 77° and was 99.3% pure by saponification.

---

[1] "Beilstein," Vol. II, first supplement, p. 70; second supplement, p. 161.

TECHNICAL DEVELOPMENT LABORATORY
U. S. INDUSTRIAL CHEMICALS, INC.
BALTIMORE, MARYLAND
RECEIVED JUNE 25, 1947

Alpha and Beta Schardinger Dextrin Nitrates

BY N. S. GRUENHUT, M. L. CUSHING AND G. V. CAESAR

French and Rundle[1] have accurately determined by X-ray diffraction and crystal density measurements the molecular weights of the α and β-Schardinger dextrins. The α-dextrin was shown to consist of six, and the β-dextrin of

---

[1] French and Rundle, THIS JOURNAL, **64**, 1651 (1942).

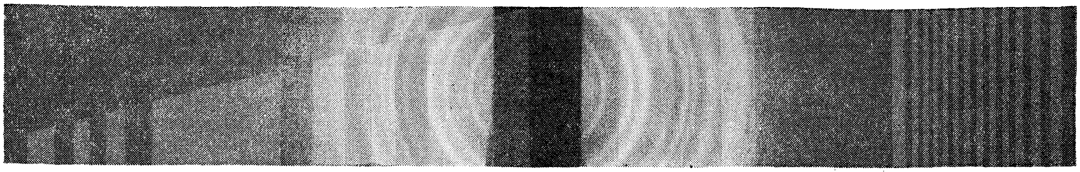


Fig. 1a.—Schardinger α-dextrin nitrate.

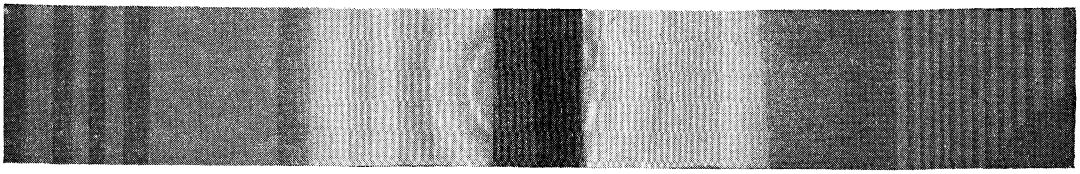


Fig. 1b.—Schardinger β-dextrin nitrate.

seven glucose residues. During the course of recent molecular weight determinations of completely nitrated starches and dextrins by means of the Barger isopiestic method[2] we decided to check the Barger technique on nitric esters of the crystalline Schardinger dextrins, compounds previously described only once.[3]

We were able to nitrate without difficulty the Schardinger α and β-dextrins, employing nitrogen pentoxide in chloroform in the presence of sodium fluoride according to a method previously described.[4]

Proof of the crystalline character of these Schardinger dextrin nitric esters is attested by the photographs (Fig. 1) of their X-ray powder patterns.[5]

The derivation $c \rightarrow 0$ of number average molecular weights, determined by the Barger method,[2] is shown graphically in Fig. 2. Values of *ca.* 1,700 for the α-dextrin nitrate and 2,000 for the β-nitrate were obtained. The observed nitrogen contents were 13.61 and 13.52%, respectively.[6] From these nitrogen values the calculated molecular weights are1, 728 and 2,009, respectively, assuming six and seven glucose residues. Complete nitration of Schardinger dextrins should yield 14.14% N. The observed degree of nitration is lower than anticipated from previous experience with starches and dextrins under similar conditions,[4] and is attributed tentatively to steric hindrance in a ring structure.

Intrinsic viscosities, $[\eta] = \lim_{c \to 0} \eta_{sp}/c$, were determined in ethyl acetate solution. The $[\eta]$ of the α-dextrin nitrate was 0.048, of the β-dextrin nitrate 0.080.

The Schardinger dextrin nitrates failed to exhibit a sharp melting point. The α-dextrin nitrate began to decompose slowly at 167–168°, the β-nitrate at 184–186°.

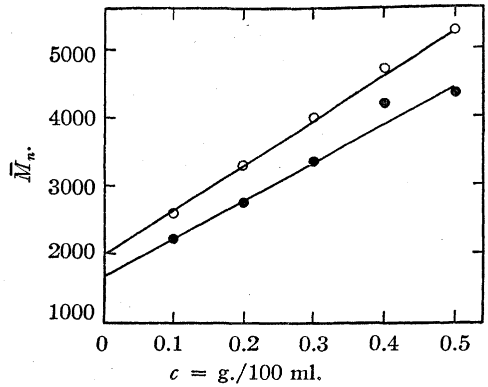


Fig. 2.—Schardinger dextrin nitrates; derivation of $\bar{M}_{nc \rightarrow 0}$ in ethyl acetate: ●, α; ○, β-dextrin.

Experimental

Preparation of Schardinger Dextrin Nitrates.—A chloroform solution of 250 ml. containing 47.3 g. of nitrogen pentoxide was cooled to −15°. Ten grams of sodium fluoride was added and the dispersion mechanically agitated during the slow addition of 10 g. of dried crystalline Schardinger dextrin.[7] The temperature was allowed to rise slowly to 8° during a reaction period of one hour. The nitrated dextrin, admixed with sodium fluoride, was removed by filtration, purified and stabilized according to the procedure elsewhere described.[4]

Molecular Weight and Intrinsic Viscosity Determinations.—These were determined according to procedures elsewhere described.[2]

X-Ray Diffraction Patterns.[5]—These (Fig. 1) were obtained with a cylindrical camera of approximately 10 cm. radius using filtered copper radiation.

Acknowledgment.—The authors wish to express their appreciation to Dr. C. S. Hudson for the Schardinger dextrins and for helpful suggestions, also to Dr. G. C. Nutting and F. R. Senti for the X-ray diffraction photographs.

RESEARCH LABORATORY
STEIN HALL AND CO.
NEW YORK, N. Y.

RECEIVED JUNE 4, 1947

---

[2] Caesar, Gruenhut and Cushing, *ibid.*, **69**, 617 (1947).

[3] Pringsheim, *et al.*, *Ber.*, **58**, 1889 (1925).

[4] Caesar and Goldfrank, THIS JOURNAL, **68**, 372 (1946).

[5] Courtesy of the Eastern Regional Research Laboratory, Phila., Pa., Phys. Chem. Sec., F. R. Senti.

[6] Nitrometer determinations by Mr. Leslie M. Redman, Organic Research Laboratory, Massachusetts Institute of Technology.

[7] Courtesy of C. S. Hudson, National Institute of Health, Bethesda, Md.

Synthesis of Ketones from Aliphatic Nitriles and Phenylmagnesium Bromide

BY CHARLES R. HAUSER, WILBERT J. HUMPHLETT AND MARTIN J. WEISS

Shriner and Turner[1] have shown that, in the synthesis of acetophenone from acetonitrile and phenylmagnesium bromide, the best result is obtained with a 300% excess of the Grignard reagent. Accordingly these workers employed this large excess of the reagent in corresponding reactions with higher homologs of acetonitrile. Apparently on this basis the statement has been made in texts[2] that, with the higher aliphatic nitriles, as well as acetonitrile, the large excess of the Grignard reagent is necessary for satisfactory yields of ketones. However, Bary[3] had reported previously that a 90% yield of butyrophenone is obtained from butyronitrile with a 50% excess of phenylmagnesium bromide.

In the present investigation, high yields of ketones have been obtained from propionitrile and higher homologs through *n*-capronitrile with only a 10% excess of phenylmagnesium bromide. These results, and also the corresponding cases reported by Shriner and Turner,[1] are given in Table I. With the three higher nitriles, our results appear even slightly better than those from the large excess of the Grignard reagent.

It should be pointed out that, with ethylmagnesium bromide and propionitrile, we have obtained only a 23% yield of diethyl ketone (b. p. 101–105°) using a 10% excess of the reagent. Earlier workers[4] have similarly reported only fair yields of ketones with this aliphatic Grignard reagent and propionitrile or butyronitrile.

TABLE I

YIELDS OF KETONES FROM ALIPHATIC NITRILES AND PHENYLMAGNESIUM BROMIDE

Nitrile	Ketones, 10% excess Grignard B. p. °C.	Mm.	Yield, %	$n^{20}D$	Ketones, 300% excess Grig.[e] B. p. °C.	Mm.	Yield, %
Aceto	201–205		33	1.5344[a]	202–205		70
Propio	105–106	17	83	1.5270[b]	115–120	21	91
n-Butyro	121–123	20	82	1.5203[c]	125–130	21	77
n-Valero	139–141	24	83	1.5146[d]	135–140	25	79
n-Capro	137–138	13	89	1.5116	145–150	19	83

[a] "International Critical Tables," Vol. VII (compiled by C. J. West, National Research Council, McGraw-Hill Book Co., New York, N. Y., 1930, p. 43) gives 1.53427 at 19.1°. [b] Wallach, *Ann.*, **332**, 317 (1904). [c] "Handbook of Chemistry and Physics" (Chemical Rubber Publishing Co., 28th edition, 1944, p. 680) gives 1.52016 at 18.25°. [d] Layraud [*Bull. soc. chim.*, (3) **35**, 223 (1906)] gives 1.5152 at 19°. [e] Ref. 1.

Procedure.—In a 1-liter three-necked round-bottomed flask equipped through ground-glass joints with a mercury-sealed stirrer, dropping funnel, and a reflux condenser (having a drying tube) was placed 300 ml. of an ether solution containing 0.275 mole of phenylmagnesium bromide. To the stirred refluxing solution was added, during fifteen to twenty minutes, 0.250 mole of the nitrile in 125 ml. of dry ether. The stirring and refluxing was continued for one to six hours[5]; during the first hour a precipitate formed. The cooled mixture was decomposed with ice and acid and the ether removed on the steam-bath under an ether still. After heating for an hour longer to ensure hydrolysis of the ketimine, the ketone was extracted with four 150-ml. portions of ether. The solvent was distilled from the dried combined ether solutions and the residue distilled through a 15 cm. Vigreux column.

---

(1) Shriner and Turner, THIS JOURNAL, **52**, 1267 (1930).

(2) Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., New York, N. Y., 1936, p. 258; Fuson and Snyder, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1942, p. 270.

(3) Bary, *Bull. soc. chim. Belg.*, **31**, 397 (1922).

(4) See ref. 3 and Baerts, *ibid.*, **31**, 184 (1922).

(5) The yields given in Table I were obtained on six-hour runs but an equally good yield (85%) has been obtained in a one-hour run with butyronitrile.

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, N. C.

RECEIVED AUGUST 18, 1947

Some Azeotropes of Alkylacetylenes and Ethyl Alcohol[1]

BY G. F. HENNION AND J. J. GROEBNER

Azeotropic distillation is a well-known means for the separation and purification of various hydrocarbons and data are available for many hydrocarbon-carrier systems. Particular attention has been given to the azeotropes of paraffins, naphthenes, olefins, diolefins and aromatics. Since there is no information on constant boiling mixtures of higher acetylenes, we have investigated four acetylene–ethyl alcohol binaries. The data are given in Table I. When the boiling points of the azeotropes are plotted against their compositions a smooth curve is obtained, similar to, but appreciably above, the one for paraffins.[2]

The lowering of the hydrocarbon boiling point achieved by azeotropic distillation is greatest for paraffins and least for aromatics; the other hydrocarbons are intermediate and usually in the order cited above.[3] When the data for the acetylenes are compared with those of the other hydrocarbons it appears that the acetylenes fall between the aromatics and the others. Thus the

TABLE I

BINARY AZEOTROPES OF ALKYLACETYLENES AND ETHYL ALCOHOL

Acetylene[a]	Properties of azeotropes B. p., °C.			Acetylene	
		$n^{25}D$	d^{25}	Mole %	Wt. %
n-Butyl	62.8	1.3880	0.7264	65.0	76.8
Diethyl	67.5	1.3922	.7399	51.7	65.6
Isoamyl	71.0	1.3857	.7490	42.0	60.2
n-Amyl	74.2	1.3818	.7586	28.5	45.4

[a] The boiling points of the pure hydrocarbons were: *n*-butylacetylene, 70.2°; diethyl-, 80.5°; isoamyl-, 90.8°; *n*-amyl-, 99.5°. Other physical properties are cited by Hennion and Banigan, THIS JOURNAL, **68**, 1381 (1946).

---

(1) Paper LI on the chemistry of substituted acetylenes; previous paper, THIS JOURNAL, **68**, 1381 (1946).

(2) Mair, Glasgow and Rossini, *J. Research Natl. Bur. Standards*, **27**, 47 (1941).

(3) Rossini, Mair and Glasgow, *Oil Gas J.*, **158**, Nov. 14 (1940).

acetylene–alcohol mixtures boil slightly higher than those of the other classes of aliphatic hydrocarbons. This may prove to be significant should the problem of separating acetylenes from hydrocarbon mixtures ever present itself.

Analysis of the constant boiling acetylene–alcohol mixtures was accomplished both by refractive index and density. A sufficient number of mixtures was prepared in each case to establish both isotherms. All distillations were done at atmospheric pressure when the barometer read 745 ± 5 mm.

The acetylenes form ternary alcohol–water heteroazeotropes also. These were not analyzed although some of the data for them were recorded (Table II).

TABLE II

TERNARY HETEROAZEOTROPES OF ALKYLACETYLENES WITH ETHYL ALCOHOL AND WATER

Acetylene	Constant b. p., °C.	Vol. % lower layer[a]	Upper layer $n^{25}D$	Upper layer d^{25}	Lower layer $n^{25}D$	Lower layer d^{25}
n-Butyl	59.9	5.6	1.3921	0.7202	1.3598	0.8597
Diethyl	64.4	14.8	1.4025	.7290	1.3674	.8539
Isoamyl	69.0	17.4	1.3955	.7371	1.3672	.9519
n-Amyl	71.0	28.6	1.3970	.7436	1.3680	.8329

[a] These values are approximate and were measured at 25°.

Experimental

The acetylenes were prepared in the usual way from the alkyl bromides and sodium acetylide in liquid ammonia.[4] Absolute ethyl alcohol (Commercial Solvents Corp.) was redried with magnesium ethoxide immediately before use; d^{25} 0.7852, $n^{25}D$ 1.3594.

A carefully purified sample of each acetylene was mixed with an excess of amount of absolute alcohol and slowly distilled through a helix packed column having an efficiency of 15 plates as determined with an ethylene bromide–benzene mixture. The distillate was collected in fractions and those of nearly the same boiling point, density and refractive index were combined and redistilled. The process was repeated until successive fractions of the distillate showed practically the same composition, not altered by redistillation.

The ternary mixtures were obtained in substantially the same way, except that water was added to the still charge and the column was provided with a special head to prevent premature phase separation. The material which distilled at constant temperature was collected separately but was not redistilled since analysis was not intended.

---

(4) Vaughn, Vogt, Hennion and Nieuwland, *J. Org. Chem.*, **2**, 1 (1937).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NOTRE DAME
NOTRE DAME, INDIANA

RECEIVED AUGUST 20, 1947

Relative Association of Hydrogen and Deuterium Fluorides in the Liquid State

BY JOEL H. HILDEBRAND AND ALLEN GEE

Claussen and Hildebrand[1] found that the vapor pressure of deuterium fluoride is greater than that of hydrogen fluoride, the ratio, P_{DF}/P_{HF} varying from 1.150 at 240° K. to 1.049 at 290° K. The vapor pressure of the deuterium compound is greater than that of the hydrogen compound also in the case of the acetic acids, but it is less in the case of the two kinds of water and ammonia and with deuterium and hydrogen chloride. It was pointed out that the first two pairs are alike in being highly associated in the gaseous phase while the last three are not.

Long, Hildebrand and Morrell[2] determined the variation in the association factors of gaseous hydrogen fluoride and deuterium fluoride with pressure and temperature, showing deuterium fluoride to be more associated. They confirmed the earlier results of Simons and Hildebrand[3], who found that the association of hydrogen fluoride could be reproduced over a wide range by assuming the single equilibrium, $6HF = (HF)_6$, with evidence for smaller polymers below a degree of association represented by the association factor, 1.3. It has been recognized that polymers other than $(HF)_6$ may be present also in the range of higher association, and that the single equilibrium that has been assumed may represent only an average of a more complex scheme of association. The only reason for a preponderance of a hexamer would appear to be a closed ring with its additional hydrogen bond and with corresponding preferred bond angles.[4] However, no independent evidence for ring structure has yet been discovered, and the recent measurements of dielectric constant by Benesi and Smyth indicate linear polymers.[5]

This does not interfere with the purpose of this communication, which is to calculate the partial pressures of the monomers, p_{HF} and p_{DF}, in the saturated vapors in order to learn whether, in the liquid state, the hydrogen compound is less strongly associated than the deuterium compound, as in the cases of water and ammonia.

The following table gives the total pressures at saturation according to Claussen and Hildebrand together with the corresponding partial pressures of the monomers, calculated by the aid of the equations of Long, Hildebrand and Morrell. The ratio, p_{HF}/p_{DF}, is greater than unity, indicating stronger association of the deuterium compound in the liquid, and bringing these com-

TABLE I

T, °K.	Total pressure P_{HF}	Total pressure P_{DF}	Monomer pressure p_{HF}	Monomer pressure p_{DF}	Ratios P_{HF}/P_{DF}	Ratios p_{HF}/p_{DF}
270	314.0	340.1	140.7	133.0	0.923	1.057
280	468.9	499.5	232.8	220.5	.939	1.056
290	681.1	714.2	371.1	351.8	.953	1.055

---

(1) Wm. M. Claussen and J. H. Hildebrand, THIS JOURNAL, **56**, 1820 (1934).

(2) R. W. Long, J. H. Hildebrand and W. E. Morrell, *ibid.*, **65**, 182 (1943).

(3) J. H. Simons and J. H. Hildebrand, *ibid.*, **46**, 2138 (1924).

(4) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 298.

(5) H. A. Benesi and C. P. Smyth, *J. Chem. Phys.*, **15**, 337 (1947).

pounds into line with the corresponding waters and ammonias.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA

RECEIVED JULY 1, 1947

Chromatography of Some Common Indicators

BY J. V. KARABINOS[1] AND P. M. HYDE

Alumina,[2] calcium carbonate, talc, Super Cel and Hyflo Super Cel have been used successfully as adsorbents for the chromatography of coal tar dyes and indicators.[3] We wish to add to this list Silene EF[4] which has already found extensive use in the carbohydrate series.[5]

The relative degree of adsorption of the indicators on Silene EF–Celite 535[6] (5:1 by weight) was determined as follows. The indicator (0.75 mg.) dissolved in 0.4 ml. of 90% dioxane (90 ml. dioxane–10 ml. water) was put on a Tswett column (10 × 100 mm.) previously wetted with 0.5 ml. of the solvent and the indicator was developed with 5.0 ml. of 90% dioxane. The position of the colored zone was easily determined since the length of the column was calibrated in mm. (0, bottom; 100 mm., top). Checks were obtained in duplicate runs. Comparative data on the relative adsorption of the indicators on Silene EF–Alumina–Celite 535 (5:5:2 by weight) are also presented.

TABLE I

RELATIVE DEGREE OF ADSORPTION OF SOME INDICATORS

Indicator	Position of zone, mm. (color) Silene EF	Silene EF–Alumina
Aurin tricarboxylic acid, ammonium salt	99–100 (Br)	99–100 (Br)
Indigo carmine	99–100 (Bl)	99–100 (Bl)
Alizarin red S	98–100 (R)	98–100 (R)
Alizarin yellow R	98–100 (Y)	98–100 (Y)
Methyl violet	68–100 (Bl)	60–93 (Bl)
Dichlorofluorescein	91–96 (O)	97–98 (Y-O)
Congo red	85–90 (R)	97–100 (O)
Brom phenol blue	73–80 (P)	95–99 (P)
Brom cresol green	62–70 (Bl)	96–99 (Bl)
Chlor phenol red	60–70 (P)	95–98 (P)
Brom cresol purple	15–25 (P)	65–75 (P)
m-Cresolsulfonphthalein	15–25 (Y)	57–63 (O)
Methyl orange	5–20 (Y)	51–60 (Y)
Tropaeolin 00	8–18 (Y)	45–55 (Y)
o-Cresolphthalein	8–18 (Y)	47–55 (Y)
Thymol blue	0–10 (Y)	25–35 (Y)
Cresol red	8–15 (Y)	48–52 (Y)
Brom thymol blue	0–4 (Y)	0–2 (Y)
m-Nitrophenol	0	0
Phenolphthalein	0	0

It is interesting to note that the highly polar dyes, *e. g.*, the sodium salts are more strongly adsorbed.

CHEMICAL LABORATORY
UNIVERSITY OF SAN FRANCISCO
SAN FRANCISCO, CALIFORNIA

RECEIVED JUNE 30, 1947

---

[1] Present address: Department of Chemistry, St. Procopius College, Lisle, Illinois.

[2] C. P. grade, J. T. Baker Chemical Company, Phillipsburg, New Jersey.

[3] P. Ruggli and P. Jensen, *Helv. Chim. Acta*, **18**, 624 (1934); **19**, 64 (1936); P. Ruggli and M. Stauble, *ibid.*, **23**, 689 (1940); H. H. Strain, THIS JOURNAL, **61**, 1292 (1939); W. Rieman, *J. Chem. Ed.*, **18**, 131 (1941).

[4] A commercial hydrated calcium silicate generously supplied by the Columbia Chemical Division, Pittsburgh Plate Glass Co., Barberton, Ohio.

[5] L. W. Georges, R. S. Bower and M. L. Wolfrom, THIS JOURNAL, **68**, 2169 (1946).

[6] Johns-Manville Co., New York, N. Y.

Preparation of Resacetophenone

BY JOSEPH R. KILLELEA AND H. G. LINDWALL

The zinc chloride method commonly employed for the preparation of resacetophenone[1] involves a vacuum distillation and yields 65% of colored product. Since the vacuum distillation of high-melting solids is a troublesome process, we have adopted a boron fluoride method which eliminates the necessity of the distillation and gives superior yields of colorless product. Details are given below.

A mixture of resorcinol, 55.0 g. (0.5 mole), acetic anhydride, 54.5 g. (50.0 ml., 0.53 mole) and commercial anhydrous ether, 75 ml., is saturated with gaseous boron fluoride in an ice-bath. The mixture is then stored in a refrigerator for ninety-six hours. The heavy, yellow crystalline mass is broken up with a glass rod and the contents of the flask transferred to a beaker containing 200 g. of crushed ice. The ether is distilled off on a water-bath or allowed to evaporate in a good hood. The light yellow solid is washed with cold water. It weighs 73.0 g. (96%) and melts at 138–142°. It may be recrystallized from 1200 ml. of boiling water (Norit), the recovery being 69.0 g. of colorless solid (91%) melting at 144–145°.

A mixed melting point of this product with a sample prepared by the zinc chloride method showed no depression. The dibenzoate, prepared by Baker's method[2] melted at 80–81° mixed with the dibenzoate prepared from Cooper's product, 80–81°.

The boron fluoride method exemplified above has been employed, with slight modifications, in this Laboratory for the preparation of other polyhydroxyacetophenones.

---

[1] Cooper, "Org. Syn.," **21**, 103 (1941).

[2] Baker, *J. Chem. Soc.*, 1384 (1933).

WM. H. NICHOLS LABORATORY
NEW YORK UNIVERSITY
UNIVERSITY HEIGHTS
NEW YORK 53, N. Y.

RECEIVED AUGUST 9, 1947

Vanadium Oxide, a Hydrogenation Catalyst[1]

BY V. I. KOMAREWSKY, L. B. BOS AND J. R. COLEY

Vanadium oxide is widely used as an oxidation catalyst. It has also been reported to be an effective catalyst for the dehydrogenation of hydro-

---

[1] Presented before the Division of Petroleum Chemistry at the Atlantic City Meeting of the American Chemical Society, April 14, 1947.

carbons,[2] the hydrogenolysis of phenols[3] and of aliphatic alcohols.[4]

In this work a direct hydrogenation of unsaturated hydrocarbons in the presence of vanadium oxide catalyst is described.

Experimental

Apparatus and Procedure.—The catalytic hydrogenation procedure employed consisted of passing a three to one (by volume) mixture of hydrogen and vaporized unsaturated hydrocarbon over a granular (8–10 mesh) catalyst bed (volume, 50 cc.) maintained at uniform temperature by an electrically heated furnace. The rate of passage of the reactants through the Pyrex glass or steel reaction tubes (i. d. 15 mm.) was varied in the range of 0.01 to 1.00 liquid space velocity. The methods of feeding the reactants and condensing and collecting the products were conventional for vapor phase catalytic procedure.

Catalysts.—The vanadium oxide–aluminum oxide (V_2O_5, 35%–Al_2O_3, 65%) catalyst was prepared by coprecipitation from solutions of sodium vanadate and aluminum nitrate. The precipitation was accomplished by the addition of a calculated amount of a sodium hydroxide–sodium vanadate solution to a well-cooled solution of aluminum nitrate. The composition of the catalyst was checked by chemical analysis.

Analysis of Products.—The per cent. unsaturation of the liquid products was determined by the bromine number method.[5] The gaseous products were analyzed by the Gockel method.[6] The per cent. of butadiene in the gaseous product was determined by the maleic anhydride method.[7] The percentage of conversion of benzene to cyclohexane was determined by the refractive index.

Discussion of Results

Olefins, diolefins and acetylene when subjected to the action of vanadium oxide–aluminum oxide (V_2O_5, 35%–Al_2O_3, 65%) catalysts at 400° and atmospheric pressure were readily hydrogenated. The per cent. hydrogenation of isobutylene, hexene-1 and octene-1 obtained was in excess of 95%.

The optimum temperature for the olefin hydrogenation procedure was found to be 400°, which corresponds closely to the optimum temperature for the activated adsorption of hydrogen on vanadium oxide, as presented by Griffith[8] (see Fig. 1).

The space velocity proved to be a critical variable for this reaction. An increase in liquid space-velocity in excess of 0.05 gave a sizeable decrease in the effectiveness of the hydrogenation at atmospheric pressure. However, it was found that the maximum allowable space velocity could be materially increased by operation under increased pressure. The limiting space velocity was increased to 0.25 by operation at 21 atmospheres pressure (Table I).

TABLE I

DATA ON THE HYDROGENATION OF OLEFIN HYDROCARBONS AT 400°

Reactant	Pressure, atm.	Liquid space velocity, hr.$^{-1}$	Per cent. hydrogenation
Isobutylene	1	0.046	98.6
Isobutylene	1	.150	60.2
Isobutylene	1	.345	15.0
Octene-1	1	.010	98.6
Octene-1	21	.25	94.9
Octene-1	21	.50	82.2
Octene-1	21	1.00	58.9

Butadiene was readily hydrogenated at 400° and atmospheric pressure. The reaction product consisted of n-butane, 77.1% and butadiene 22.9%. No butenes were detected in the product.

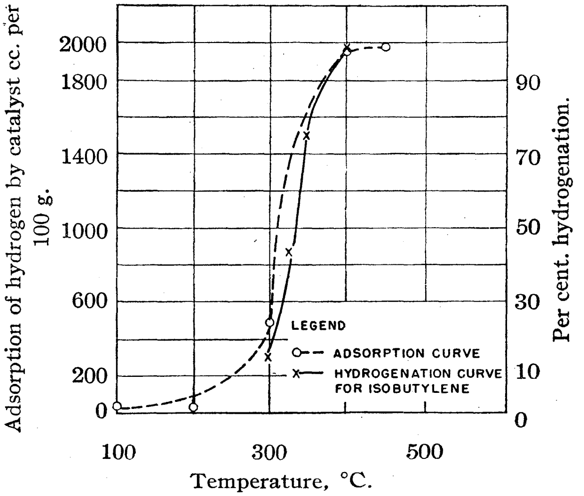


Fig. 1.—Comparison of hydrogenation curve for isobutylene and hydrogen adsorption curve—vanadium oxide catalyst.

Acetylene was hydrogenated successfully under the same reaction conditions. The reaction product consisted of 92.9% ethane, 0.2% acetylene and 6.9% ethylene.

Attempts to hydrogenate benzene at atmospheric pressure and 400° were unsuccessful. However, at 475° and 115 atmospheres, a yield of 27% cyclohexane was obtained. These particular high pressure experiments were carried out in a rotating autoclave.

An important feature of the vanadium oxide catalyst is its resistance to sulfur poisoning. The addition of 1% by weight of thiophene to hexene-1 and t-amyl mercaptan to octene-1 did not produce any noticeable decrease in the per cent. hydrogenation of either of these olefins. Sulfur analyses showed that 61.0% of the organic sulfur was removed by the catalytic hydrogenation for the hexene-1–thiophene mixture.

Vanadium oxide was shown to be an effective high temperature, low pressure, sulfur resistant

---

(2) Sachanen, "Conversion of Petroleum," Reinhold Publishing Corporation, New York, N. Y., 1940, p. 16.

(3) Griffith, "Mechanism of Contact Catalysis," Oxford University Press, London, 1936, pp. 17, 149.

(4) Komarewsky, Price and Coley, THIS JOURNAL, **69**, 238 (1947).

(5) Universal Oil Products Laboratory Test Methods for Petroleum and its Products, Universal Oil Company, Chicago (1940), method H-44-40.

(6) *Ibid.*, method G-84-40.

(7) *Ibid.*, method G-17-43.

(8) Griffith, "The Mechanism of Contact Catalysis," Oxford University Press, London, 1936, p. 186.

catalyst for the hydrogenation of unsaturated hydrocarbons.

DEPARTMENT OF CHEMICAL ENGINEERING
ILLINOIS INSTITUTE OF TECHNOLOGY
CHICAGO 16, ILLINOIS
RECEIVED JUNE 16, 1947

---

levo-2,3-Dinitroxybutane

BY A. F. MCKAY, R. H. MEEN AND GEORGE F WRIGHT

In 1938, a diastereomeric mixture of 2,3-dinitroxybutanes was reported in 16% yield as one of the products arising from electrolysis of sodium methylethylacetate in aqueous solution of sodium nitrate.[1] Later sodium pentanoate was electrolyzed in the same way to yield a little of the nitrate ester, which was in the *dd, ll* form according to the dicarbanilide which it yielded after iron–acetic acid reduction.[2] Dinitroxybutane was finally reported in good yield from 2,3-butanediol, but the author does not specify the stereochemical configuration of this diol.[3]

In connection with studies involving plasticization of nitrocellulose, we wished to obtain 2,3-dinitroxybutane as a pure stereochemical compound. The availability of *levo*-butanediol through the courtesy of the Canadian National Research Council made this possible. The nitrate-esterification with mixed acid proceeded without incident. The crude product was sufficiently pure that its refractive index was not changed by subsequent fractional distillation. The distilled product was still clear after four years, when it gave an Abel Heat Test of two minutes at 100°. Its sensitiveness to impact between steel surfaces (glancing blow) was approximately the same as that of crystalline TNT. The compound was found to be a poor plasticizer for nitrocellulose of 13.1% nitrogen content.

Although the 2,3-butanediol from which this ester was prepared had a high *levo* rotation (−12.89°) the *levo* rotation of the resulting dinitroxybutane was less than 1°. This low rotation suggested that racemization might have occurred during nitration. This was found not to be the case. Catalytic reduction with the catalyst recommended by Kuhn[4] regenerated 2,3-butanediol with *levo* rotation of −12.90°.

Experimental

To a mechanically stirred solution of 228 cc. (5.4 moles) of 98% nitric acid in 219 cc. (3.79 moles) of 96% sulfuric acid was added dropwise, over one hundred and sixty minutes, 185.5 g. (2.06 moles) of *levo*-2,3-butanediol, b. p. 81.0° (18 mm.), $n^{25}D$ 1.4315, $[\alpha]^{20}D$ −12.89°. The reaction temperature was held at 0–5° during this addition and was maintained thus for a further fifteen minutes. The cold solution was then poured into 100 g. of ice and further diluted with 500 cc. of water. The oily layer was not freed completely from acid by washing with 1 liter of 2% sodium carbonate solution. The deacidification was therefore completed by further washing with 200 cc. of 2% aqueous ammonia and then with water until neutral to litmus.

The product was dried under 25-mm. pressure to weigh 337.5 g. or 91% of theoretical, $n^{20}D$ 1.4405. This refractive index was not changed by distillation at 99–100° (15 mm.) or 91.5° (10 mm.). *levo*-Dinitroxybutane melts at 0 to 4°. Other constants are: d^{20}_4 1.297; MR_D calcd. 36.94,[5] found 36.63; $[\alpha]^{20}D$–0.88.

Reduction of 2,3-Dinitroxybutane.—A 10% solution of 20 g. (0.11 mole) of 2,3-dinitroxybutane in absolute ethanol was reduced with 0.54 mole of hydrogen, initially at 500 lb. gage pressure, in presence of 0.5 g. of the palladium-on-charcoal catalyst recommended by Kuhn. It was necessary to heat the bomb to 48° in order to complete this reduction in seven hours. The hydrogenolysis was complete in twenty-two minutes when 2 g. of catalyst was used per 6 g. of ester. There was less evidence of ammonia formation in the quick reduction, but the reaction mixture became quite hot. The catalyst was filtered off and the filtrate distilled, finally under 14 mm. The yield of 2,3-butanediol distilling at 75–76° was 9.6 g. or 96% of theoretical. Its rotation was $[\alpha]^{20}D$° −12.90°.

---

[1] F. Fichter and P. Suter, *Helv. Chim. Acta* **21**, 1401–1407 (1938).

[2] M. Rudin, *ibid.*, **25**, 636–640 (1942).

[3] L. J. DeKreuk, *Rec. trav. chim.*, **61**, 819–830 (1942).

[4] L. Kuhn, THIS JOURNAL, **68**, 1761–1762 (1946).

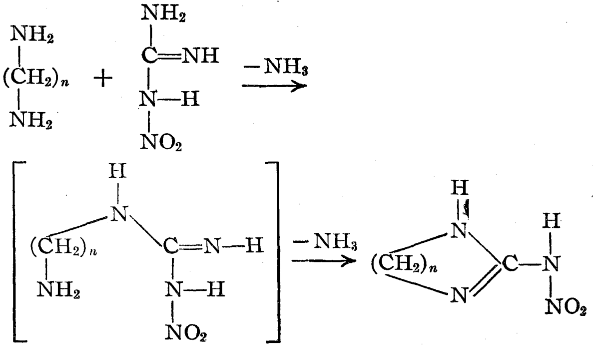
[5] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley & Sons Inc., New York, N. Y., 1945.

UNIVERSITY OF TORONTO
TORONTO, ONTARIO
RECEIVED AUGUST 4, 1947

Preparation and Properties of 2-Nitramino-Δ^2-1,3-diazacycloalkenes

BY A. F. MCKAY AND GEORGE F WRIGHT

Davis and his co-workers[1,2] have shown that monoalkylamines react with nitroguanidine in aqueous solution to give the corresponding N-alkyl-N′-nitroguanidines. If these alkylnitroguanidines are treated with excess alkylamine then the nitramino group is replaced to give, among other products, the *sym*-dialkylguanidines.[3] One might then expect that, if nitroguanidine were treated with an alkyldiamine, both reactions would occur to give a cyclic derivative from which the nitramino group had been eliminated. However, the reaction follows an alternative course. Ammonia is, indeed, liberated by the reaction of the amino group in nitroguanidine with one of the amino groups in the diamine, but the second evidently adds to the imino group in the resulting



---

[1] T. L. Davis and A. J. J. Abrams, *Proc. Am. Acad. Sci.*, **61**, 437 (1936).

[2] T. L. Davis and S. B. Luce, THIS JOURNAL, **49**, 2303 (1927).

[3] T. L. Davis and R. C. Elderfield, *ivid.*, **55**, 731(1933).

TABLE I

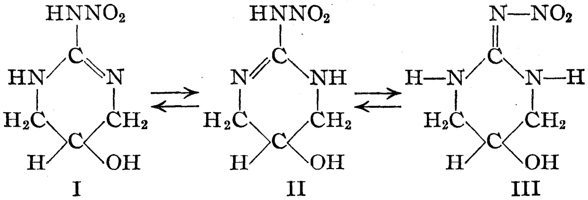
2-NITRAMINO-Δ^2-1,3-DIAZACYCLOALKENES

Compound	Yield, %	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
2-Nitramino-Δ^2-1,3-diazacyclopentene	65.4	220–221 dec.	27.9	27.8	4.61	4.52	43.1	43.0
4(or 5)-Methyl-2-nitramino-Δ^2-1,3-diazacyclopentene	64.0	170.5	33.3	33.5	5.54	5.60	38.9	39.2
2-Nitramino-Δ^2-1,3-diazacyclohexene	55.0	251–252 dec.	33.3	33.3	5.54	5.55	38.9	38.7
4(or 6)-Methyl-2-nitramino-Δ^2-1,3-diazacyclohexene	40.0	147–148.5	38.0	37.9	6.33	6.70	35.4	35.8
2-Nitramino-Δ^2-1,3-diazacycloheptene	64.3	219–220 dec.	38.0	38.4	6.33	6.68	35.4	35.5
5-Hydroxy-2-nitramino-Δ^2-1,3-diazacyclohexene	59.0	233–233.5 dec.	30.0	29.6	5.00	5.05	35.0	34.6

aminoalkylnitroguanidine to give a cyclic nitramine after a second molecule of ammonia is liberated. Five, six and larger membered rings can thus be synthesized.

It has been found[4] that the yields of alkylnitroguanidines can be improved over those previously reported, by treating nitroguanidine dissolved in aqueous alkali with the alkylamine hydrochloride. The mixture is heated to 60–70° for twenty to thirty minutes, cooled and the product recovered by filtration. This revised method is also found considerably to increase (by 15–55%) the yields of 2-nitramino-Δ^2-1,3-diazacycloalkenes (1, $n = 2$ to 4) obtained from the reaction of alkyldiamines with nitroguanidine. The synthesis is found to be successful with diamines containing branched as well as straight chains. The compounds which have been prepared thus far are listed in Table I. No tautomeric forms have yet been detected. Although the products isolated from the reaction of the unsymmetrical diamines with nitroguanidine are chemical individuals, we cannot at present assign definite positions to the methyl groups.

It is interesting to note that in the substituted 2-nitramino-Δ^2-1,3-diazacycloalkenes described in Table I an asymmetric carbon atom occurs. Thus the 4(or 5)-methyl-2-nitramino-Δ^2-1,3-diazacyclopentene and 4(or 6)-methyl-2-nitramino-Δ^2-1,3-diazacyclohexene are racemates. Especially interesting is the 5-hydroxy-2-nitramino-Δ^2-1,3-diazacyclohexene. If a labile tautomerism exists between I and II, or if the acid salts of I are resonance hybrids, then resolution would be impossible. If, on the other hand, the tautomeric nitrimino form III were stable then resolution of the allene-like structure should be possible.



I II III

Work on structure and synthesis of these 2-nitramino-Δ^2-1,3-diazacycloalkenes is in progress. The authors are grateful to Messrs. Scott and Farmer of London, England, from whom the original idea of cyclization was obtained. The National Research Council of Canada has supported this work by a grant-in-aid.

Experimental

Preparation of 2-Nitramino-Δ^2-1,3-diazacycloalkenes.—One mole of nitroguanidine is dissolved in 250–300 cc. of water containing two moles of potassium hydroxide and then one mole of the diamine dihydrochloride is added with stirring. A thick sludge forms which is heated at 65–70° with stirring over a period of twenty to thirty minutes. During this time the sludge becomes less viscous and it may dissolve completely. At the end of the reaction time, the reaction mixture is cooled to 1° in an ice–salt-bath and the white solid is recovered by filtration. The occluded potassium chloride may be removed by trituration with water. The final yields vary from 40–65% of theoretical, depending on the specific compound.

CHEMICAL LABORATORIES OF THE
UNIVERSITY OF TORONTO AND
QUEEN'S UNIVERSITY
TORONTO AND KINGSTON, ONTARIO

RECEIVED AUGUST 14, 1947

---

[4] A. F. McKay and G. F. Wright, THIS JOURNAL, 69, 3028 (1947).

The Addition of Methyl Alcohol to Fluoroethylenes[1]

BY WILLIAM T. MILLER, JR.,[2] EDWARD W. FAGER[3] AND PAUL H. GRISWOLD[4]

The addition of alcohols to tetrafluoroethylene and to chlorotrifluoroethylene[5] has been reported in the patent literature. In the present work, which was carried out independently, the base catalyzed addition of methyl alcohol to these substances and to *unsym*-dichlorodifluoroethylene was shown to occur. Reaction occurred rapidly and exothermically at from zero to room temperature with a reagent prepared by dissolving two moles of sodium in 500 cc. of absolute methanol. The tetrafluoroethylene was added in portions as a gas at 20 atm. pressure to the methylate solution in a steel bomb of the rocker type with the temperature maintained below 40°. The other olefins were added at atmospheric pressure to the stirred methylate solution cooled in an ice-bath.

---

[1] This paper was largely based on work done for the Manhattan Project under Contract No. W-7405-Eng-50 at S. A. M. Laboratories, Columbia University and under contract No. W-7405-Eng-26, Supplement No. 4 at S. A. M. Laboratories Carbide and Carbon Chemicals Corporation, New York City. Part of the information contained in this document will appear in Volume I of Division VII of the Manhattan Project Technical Series.

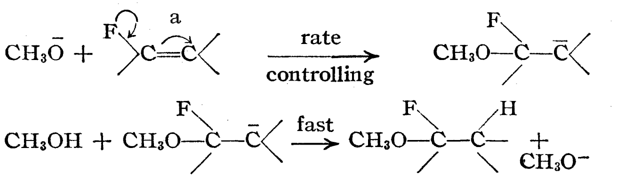
Present addresses: (2) Department of Chemistry, Cornell University, Ithaca, N. Y.; (3) Department of Chemistry, University of Chicago, Chicago, Illinois; (4) Department of Chemistry, Yale University, New Haven, Connecticut.

[5] Hanford and Rigby, U. S. Patent 2,409,274, Oct. 15, 1946.

Trichlorofluoroethylene was also observed to react readily but with some loss of halogen acid, while tetrachloroethylene did not react at 0°.

The physical properties and analytical data for the three ethers obtained pure are summarized in Table I. All three ethers were saturated to permanganate solution. They yielded fluoride ion in large amount when heated with alcoholic potash along with trace amounts of chloride ion from the chlorine containing compounds. The structures assigned are consistent with the above observation, and the presence of $-CF_2-$groupings alpha to oxygen explained the observed stability toward the sodium methylate reagent.

The mechanism of addition is postulated as follows



The role of fluorine relative to chlorine in promoting addition of nucleophilic type reagents and effecting the orientation of addition is considered to be due to its greater tendency to enter into resonance with the double bond so as to predispose the system to polar activation of the type indicated above (arrow *a*). There is also considerable reason to believe that fluorine is capable of electron release relative to chlorine as an activation mechanism.[7] The general electron withdrawal (inductive effect) by the halogens on the double bond favors the development of acceptor activity by activation in marked contrast to the exclusively nucleophilic reactivity shown by simple ethylenic hydrocarbons.

TABLE I

	CH_3OCF_2-CHF_2	CH_3OF_2-$CHClF$	$CH_3OCF_2CHCl_2$
F. p., °C.	−107	−92[a]	− 35
B. p., °C.	+ 36.5	+70.6	+105
$n^{20}D$	<1.3	1.3340	1.3861
d^{20}_4	1.2939	1.3636	1.4262
*MR*D		22.46	27.18
ARE[b]		1.01	0.97
% C calcd.	27.3	24.3	21.8
% C found	27.4	24.4	21.9
% H calcd.	3.03		2.42
% H found	3.11		2.51
Mol. wt. calcd.	132	148.5	164.9
Mol. wt. found	135	149	167

[a] A second crystalline form m. p. −109° was also indicated. [b] Calculated using atomic refractivities listed by Gilman.[6]

ITHACA, N. Y.

RECEIVED APRIL 30, 1947

---

[6] Gilman, "Organic Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1938, p. 1739.

[7] See for example Watson, "Modern Theories of Organic Chemistry," 2nd ed., Oxford University Press, London, 1941, p. 101.

Occurrence of Pectic Materials in Wood

BY W. W. PIGMAN, E. ANDERSON AND R. L. LEAF, JR.

Hardwoods contain small amounts (usually less than 0.5%) of materials that yield furfural and carbon dioxide when distilled with 12% hydrochloric acid.[1,2] After hydrolysis of a hemicellulose fraction of beechwood O'Dwyer[1] isolated a cinchonine salt similar to that reported for D-galacturonic acid. Anderson has isolated fractions from hardwoods and softwoods that have specific rotations and solubility characteristics similar to fruit pectins.[2] By hydrolysis of the material in the presence of bromine he produced mucic acid. This evidence proves qualitatively the presence of galacturonic acid in the original wood, which on the basis of O'Dwyer's identification is apparently the D-isomer.

In order to demonstrate more conclusively the presence of pectic materials[3] in a typical wood, it was decided to isolate galacturonic acid n ithe form of the difficultly soluble sodium calcium D-galacturonate[4] after enzymic hydrolysis[5] of wood pectic material. To give some quantitative aspects to the procedure the results were compared with those obtained with citrus pectic acid under the same conditions. Unfortunately for the quantitative aspects, the yields are greatly affected by the purity of the pectic material.[6]

Pectic material isolated from the inner bark of black spruce, in which it occurs in fairly large amounts (10%),[7] was treated with a commercial enzyme preparation. Crystalline sodium calcium galacturonate was isolated in a yield of 28% of the theoretical. Citrus pectic acid under the same conditions gave a yield of 53%. The product had the same calcium analysis and specific rotation as described by Isbell and Frush.[4] On oxidation with bromine under slightly acid conditions it gave mucic acid in a yield of 64% of the theoretical.

On the basis of this work there is no doubt that D-galacturonic acid occurs in the inner bark of the black spruce in a polymerized form. Since enzymic reactions are generally very specific, it is likely that the polymerized form is structurally similar to citrus pectic acid and that wood pectins are closely related to citrus pectins.

Experimental

The pectic acid was made by direct extraction with 5%

---

[1] M. H. O'Dwyer, *Biochem. J.*, **20**, 656 (1926); I. A. Preece, *Biochem. J.*, **25**, 1304 (1931).

[2] E. Anderson, *J. Biol. Chem.*, **165**, 233 (1946), and earlier papers.

[3] In the present sense a pectic material is one which, on hydrolysis, yields a substantial amount of D-galacturonic acid.

[4] H. S. Isbell and H. L. Frush, *J. Research Natl. Bur. Standards*, **32**, 77 (1944); R. Pasternack and P. P. Regna, U. S. patent 2,338,534 (1944).

[5] H. H. Mottern and H. L. Cole, THIS JOURNAL, **61**, 2701 (1939); W. W. Pigman, *J. Research Natl. Bur. Standards*, **25**, 301 (1940).

[6] H. S. Isbell and H. L. Frush, *J. Research Natl. Bur. Standards*, **32**, 90 (1944).

[7] E. Anderson and W. W. Pigman, *Science*, **105**, 601 (1947).

ammonium hydroxide of the inner bark of the black spruce (*Picea mariana* B. S. P.) and of holocellulose from the inner bark.[7] It was precipitated as calcium pectate. By treatment with hydrochloric acid the calcium pectate was converted to an impure pectic acid with $[\alpha]^{20}D$ +80° (3% NaOH) and containing 66.5% uronic anhydride (on an oven-dry basis).

A control experiment using commercial pectic acid[8] containing 77% uronic anhydride gave sodium calcium galacturonate in 53% of the theoretical yield.

The hydrolyses were carried out according to the directions of Isbell and Frush[6] except that: (1) an aqueous dispersion of pectic acid was treated with sodium bicarbonate until the *p*H was 3.8; (2) the hydrolysis time was twelve days at 38°; 12 g. of pectic substance (oven-dried) was used.

From 13 g. of wood pectic material (containing 11% moisture) 3.1 g. of sodium calcium D-galacturonate $[NaCa(C_6H_9O_7)_3 \cdot 6H_2O]$ was obtained; this yield is 28% of the theoretical value. The equilibrium specific rotation in 0.1 *N* nitric acid was $[\alpha]^{20}D$ +43.4 (*c*, 2%), whereas Isbell and Frush reported $[\alpha]^{20}D$ +44.0. The product contained 5.26% calcium; this value compares with 5.35% calculated for the above formula.

When 0.601 g. of the above product was dissolved in dilute hydrochloric acid and treated with bromine for four hours at room temperature 0.257 g. of insoluble material separated. A further crop of 0.066 g. was obtained from the mother liquor. The melting point of the material was 208–210° (dec.). Upon the basis of the insolubility and melting point the material must be mucic acid. The yield was 64% of the theoretical value.

---

(8) California Fruit Grower Exchange, Ontario, Cal.

INSTITUTE OF PAPER CHEMISTRY
APPLETON, WISCONSIN
UNIVERSITY OF ARIZONA
TUCSON, ARIZONA

RECEIVED SEPTEMBER 12, 1947

Trimethylhalosilane Preparations[1]

BY B. O. PRAY,[2] L. H. SOMMER, G. M. GOLDBERG, G. T. KERR, P. A. DI GIORGIO[3] AND F. C. WHITMORE

Previously reported preparations of trimethylfluorosilane have utilized the reaction of trimethylchlorosilane with zinc fluoride,[4] and with antimony trifluoride in the presence of antimony pentachloride.[5]

We have found that trimethylfluorosilane can be prepared directly in about 80% yield by the addition of ammonium fluoride to a solution prepared from hexamethyldisiloxane and concentrated sulfuric acid.[6]

$$(CH_3)_3SiOSi(CH_3)_3 \xrightarrow[H_2SO_4]{NH_4F} 2(CH_3)_3SiF$$

A similar procedure, using ammonium chloride, constitutes an excellent method for the preparation of trimethylchlorosilane in good yield (85%) and high purity. This method for trimethylchlorosilane gives better yields and is more convenient than that involving reaction of methylmagnesium halide with silicon tetrachloride.[7] The latter forms an azeotrope with trimethylchlorosilane[8] and careful fractionation is required to effect separation from dimethyldichlorosilane and methyltrichlorosilane which are also formed.[7] The present method gives only trimethylchlorosilane. Thus, hexamethyldisiloxane is a convenient starting material for three of the trimethylhalosilanes.[9]

In the present work, trimethylbromosilane[9] and trimethyliodosilane have been prepared by fission of the phenyl–silicon bond in phenyltrimethylsilane with bromine and iodine, respectively.[10]

$$C_6H_5Si(CH_3)_3 \xrightarrow{X_2} C_6H_5X + (CH_3)_3SiX$$

The above synthesis of trimethyliodosilane completes the series of trimethylhalosilanes. Trimethyliodosilane is a colorless liquid which fumes vigorously in moist air and acquires an iodine color on standing.

Experimental

Hexamethyldisiloxane from Ethyl Orthosilicate.[11]—Ethyl orthosilicate, 8.7 moles, was added with vigorous stirring during thirty minutes to 28 moles of methylmagnesium bromide in 12 liters of ether while keeping the reaction mixture at 10°. Stirring and cooling were continued for one hour followed by refluxing for two hours. Ether and product were then distilled. After removal of the ether, the product was dissolved in 700 cc. of concentrated sulfuric acid, and the resulting solution was added to ice. Fractionation of the upper layer, after washing and drying, gave 380 g. (2.35 moles) of hexamethyldisiloxane, b. p. 99–100°, $n^{20}D$ 1.3771, 54% yield.

Trimethylfluorosilane.—Ammonium fluoride, 24.2 g. (0.7 mole) was added from a dropping bottle to a stirred ice-cold solution of 32.4 g. (0.2 mole) of hexamethyldisiloxane in 60 cc. of concentrated sulfuric acid during one hour. Warming gave 31 g. of distillate of clear colorless liquid. Fractionation gave 3.2 g., b. p. 15.4°, and 27.8 g., b. p. 15.8° at 734 mm., of pure trimethylfluorosilane.

Anal. Calcd. for C_3H_9SiF: F, 20.6. Found: F, 20.3, 20.4.

A molecular weight determination by the vapor density method gave mol. wt. 92 (calcd. 94).

Trimethylchlorosilane.—Dry powdered ammonium chloride, 321 g. (6 moles), was added during three hours with vigorous stirring to a solution prepared from 324 g. (2 moles) of hexamethyldisiloxane and 1000 g. of concentrated sulfuric acid. During the addition the flask was cooled in an ice-bath. Upon completion of the addition, *the upper layer was separated as quickly as possible.* Fractional distillation gave 369 g. (3.4 moles) of trimethylchlorosilane, b.p. 58° (734 mm.), $n^{20}D$ 1.3884, d^{20} 0.8581, a yield of 85%.

Trimethylbromosilane.—Using the method of Bygden,[12] phenyltrimethylsilane, b. p. 168 (734 mm.), $n^{20}D$ 1.4900, was prepared in 72% yield by the reaction of phenyltrichlorosilane with methylmagnesium bromide. Liquid bromine, 162 g. (1 mole), was added with stirring to 150 g. (1 mole) of phenyltrimethylsilane in a flask cooled with cold tap-water, and the reaction mixture was heated on the steam-bath for one hour. Fractional distillation gave

---

(1) Paper XI in a series on organsilicon compounds; paper X, THIS JOURNAL, **69**, 2108 (1947).

(2) Present address: Pittsburgh Plate Glass Co., Barberton, Ohio.

(3) Present address: General Electric Research Laboratory, Schenectady, N. Y.

(4) Newkirk, THIS JOURNAL, **68**, 2736 (1946).

(5) Booth and Suttle, *ibid.*, **68**, 2658 (1946).

(6) *Cf.* Flood, *ibid.*, **55**, 1735 (1933).

(7) Gilliam and Sauer, *ibid.*, **66**, 1793 (1944).

(8) Sauer, U. S. Patent 2,381,139, *C. A.*, **39**, 4890 (1945).

(9) The preparation of trimethylbromosilane from hexamethyldisiloxane has been reported by Gilliam, Meals and Sauer, THIS JOURNAL, 1161 (1946).

(10) Grüttner and Cauer, *Ber.*, **51**, 1289 (1918), have reported a similar fission of *p*-di-(triethylsilyl)-benzene with bromine.

(11) *Cf.* Daudt, U. S. Patent 2,386,441; *C. A.*, **40**, 1866 (1946).

(12) Bygden, *Ber.*, **40**, 2274 (1907).

130 g. (0.85 mole) of trimethylbromosilane,[9] b. p. 79° (744 mm.), a yield of 85%, and 130 g. (0.84 mole) of bromobenzene. The bromosilane was analyzed for bromine content.

Anal. Calcd. for C_3H_9SiBr: Br, 52.3. Found: Br, 52.3, 52.3.

Trimethyliodosilane.—In a 500-cc. round-bottomed flask there were placed 75 g. (0.5 mole) of phenyltrimethylsilane and 127 g. (0.5 mole) of iodine crystals. After refluxing the reaction mixture for twelve hours, unreacted iodine was removed by adding 15 g. of powdered antimony. Fractional distillation gave 56 g. (0.28 mole) of trimethyliodosilane, b. p. 106.5° (734 mm.), d^{20} 1.47, a yield of 56%.

Anal. Calcd. for C_3H_9SiI: I, 63.5. Found: I, 63.0, 62.8.

DEPARTMENT OF CHEMISTRY
SCHOOL OF CHEMISTRY AND PHYSICS
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PA.

RECEIVED MAY 17, 1947

Competitive Reactions between Trialkylchlorosilanes and Alkylmagnesium Bromides[1]

BY LEO H. SOMMER, GEORGE T. KERR AND FRANK C. WHITMORE

In connection with studies in the chemistry of trialkylsilyl compounds, it was of interest to determine the effect of structural variations on the reactivity of trialkylchlorosilanes with alkylmagnesium bromides. Three studies of this type are reported in the present paper.

In one experiment, methyl- and ethylmagnesium bromides, 0.42 mole of each, were allowed to compete for 0.42 mole of triethylchlorosilane. The latter reacted exclusively with the methylmagnesium bromide.

$$CH_3MgBr + C_2H_5MgBr + (C_2H_5)_3SiCl \longrightarrow (C_2H_5)_3SiCH_3 \quad (1)$$

This result is in line with the generally observed greater reactivity of the shorter-chain aliphatic Grignard reagents with purely organic compounds.[2]

Treatment of a mixture of trimethylchlorosilane and triethylchlorosilane, 0.5 mole of each, with ethylmagnesium bromide, 0.5 mole, gave ethyltrimethylsilane and tetraethylsilane in a mole ratio of approximately 2 to 1.

$$2(CH_3)_3SiCl + (C_2H_5)_3SiCl + 3C_2H_5MgBr \longrightarrow 2(CH_3)_3SiC_2H_5 + (C_2H_5)_4Si \quad (2)$$

n-Propylmagnesium bromide, which is generally less reactive than ethylmagnesium bromide, gave stronger emphasis to the difference in the reactivity of trimethyl- and triethylchlorosilane. No appreciable amount of *n*-propyltriethylsilane was found.

$$(CH_3)_3SiCl + (C_2H_5)SiCl + C_3H_7MgBr \longrightarrow (CH_3)_3SiC_3H_7 \quad (3)$$

In general, the decreased activity toward Grignard reagents with increased size of the alkyl groups on silicon, as in reactions 2 and 3, is paralleled by a similar change in reactivity with structure of other trialkylsilyl compounds toward other reagents. For example, trimethylsilanol is far more susceptible toward intermolecular dehydration to the disiloxane than is triethylsilanol.[3]

Experimental

Reaction of Triethylchlorosilane with Methyl- and Ethylmagnesium Bromides.—In a 3-liter, three-necked flask, fitted with a mercury-sealed stirrer, a reflux condenser and a separatory funnel, were placed 139 cc. (0.42 mole) of methylmagnesium bromide and 165 cc. (0.42 mole) of ethylmagnesium bromide. To a mixture of Grignard reagents in ether solution was added, during fifteen minutes, with stirring and cooling, 63.0 g. (0.42 mole) of triethylchlorosilane. The mixture was refluxed for four hours, and then the reaction flask was fitted with a condenser for distillation of material volatile at steam-bath temperature. Completion of the distillation after four hours was followed by heating of the residue on the steam-bath for eight hours. The distillate was then returned to the flask, and 500 cc. of water was slowly added with stirring in order to decompose unreacted Grignard reagent. The resulting product was steam-distilled, the organic layer was separated and the aqueous layer extracted with 65 cc. of ether. Ether was removed from the product by distillation and the residue was refluxed with dilute hydrochloric acid for eight hours in order to convert any triethylsilanol (from the hydrolysis of unreacted triethylchlorosilane) to hexaethyldisiloxane. The organic layer was separated, washed free of acid, and dried over anhydrous magnesium sulfate. Fractionation in a glass-helix packed column of about 20 theoretical plates gave 36.1 g. (0.28 mole) of methyltriethylsilane,[4] b. p. 126° (729 mm.), n^{20}_D 1.4160, and no tetraethylsilane.

Reaction of Ethylmagnesium Bromide with Trimethyl- and Triethylchlorosilanes.—Addition of a mixture of trimethyl- and triethylchlorosilane (0.5 mole of each) to ethylmagnesium bromide (0.5 mole) was followed by a treatment similar to that employed above. Fractionation gave: 18.3 g. (0.18 mole) of ethyltrimethylsilane,[4] b. p. 62° (734 mm.), n^{20}_D 1.3819–1.3821, and 13.6 g. (0.095 mole) of somewhat impure tetraethylsilane,[4] b. p. 152–156° (734 mm.), n^{20}_D 1.4259–1.4245. In addition, there were obtained 18.5 g. (0.091 mole) of 1,1,1-trimethyl-3,3,3-triethyldisiloxane,[5] b. p. 172° (724 mm.), n^{20}_D 1.4104 and 25.1 g. (0.101 mole) of hexaethyldisiloxane,[6] b. p. 128° (30 mm.), n^{20}_D 1.4335.

Reaction of *n*-Propylmagnesium Bromide with Trimethyl- and Triethylchlorosilanes.—Addition of a mixture of trimethyl- and triethylchlorosilane (0.5 mole of each) to *n*-propylmagnesium bromide (0.5 mole) was followed by treatment of the reaction mixture in a manner similar to that above, except that the crude reaction product was treated with 50 cc. of cold concentrated sulfuric acid prior to fractionation in an attempt to separate tetraalkylsilane, which is known to be insoluble in concentrated sulfuric acid, from the disiloxanes which are soluble. The upper layer, containing tetraalkylsilane, was washed free of acid with water and sodium bicarbonate solution, and was then dried with anhydrous sodium sulfate. Fractionation of the product gave 33.3 g. (0.287 mole) of *n*-propyltrimethylsilane,[4] b. p. 89° (729 mm.), n^{20}_D 1.3930, and no appreciable quantity of *n*-propyltriethylsilane. In addition, there was obtained 22.1 g., (0.090 mole) of hexaethyldisiloxane, b. p. 129° (30 mm.), n^{20}_D 1.4340.

---

(1) Paper XII in a series on organosilicon compounds; for Paper XI see THIS JOURNAL, **69**, 433 (1947).

(2) Gilman, St. John, St. John and Lichtenwalter, *Rec. trav. chim.*, **55**, 577, 588 (1936).

(3) Sauer, THIS JOURNAL, **66**, 1707 (1944); Sommer, Pietrusza and Whitmore, *ibid.*, **68**, 2282 (1946).

(4) Whitmore, Sommer, Di Giorgio, Strong, Van Strien, Bailey, Hall, Pietrusza and Kerr, THIS JOURNAL, **68**, 475 (1946).

(5) Sauer, *ibid.*, **68**, 954 (1946).

(6) Di Giorgio, Strong, Sommer and Whitmore, *ibid.*, **68**, 1380 (1946).

The lower sulfuric acid layer from treatment of the original crude product (see above) was treated with ice-water, the organic layer was separated, washed free of acid, dried over anhydrous sodium sulfate and fractionated. There was obtained 9.5 g. (0.045 mole) of 1,1,1-trimethyl-3,3,3-triethyldisiloxane, b. p. 80° (30 mm.), $n^{20}\mathrm{D}$ 1.4105, and 10 g. (0.040 mole) of hexaethyldisiloxane, b. p. 137° (29 mm.), $n^{20}\mathrm{D}$ 1.4332.

DEPARTMENT OF CHEMISTRY
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PA.
RECEIVED MAY 17, 1947

Some Reactions of Trialkylaminosilanes[1]

BY D. L. BAILEY,[2] L. H. SOMMER AND F. C. WHITMORE

In continuation of previous studies on the chemistry of trialkylsilyl compounds, the present paper reports reactions of triethylaminosilane (I)[3] and α-chloroethyldiethylaminosilane (II).

Compounds I and II were prepared from the corresponding chlorosilanes[4,5] by treatment with liquid ammonia, a method previously used by Sauer.[3]

$$R(C_2H_5)_2SiCl + 2NH_3 \longrightarrow R(C_2H_5)_2SiNH_2 + NH_4Cl$$

(R is C_2H_5— in compound I, and CH_3CHCl— in compound II)

Conversion of compounds I and II to halosilanes[6] was achieved with hydrogen chloride, hydrogen bromide, concentrated hydrochloric acid, concentrated hydrofluoric acid, and hydrobromic–sulfuric acid mixture.

$$R(C_2H_5)_2SiNH_2 + 2HX \longrightarrow R(C_2H_5)_2SiX + NH_4X$$

These reactions indicate possible use of trialkylaminosilanes as intermediates for the preparation of other halosilanes from chlorosilanes. They further emphasize the great differences in the reactions of the silicon–amino and carbon–amino bonds.

Experimental

Triethylaminosilane.[3]—A description of our procedure may be useful in view of the low yield (26%) originally reported for this compound.

In a 200-cc., three-necked flask equipped with dropping funnel, mercury-sealed stirrer and reflux condenser there was placed 100 cc. of liquid ammonia. The flask was then immersed in a Dry Ice and acetone-bath and 75 g. (0.5 mole) of triethylchlorosilane was added from the dropping funnel during one-half hour. After stirring for one hour, the excess ammonia was evaporated and the contents of the flask were diluted with ether and filtered to remove ammonium chloride. The ether was then removed from the product which was fractionally distilled in a glass-helix packed column of about 20 theoretical plates. There was obtained 46 g. (0.35 mole) of triethylaminosilane, b. p. 134°, $n^{20}\mathrm{D}$ 1.4267, a yield of 70%. Weighed samples added to a mixture of methanol and excess standard acid followed by back-titration with standard alkali gave a neutral equivalent of 132. Calcd. neutral equivalent for complete hydrolysis of the silicon–amino bond, 131. The compound was also analyzed by the Kjeldahl method.

Anal. Calcd. for $C_6H_{17}SiN$: N, 10.69. Found: N, 10.69, 10.70.

α-Chloroethyldiethylaminosilane.—Addition of 93 g. (0.5 mole) of α-chloroethyldiethylchlorosilane[5] to 100 cc. of liquid ammonia and use of a procedure similar to that employed for the triethylaminosilane gave 72 g. (0.44 mole) of α-chloroethyldiethylaminosilane, b. p. 93° (38 mm.), $n^{20}\mathrm{D}$ 1.4570, d^{20} 0.9604, a yield of 88%.

Anal. Calcd. for $C_6H_{16}SiClN$: Cl, 21.40; neut. equiv., 166. Found: Cl, 21.36; neut. equiv., 166.

Reactions

A. With Concentrated Hydrochloric Acid.—In a 200-cc., three-necked flask equipped with a reflux condenser, dropping funnel, and mercury-sealed stirrer, there was placed 160 cc. of concentrated hydrochloric acid. This was cooled in an ice-bath and 13 g. (0.1 mole) of triethylaminosilane was added by means of the dropping funnel. After stirring for thirty minutes, the reaction mixture was placed in a separatory funnel and the two layers were separated. Upon drying with sodium sulfate, the undistilled triethylchlorosilane, 14.5 g. (0.09 mole), analyzed for 23.3% Cl (calcd. for triethylchlorosilane, 23.5%). Distillation of this material gave 12 g. (0.08 mole) of triethylchlorosilane, b. p. 144–145°, d^{20} 0.8977, a yield of 80%.

α-Chloroethyldiethylaminosilane, 13 g. (0.08 mole), was treated with concentrated hydrochloric acid by a procedure similar to that used for triethylaminosilane. Distillation of the product gave 11.5 g. (0.062 mole) of α-chloroethyldiethylchlorosilane,[5] b. p. 178–179°, d^{20} 1.0399, a yield of 79%.

B. With Hydrofluoric Acid.—In a 200-cc. flask there was placed 60 cc. of 48% hydrofluoric acid. This was cooled in an ice-bath and 12 g. (0.09 mole) of triethylaminosilane was added from the dropping funnel during five minutes. After agitation of the reaction mixture for ten minutes, the resulting two layers were separated and the upper layer dried over sodium sulfate. Distillation gave 10.5 g. (0.08 mole) of triethylfluorosilane,[7] b. p. 109–110°, d^{20} 0.8380, F, 13.9% (calcd. 14.1%), a yield of 89%.

Treatment of α-chloroethyldiethylaminosilane, 11 g. (0.066 mole), with hydrofluoric acid (48%) gave 9 g. (0.053 mole) of α-chloroethyldiethylfluorosilane,[5] b. p. 149–150°, d^{20} 0.9961, F, 11.3% (calcd. 11.3%), in 82% yield.

C. With Hydrogen Chloride.—In a 200-cc. three-necked flask equipped with a reflux condenser, mercury-sealed stirrer, and gas delivery tube there were placed 150 cc. of dry ether and 20 g. (0.152 mole) of triethylaminosilane. Dry hydrogen chloride was passed into the reaction mixture until the solution was saturated. The ammonium chloride was filtered and the ether was evaporated on the steam-bath. Distillation of the residual liquid gave 16 g. (0.106 mole) of triethylchlorosilane, b. p. 143–145°, d^{20} 0.8974, Cl, 23.4% (calcd. 23.5%), a yield of 70%.

An ether solution of α-chloroethyldiethylaminosilane, 18 g. (0.11 mole) was treated with hydrogen chloride gas to give 15.5 g. (0.084 mole) of α-chloroethyldiethylchlorosilane,[5] b. p. 179–181°, d^{20} 1.0385, $n^{20}\mathrm{D}$ 1.4553, a yield of 76%.

D. With Hydrogen Bromide.—An ether solution of triethylaminosilane, 39 g. (0.30 mole) was treated with dry hydrogen bromide by a procedure similar to that used for the reaction of hydrogen chloride with this compound. There was obtained 41.5 g. (0.21 mole) of triethylbromosilane,[8] b. p. 162–163°, $n^{20}\mathrm{D}$ 1.4563, d^{20} 1.1403, a yield of 70%.

---

[1] Presented at the 109th Meeting of the American Chemical Society in Atlantic City, New Jersey, April 9, 1946. Paper XIII in a series on organosilicon compounds. For paper XII see THIS JOURNAL, **70**, 434 (1948).

[2] Gulf Oil Corporation Fellow, 1946–1947.

[3] Sauer and Hasek, THIS JOURNAL, **68**, 241 (1946).

[4] Triethylchlorosilane was prepared by the method of Di-Giorgio, Strong, Sommer and Whitmore, *ibid.*, **68**, 1380 (1946).

[5] α-Chloroethyldiethylchlorosilane was prepared by the method of Sommer, Bailey, Strong and Whitmore, *ibid.*, **68**, 1881 (1946).

[6] The conversion of hexamethyldisilazane to trimethylchlorosilane using hydrogen chloride has been reported in ref. 3.

[7] Flood, THIS JOURNAL, **55**, 1735 (1933).

[8] Grüttner and Cauer, *Ber.*, **51**, 1289 (1918).

Anal. Calcd. for $C_6H_{15}SiBr$: Br, 40.95; neut. equiv., 195. Found: Br, 40.93; neut. equiv., 196.

An ether solution of α-chloroethyldiethylaminosilane, 24 g. (0.145 mole) was treated with dry hydrogen bromide to give 12 g. (0.052 mole) of α-chloroethyldiethylbromosilane, b. p. 194–196°, $n^{20}D$ 1.4762, a yield of 26%. A product of higher purity was obtained in the reaction with hydrobromic–sulfuric acid mixture.

Anal. Calcd. for $C_6H_{14}SiClBr$: Br, 34.81; neut. equiv., 230. Found: Br, 33.99; neut. equiv., 234.

E. With Hydrobromic–Sulfuric Acid Mixture.—In a one-liter three-necked flask equipped with reflux condenser, mercury-sealed stirrer, and dropping funnel, there was placed 300 cc. of 48% hydrobromic acid. This was cooled in an ice-bath and 200 cc. of concentrated sulfuric acid was added. To the mixture there was then added through the dropping funnel 41 g. (0.31 mole) of triethylaminosilane. After stirring the reaction mixture for twenty minutes, the resulting two layers were separated and the organic layer dried over sodium sulfate. Fractionation gave 33.5 g. (0.17 mole) of triethylbromosilane, b. p. 78–79° (45 mm.), $n^{20}D$ 1.4561, Br, 40.8% (calcd. 40.95%), a yield of 55%.

α-Chloroethyldiethylaminosilane, 52 g. (0.31 mole), was treated with hydrobromic–sulfuric acid by a procedure similar to that used for triethylaminosilane. Distillation of the product gave 58.5 g. (0.255 mole) of α-chloroethyldiethylbromosilane, b. p. 105–106° (46 mm.), $n^{20}D$ 1.4784, d^{20} 1.2661, Br, 34.8% (calcd. 34.81%), a yield of 81%.

DEPARTMENT OF CHEMISTRY
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PENNSYLVANIA
RECEIVED MAY 17, 1947

Conductivities of Aqueous Solutions of Dodecylammonium Chloride

BY A. W. RALSTON AND D. N. EGGENBERGER

We are currently engaged in a study of the effects of inorganic electrolytes and of various organic compounds upon the electrical behavior of solutions of cationic colloidal electrolytes. During the course of this investigation we have redetermined the equivalent conductivities of aqueous solutions of dodecylammonium chloride at various temperatures and have found that the values are somewhat lower than those which we have previously reported.[1,2] We are of the opinion that the dodecylammonium chloride which was used in our earlier work contained traces of impurities, since our present values have been reproduced with several quite pure samples of this amine salt prepared by different investigators. The values herein reported, when plotted against the square root of the volume normality, $\sqrt{N_v}$, show a decidedly less steep slope within the first range, although the concentrations of amine salt at the critical points for micelle formation are in agreement with those reported previously.

The values of the equivalent conductivities of aqueous solutions of dodecylammonium chloride at various temperatures are shown in Table I.

TABLE I

EQUIVALENT CONDUCTIVITIES OF AQUEOUS SOLUTIONS OF DODECYLAMMONIUM CHLORIDE

N_v 20°	Λ	N_v 25°	Λ	N_v 30°	Λ	N_v 40°	Λ	N_v 50°	Λ	N_v 60°	Λ
0.000507	87.6	0.000777	96.0	0.000985	106.4	0.000801	127.7	0.000968	148.6	0.000905	172.1
.00127	86.5	.00177	95.2	.00179	105.7	.00186	126.0	.00212	147.4	.00194	169.5
.00284	85.0	.00398	93.1	.00335	104.8	.00405	124.0	.00445	145.5	.00466	166.7
.00402	84.4	.01003	91.3	.00384	104.4	.00728	123.0	.00820	142.4	.01433	160.6
.00635	83.0	.01025	90.9	.00608	103.5	.00806	121.5	.00933	141.8	.0180	155.0
.00934	81.7	.0156	86.6	.00842	102.4	.01455	119.7	.01417	140.7	.0248	130.0
.01025	81.4	.0168	83.1	.01137	101.5	.0177	107.2	.0181	128.6	.0439	96.0
.0170	74.1	.0172	80.7	.01354	100.7	.0207	96.5	.0223	112.5	.0729	79.7
.0181	70.3	.0196	73.5	.0150	98.9	.0480	61.8	.0240	109.0	.1345	70.8
.0208	64.1	.0223	68.4	.0173	90.5	.0796	52.1	.0423	80.5		
.0265	54.3	.0437	45.7	.0226	75.4	.1353	47.2	.0682	67.0		
.0484	38.1	.0769	36.3	.0235	72.9			.1383	58.4		
.0782	31.1	.1371	31.7	.0384	54.9						
.1397	26.8			.0622	43.7						
				.1008	38.7						
				.1493	36.4						

Experimental

Preparation of Dodecylammonium Chloride.—Commercially distilled dodecylamine was fractionated through a Stedman packed column and the fraction boiling at 111.5° at 4 mm. retained. This fraction melted at 28.30°. The amine (200 g.) was dissolved in benzene (2 liters) and treated with dry hydrogen chloride. Upon cooling, crystals of dodecylammonium chloride precipitated. The crystals were removed by filtration and crystallized three times from benzene. The sample was analyzed by a previously described procedure.[3] (*Anal.* Calcd. for $C_{12}H_{25}NH_2$, 83.54; Cl, 16.00. Found: $C_{12}H_{25}NH_3$, 83.84; Cl, 16.06).

Conductivity Determinations.—Conductivities were determined in the manner and with the equipment previously described.[1]

---

(1) Ralston, Hoerr and Hoffman, THIS JOURNAL, **64**, 97 (1942).

(2) Ralston and Hoerr, *ibid.*, **64**, 772 (1942).

(3) Ralston and Hoerr, *Ind. Eng. Chem., Anal. Ed.*, **16**, 459 (1944).

RESEARCH LABORATORY OF ARMOUR AND COMPANY
CHICAGO, ILLINOIS
RECEIVED JULY 14, 1947

Trimethylgermanium Chloride

BY EUGENE G. ROCHOW[1]

The preparation of methylgermanium trichloride and dimethylgermanium dichloride by the

---

(1) Research Laboratory, General Electric Company.

action of methyl chloride upon elementary germanium in the presence of a copper catalyst has been described in a previous paper.[2] In that investigation, no trimethylgermanium chloride was found in the product of the direct reaction, although the compound may have been present in an amount too small to be recovered in the distillation.

In order to round out the series of methylgermanium chlorides, some of the pure dimethylgermanium dichloride obtained in the direct reaction has been methylated with Grignard reagent.

Experimental

One-half mole of methylmagnesium chloride was allowed to drip slowly into a solution of 0.5 mole of dimethylgermanium dichloride in 300 cc. of dry ether. The mixture stood overnight and the magnesium chloride was filtered off. Ether was distilled from the liquid product, and the residue was fractionated. Nineteen grams of trimethylgermanium chloride was isolated. *Anal.* Calcd.: Cl, 23.15. Found: Cl, 23.3, 23.5. Because of the complete analysis of its progenitor[2] and the impossibility of halogen exchange in the system used, no further analyses were considered necessary.

Trimethylgermanium chloride is a colorless liquid which boils at 115°, melts at −13°, and has a refractive index of 1.4314 at 29° for sodium light. It hydrolyses rather slowly in water to form volatile products.

This compound completes the series

$GeCl_4$	b. p.	83.1°
CH_3GeCl_3	b. p.	111°
$(CH_3)_2GeCl_2$	b. p.	124°
$(CH_3)_3GeCl$	b. p.	115°
$(CH_3)_4Ge$	b. p.	43.4°

It is seen that the substitution of methyl groups for chlorine in $GeCl_4$ does not bring about a gradual lowering of the boiling point to that of $(CH_3)_4Ge$, but causes a rise and then a decline, with a maximum at $(CH_3)_2GeCl_2$. The "abnormally" high maximum boiling points for the disubstituted compounds $(CH_3)_2SiCl_2$ and $(CH_3)_2GeCl_2$ correspond to a lower reactivity in some reactions,[3] and the association therefore may be considered as a form of self-stabilization.

---

(2) Rochow, THIS JOURNAL, **69**, 1729 (1947).

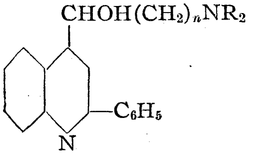
(3) Fuoss, *ibid.*, **65**, 2406 (1943).

SCHENECTADY, NEW YORK RECEIVED JUNE 27, 1947

Synthesis of Antimalarials. VIII.[1] 1-(7-Chloro-2-phenylquinolyl-4)-6-diethylaminohexanedione-1,3 and Certain Other Compounds

BY JOSEPH C. SHIVERS[2] AND CHARLES R. HAUSER

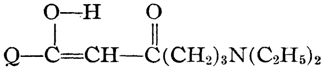
Various workers[3] have synthesized 4-quinolinemethanols (I) certain of which possess considerable antimalarial activity. The present note describes the synthesis of the β-diketone (II),[4] which, in its enol form (III),[4] resembles 4-quinolinemethanols. An attempt was made to prepare the 1,3-diol (IV)[4] from the β-diketone but a pure product was not isolated.



(I)

$Q{-}COCH_2CO(CH_2)_3N(C_2H_5)_2$

(II)



$Q{-}\overset{\text{O—H}}{\overset{|}{C}}{=}CH{-}\overset{\text{O}}{\overset{\|}{C}}(CH_2)_3N(C_2H_5)_2$

(III)

$Q{-}CHOHCH_2CHOH(CH_2)_3N(C_2H_5)_2$

(IV)

$CH_3CO(CH_2)_3N(C_2H_5)_2$

(V)

$Q{-}CO_2C_2H_5$

(VI)

The crude β-diketone (II–III)[4] was obtained in good yield by acylating ketone (V) with ester (VI)[4] by means of sodium amide; however, the pure product was isolated in only 15% yield. The acylation practically failed in the presence of sodium ethoxide. An attempt to acylate ketone (V) with ethyl 2-(3′-nitrophenyl)-cinchoninate by means of sodium amide produced tars.

Experimental[5]

2-Phenyl-7-chlorocinchoninic acid was prepared from benzaldehyde, *m*-chloroaniline and pyruvic acid by the Doebner reaction using a modification of the procedure kindly furnished by Elderfield, Gensler and Brody of Columbia University who based their procedure on that of earlier workers.[6] Our modification[7] consisted in first isolating N-benzal-3-chloroaniline and in treating it in refluxing commercial absolute ethanol with the pyruvic acid; the yield of 2-phenyl-7-chlorocinchoninic acid was 30%. The intermediate anil, b. p. 155° at 2 mm. (reported b. p. 338° at atm. press.)[8] was obtained in 90% yield by allowing a mixture of benzaldehyde and *m*-chloroaniline to stand overnight, extracting with ether and distilling the dried ether solution.

Ethyl 2-phenyl-7-chlorocinchoninate (VI), m. p. 88° (reported m. p. 89–89.5°)[9] was obtained in 75% yield by esterification of the crude acid using the common sulfuric acid method.

2-(3′-Nitrophenyl)-cinchoninic acid was obtained in 47% yield from pyruvic acid and 3-nitrobenzalaniline (m. p. 68°, reported m. p. 66°)[10] which was prepared in 86% yield from 3-nitrobenzaldehyde and aniline. After recrystallization from glacial acetic acid, a sample of the acid melted at 257°, darkening at 245°.

Anal. Calcd. for $C_{16}H_{10}O_4N_2$: C, 65.30; H, 3.43; N, 9.52. Found: C, 65.12; H, 3.72; N, 9.70.

Ethyl 2-(3′-nitrophenyl)-cinchoninate, m. p. 110–112°, was obtained in 70% yield by the esterification of the crude acid by the sulfuric acid method, and recrystallization from ethanol–water using charcoal. A second recrystallization gave light tan crystals, m. p. 112–113°.

---

(1) Part of this work was done under an O. S. R. D. contract. For paper VII of this series see THIS JOURNAL, **68**, 1544 (1946).

(2) Present address: E. I. du Pont de Nemours and Company, Inc., Pioneering Research Section, Buffalo, New York.

(3) See especially King and Work, *J. Chem. Soc.*, 1307 (1940); 401 (1942); Lutz, *et al.*, THIS JOURNAL, **68**, 1813 (1946); Winstein, Jacobs, *et al.*, *ibid.*, **68**, 1831 (1946); Campbell and Kerwin, *ibid.*, **68**, 1837 (1946); Campbell, Helbing and Kerwin, *ibid.*, **68**, 1840 (1946); Buchman, Sargent, Meyers and Seneker, *ibid.*, **68**, 2692 (1946).

(4) Q = 7-chloro-2-phenyl-4-quinolyl.

(5) Analyses by Oakwold Laboratories, Alexandria, Va.

(6) Borsche, *Ber.*, **41**, 3884 (1908); John, *J. prakt. Chem.*, [2] **130**, 314 (1931).

(7) This was devised by M. J. Weiss and G. A. Reynolds of this Laboratory.

(8) Lachowicz, *Monatsh.*, **9**, 697 (1889).

(9) Tarbell and co-workers, THIS JOURNAL, **67**, 1583 (1945).

(10) Schwalbe, *Chem. Zentr.*, **74**, I, 231 (1903).

Anal. Calcd. for $C_{18}H_{14}O_4N_2$: C, 67.07; H, 4.38; N, 8.70. Found: C, 67.39; H, 4.50; N, 8.86.

1-(7′-Chloro-2′-phenylquinoline-4′)-5-diethylaminohexanedione-1,3 (II) was prepared by acylating 1-diethylaminopentanone-4 (V) with ethyl 2-phenyl-7-chlorocinchoninate (VI) by means of sodium amide according to an adaptation of the method developed in this Laboratory.[11] To a stirred suspension of 0.4 mole of sodium amide[11] in 500 ml. of liquid ammonia was added rapidly 0.4 mole of the ketone in 75 ml. of dry ether. After replacing the ammonia by ether,[11] 0.2 mole of the ester in one liter of dry ether was added and the mixture refluxed five hours and then allowed to stand overnight. The mixture was poured onto 750 ml. of 10% acetic acid and crushed ice; after shaking thoroughly, the ether phase was extracted with 500 ml. of 10% acetic acid and combined with the aqueous phase. To the combined acetic acid solution was added cold 20% sodium hydroxide solution to a *p*H of 11 (oil separating). Carbon dioxide was passed into the mixture to a *p*H of 9, and the oil extracted with ether. The solvent was distilled from the dried ether solution leaving the crude oily β-diketone (79%) which, after drying over phosphorus pentoxide in a vacuum desiccator, was recrystallized from a mixture of benzene and 30–60° petroleum ether, freezing out with dry ice. There was obtained a 15% yield of pure β-diketone, melting at 88°; this melting point was not raised by further recrystallization but was depressed by admixture with the cinchoninic ester (VI).

Anal. Calcd. for $C_{25}H_{27}O_2Cl$: C, 70.98; H, 6.44; N, 6.62. Found: C, 70.96, 70.61; H, 6.34, 6.17; N, 6.63, 6.40.

The β-diketone gave a deep red enol test with alcoholic ferric chloride, and formed a 2,4-dinitrophenylhydrazone which soon became oily. Attempts to convert the crude β-diketone to a picrate, pyrazole, hydrochloride or a copper salt failed. The crude β-diketone, which was entirely soluble in dilute hydrochloric acid, appeared to decompose on distillation at 0.1 mm., since the distillate, b. p. 175–190°, was not entirely soluble in the acid.

Hydrogenation of the crude β-diketone in glacial acetic acid at room temperature and low pressure in the presence of Adams catalyst[12] absorbed the calculated amount of hydrogen within two hours and produced an oil, b. p. 240–250° at 0.1 mm., which, as should be expected, failed to give the enol test with alcoholic ferric chloride; however, the pure 1,3-diol or a solid derivative of it has not been isolated.

---

(11) Adams and Hauser, THIS JOURNAL, **66**, 1220 (1944); Levine, Adams, Conroy and Hauser, *ibid.*, **67**, 1510 (1945).

(12) Adams, Voorhees and Shriner, "Organic Syntheses," Coll. Vol. I, 463 (1946).

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, NORTH CAROLINA

RECEIVED JUNE 5, 1947

Identification of Esters of Dibasic Acids by the Use of Ethanolamine

BY WILLIAM H. RAUSCHER AND WILLIAM H. CLARK

In an attempt to find a rapid and satisfactory method for the identification of esters, their ammonolysis by ethanolamine in the absence of water has been investigated. It was hoped that on refluxing esters with ethanolamine that solid amides which would suitably characterize the acid would be formed, and that the alcohol simultaneously formed could be distilled out of the reaction mixture in such a state of purity that it could be easily identified in the usual manner.

On refluxing a number of esters with ethanolamine it was found that they were rapidly ammonolyzed, and that the alcohol could be distilled from the reaction mixture at a temperature very close to its boiling point. A redistillation of the alcohol from a simple distilling flask gave a product of correct boiling point from which a standard solid derivative of correct melting point was made. The reaction mixture from which the alcohol had been distilled did not yield solid amides on cooling in the case of most esters of monobasic acids which were investigated. However, the series of esters of dibasic acids shown in the table did give solid amides on cooling the reaction mixture after distilling off the alcohol. After a recrystallization the amides proved to have melting points suitable for purposes of identification.

Experimental

The reflux apparatus consisted of a 50-cc. flask and water cooled reflux condenser, both with ground joints. A mixture of 5 g. of the ester and 15 g. of ethanolamine was refluxed for fifteen minutes. After cooling below the boiling point of the alcohol, the condenser was replaced by a short Vigreux column and the alcohol distilled off. The residue was cooled to room temperature to obtain a solid product in the case of the esters of dibasic acids listed in the table. The amides were recrystallized from a 1:1 solution of alcohol and benzene. The alcohol which had been distilled from the reaction mixture was redistilled from a simple distilling flask, its boiling point checked and at least one solid derivative prepared from the distillate by standard procedures.

TABLE I

N,N′-DI-β-HYDROXYAMIDES OF DIBASIC ACIDS

Ester	M. p. (cor.), °C.	Nitrogen, %	
		Calcd.	Found
Methyl oxalate[a]	169–169.2	15.95	15.90–16.03
Ethyl oxalate[a]	169–169.2	15.95	
n-Butyl oxalate[a]	169–169.2	15.95	
Ethyl malonate	127.0–127.5	14.71	14.73–14.81
Ethyl succinate	156.2–156.7	13.69	13.55–13.61
Ethyl glutarate[b]	119.6–120.0	12.85	12.86–12.99
Ethyl adipate	130.2–130.7	12.08	12.02–12.05
Ethyl suberate	138.5–138.9	10.77	10.88–10.79
Ethyl azelate	125.5–125.9	10.22	10.33–10.81
Methyl sebacate	144.5–145.0	9.72	9.77– 9.89

[a] Required no refluxing. [b] Dioxane used for recrystallization of amide.

DEPARTMENT OF CHEMISTRY
RENSSELAER POLYTECHNIC INSTITUTE
TROY, N. Y.

RECEIVED AUGUST 12, 1947

NEW COMPOUNDS

α-Amino-β-mercapto-*n*-valeric Acid Hydrochloride

α-Amino-β-mercapto-*n*-valeric acid hydrochloride was prepared by following the procedure of Carter, Stevens and Ney[1] for the corresponding butyric acid.

2-Phenyl-4-*n*-propylidene-5-oxazolone was synthesized by the method of Carter, Handler and Melville[2] using

---

(1) Carter, Stevens and Ney, *J. Biol. Chem.*, **139**, 247 (1941).

(2) Carter, Handler and Melville, *ibid.*, **129**, 359 (1939).

slight modifications. The mixture of 72 g. of hippuric acid, 33 g. of anhydrous sodium acetate and 200 ml. of acetic anhydride was maintained at 30° under a reflux condenser while 250 ml. of propionaldehyde was added over a period of one hour. The mixture was then heated about forty-five minutes at 50–60° until an almost clear orange solution resulted. Decomposition with ice yielded a semi-crystalline mass which was washed several times with ice water. The small amount of oil present was dissolved by adding 300 ml. of 70% ethanol and the resulting mixture was filtered by suction to give light yellow crystals. These crystals were sucked as dry as possible, washed several times with water and air dried. The yield of crude azlactone was 30–33 g., m. p.[3] 79–81°. Recrystallization from 50% ethanol gave white needles, m. p. 81–83°.

Anal. Calcd. for $C_{12}H_{11}NO_2$: N, 6.96. Found: N, 6.94.

If the temperature of the reaction were allowed to rise above 60° or the time of heating were prolonged, the yield suffered markedly and the majority of the resultant product was the dark red oil. The crude material was entirely satisfactory for the next step.

α-Benzoylamino-β-benzylmercapto-*n*-valeric Acid.—To a solution of 0.67 g. of sodium in 140 ml. of dry methanol was added 17.2 g. of benzyl mercaptan. Then a solution of 27 g. of 2-phenyl-4-*n*-propylidene-5-oxazolone in 140 ml. of dry benzene was added, with stirring, over a period of one hour. The mixture was allowed to stand at room temperature for fourteen hours. The product was isolated as described for the butyric acid derivative[1] except that the mixture was stirred and heated on the steam-bath for five hours. It was chilled and diluted with 250 ml. of water. A dark brown, gummy mass precipitated and tended to solidify after standing for several hours. It was washed with water and dissolved in 150 ml. of benzene. The water which had been entrapped was removed and the benzene solution was filtered. The solution was diluted with 500 ml. of gasoline causing the separation of an oil that soon solidified into light gray crystals. The yield of crude α-benzoylamino-β-benzylmercapto-*n*-valeric acid was 15 g., m. p. 102–104°. A small sample was recrystallized from the benzene–gasoline mixture, m. p. 103–105°.

Anal. Calcd. for $C_{19}H_{21}NO_3S$: N, 4.08. Found: N, 3.84.

The crude material was sufficiently pure for use in the following step.

A larger run from 60 g. of the oxazolone yielded 60 g. of the acid melting at 102–104°.

α-Amino-β-benzylmercapto-*n*-valeric Acid.—A mixture of 30 g. of α-benzoylamino-β-benzylmercapto-*n*-valeric acid, 230 ml. of commercial formic acid (87%), 230 ml. of concentrated hydrochloric acid and 230 ml. of water was heated under reflux for twelve hours. After the mixture had been cooled in an ice-bath, starting material (15 g.) was removed by filtration. The clear filtrate was evaporated to dryness *in vacuo* and the residue was taken up in 500 ml. of water. A small amount of a brown insoluble substance was removed by filtration. The filtrate was made slightly alkaline with ammonium hydroxide and then was evaporated to remove excess ammonia. α-Amino-β-benzylmercapto-*n*-valeric acid crystallized in white plates, yield 7.5 g., m. p. 172–174°. A small sample was recrystallized from water, m. p. 177–179°.

Anal. Calcd. for $C_{12}H_{17}NO_2S$: N, 5.87. Found: N, 5.98.

α-Amino-β-mercapto-*n*-valeric Acid Hydrochloride.—Sodium (about 2.5 g.) in small pieces was added with vigorous stirring to a solution of 7 g. of the above acid in 100 ml. of liquid ammonia. The metal was added until a deep blue color persisted. This color was discharged by the addition of sufficient solid ammonium chloride. The ammonia was then allowed to evaporate, eventually at reduced pressure to remove final traces. The residue was washed with ether and again evaporated *in vacuo*. The white product was dissolved in 50 ml. of dilute hydrochloric acid and the solution was extracted twice with 50-ml. portions of ether. Again the solution was evaporated to dryness *in vacuo*.

This residue was extracted with 150 ml. of absolute ethanol and the ammonium and sodium chlorides were removed by filtration. The alcohol solution was evaporated to dryness at reduced pressure. The light yellow solid was redissolved in 100 ml. of absolute ethanol and this solution was treated with decolorizing charcoal, filtered and evaporated *in vacuo*.

The white crystalline solid was dissolved in 75 ml. of absolute ethanol. Anhydrous ether was added until a slightly cloudy solution resulted. After the mixture had stood for fiteen minutes, the amino acid hydrochloride began to crystallize in small, white platelets. The mixture was then chilled for several hours and filtered. The yield of white, crystalline α-amino-β-mercapto-*n*-valeric acid hydrochloride was 3 g., m. p. 154–156°. More acid was obtained by working up the ether–ethanol mother liquor. The product gave a strong nitroprusside test to indicate the presence of the sulfhydryl rather than sulfide group.

After two further recrystallizations, the melting point was 163–165°. The nitroprusside test was still strongly positive.

Anal. Calcd. for $C_5H_{11}NO_2S{\cdot}HCl$: N, 7.54. Found: N, 7.32.

Throughout this synthesis no attempt was made to separate the two theoretically possible racemic modifications in pure form or to determine if more than one form were present.

THE LILLY RESEARCH LABORATORIES
ELI LILLY AND COMPANY
INDIANAPOLIS, INDIANA

JOSEPH CORSE[4]
E. C. KLEIDERER
QUENTIN F. SOPER

RECEIVED SEPTEMBER 2, 1947

---

(3) Melting points were determined by means of a Fisher–Johns melting-point block.

(4) Present address, University of California at Los Angeles, Los Angeles, California.

4-Fluoroanthranilic Acid

4-Fluoro-2-nitrotoluene.—3-Nitro-4-toluidine (228 g., 1.5 moles)[1] was suspended in a mixture of 313.5 cc. of concd. hydrochloric acid and 450 cc. of water, chilled to 0° and diazotized using 130 g. of sodium nitrite (as a 35% solution). The filtered diazonium solution was stirred at 0° while 451 g. of 40% fluoboric acid solution was added (*ca.* ten minutes), and stirred for half an hour. After washing (ice-water, methanol, and ether), the cream-colored crystalline diazonium borofluoride was dried, first in air, then *in vacuo* (over paraffin and phosphoric anhydride); yield, 202 g. (54%).

The diazonium borofluoride was decomposed by heating it alone or mixed with an equal weight of acid-washed sand in an apparatus with wide-bore tubing (25 mm.) connected to several traps (*cf.* ref. 2). All products of the reaction, including the residual ashes in the decomposition flask, were combined and distilled with steam. The distillate was extracted with ether, and the extracts freed of phenolic matter by washing with 5% sodium hydroxide and saturated salt solution. After drying (Na_2SO_4), the extract was fractionated[3]; 125–134 g. (67–71%) of yellow liquid was collected at 75–76° (5 mm.) or 108–109° (23 mm.), $n^{25}\mathrm{D}$ 1.5212. 4-Fluoro-2-nitrotoluene was previously obtained by the nitration of 4-fluorotoluene[4]; b. p. 102.4° (20 mm.), $n^{25}\mathrm{D}$ 1.51997.

5-Fluoro-2-acetotoluidide.—Reduction of 4-fluoro-2-nitrotoluene by the method of West,[5] using aqueous

---

(1) Noelting and Collin, *Ber.*, **17**, 263 (1884).

(2) Flood, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 295.

(3) A 25 cm. vacuum-jacketed Vigreux column was used in the distillation.

(4) Desirant, *Bull. sci. acad. roy. Belg.*, **19**, 325 (1933); *C. A.*, **27**, 4781^8 (1933).

(5) West, *J. Chem. Soc.*, 494 (1925).

methanol as the milieu, gave the pure amine in yields of 80–86%. 5-Fluoro-2-toluidine was a colorless liquid, b. p. 100–101° (16 mm.),[3] $n^{25}\text{D}$ 1.5379.

Anal. Calcd. for C_7H_8FN: N, 11.21. Found: N, 11.15.[6]

The amino compound was interacted with acetic anhydride to give 5-fluoro-2-acetotoluidide in 96% yield. It separated from aqueous alcohol in the form of white prismatic needles, m. p. 133.5–134°.

Anal. Calcd. for $C_9H_{10}FNO$: N, 8.38. Found: N, 8.54.

4-Fluoranthranilic Acid.—Five and three-tenths grams (0.0317 mole) 5-fluoro-2-acetotoluidide was added to a solution (at 75–80°) containing 10.3 g. of magnesium sulfate heptahydrate and 14.5 g. of potassium permanganate in 750 cc. of water. The mixture was stirred at 75–80° for two hours, then filtered and the filtrates acidified with dilute sulfuric acid. When crystallized from aqueous ethanol, 4.95 g. (79%) of 4-fluoroacetylanthranilic acid was obtained; the white platelets melted 209–209.5°.

Anal. Calcd. for $C_9H_8FNO_3$: N, 7.10. Found: N, 7.04.

Hydrolysis of the acetyl compound with boiling 6 *N* hydrochloric acid or 6 *N* sodium hydroxide gave 78–85% yields of 4-fluoroanthranilic acid. The compound crystallized from water as white needles of melting point 192.5–193°.

Anal. Calcd. for $C_7H_6FNO_2$: C, 54.19; H, 3.90; N, 9.03. Found: C, 54.07; H, 3.65; N, 9.11.

---

[6] All analyses were carried out under the direction of Mr. M. E. Auerbach in the analytical laboratories of this Institute.

THE STERLING–WINTHROP RESEARCH INSTITUTE
RENSSELAER, NEW YORK
EDGAR A. STECK
LYNN T. FLETCHER

RECEIVED SEPTEMBER 13, 1947

Ethyl α-Ethoxalylvalerate

The Claisen reaction of diethyl oxalate with ethyl valerate[1] was carried out in dry benzene using commercial sodium methoxide in essentially the manner described for ethyl α-ethoxalylpropionate.[2] An excess of ethyl valerate was used. The crude ester was difficult to distil satisfactorily, and the pure ethyl α-ethoxalylvalerate was obtained in yields of 20–24.5%, based upon diethyl oxalate employed; a 25-cm. vacuum-jacketed Vigreux column was required in the distillation, b. p. 78–80° (0.2 mm.), $n^{25}\text{D}$ 1.4319. This compound was prepared, but not obtained in a pure condition, by Adickes and Andresen.[3]

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found[4]: C, 57.18; H, 7.66.

To determine the position of entrance of the ethoxalyl group, a sample of the ester was heated at 165–175° with powdered glass during three hours. Decarbonylation led to a 53% yield of diethyl propylmalonate, b. p. 78–80° (2 mm.), $n^{25}\text{D}$ 1.4201. An authentic sample of the malonic ester boiled at 79–81° (2 mm.), $n^{25}\text{D}$ 1.4206.

The **2,4-dinitrophenylhydrazone**, prepared in the customary fashion, separated from 80% alcohol in the form of golden leaflets, m. p. 87–87.5° (lit.[3] value, 85–86°—only this derivative was prepared, using crude ester).

Anal. Calcd. for $C_{17}H_{22}N_4O_8$: N, 13.65. Found: N, 13.80.

---

[1] Purchased from Northeastern Chemical Co., Wauwatosa, Wis.

[2] Steck, Hallock and Holland, THIS JOURNAL, **68**, 131 (1946).

[3] Adickes and Andresen, *Ann.*, **555**, 55 (1943).

[4] All analyses were carried out under the direction of Mr. M. E. Auerbach in the analytical laboratories of this Institute.

THE STERLING–WINTHROP RESEARCH INSTITUTE
RENSSELAER, NEW YORK
EDGAR A. STECK
ARNOLD J. HOLLAND

RECEIVED SEPTEMBER 13, 1947

COMMUNICATIONS TO THE EDITOR

THE STRUCTURE OF CITRININ

Sir:

Hetherington and Raistrick[1] degraded citrinin (I, $C_{13}H_{14}O_5$) with dilute acid to II ($C_{11}H_{16}O_3$), which was fused with alkali to give III ($C_9H_{12}O_2$), which in turn was methylated and oxidized to two carboxylic acids IV ($C_{11}H_{14}O_4$) and V ($C_{10}H_{12}O_4$). The compound 4-methyl-5-ethylresorcinol has now been synthesized by two methods, and a comparison of this substance with III (prepared from citrinin) shows that they have the same structure. Two acids, 2-ethyl-4,6-dimethoxybenzoic acid and 2-methyl-3,5-dimethoxybenzoic acid have also been synthesized, and their properties correspond to those reported for IV and V, respectively. No degradation products of citrinin have been previously synthesized.

Formylation of 5-ethylresorcinol[2] with zinc cyanide and hydrogen chloride produced 2-ethyl-4,6-dihydroxybenzaldehyde[3]; the two phenolic hydroxyl groups were methylated to give 2-ethyl-4,6-dimethoxybenzaldehyde, which was in turn oxidized to 2-ethyl-4,6-dimethoxybenzoic acid, m. p. 99–100° (Hetherington, *et al.*,[1] reported a melting point of 98–99° for IV).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.76; H, 6.71.

Reduction of 2-ethyl-4,6-dimethoxybenzaldehyde to 2-methyl-3,5-dimethoxyethylbenzene, followed by demethylation of the two methoxyl groups produced 4-methyl-5-ethylresorcinol, m. p. 67–69°. A mixed melting point of this compound

---

[1] Hetherington and Raistrick, *Trans. Roy. Soc.* (London), **B220**, 1–10 (1931).

[2] This compound was prepared by the procedure of Asahina and Ihara, *J. Pharm. Soc. Japan*, **48**, 28 (1928).

[3] This substance had been prepared previously by Geissman and Tulagin (unpublished work).

with III[4] prepared from citrinin gave no depression. The bis-(*p*-nitrobenzoate) of 4-methyl-5-ethylresorcinol was prepared (m. p. 205–6°) and compared with the bis-(*p*-nitrobenzoate) of III (m. p. 205–6°). A mixed melting point determination gave 205–206°. *Anal.* Calcd. for $C_{23}H_{18}O_8N_2$: C, 61.33; H, 4.03. Found: C, 61.50; H, 4.03.

Methylation of the hydroxyl groups of 2-methyl-3,5-dihydroxybenzoic acid (prepared by the method of Jacobsen and Wierss[5]) gave 2-methyl-3,5-dimethoxybenzoic acid, m. p. 157–158° (Hetherington, *et al.*,[1] reported m. p. 142–146° for V). *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.16; neut. equiv., 196.2. Found: C, 61.35; H, 6.55; neut. equiv., 195. This acid was converted to the amide which was treated with methylmagnesium bromide to give 2-methyl-3,5-dimethoxyacetophenone, m. p. 46–47°. Reduction of this ketone with hydrazine followed by demethylation produced 4-methyl-5-ethylresorcinol, m. p. 67–69°. Admixture of this sample with III or with the sample prepared from 5-ethylresorcinol produced no depression.

The above evidence completely eliminates the formulas advanced by Coyne, Raistrick and Robinson[6] for citrinin, II, III, IV and V.

Terminal-methyl number determinations were run on citrinin (2.68 and 2.76) and on II (2.57 and 2.51). Since II couples with two moles of benzenediazonium chloride in an apparently normal manner (Gore, *et al.*[4]), and since the molecule must have at least three terminal methyl groups, II would appear to be 4-methyl-5-(1-methyl-2-hydroxypropyl)-resorcinol. The synthesis of this substance has been undertaken.

[4] Hetherington, *et al.*,[1] reported a melting point of 97–99° which changed to 65–70° after the sample stood for some time. Gore, Panse and Venkatarumen [*Nature*, **157**, 333 (1946)] reported 65–70° and Spranger and Ruoff [*J. Org. Chem.*, **11**, 189 (1946)] 67–70° as the melting point of III.

[5] Jacobson and Wierss, *Ber.*, **16**, 1960 (1883).

[6] Coyne, Raistrick and Robinson, *Trans. Roy. Soc.* (London), **B220**, 297–300 (1931).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
LOS ANGELES, CALIFORNIA DONALD J. CRAM

RECEIVED NOVEMBER 10, 1947

REDUCTION OF CARBON DIOXIDE TO METHANOL BY LITHIUM ALUMINUM HYDRIDE[1]

Sir:

Carbon dioxide is rapidly absorbed by lithium aluminum hydride in ether solution. From such mixtures formaldehyde was isolated, as the dimethone derivative and as hexamethylenetetramine, in yields not over 25%. Schlesinger and Finholt[2] found two moles of carbon dioxide absorbed per mole of hydride, which is consistent with reduction to the formaldehyde stage but does not exclude further reduction followed by partial carbonation of the resultant methoxide.

We then found that, with lithium aluminum hydride in excess, 0.75 mole of hydride is consumed per mole of carbon dioxide and hence that the reduction under these conditions proceeds to the methanol stage.

However, the isolation of methanol proved troublesome. The best of many different procedures for the recovery of small amounts of methanol from ether–water mixtures gave yields, based on carbon dioxide, of less than 50%. The conventional procedure for effecting reductions with lithium aluminum hydride was eventually abandoned in favor of one which is better with respect to yield and better adapted to isotopic synthesis since it involves fewer operations.

A relatively non-volatile solvent, diethyl carbitol, replaces diethyl ether, and a high-boiling alcohol, *n*-butylcarbitol, is used both to decompose the excess hydride and to liberate methanol by alcoholysis. Methanol, the most volatile component of the system, is then obtained in a simple distillation employing an inert entraining gas. The over-all process is shown below:

First Stage

$$4CO_2 + 3LiAlH_4 = LiAl(OCH_3)_4 + 2LiAlO_2$$

Second Stage (R = *n*-butylcarbityl)

$$LiAlH_4 + 4ROH = LiAl(OR)_4 + 4H_2$$

$$LiAl(OCH_3)_4 + 4ROH = LiAl(OR)_4 + 4CH_3OH$$

In a typical experiment, the carbon dioxide generated from 13.0 g. of barium carbonate by the slow addition of 30% perchloric acid, and diluted by a stream of nitrogen, was passed through drierite into a solution of 3.8 g. of lithium aluminum hydride in 500 cc. of diethyl carbitol. Shortly thereafter, 120 g. of *n*-butylcarbitol was added and, with continued flow of nitrogen gas, the mixture was heated. The product, collected in a trap cooled by a Dry Ice freezing mixture,[3] was redistilled to separate a small residue of high-boiling material and there was obtained as distillate 1.71 g. of methanol, $n^{20}\text{D}$ 1.3310, identified further as the N-(α-naphthyl)-carbamate, m. p. 124°. The yield of methanol was thus 81% based on barium carbonate. A small fraction, 1.7%, of unreacted carbon dioxide was collected in an ascarite tube through which the effluent gas passed.

CLINTON NATIONAL LABORATORY ROBERT F. NYSTROM
OAK RIDGE, TENNESSEE WILLIAM H. YANKO[4]
GEORGE HERBERT JONES LABORATORY
THE UNIVERSITY OF CHICAGO
CHICAGO, ILLINOIS WELDON G. BROWN

RECEIVED DECEMBER 16, 1947

---

[1] Experimental work started at George Herbert Jones Laboratory, The University of Chicago, and continued at Clinton National Laboratory, Oak Ridge, operating under Contract No. W-35-058-eng-71 with the Atomic Energy Project.

[2] Schlesinger and Finholt, unpublished work.

[3] An improvement in yield might result from liquid nitrogen cooling since methanol is appreciably volatile at Dry Ice temperatures.

[4] Present address: Monsanto Chemical Company, Central Research Laboratory, Dayton, Ohio.

THE PREPARATION OF TECHNETIUM METAL

Sir:

Element number 43, technetium, which was discovered by Perrier and Segre[1] has now been prepared in metallic form from two separate samples of technetium compounds which were obtained from Dr. G. W. Parker of Clinton Laboratories, Oak Ridge, Tennessee. Both original samples were reported to be the ammonium "per" salt, probably NH_4TcO_4 and were shown by spectrographic analysis to contain negligible amounts of impurities.

The first sample was obtained from Oak Ridge as a pink deposit, weighing 119 micrograms, on a platinum plate. Hydrogen sulfide was passed, for a period of one hour, over a pink solution of the solid in 100 microliters of 4 *N* hydrochloric acid in a microcone placed in a water-bath at 80°, and a brownish, flaky precipitate formed slowly. This was centrifuged, washed and dried *in vacuo* at room temperature. A sample of this sulfide which was submitted for analysis gave an X-ray diffraction pattern which has not yet been interpreted.

The sulfide was transferred to a thin-walled quartz capillary (i. d. 0.15 mm., wall thickness 0.015 mm.) which was attached to a vacuum line in such a manner that hydrogen could be admitted onto the heated sulfide and then removed by pumping.

When the compound was treated with hydrogen at 1000° for three two-minute intervals with intervening evacuation a black cindery mass resulted and a yellow material sublimed out, presumably sulfur. The black material was transferred to an X-ray capillary and submitted for X-ray analysis. It was reported by Dr. R. C. L. Mooney to be technetium metal, isomorphous with rhenium, osmium and ruthenium.[2]

The second sample of technetium was obtained as a pink sirup in a sealed quartz tube. The sirup, which was reported to contain *ca.* 200 micrograms of technetium, was dissolved in 100 microliters of 4 *N* hydrochloric acid as before. This time when hydrogen sulfide was passed over the heated solution a black precipitate immediately formed. This compound gave no X-ray diffraction pattern.

On treatment of the dried solid with hydrogen at 900°, a substance was formed yielding an X-ray diffraction pattern totally unlike that obtained before. The product was then treated with hydrogen at 1000° and the pattern obtained was again different but may have contained some metal. Finally, it was treated with hydrogen at 1100° and a silvery, sintered mass was obtained which proved to give the same pattern as the first metal obtained.

Technetium metal does not dissolve in hydrogen peroxide–ammonium hydroxide mixture or in hydrogen peroxide alone as does rhenium metal, nor does it dissolve in hydrochloric acid.

The patterns obtained at 900 and 1000° may be due to lower sulfides of technetium and these compounds will be investigated further.

The disparate results on the precipitation of the technetium sulfides may be due to the fact that two distinct oxidation states were involved.

CHEMISTRY DIVISION
ARGONNE NATIONAL LABORATORY SHERMAN FRIED
CHICAGO, ILLINOIS

RECEIVED DECEMBER 24, 1947

---

(1) Perrier and Segre, *J. Chem. Phys.*, **5**, 712 (1937).

(2) Mooney, *Phys Rev.*, **72**, 1269 (1947).

PREPARATION OF CARBON MONOXIDE[1]

Sir:

Because of the wide interest in carbon monoxide as an intermediate in the synthesis of isotopically labeled organic compounds, and in view of the recent report by Kummer[2] on the preparation of $C^{14}O$ by an exchange reaction with $C^{14}O_2$, I am prompted to describe a method which, because of its extreme simplicity, is applicable not only to the preparation of isotopic carbon monoxide, but also to the ordinary laboratory preparation of this gas. It consists simply in heating a mixture of calcium carbonate and zinc dust, whereupon the following reaction occurs

$$CaCO_3 + Zn \longrightarrow CaO + ZnO + CO$$

This reaction was reported many years ago by Kinnicutt[3] and Schwartz,[4] but appears to have been overlooked, since the only subsequent reference found is a brief mention by Mellor. Investigation revealed that at 700–750° a mixture of dry, powdered calcium carbonate with twice the theoretical quantity of zinc dust[5] gives a quantitative yield of carbon monoxide of high purity. For small-scale preparations (1–10 mM.) it was found convenient to heat the reactants in a quartz tube attached to an evacuated system of known volume, the rate and extent of gas evolution being measured by means of a manometer. In a typical run, 10 mM. of calcium carbonate and 20 mM. of zinc yielded 216 ml. N.T.P. of gas consisting of CO, 99.1%; CO_2, 0.9%; H_2 and H_2O, traces; as determined by mass-spectrometric analysis. Larger-scale preparations (up to 5 liters) have been made at atmospheric pressure by heating the reactants in a Pyrex test-tube and collecting the gas by displacement of a liquid (water or oil).

The rate of gas evolution is easily controlled by varying the temperature of the reaction vessel. The reaction doubtless depends upon dissociation of calcium carbonate, since the more stable barium carbonate gives no trace of carbon monoxide under the same conditions.

---

(1) This work was sponsored by the Sun Oil Company, Philadelphia, Pa.

(2) Kummer, THIS JOURNAL, **69**, 2239 (1947).

(3) Kinnicutt, *Am. Chem. J.*, **5**, 43 (1883).

(4) Schwartz, *Ber.*, **19**, 1141 (1886).

(5) An excess of zinc is necessary because some distils at the temperature employed.

Although this procedure was investigated primarily for the synthesis of C^{13} labeled methanol, it should also be useful for the preparation of isotopic phosgene and perhaps other compounds. An important advantage of this method, particularly with C^{13}, is that there is no dilution of the isotope concentration, as would occur in an exchange reaction.

THE RESEARCH INSTITUTE OF
TEMPLE UNIVERSITY, PHILA.,
AND THE HOUDRY PROCESS CORP. OF
MARCUS HOOK, PENNSYLVANIA
SIDNEY WEINHOUSE

RECEIVED OCTOBER 20, 1947

NEW BOOK

Essentials of Physiological Chemistry. By ARTHUR K. ANDERSON, Professor of Physiological Chemistry, The Pennsylvania State College. Third Edition. John Wiley and Sons, Inc., 440 Fourth Ave., New York 16, N. Y., 1947. vii + 395 pp. 38 figs. 15 × 23.5 cm. Price, $3.50.

This excellent elementary text-book has been revised and reasonably well brought up to date. It can be recommended either for students taking a one semester course in biochemistry or for others who have had a satisfactory background of organic chemistry but who have not been able to take a formal course in biochemistry. The fundamental facts of biochemistry are set forth in an interesting manner. Good reviews of carbohydrates and lipids are presented. It is to be regretted, however, that no serious attempt has been made to give the student an adequate picture of the protein molecule as established by modern physical and chemical methods of investigation. The usual topics, such as enzymes, hormones, vitamins, metabolism and blood chemistry, have been handled well. In a later edition, it might be advisable to adopt uniformly the current method for representing the benzenoid ring. As is usual with any text-book, criticisms may be directed at certain statements; considering the excellence and general accuracy of the text, however, such criticisms become relatively unimportant.

HUGH J. CREECH

BOOKS RECEIVED

November 10, 1947–December 10, 1947

ERNEST BALDWIN. "Dynamic Aspects of Biochemistry." The Macmillan Company, 60 Fifth Avenue, New York 11, N. Y. 457 pp. $4.00.

CHARLES E. CLIFTON, Editor, SIDNEY RAFFEL AND H ALBERT BARKER, Associate Editors. "Annual Review of Microbiology." Vol. I, 1947. Annual Reviews, Inc., Stanford University P.O., California. 404 pp.

RAYMOND E. KIRK AND DONALD F. OTHMER, Editors. "Encyclopedia of Chemical Technology." Volume I. "A to Anthrimides." The Interscience Encyclopedia, Inc., 215 Fourth Ave., New York 3, N. Y. 982 pp. $20.00. (Complete in 10 volumes of approximately 960 pages per volume. Two to three volumes to appear per year.)

WALTER O. LUNDBERG. "The Hormel Institute of the University of Minnesota." Publication No. 20. "A Survey of Present Knowledge, Researches and Practice in the United States Concerning the Stabilization of Fats." Printed at the University of Minnesota, Minneapolis, Minn. 45 pp.

E. B. MAXTED. "Modern Advances in Inorganic Chemistry." The Oxford University Press, Inc., 2 West 17th St., New York 11, N. Y. 296 pp. $7.00.

EDNA C. MORSE. "College Chemistry in Nursing Education." The Macmillan Company, 60 Fifth Ave., New York, N. Y. 260 pp. $4.00.

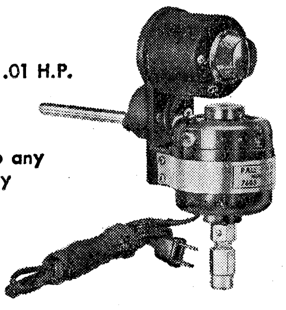
GEORGE ROSEN AND BEATE CASPARI-ROSEN. "400 Years of a Doctor's Life." Henry Schuman, Publisher, 20 East 70th Street, New York 21, N. Y. 429 pp. $5.00.

ALBIN H. WARTH. "The Chemistry and Technology of Waxes." The Reinhold Publishing Corporation, 330 West 42nd Street, New York 18, N. Y. 519 pp. $10.00.

LABORATORY STIRRERS
with Complete Speed Control

WRITE FOR BULLETIN 3404-F

- Rheostat speed control to 5,000 R.P.M.
- Standard motor, continuous duty.
- Plenty of power—.01 H.P.
- Stainless steel mounting rod.
- Can be clamped to any standard laboratory support.
- Rugged chuck, for ¼″ rod.
- Operates on 110 volts AC or DC.



MODEL 7605
$17²⁵

This is just *one* of our complete line of high quality laboratory stirrers—of all kinds, for all purposes. Tell us your needs. We will be glad to advise you.

Our New COMPLETE CATALOG IS NOW READY. Write today for your copy.

PALO-MYERS INC.
81 READE STREET • NEW YORK 7, N.Y.

TRADE MARK
HEVI-DUTY
REGISTERED U.S. PAT. OFFICE

HEVI DUTY
PRECISION ELECTRIC
HEAT TREATING FURNACES

. . . embrace most laboratory and industrial heat treating operations requiring temperatures to 2500° F. They are available in a large range of types and sizes or custom built to your own special requirements. Hevi Duty Furnaces are standard production equipment in many national industries. Ask for detailed bulletins or send us your specifications.

HEVI DUTY ELECTRIC COMPANY
HEAT TREATING FURNACES HEVI-DUTY ELECTRIC EXCLUSIVELY
MILWAUKEE 1, WISCONSIN

Single Copy and Back Issue Prices

ACS JOURNALS

The necessity for reprinting many numbers of back issues of ACS journals has required an increase in the back number prices of these journals in order to meet costs of reproduction. The following schedules are now in effect.

SINGLE COPY PRICES

Journal	Current Year		Back Years		
	Member	Non-Member	Member	Non-Member	Foreign Postage
ANALYTICAL CHEMISTRY	$0.40	$0.50	....	....	$0.15
Analytical Edition (I&EC)					
Volumes 1–4	....	....	$1.00	$1.25	.15
Volumes 5–8	....	....	.68	.85	.15
Volumes 9 et seq.	....	....	.48	.60	.15
CHEMICAL ABSTRACTS					
Numbers 1–22, each	.60	.75	.80	1.00	.15
Numbers 23 and 24, each	2.00	2.50	2.40*	3.00*	.45
CHEMICAL AND ENGINEERING NEWS	.15	.15	.15	.15	.05
INDUSTRIAL AND ENGINEERING CHEMISTRY	.60	.75	....	....	.15
INDUSTRIAL AND ENGINEERING CHEMISTRY (Industrial Edition)	....	....	.72	.90	.15
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY	.80	1.00	.80	1.00	.15

Canadian Postage: Five cents per copy with the exception of Chemical Abstracts, Nos. 23 and 24 each, 15 cents. Copies of Chemical and Engineering News, postage free.

* Except Subject Index, Volume 40. This is in two parts and each part sells for $2.00 (subject to 20% discount to members). Part 1 contains Subject Index. Part 2 contains Formula Index, Numerical Patent Index, and List of Periodicals Abstracted.

VOLUME PRICES

	Member	Non-Member	Foreign Postage	Canadian Postage
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY	$ 9.60	$12.00	$1.50	$0.50
CHEMICAL ABSTRACTS	16.00	20.00	2.40	.80
INDUSTRIAL AND ENGINEERING CHEMISTRY	7.20	9.00	2.25	.75
ANALYTICAL EDITION	4.80	6.00	.75	.25
CHEMICAL AND ENGINEERING NEWS (1–24)	2.40	3.00	2.25	.75
CHEMICAL AND ENGINEERING NEWS (25 et seq.)	4.80	6.00	2.25	.75

Please address all orders and inquiries to:

AMERICAN CHEMICAL SOCIETY
BACK NUMBERS DEPT.
1155 Sixteenth Street, N.W. • Washington 6, D. C.

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 70 MARCH 5, 1948 NUMBER 2

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Reactions of Trimethylsilyl Sulfate[1]

BY LEO H. SOMMER, GEORGE T. KERR AND FRANK C. WHITMORE

The Flood Reaction.—In 1933 Flood reported that treatment of a concentrated sulfuric acid solution of hexaethyldisiloxane with ammonium chloride or fluoride gives triethylchlorosilane or the corresponding fluoro compound.[2] In connection with studies of organosilicon compounds, we have found this reaction extremely convenient for the preparation of large amounts of trialkylchloro- and trialkylfluorosilanes, when certain modifications of the procedure reported by Flood are employed.[3] During a study of the mechanism of the reaction, we isolated trimethylsilyl sulfate, a white crystalline solid, m. p. 56–58°, from the reaction of hexamethyldisiloxane with fuming sulfuric acid.[4]

In the present work it has been found that the use of concentrated sulfuric acid and continuous extraction of the reaction mixture with pentane gives improved yields and a consistently purer product.

$$[(CH_3)_3Si]_2O + H_2SO_4 \longrightarrow [(CH_3)_3Si]_2SO_4 + H_2O \quad (1)$$

To 162.0 g. (1.00 mole) of hexamethyldisiloxane was added dropwise over a two-hour period, with stirring and salt–ice cooling, 260 g. (2.5 moles) of concentrated sulfuric acid. The final reaction mixture was a white, crystalline slurry. It was continuously extracted with dry pentane for forty-eight hours while keeping the reaction mixture ice-cold. The pentane was removed from the extract under vacuum and there was obtained 161.0 g. (0.67 mole) of white crystalline trimethylsilyl sulfate. A weighed sample gave: % SO_4, 38.9 (calcd., 39.6). The acid residue remaining after extraction was hydrolyzed and there was recovered 48 g. (0.30 mole) of hexamethyldisiloxane. The yield of sulfate was 66% based on the total starting material and 94% based on unrecovered starting material.

Treatment of a heptane solution of trimethylsilyl sulfate with hydrogen chloride gas in the presence of ammonium sulfate gives an instantaneous reaction affording an 88% yield of trimethylchlorosilane.

$$[(CH_3)_3Si]_2SO_4 + 2HCl \longrightarrow 2(CH_3)_3SiCl + H_2SO_4 \quad (2)$$

Dry hydrogen chloride passed into a mixture of 20.0 g. (0.15 mole) of ammonium sulfate and 200 cc. of a *n*-heptane solution of 30.0 g. (0.124 mole) of trimethylsilyl sulfate gave immediate precipitation of droplets of sulfuric acid. After completion of the reaction (one and one-half hours), the upper layer was fractionated to give 24.0 g. (0.22 mole) of trimethylchlorosilane, b. p. 56–58°, 88% yield.

Reactions 1 and 2 suggest that the preparation of trialkylchlorosilanes by the Flood reaction involves (a) formation of the sulfate from disiloxane and sulfuric acid, and (b) reaction of the sulfate with hydrogen chloride to give the chlorosilane.

$$(R_3Si)_2O + H_2SO_4 \longrightarrow (R_3Si)_2SO_4 + H_2O \quad (a)$$
$$(R_3Si)_2SO_4 + 2HCl \longrightarrow 2R_3SiCl + H_2SO_4 \quad (b)$$

Both of these reactions are reversible. Hydrolysis of trimethylsilyl sulfate with water readily gives the disiloxane. An effective reversal of (b) has been utilized by Patnode and Schmidt[5] in the preparation of trimethylsilyl sulfate from trimethylchlorosilane and concentrated sulfuric acid.

In the Flood reaction, isolation of trimethylchlorosilane in good yield is made possible by the presence of ammonium bisulfate, from the reaction of ammonium chloride with sulfuric acid, which effectively prevents the reversal of (b).

Addition of 108 g. (1.0 mole) of trimethylchlorosilane to a mixture of 245 g. (2.5 moles) of concentrated sulfuric acid and 99 g. (0.75 mole) of ammonium sulfate, followed by stirring for fifteen minutes gave a very slight evolution of hydrogen chloride. Separation of the upper layer,

---

[1] Presented at the 110th Meeting of the American Chemical Society, Chicago, Ill., September 1946. Paper XIV in a series on organosilicon compounds. For paper XIII see THIS JOURNAL, **70**, 435 (1948).

[2] Flood, *ibid.*, **55**, 1735 (1933).

[3] See Di Giorgio, Strong, Sommer and Whitmore, *ibid.*, **68**, 1380 (1946); Sommer, Bailey, Strong and Whitmore, *ibid.*, **68**, 1881 (1946); Pray, Sommer, Goldberg, Kerr, Di Giorgio and Whitmore, *ibid.*, **70**, 433, (1948).

[4] Sommer, Pietrusza, Kerr and Whitmore, *ibid.*, **68**, 156 (1946).

[5] Patnode and Schmidt, *ibid.*, **67**, 2272 (1945).

followed by fractionation, gave 94.6 g. (0.87 mole) of trimethylchlorosilane, a recovery of 87%.

Although hydrogen chloride gave no apparent reaction with a solution prepared from hexamethyldisiloxane and concentrated sulfuric acid in the absence of added ammonium sulfate, the following procedure gave a 65% yield of trimethylchlorosilane. Dry hydrogen chloride was passed into a stirred solution (at 0°) prepared from 162 g. (1.0 mole) of hexamethyldisiloxane and 250 g. (2.5 moles) of concentrated sulfuric acid, while adding ammonium sulfate intermittently to the reaction mixture over a three-hour period until a total of 200 g. (1.5 moles) had been added. Hydrogen chloride was then passed in for an additional two hours, until fumes of hydrogen chloride were evolved from the condenser. The upper layer was separated and fractionated, yielding 141 g. (1.13 moles) of trimethylchlorosilane, 60% yield. On cooling, the residue from the fractionation gave 68.0 g. (0.25 mole) of trimethylsilyl sulfate crystals. Thus 90% of the hexamethyldisiloxane was accounted for.

It has recently been reported that hydrogen chloride and hexamethyldisiloxane react to give trimethylchlorosilane.[6] Thus it is possible that the following reaction of hexamethyldisiloxane, or an oxonium salt thereof, should be added to reactions (a) and (b) above in order to fully represent the Flood reaction.

$$(R_3Si)_2O + 2HCl \longrightarrow 2R_3SiCl + H_2O \qquad (c)$$

Reaction (c), like (a) and (b), is reversible.

Other Reactions of Trimethylsilyl Sulfate.—Like trimethylchlorosilane,[7] trimethylsilyl sulfate reacts with ammonia gas to give hexamethyldisilazane, and with dilute alkali to give azeotropic hexamethyldisiloxane–trimethylsilanol and hexamethyldisiloxane.

$$[(CH_3)_3Si]_2SO_4 \xrightarrow{NH_3} [(CH_3)_3Si]_2NH$$

$$[(CH_3)_3Si]_2SO_4 \xrightarrow[H_2O]{NaOH} [(CH_3)_3Si]_2O + (CH_3)_3SiOH$$

Treatment of 300 cc. of an ether solution of 35.0 g. (0.145 mole) of trimethylsilyl sulfate with dry ammonia gas gave immediate reaction. When ammonia was no longer absorbed (three hours), filtration of the product to remove the precipitated ammonia salt followed by fractional distillation gave 16.5 g. (0.102 mole) of hexamethyldisilazane, b. p. 124°, $n^{20}D$ 1.4077, 71% yield.

Trimethylsilyl sulfate, 60 g. (0.25 mole), dissolved in 150 cc. of dry ether, was added (two hours) with vigorous stirring to 200 cc. of ice-cold 20% aqueous sodium hydroxide by means of a separatory funnel having a capillary stem extending below the surface of the alkali. The ether layer was separated, the aqueous layer extracted with three 100-cc. portions of ether, and the ether solution of the product dried with potassium carbonate. Fractionation gave 14.7 g. of azeotropic hexamethyldisiloxane–trimethylsilanol, b. p. 90–93°, $n^{20}D$ 1.3778–1.3790, and 13.3 g. of hexamethyldisiloxane, b. p. 97–100°, $n^{20}D$ 1.3774.

Trimethylsilyl sulfate gave the tetraalkylsilane in good yield when treated with ethyl- or *n*-propylmagnesium bromide. Isopropylmagnesium bromide gave mainly trimethylbromosilane in one experiment, and a 34% yield of isopropyltrimethylsilane in another experiment when a longer reaction time was used.

Ethylmagnesium Bromide.—A solution of 30.0 g. (0.33 mole) of trimethylsilyl sulfate in 200 cc. of dry ether was added, with stirring, to 0.9 mole of ethylmagnesium bromide in 250 cc. of ether during ten minutes. There was no vigorous reaction at first, but addition of about two-thirds of the sulfate resulted in the formation of two layers. The reaction mixture was then slowly heated on the steam-bath until all of the volatile material was distilled and collected. After heating for six hours, the solid in the flask appeared to be dry, and was allowed to cool. Hydrolysis with dilute acid and extraction gave no additional product. After removal of ether, the distillate from the reaction mixture was fractionally distilled. There was obtained 36.0 g. (0.55 mole) of ethyltrimethylsilane,[8] b. p. 62°, $n^{20}D$ 1.3820, a yield of 83.5%.

***n*-Propylmagnesium Bromide.**—Using a procedure similar to that above, 0.8 mole of *n*-propylmagnesium bromide was treated with 73 g. (0.3 mole) of trimethylsilyl sulfate. Fractional distillation indicated that the product was a mixture of *n*-propyltrimethylsilane and trimethylbromosilane.[9] Since these compounds were somewhat difficult to separate, the trimethylbromosilane (*ca.* 10%) was removed by hydrolysis followed by treatment with concentrated sulfuric acid which dissolved the formed hexamethyldisiloxane and left *n*-propyltrimethylsilane as a clear upper layer. The yield of *n*-propyltrimethylsilane,[8] b. p. 90°, $n^{20}D$ 1.3929, was 55%.

Isopropylmagnesium Bromide. Run 1.—A solution of 73 g. (0.30 mole) of trimethylsilyl sulfate in 150 cc. of dry ether was added to 0.7 mole of isopropylmagnesium bromide in 350 cc. of ether. The reaction mixture was stirred at room temperature for one hour and was then heated on the steam-bath for six hours to distil all of the volatile product. The distillate fumed vigorously on exposure to air. Fractionation gave 47.5 g. (0.31 mole) of trimethylbromosilane,[9] b. p. 80°, a yield of 51.5%.

Run 2.—A run similar to that above was made, except that the reaction mixture was stirred at reflux temperature for eight days before distillation of the product. Fractionation gave 15.7 g. (0.155 mole) of isopropyltrimethylsilane, b. p. 89°, $n^{20}D$ 1.3958, a yield of 34%.

Anal. Calcd. for $C_6H_{16}Si$: Si, 24.1. Found: Si, 23.9.

The physical properties of this material check those of another sample prepared from *i*-propyltrichlorosilane[10] and methylmagnesium bromide.

Heating of trimethylsilyl sulfate with dry ammonium chloride gave trimethylchlorosilane in fair yield.

$$[(CH_3)_3Si]_2SO_4 \xrightarrow{NH_4Cl} 2(CH_3)_3SiCl$$

In a 250-cc. distilling flask were placed 40.0 g. (0.166 mole) of trimethylsilyl sulfate and 16.0 g. (0.33 mole) of dry powdered ammonium chloride. The flask was fitted with a thermometer, whose bulb was just below the side-arm, and a water-cooled condenser attached to an adaptor. The reaction mixture was heated gently and almost immediately vapor entered the condenser. The reaction mixture was heated until it was dry, and the distillate was fractionally distilled. There was obtained 15.0 g. (0.138 mole) of trimethylchlorosilane,[11] b. p. 56–58°, 32.5% Cl (calcd. 32.6% Cl), 42% yield.

Using a procedure similar to that above, very poor yields of trimethylchlorosilane (5–10%) were obtained with cupric chloride and cuprous chloride.

It is of interest to note that one of the most striking differences between trimethylsilyl sulfate and alkyl sulfates is the tendency of the latter to give reaction of only one of the alkyl groups.[12]

---

[6] Krieble and Elliott, THIS JOURNAL, **68**, 2291 (1946).

[7] Sauer, *ibid.*, **66**, 1707 (1944).

[8] Whitmore, Sommer, Di Giorgio, Strong, Van Strien, Bailey, Hall, Pietrusza and Kerr, *ibid.*, **68**, 475 (1946).

[9] Gilliam, Meals and Sauer, *ibid.*, **68**, 1161 (1946).

[10] Booth and Spessard, *ibid.*, **68**, 2660 (1946).

[11] Taylor and Walden, *ibid.*, **66**, 842 (1944); Gilliam and Sauer, *ibid.*, **66**, 1793 (1944).

[12] Suter, "Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 48.

This is in line with the increase in reactivity of electronegative groups which generally results from substitution of silicon for carbon.

Summary

1. Trimethylsilyl sulfate has been prepared by an improved method.

2. Reactions of trimethylsilyl sulfate have been studied.

3. A mechanism for the Flood reaction has been proposed.

STATE COLLEGE, PENNA. RECEIVED MAY 9, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY, THE OHIO STATE UNIVERSITY]

The Isolation of β-Amyrin and a Fatty Acid of High Molecular Weight from *Solidago leavenworthii* T. and G.

BY R. C. BURRELL AND FORREST G. HOUSTON

In the usual process for obtaining rubber from goldenrod the leaf material is first exhaustively extracted with acetone to remove waxes and resinous materials. On evaporation of the acetone from this extract a dark green tar is obtained. Polhamus[1] reports a mean of 21.03% of tar from five samples of *Solidago minor*. At the Southern Regional Research Laboratory of the U. S. D. A., Guthrie, *et al.*,[2] obtained a good yield of quercitrin and its aglycone from such tar prepared from the leaves of *Solidago leavenworthii* T. and G. Through the kindness of Dr. Guthrie a sample of this tar was obtained by us and the benzene soluble fraction of it was subjected to further investigation.

Experimental Results

Isolation of β-Amyrin.—Three kg. of the above mentioned tar were extracted with 2 l. of boiling benzene followed by five extractions with one-liter portions of hot benzene. The combined extracts were filtered through paper pulp and the green pigments removed by treatment with activated charcoal. A dark brown solution resulted from which the benzene was distilled, thereby yielding 950 g. of a brown viscous oil. This oil was refluxed for two hours with 1500 cc. of 20% alcoholic potassium hydroxide. The mixture was cooled and 2 liters of water added. It was made slightly acid to litmus with 10 *N* sulfuric acid. Two layers were formed, the upper a brown oil and the lower a greenish colored water solution. The oily layer was separated and treated with one liter of 10% sodium hydroxide solution and 3 liters of water and shaken vigorously for an hour. This mixture was then repeatedly extracted with ether, the extracts united, washed and dried over anhydrous sodium sulfate.

The sodium hydroxide solution which remained after the ether extraction was set aside for further investigation.

The ether was distilled from the dried extract leaving a deep yellow greasy residue. This was dissolved in one liter of acetic anhydride and refluxed for two hours. After standing overnight a heavy deposit of yellow needles formed. The liquid was then decanted and the crystals washed twice with one-liter portions of hot 95% ethyl alcohol and finally with petroleum ether until colorless. Nineteen grams of vacuum dried crystals was obtained, amounting to a yield of about 0.13% of the dried leaf material.

These crystals (acetate) melted at 231–233°. The saponification equivalent was 467 to 471 and the specific rotation in chloroform was $[\alpha]^{28}\text{D}$ +78°. The saponified compound after recrystallization from a large volume of 95% ethyl alcohol gave long colorless needles which melted at 190–192°. The benzoate melted at 229–230°. The Liebermann–Burchard reaction was positive. These properties correspond quite closely to those recorded for β-amyrin.[3,4]

Isolation of a High Molecular Weight Fatty Acid.—The fraction of saponified oil that was soluble in 10% sodium hydroxide (see β-amyrin preparation above) was neutralized with 10 *N* sulfuric acid. A brown oily liquid rose to the surface. This oil was removed by extraction with ether, the ether extract was thoroughly washed with water and dried, the ether removed by distillation and the residue dissolved in 1500 cc. of hot 95% ethyl alcohol. This solution was partially cleared with activated charcoal. On cooling a slightly yellow flocculent precipitate formed. This was reprecipitated four times from 95% alcohol. The 5 g. of colorless, amorphous material thus obtained was saponified for six hours with 20% alcoholic potassium hydroxide. This solution was then cooled and diluted with an equal volume of water. A slightly yellowish soapy precipitate formed which was filtered off, washed with dilute sulfuric acid, dried over a steam-bath and dissolved in 30 cc. of hot glacial acetic acid. On slow cooling colorless rosets of crystals were deposited (dry wt. 1 g.) which melted at 82°. The molecular weight by the Rast method was 433. Due to the hydrocarbon-like properties of the compound neutralization equivalent values were erratic. The acid amide melted at 108–110°.

Anal. Calcd. for $C_{28}H_{56}O_2$ (424.4): C, 79.17; H, 13.29. Found: C, 79.27; H, 13.25.

Summary

The isolation of β-amyrin and a high molecular weight fatty acid from the acetone extract of leaves of *Solidago leavenworthii* T. and G. is described.

COLUMBUS, OHIO RECEIVED AUGUST 25, 1947

---

[1] L. G. Polhamus, *J. Agr. Research*, **47**, 149 (1933).

[2] J. D. Guthrie, R. T. O'Connor, M. F. Stansbury and T. R. Savich, THIS JOURNAL, **66**, 1794–1795 (1944).

[3] Abderhalden, "Biochemisches Handlexikon VII," 729 (1912).

[4] I. M. Heilbron, G. L. Moffet and F. S. Spring, *J. Chem. Soc.*, 1583 (1934).

[CONTRIBUTION FROM THE SCHOOL OF PHARMACY, UNIVERSITY OF GEORGIA]

Some Hemiacetals of Chloral with Cyclic Alcohols

BY W. T. SUMERFORD[1] AND F. MAIER CRONIC[2]

Introduction

Some interest has been shown in the hemiacetals of chloral, $CCl_3CHOH(OR)$, as neurophilic agents.[3] This paper describes the synthesis of some hemiacetals of chloral with cyclic alcohols, and reports preliminary pharmacological data on one of them.

Experimental

The chloral used in this work was obtained by mixing U. S. P. grade chloral hydrate with 1.8 times its weight of concentrated sulfuric acid, allowing the chloral to separate, and then distilling it off in an all-glass apparatus. The cyclohexanol and *p*-methylcyclohexanol, obtained from the Eastman Kodak Company, the 1-ethynylcyclohexanol from Farchan Laboratories, and the 3,3,5-trimethylcyclohexanol from the Carbon and Carbide Chemicals Corporation, were dried over anhydrous sodium sulfate, and used without further purification.

One-tenth mole each of chloral and the cyclic alcohol in separate flasks were cooled to 2°. The alcohol was added in ten equal portions at ten-minute intervals to the chloral, placing both flasks in the refrigerator after each addition. The mixture was kept at 2° until it solidified, which required not more than three days, stored for several days in an evacuated desiccator containing calcium chloride and then recrystallized from petroleum ether, b. p. 75–85°.

TABLE I

HEMIACETALS OF CHLORAL WITH CYCLIC ALCOHOLS $CCl_3CHOH(OR)$

R	Formula	Yield, %	M. p., °C.	C analyses, % Calcd.	C analyses, % Found	H analyses, % Calcd.	H analyses, % Found
Cyclohexyl	$C_8H_{13}O_2Cl_3$	82	64	38.88	39.01	5.25	5.45
p-Methylcyclohexyl	$C_9H_{15}O_2Cl_3$	30	60	41.30	41.24	5.73	5.74
1-Ethynylcyclohexyl	$C_{10}H_{14}O_2Cl_3$	41	55	44.19	43.71	4.78	4.70
3,3,5-Trimethylcyclohexyl	$C_{11}H_{19}O_2Cl_3$[a]	33	73	45.61	46.05	6.57	7.17

[a] This compound was prepared also from a sample of 3,3,5-trimethylcyclohexanol which is distributed under the name "Cyclonol" as a synthetic substitute for menthol by W. J. Bush and Co., Inc.

The high solubility of these hemiacetals (Table I) in a wide variety of solvents makes difficult their isolation and purification. Of the many solvents and combinations of solvents tried, only ligroin was suitable, and the fraction boiling between 75–85° gave the best results.

Several cyclic alcohols, *o*-methylcyclohexanol, *m*-methylcyclohexanol and *p*-*t*-butylcyclohexanol, gave hemiacetals with chloral which did not solidify under the experimental conditions. Efforts to purify them by careful distillation at pressures ranging from 2 to 20 mm. and at atmospheric pressure, with the use of glass wool,[4] resulted in their almost complete dissociation into chloral and the alcohol.

Pharmacological.—1-Cyclohexoxy-2,2,2-trichloroethanol in a dosage of 800 mg./kg. narcotized all of five rats injected for an average latent period of fifty minutes, and in a dosage of 1500 mg./kg. gave 100% mortality in a like number of rats.

Acknowledgments.—The authors wish to thank the Advisory Faculty Council of the University Center in Georgia for a grant-in-aid in support of this work. The pharmacological data on the 1-cyclohexoxy-2,2,2-trichloroethanol was kindly supplied by Dr. Y. SubbaRow of the Lederle Laboratories, Inc., Pearl River, N. Y.

Summary

Four new hemiacetals of chloral with cyclic alcohols have been synthesized and described. The relative narcotic activity and toxicity in rats of one of these compounds have been ascertained.

BATON ROUGE, LA. RECEIVED MAY 2, 1947

---

[1] Present address: Coates Chemical Laboratories, Louisiana State University, Baton Rouge, La.

[2] Undergraduate student, School of Pharmacy, University of Georgia.

[3] (a) Personne, *Compt. rend.*, **69**, 1363 (1869); (b) Adams, *J. Pharmacol. Exptl. Ther.*, **78**, 340 (1943); (c) Chechik, *J. Am. Pharm. Assoc.*, **19**, 320 (1930); Kuntze, *Arch. Pharm.*, **246**, 91 (1908); Martius and Mendelssohn-Bartholdy, *Ber.*, **3**, 443 (1870); (d) Minguin, *Bull. soc. chim.*, (iii) **27**, 683 (1902); (e) Schmitt, *Compt. rend. soc. biol.*, **42**, 678 (1890).

[4] Morton, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1938, p. 104.

[CONTRIBUTION FROM NATIONAL RESEARCH INSTITUTE OF CHEMISTRY, ACADEMIA SINICA]

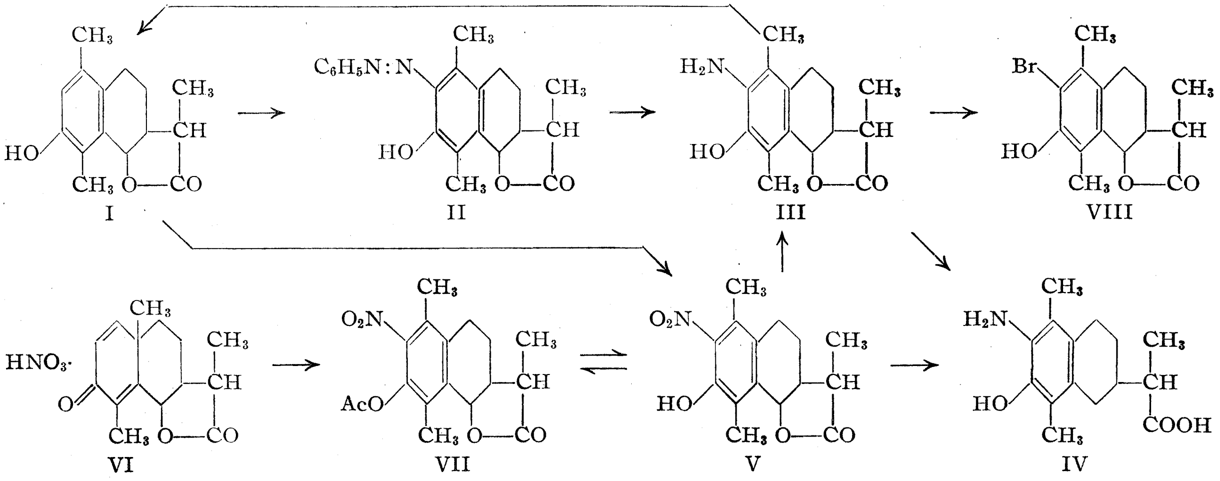
Studies in the Santonin Series. III.[1,2,3] The Introduction of Nitrogen into the Desmotroposantonin Molecule

BY HUANG-MINLON[4] AND SHAO-CHI CHENG

Some time ago E. Wedekind[5] studied the introduction of nitrogen in the form of a salt-forming group into the desmotroposantonin molecule (I), with a view to obtain basic derivatives resembling the alkaloids and to determine pharmacologically the possible variation of the physiological properties of santonin. He attempted to transform benzene-azo-*d*-β-desmotroposantonin (II),[6] prepared from *d*-β-desmotroposantonin (I),[7] into aminodesmotroposantonin (III) by reduction with stannous chloride and hydrochloric acid. However, he obtained not the desired product but an amino acid melting at 206°, which as he recognized arose from benzene-azo-desmotroposantonin through the simultaneous reduction of the lactone ring. The product, therefore, according to him is an aminodesmotroposantonous acid (IV). He further reported that the attempt to employ nitrodesmotroposantonin (V) as the starting material for the preparation of aminodesmotroposantonin had likewise a negative result, and therefore emphasized in his report that in general the preparation of such a substance, on account of the sensitiveness toward reducing agents, would be difficult.

After we had found the interesting rearrangement and isomerization of santonin and desmotroposantonin[2] as well as of its bromination products[3] we wished to ascertain whether or not nitrogen containing derivatives of santonin and desmotroposantonin could give similar reactions. We started with the preparation of nitrodesmotroposantonins (V). The nitro derivative of *d*-β-desmotroposantonin had already been prepared by Andreocci,[8] but under the conditions briefly described by him the nitration did not proceed uniformly. Nitric acid, even in the cold, produces a small amount of the desired nitrodesmotroposantonin and a product melting at 250°, which is perhaps identical with the so-called hydroxynitrodesmotroposantonin obtained by Andreocci[8] by the nitration of *d*-β-desmotroposantonin at room temperatures.

When the nitration is carried out in glacial acetic acid solution and under the controlled conditions described in the experimental part a much better yield of the nitrodesmotroposantonins was obtained. We have prepared up to the present only two of them: the dextro-rotatory nitro-*d*-β-desmotroposantonin, melting at 191–192°, from *d*-β-desmotroposantonin, and the new levo-rotatory nitro-*l*-α-desmotroposantonin, melting at 216°, from *l*-α-desmotroposantonin. The nitro compound melting at 216° can also be prepared by treatment of the addition product of santonin and nitric acid (VI)[9] with acetic anhydride and a drop of concentrated sulfuric acid, followed by



---

(1) This work was done in 1943; publication was delayed because it was impossible to make the stipulated analyses of the new compounds in China during wartime. The analytical data supplied here were performed by Margaret Racich Reese, Chemical Laboratories, Harvard University, to whom the authors are greatly indebted.

(2) Huang-Minlon, Lo and Chu, THIS JOURNAL, **65**, 1780 (1943).

(3) Huang-Minlon, Lo and Chu, *ibid.*, **66**, 1954 (1944).

(4) Present address: Department of Chemistry, Harvard University, Cambridge, Mass.

(5) Wedekind, *Z. physiol. Chem.*, **43**, 240 (1904).

(6) Wedekind and Schmidt, *Ber.*, **36**, 1386 (1903).

(7) For nomenclature of desmotroposantonins and desmotroposantonous acids see Reference 2.

(8) Andreocci, *Atti Acad. Lincei*, [5] **5**, II, 311 (1897); *Chem. Centr.*, **68**, I, 165 (1897); Bargellini and Daconto, *Gazz. chim. ital.*, **38**, II, 42 (1908).

(9) Andreocci, *Atti Acad. Lincei*, [5] **5**, II, 310 (1896); Wedekind and Koch, *Ber.*, **38**, 425 (1905).

saponification of the resulting acetate (VII) which melts at 230–231°. Compound VII has been proved to be identical with the acetylation product of nitro-*l*-α-desmotroposantonin, melting at 230–231°. The mechanism of the reaction is similar to that of the transformation of santonin into *l*-α-desmotroposantonin.[2] But it is more interesting in this case since, in addition to the aromatization of the first ring the rearrangement of the angular methyl group, an indirect nitration has taken place.

The nitrodesmotroposantonins (V), unlike the desmotroposantonins[2] and bromodesmotroposantonins,[3] are not so readily transformable into each other. They remain unchanged after treatment with sulfuric acid and decompose readily on alkali fusion. On reduction under mild conditions with zinc dust and ammonium chloride in alcoholic solutions both of the nitrodesmotroposantonins give the corresponding, previously unknown, aminodesmotroposantonins (III): the dextro-rotatory amino-*d*-β-desmotroposantonin, melting at 197–198°, and the levo-rotatory amino-*l*-α-desmotroposantonin, melting at 170°. Both of the amino compounds are soluble in alcohol but not in water and sodium carbonate solution, and they form water-soluble hydrochlorides. From the aqueous solution of their salts the corresponding aminodesmotroposantonins can be precipitated by the addition of sodium carbonate solution.

The constitution of amino-*d*-β-desmotroposantonin was established by the fact that by the Sandmeyer reaction it is transformed into the already known bromo-*d*-β-desmotroposantonin (VIII).[3] Besides, it is reconverted into *d*-β-desmotroposantonin (I) on diazotization and replacement of the diazo group with hydrogen. These transformations further demonstrate that amino-*d*-β-desmotroposantonin and of course nitro-*d*-β-desmotroposantonin, in respect to the three asymmetric carbon atoms in the lactone ring, must have the same configuration as their parent substance, *d*-β-desmotroposantonin.

Owing to the scarcity of material amino-*l*-α-desmotroposantonin has not yet been converted into compounds of known constitution. We believe, however, that there should be little doubt about this conversion because the *l*-α-isomer is obtained by the same methods and under exactly the same experimental conditions, from *l*-α-desmotroposantonin, as those under which amino-*d*-β-desmotroposantonin is formed from *d*-β-desmotroposantonin. Its levo-rotatory character, as well as its conversion to a dextro-rotatory amino acid which will be discussed later, further illustrates that it retains the configuration of *l*-α-desmotroposantonin with regard to the lactone ring. As in the case of the nitrodesmotroposantonins, the attempt to convert the aminodesmotroposantonins by acid or alkali into their respective stereoisomers gave negative results.

By reduction with zinc dust and acetic acid amino-*d*-β-desmotroposantonin and amino-*l*-α-desmotroposantonin are converted into the corresponding aminodesmotroposantonous acids (IV) melting at 190 and 197°, respectively. These aminodesmotroposantonous acids, like desmotroposantonous acids, show directions of specific rotation opposite to those of their respective parent substances so that they are denoted as amino-*l*-β-desmotroposantonous and amino-*d*-α-desmotroposantonous acid.

Both of these amino acids can also be obtained directly from the appropriate nitrodesmotroposantonin (V), but our amino-*l*-β-desmotroposantonous acid is not identical with that obtained by Wedekind, although he also used *d*-β-desmotroposantonin as the starting material. Our acid and its hydrochloride are levorotatory and it forms an unstable hydrochloride in opposition to the properties of Wedekind's acid; furthermore, the melting point of our acid is lower than and depressed by admixture of Wedekind's acid.

We believe that our compound is the true amino-*l*-β-desmotroposantonous acid because all known desmotroposantonous acids and their substitution products show a direction of specific rotation opposite to that of their parent compounds. The specific rotation reported by Wedekind is that of the hydrochloride rather than that of the free amino compound, but we do not believe that a change of sign of rotation accompanies salt formation in this case since all the hydrochlorides of the amino compounds of the santonin series show the same direction of rotation as the free amino compounds.[10]

Owing to lack of specific information exact repetition of Wedekind's work was not feasible, but on treatment of benzene-azo-*d*-β-desmotroposantonin with stannous chloride we did obtain an amino acid melting at 206° and not identical with amino-*l*-β- and amino-*d*-α-desmotroposantonous acid, which probably is the same product that Wedekind had. Unfortunately lack of material prevented further characterization of the 206°-acid. Contrary to his findings, however, we also isolated amino-*d*-β-desmotroposantonin from the reduction mixture.

Experimental

Nitro-*d*-β-desmotroposantonin (V).—A suspension of ground *d*-β-desmotroposantonin (10 g.) in glacial acetic acid (100 cc.) was cooled to 6–7°. A 10% solution of concentrated nitric acid in glacial acetic acid (40 cc.) was added dropwise from a buret to the stirred suspension in eighty minutes. Stirring was continued for ten more minutes after complete addition; the mixture was poured into ice-water and filtered. Recrystallization of the separated solid from alcohol gave nitro-*d*-β-desmotroposantonin (8 g.) as yellow prisms, m. p. 191–192°, $[\alpha]^{24}\text{D}$ +119.5° (*c*, 0.4% in alcohol).

Anal. Calcd. for $C_{15}H_{17}O_5N$: C, 61.88; H, 5.88. Found: C, 62.19; H, 5.79.

---

[10] Examples for the generalization concerning the sign of rotation are: amino-*d*-β-desmotroposantonin and *d*-hydrochloride, amino-*l*-α-desmotroposantonin and *l*-hydrochloride (see text), *l*-aminohyposantonin and *d*-aminohyposantonous acid hydrochloride [Asahina and Momose, *Ber.*, **71**, 1425 (1938)].

Amino-*d*-*β*-desmotroposantonin (III).—Nitro-*d*-*β*-desmotroposantonin (8 g.) and ammonium chloride (1.5 g.) were dissolved in dilute alcohol (600 cc. of alcohol in 300 cc. of water) and heated to 62–67°, when zinc dust (1.5 g.) was added slowly. The reaction mixture was kept at this temperature for one hour. The filtrate on cooling precipitated long thin plates (2.85 g.), m. p. 195–196°. The mother liquid, after distillation of the major part of the alcohol, gave a second crop (0.88 g.). The combined precipitate was then recrystallized from alcohol; amino-*d*-*β*-desmotroposantonin was obtained as plates, m. p. 197–198°, $[\alpha]^{23}\mathrm{D}$ +113.8°, (*c*, 0.44% in alcohol).

Anal. Calcd. for $C_{15}H_{19}O_3N$: C, 68.95; H, 7.31. Found: C, 69.24; H, 7.03.

It gave the hydrochloride as long prisms by dissolving in a small amount of hot 5% hydrochloric acid and cooling; m. p. 265–267° (dec.), $[\alpha]^{25}\mathrm{D}$ +66.4° (*c*, 0.34% in alcohol).

Anal. Calcd. for $C_{15}H_{20}O_3NCl$: Cl, 11.92. Found: Cl, 11.47.

Amino-*l*-*β*-desmotroposantonous Acid (IV).—(a) Nitro-*d*-*β*-desmotroposantonin (10 g.), zinc dust (37 g.) and 70% acetic acid (300 cc.) were refluxed for ten hours. The filtrate was diluted with 4–5 times its volume of water, when a white precipitate settled out. Dissolution of the separated solid in sodium carbonate solution followed by acidification of the filtrate gave the product in a purer state. The purified solid was then recrystallized from alcohol; amino-*l*-*β*-desmotroposantonous acid (1.44 g.) separated as plates, m. p. 190°, $[\alpha]^{25}\mathrm{D}$ −56.3°, (*c*, 0.8% in alcohol). (b) Amino-*d*-*β*-desmotroposantonin (1 g.), zinc dust (5 g.) and 70% acetic acid (43 cc.) were treated as described in (a); m. p. 189–190°, not depressed by admixture with the product obtained from nitro-*d*-*β*-desmotroposantonin.

Anal. Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.03. Found: C, 68.38; H, 8.10.

The hydrochloride was prepared by dissolving the amino acid in small amount of hot alcohol and followed by addition of concentrated hydrochloric acid; m. p. 245–246°, $[\alpha]^{24}\mathrm{D}$ −59.2° (*c*, 0.6% in alcohol). The fact that several determinations gave about the same but lower value for the chloride content may be due to the loss of hydrogen chloride during drying, because the substance reverts to the free base on standing overnight in a vacuum desiccator over potassium hydroxide or on recrystallization from alcohol.

Anal. Calcd. for $C_{15}H_{22}O_3NCl$: Cl, 11.83. Found: Cl, 10.65.

Conversion of Amino-*d*-*β*-desmotroposantonin into Bromo-*d*-*β*-desmotroposantonin.—A mixture of copper sulfate (1 g.), copper powder (0.35 g.), sodium bromide (2.5 g.), concentrated sulfuric acid (0.3 cc.) and water (16 cc.) was boiled for three to four hours until the solution had become yellow. Amino-*d*-*β*-desmotroposantonin (0.4 g.) dissolved in a little water containing three drops of sulfuric acid was diazotized with sodium nitrite (0.12 g.) in the presence of copper sulfate (0.1 g.). The diazotized mixture was then poured into the cuprous bromide solution at 60–70°. After cooling the brown precipitate was filtered and dissolved in alcohol. Narrow thin plates separated overnight. After being decolorized with bone char it was recrystallized from alcohol giving bromo-*d*-*β*-desmotroposantonin in prismatic needles (0.03 g.), m. p. 209–210°, unchanged by admixture with an authentic specimen of bromo-*d*-*β*-desmotroposantonin.[3] The product gave a positive Beilstein test. Its racemic compound with bromo-*l*-*β*-desmotroposantonin[3] was found to be identical with bromo-*dl*-*β*-desmotroposantonin[3] both in crystal form and in melting point. A mixture of the two showed no melting point depression.

Conversion of Amino-*d*-*β*-desmotroposantonin into *d*-*β*-Desmotroposantonin.—Amino-*d*-*β*-desmotroposantonin (0.2 g.) dissolved in alcohol (10 cc.) containing two drops of concentrated sulfuric acid was diazotized with sodium nitrite (0.06 g.). After standing for twenty minutes in an ice-bath the diazotized compound was decomposed by boiling for twenty minutes in the presence of a small amount of zinc dust. Dilution of its filtrate with water gave a yellow precipitate (0.1 g.) which was then dissolved in alcohol and decolorized with bone char. Concentration and cooling of the decolorized filtrate yielded *d*-*β*-desmotroposantonin in prisms, m. p. 259–260°, unchanged by admixture with an authentic specimen of *d*-*β*-desmotroposantonin. The product gave with *l*-*β*-desmotroposantonin a racemic compound that was identical with *dl*-*β*-desmotroposantonin.[2]

Nitro-*l*-*α*-desmotroposantonin (V).—(*a*) This was obtained from *l*-*α*-desmotroposantonin (10 g.) by the same procedure as described in the nitration of *d*-*β*-desmotroposantonin. It crystallized from alcohol as yellow prisms (7.8 g.), m. p. 216–217°, $[\alpha]^{25}\mathrm{D}$ −105°, (*c*, 0.4% in alcohol).

Anal. Calcd. for $C_{15}H_{17}O_5N$: C, 61.88; H, 5.88. Found: C, 62.20; H, 5.46.

(*b*) Santonin (2 g.) was dissolved in concentrated nitric acid while warm. Upon cooling there separated the addition compound of santonin and nitric acid of m. p. 140–142°, which after filtration and drying over potassium hydroxide in the desiccator was added with water cooling to acetic anhydride (8 cc.) containing a drop of concentrated sulfuric acid. The reaction mixture was heated on a water-bath for about ten minutes. Dilution with water gave the acetate (VII) at first as an oil and then as a semisolid which, after recrystallization from chloroform–alcohol, melted at 230–231°, unchanged by admixture with the acetylation product of nitro-*l*-*α*-desmotroposantonin.

For saponification the product was refluxed with a 10% postassium hydroxide solution for half an hour when it dissolved rapidly to form a deep red solution. Acidification of the resulting reaction mixture gave the nitro compound in prisms, m. p. 215–216°. This was shown to be identical with the product obtained from (a) in crystal form, solubility and melting point. A mixture of the two showed no melting point depression. It was reconverted into the acetate of m. p. 230–231° on being refluxed with acetic anhydride for half an hour.

Amino-*l*-*α*-desmotroposantonin (III).—On reduction under the same conditions as those described in the reduction of nitro-*d*-*β*-desmotroposantonin, nitro-*l*-*α*-desmotroposantonin (1 g.) gave amino-*l*-*α*-desmotroposantonin as prisms (0.41 g.), m. p. 170°, $[\alpha]^{25}\mathrm{D}$ −157.5° (*c*, 0.4% in alcohol).

Anal. Calcd. for $C_{15}H_{19}O_3N$: C, 68.95; H, 7.31. Found: C, 69.34; H, 7.42.

Amino-*l*-*α*-desmotroposantonin Hydrochloride.—This hydrochloride (0.13 g.) was obtained from amino-*l*-*α*-desmotroposantonin (0.15 g.) by the same procedure as that described for the preparation of amino-*d*-*β*-desmotroposantonin hydrochloride. It crystallized from 5% hydrochloric acid solution as plates, m. p. 273–274°, $[\alpha]^{25}\mathrm{D}$ −125°, (*c*, 0.4% in alcohol).

Amino-*d*-*α*-desmotroposantonous Acid (IV).—This was obtained from either nitro-*l*-*α*-desmotroposantonin or amino-*l*-*α*-desmotroposantonin. The procedures were exactly the same as those described in the preparation of amino-*l*-*β*-desmotroposantonous acid. It crystallized from alcohol as prisms, m. p. 197°, $[\alpha]^{25}\mathrm{D}$ +76.2° (*c*, 0.4% in alcohol); yield, 0.12 g. from 1 g. of nitro-*l*-*α*-desmotroposantonin.

Anal. Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.03. Found: C, 68.29; H, 8.05.

Amino-*d*-*β*-desmotroposantonin and the Amino Acid of m. p. 206° from Benzene-azo-desmotroposantonin.—A hot solution of benzene-azo-desmotroposantonin (0.6 g.) in glacial acetic acid (110 cc.) was added to a solution of stannous chloride (4 g.) in boiling concentrated hydrochloric acid (20 cc.). After dilution with water the reaction mixture was treated with hydrogen sulfide. The filtrate was evaporated at first on a water-bath and then distilled under vacuum until a white precipitate separated.

Treatment with sodium carbonate solution separated the precipitate into a soluble and an insoluble portion. The latter on recrystallization from alcohol gave amino-*d*-β-desmotroposantonin in plates, m. p. 196–197°, unchanged by admixture with an authentic specimen of amino-*d*-β-desmotroposantonin. Acidification of the sodium carbonate soluble portion followed by recrystallization of the separated solid from alcohol gave a product in prismatic needles, m. p. 205–206°, depressed to 170° by admixture with amino-*l*-β-desmotroposantonous acid and to 176° by admixture with amino-*d*-α-desmotroposantonous acid. Its hydrochloride crystallized from dilute hydrochloric acid in plates.

Summary

1. Amino-*d*-β- and amino-*l*-α-desmotroposantonin have been prepared from the corresponding nitro compounds, the former also from benzene-azo-α-β-desmotroposantonin.
2. The corresponding aminosantonous acids were prepared from the aminodesmotroposantonins.
3. The constitution and configuration of the new compounds are discussed.

CAMBRIDGE, MASS. RECEIVED JUNE 16, 1947

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

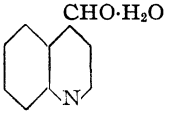
Cinchoninaldehyde and Reactive Methylene Compounds. IV[1]

BY ARTHUR P. PHILLIPS

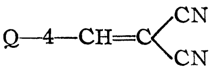
This paper reports the reaction of cinchoninaldehyde (I)[2] with a variety of malonic acid type compounds, with several of the lower nitroalkanes, and with cyclohexanone.

Cinchoninaldehyde (I) reacted so rapidly with one equivalent of malononitrile that no catalyst was used and a nearly theoretical yield of II was obtained. Use of two molecular equivalents of malononitrile in this reaction, in an attempt to obtain the "2 to 1" type of condensation product, gave only II though in poorer yield.

CHART OF COMPOUNDS

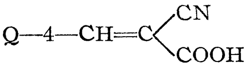


I



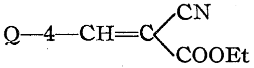
$\mathrm{Q{-}4{-}CH{=}C(CN)_2}$

II



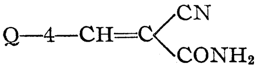
$\mathrm{Q{-}4{-}CH{=}C(CN)COOH}$

III



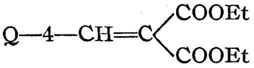
$\mathrm{Q{-}4{-}CH{=}C(CN)COOEt}$

IV



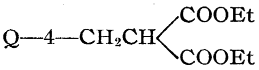
$\mathrm{Q{-}4{-}CH{=}C(CN)CONH_2}$

V



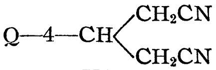
$\mathrm{Q{-}4{-}CH{=}C(COOEt)_2}$

VI



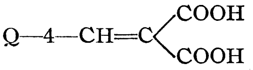
$\mathrm{Q{-}4{-}CH_2CH(COOEt)_2}$

VII



$\mathrm{Q{-}4{-}CH(CH_2CN)_2}$

VIII



$\mathrm{Q{-}4{-}CH{=}C(COOH)_2}$

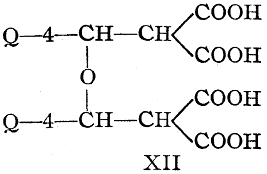
IX

$\mathrm{Q{-}4{-}CH{=}CHCOOH}$

X

$\mathrm{Q{-}4{-}CH{=}CHCOOEt}$

XI

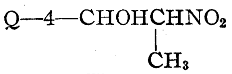


$\mathrm{[Q{-}4{-}CH(CH(COOH)_2)]_2O}$

XII

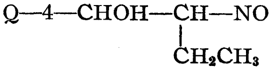
$\mathrm{Q{-}4{-}CHOHCH_2NO_2}$

XIII



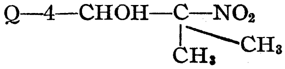
$\mathrm{Q{-}4{-}CHOHCH(NO_2)CH_3}$

XIV



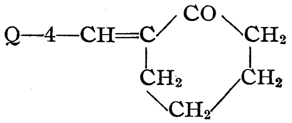
$\mathrm{Q{-}4{-}CHOH{-}CH(NO_2){-}CH_2CH_3}$

XV

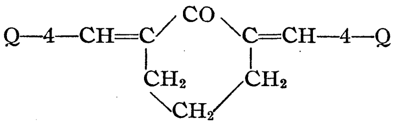


$\mathrm{Q{-}4{-}CHOH{-}C(NO_2)(CH_3)_2}$

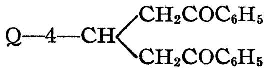
XVI



XVII



XVIII



$\mathrm{Q{-}4{-}CH(CH_2COC_6H_5)_2}$

XIX

Cyanoacetic acid, cyanoacetic ester, cyanoacetamide, malonic ester and malonic acid, when condensed with I in alcohol, aqueous or aqueous alcohol solution, with diethylamine (or piperidine) catalyst gave excellent yields of the products: III, IV, V, VI, IX.

When cyanoacetic ester was condensed with I by means of sodium ethylate in ethanol, acidification of the reaction mixture gave only the corresponding acid, III. Hydrolysis had resulted presumably as a consequence of using the aldehyde hydrate. Esterification of this acid by the Fischer method produced the same substance, IV, obtained earlier by combination of the reactants in the presence of diethylamine.

The malonic ester product was obtained in poorer yield (60%) and no sharp boiling point was observed. Since the base showed no tendency to crystallize, this product was purified as its hydrochloride.

When the condensation with malonic acid was varied by the use of pyridine as solvent with a little piperidine as catalyst, excellent yields of quinolyl-4-acrylic acid (X) resulted rapidly and

---

[1] For paper III of this series see THIS JOURNAL, **69**, 865 (1947).

[2] For the method of preparation of I see reference (4).

TABLE I

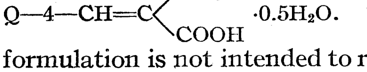
PRODUCTS AND REACTION CONDITIONS

Reactant	Mole react./Mole ald.	Reaction medium[a]	Catalyst	Reaction time, hr.	Product	Yield, %	Cryst.[a] solvent
Malononitrile	1 (or 2)	A	None (Et_2NH)	0.1^b	II	98 (65)	A
Cyanoacetic ester	1	A	NaOEt (1 *M*)	1.5^b	III	70	Nt.
Cyanoacetic ester	6	Aq.	Et_2NH (trace)	24^c	IV	90	H
III	...	A	H_2SO_4	5^b	IV	90	H
Cyanoacetamide	1	A	Et_2NH (trace)	0.5^b	V	90	A
Malonic ester	1	None	Piperidine (trace)	15^b	VI.HCl	57	A. E.
VI	...	A	H_2 + Pt.	0.3^c	VII.HCl	80	A. E.
Cyanoacetic acid	2	A	Et_2NH (trace)	1^b	III	100	Nt.
Cyanoacetic acid	1	A.Aq	KOH (1 *M*)	12^c	III	50	Nt.
Cyanoacetic acid	2	Py	Piperidine (trace)	0.5^b	III	80	Nt.
IV	...	A	KOH	48^c	III	95	Nt.
IV	...	20% HCl	.....	0.75^d	III	100	Nt.
Cyanoacetic acid	3.5	Py	Piperidine (trace)	4^b	VIII	73	B. H.
Malonic acid	1.5	A^e	Piperidine (trace)	4^b	IX	80	Nt.
Malonic acid	1.5	Py	Piperidine (trace)	6^b	X	83	Nt.
X	...	A	HCl	5^b	XI.HCl	50	A. E.
Malonic acid	1.5	A^f	Piperidine (trace)	4^c	(XII)	90	Nt.
Nitromethane	1.2	50%A.Aq	Et_2NH (trace)	5^c	XIII	93	B. H.
Nitromethane	1.2	A	KOH (2 *M*)	0.5^c	$XIII^{g,h}$	70	B. H.
Nitroethane	1.3	50%A.Aq	Et_2NH (trace)	24^c	XIV	95	B. H.
1-Nitropropane	1.1	50%A.Aq	Piperidine (trace)	24^c	XV	100	Et. H
2-Nitropropane	1.1	50%A.Aq	Piperidine (trace)	24^c	XVI	95	Et
Cyclohexanone	1.1	90%A.Aq	KOH (excess)	2^b	XVII	73	Py.Aq
Cyclohexanone	2	Aq	KOH (excess)	24^c	XVIII	20	Et. H
Acetophenone	1	50%A.Aq	KOH (excess)	5^c	XIX	30	H

[a] A = ethanol; Aq = H_2O; Py = pyridine; H = hexane; B = benzene; E = ether; Et = ethyl acetate; Nt = reprecipitated from dilute alkali with dilute acid. [b] At 100°. [c] At room temperature. [d] At reflux temperature. [e] 4.5 g. of I and 3.6 g. malonic acid in 100 cc. of EtOH and piperidine catalyst. Heated on steam-bath for four hours, when a white solid gradually formed and settled out. [f] 4.5 g. of I and 3.6 g. malonic acid in 10 cc. EtOH and piperidine. Mixture was heated 1–2 minutes on steam-bath to dissolve reactants, then on addition of catalyst a heavy white precipitate formed instantaneously. [g] The product first obtained from the reaction mixture by treatment with an excess of concentrated HCl was XIII·HCl. XIII base was obtained by neutralization of the HCl with NH_3. [h] This compound was previously known, see ref. 3.

simply. This compound had been prepared earlier by other workers by the hydrolysis of the condensation product of lepidine and chloral.[3] The ethyl ester (XI) of this acid was made by the Fischer method and was characterized as its hydrochloride.

A variation from the normal malonic acid product, IX, was obtained by modifying the reaction conditions slightly. Thus, condensation of malonic acid and I in more concentrated solution with secondary amine catalyst and no heating gave rapid and nearly quantitative precipitation of a quite different substance. Carbon, hydrogen, and neutral equivalent determinations agree well with a compound having an empirical structure:



$$Q\text{—}4\text{—}CH{=}C\begin{matrix}\diagup COOH\\ \diagdown COOH\end{matrix}\cdot 0.5H_2O$$

This hemi-hydrate formulation is not intended to represent the molecular formula of the compound. In fact, it would seem quite unreasonable to hypothesize a simple hydrate as differing persistently from the normal product, IX, since all of these acid compounds were purified by repeated reprecipitations from dilute aqueous alkaline solutions by addition of dilute mineral acids. Thus, if the hydrate represented a stable structure under those conditions it should have been impossible to get the other product, IX, under the identical conditions of purification. A more reasonable structure for this substance is XII, particularly in view of the previously observed tendency of cinchoninaldehyde to form stable aldol-like addition products. XII, having the same empirical formula as the hemi-hydrate, likewise fits the analytical data.

When compound IX was refluxed with strong (20%) hydrochloric acid the acrylic acid X resulted by decarboxylation. When either IX or XII was heated in pyridine solution in the presence of a trace of piperidine good yields (70%) of X were formed.

Since under certain conditions condensation with malonic acid permitted the easy attainment of the cinnamic acid analog, it was hoped that reaction with cyanoacetic acid under the same conditions might lead to the cinnamonitrile-like product. Contrary to expectations, however, when pyridine was used as solvent with piperidine as catalyst different results were obtained. When only a moderate excess of cyanoacetic acid was used and the heating period was brief (thirty minutes) a good yield of the product III resulted,

---

(3) Koenigs and Müller, *Ber.*, **37**, 1338 (1904).

TABLE II

ANALYTICAL DATA

Product	M. p., °C.	Analyses Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	M. wt.[a] (N. E.) Calcd.	Found
II	146–147	76.10	76.04	3.44	3.19		
III	238–239 (dec.)	69.61	69.48	3.61	3.77	224.1	224
IV	98–99	71.43	71.48	4.80	4.66		
V	253	69.96	70.14	4.02	4.07		
VI·HCl	151–152	60.80	60.82	5.36	4.82		
VII·HCl	160–161.5	60.44	59.73	5.97	5.75		
VIII	130–131	76.02	76.04	5.02	5.15		
IX	254–255 darkens 230–250	64.18	64.11	3.73	3.95	243.1	240
X	272–273 (dec. gas evol.)	72.33	72.35	4.57	4.38	199.1	200
XI.HCl	194–195	63.73	63.49	5.35	5.08		
XII	190–191	61.95	61.88	3.97	4.12	504	500
			61.66		4.01		
XIII	140–141	60.52	60.90	4.63	4.71		
XIV	167–168	62.04	62.04	5.21	5.21		
XV	138	63.38	63.31	5.73	5.79		
XVI	183	63.38	63.58	5.73	5.87		
XVII	277–278	81.01	81.29	6.38	6.20		
						N	
XVIII	153	82.93	82.45	5.36	5.17	7.44	7.47
XIX	148–149	82.28	82.25	5.58	5.46		

[a] Molecular weights listed here are actually neutral equivalents × number of acid groups.

with no decarboxylation. But when 2.5–3 moles of cyanoacetic acid per mole of aldehyde was used and when heating was more extended (four hours) the product was VIII, which involves condensation between one mole of aldehyde and two moles of acid with loss of the two carboxyl groups.

The cyanoacetic acid product III was also obtained by condensation of the reactants in aqueous potassium hydroxide. III was further obtained in good yield by the hydrolysis of the corresponding ethyl ester IV by refluxing with 20% hydrochloric acid, or by allowing it to stand at room temperature with aqueous potassium hydroxide, followed by acidification.

Cinchoninaldehyde condensed readily with nitromethane, nitroethane, 1-nitropropane and 2-nitropropane in 50% aqueous alcohol with a trace of diethylamine as catalyst and a reaction time of several hours at room temperature. The yields were well over 90% and the products were of the aldol-like nitroalcohol type (XIII, XIV, XV, XVI), although usually the products obtained from aromatic aldehydes and nitroalkanes possess the  $\mathrm{RCH{=}\underset{|}{C}{-}NO_2}$ structure. This represents another instance of the strong tendency of cinchoninaldehyde to form products with a stable aldol-like configuration. Thus, nitromethane was condensed with the aldehyde in the presence of aqueous potassium hydroxide with subsequent liberation of the product by addition of concentrated hydrochloric acid. Under these conditions many aromatic aldehydes give nitrostyrenes, but cinchoninaldehyde gave the same aldol, XIII, resulting under the milder conditions.

Cyclohexanone condensed readily with I in equimolecular amounts in aqueous or alcoholic solution in the presence of potassium hydroxide to give good yields of XVII. In very dilute aqueous alkaline solution small amounts of XVIII were also produced.

Acetophenone with I in 50% aqueous alcohol and alkali gave XIX previously reported by Kwartler and Lindwall.[4] Further work with ketones is in progress.

Experimental details are listed in Tables I and II.

Acknowledgment.—Thanks are due Mr. Samuel W. Blackman for the microanalyses included here.

Summary

The condensation of certain reactive methylene compounds with cinchoninaldehyde has been reported.

TUCKAHOE 7, NEW YORK RECEIVED JULY 26, 1947

---

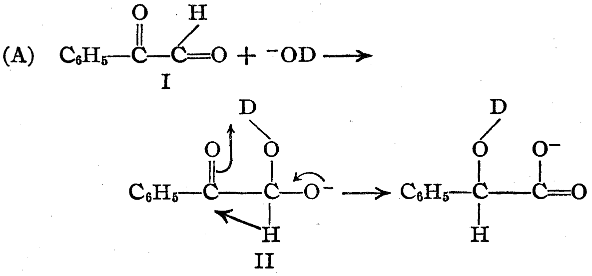
[4] Kwartler and Lindwall, THIS JOURNAL, **59**, 524 (1937).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

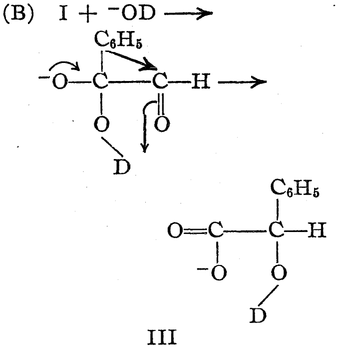
Mechanism of the Conversion of Phenylglyoxal to Mandelic Acid

BY W. V. E. DOERING, T. I. TAYLOR AND E. F. SCHOENEWALDT

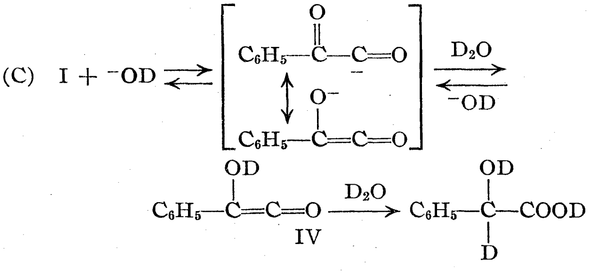
Three reasonable mechanisms may be considered for the base-catalyzed conversion of phenylglyoxal (I) to mandelic acid. Mechanism A,[1] an intramolecular version of one of the attractive mechanisms of the Cannizzaro reaction,[2] involves the intramolecular migration of a hydrogen atom in the intermediate anion II. Mechanism B,[1]



similar to that of the benzil–benzilic acid conversion,[3] involves migration of the phenyl group in III, an intermediate



closely related to II. Finally, in mechanism C direct removal of a proton from I establishes equilibrium with the tautomeric hydroxy-ketene IV which adds water forming mandelic acid.

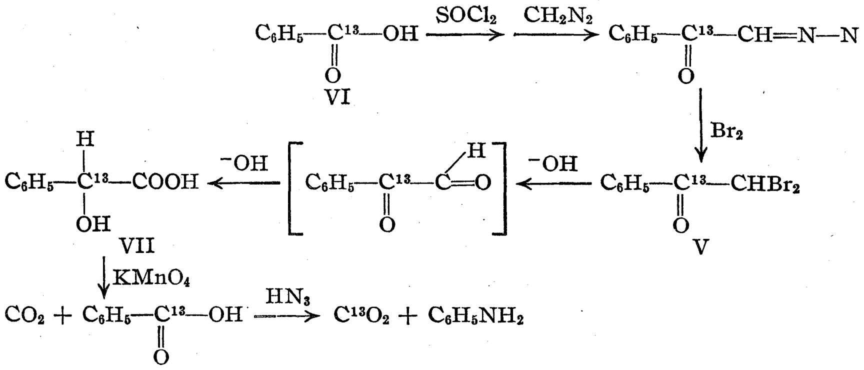


however, impossible to distinguish between mechanisms A, B and C on a kinetic basis alone.

Alexander, finding that the rate of the phenylglyoxal–mandelic acid reaction follows second-order kinetics, has supported mechanism A. It is,

Fredenhagen and Bonhoeffer[4] have invalidated mechanism C for the conversion of glyoxal to glycolic acid only by showing that solvent deuterium does not intervene in this reaction. They have not extended their experiments to I or any other monosubstituted glyoxal.

The following experiments afford evidence that there is no rearrangement of the carbon skeleton in the phenylglyoxal–mandelic acid transformation, mechanism B thereby being excluded. ω,ω-Dibromoacetophenone (V), prepared in two steps from benzoic acid containing 2.32% C^{13} in the carboxyl group (VI), is hydrolyzed with potassium hydroxide.[5] Oxidation of the resulting mandelic acid (VII) with permanganate has given carbon dioxide of normal C^{13} content and benzoic acid from which carbon dioxide containing 2.24% C^{13} has been obtained by the Schmidt reaction.[6,6a]



Extension of Bonhoeffer's work[4] to phenylglyoxal has invalidated mechanism C for a monosubstituted glyoxal. When I is treated with barium oxide in deuterium oxide there is obtained mandelic acid which, after equilibration with excess 0.5 N barium hydroxide,[7] contains no deuterium.

Only mechanism A is consistent with the available facts: no rearrangement of the carbon skeleton; the intramolecular transfer of hydrogen; the facile reaction of mesitylglyoxal[8]; and the

---

(1) Ayres and Hauser, THIS JOURNAL, **65**, 1095 (1943).

(2) Alexander, *ibid.*, **69**, 289 (1947).

(3) Westheimer, *ibid.*, **58**, 2209 (1936).

(4) Fredenhagen and Bonhoeffer, *Z. physik. Chem.*, **A181**, 379 (1938).

(5) Ayres and Hauser[1] have isolated I as an intermediate in this reaction.

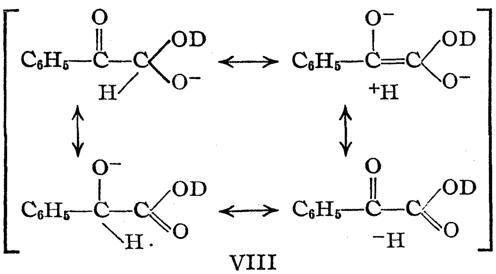
(6) Oesterlin, *Z. angew. Chem.*, **45**, 536 (1932).

(6a) *Added in proof:* O. Kenton Neville and Weldon G. Brown, [American Chemical Society, New York Meeting, September 18, 1947] have excluded mechanism B by a series of reactions differing significantly from ours.

(7) Two experiments prove that deuterium is not removable from the α-carbon of mandelic acid during the equilibration: the one in which α-hydroxyphenylacetic-*d* acid loses no deuterium in aqueous baryta at room temperature; the other, by McKenzie and Wren [*J. Chem. Soc.*, **115**, 603 (1918)], in which (−)-mandelic acid is racemized only 2.2% on treatment with 0.93 *N* potassium hydroxide for a week at room temperature.

(8) Gray and Fuson, THIS JOURNAL, **56**, 739 (1934).

second order kinetics.[2] While this mechanism has been considered to involve the shift of a hydride ion,[9] we believe that the reactive intermediate is better described by a transition state involving at least four resonance structures (VIII).



VIII

Experimental

Determination of C^{13} in Benzoic Acid (VI).—A mixture of 0.0330 g. of benzoic acid containing an enriched content of C^{13} in the carboxyl group, 0.25 cc. of purified chloroform and 0.25 cc. of concentrated sulfuric acid was introduced into a reaction vessel through which was passed continuously a slow stream of prepurified nitrogen, freed of carbon dioxide and saturated with dry chloroform at 45°. C. P. sodium azide (0.1036 g.) was tapped from a side-arm into the stirred, heated (40–44°) reaction mixture. The effluent gas was bubbled through two traps (separatory funnels) containing clear solutions of 0.26 *N* barium hydroxide. After thirty minutes, the precipitated barium carbonate was collected under nitrogen, washed with carbon dioxide-free water, and dried (29.3 mg., 55% yield).

Carbon dioxide for the mass spectrometric analyses was liberated from the barium carbonate in a standard sample conversion apparatus.[10] The abundance ratios of $C^{12}O_2$ to $C^{13}O_2$ were determined with a Nier-type mass spectrometer.[11] From a plot of the positive ion current against the accelerating voltage it was found that because of incomplete resolution ions of mass 44 ($C^{12}O_2^+$) contributed about 5% to the peak at mass 45 ($C^{13}O_2^+$). Consequently a correction of 5% was made on the averages of the observed abundance ratios.

Anal. Abundance ratio $C^{12}O_2/C^{13}O_2$: 39.7, 41.5, 41.8, 39.5, 38.9: 40.3 ± 1.1. Corrected for resolution: 42.3, corresponding to 2.32% $C^{13}O_2$.

Normal carbon dioxide abundance ratio: 81.8, 80.9, 81.2, 81.5: 81.4 ± 0.3. Corrected for resolution: 85.5, corresponding to 1.16% $C^{13}O_2$.

Preparation of Labeled Mandelic Acid (VI).—An ethereal solution of benzoyl chloride prepared from 0.3014 g. of benzoic acid (I) (2.32% C^{13} in the carboxyl group) by treatment with thionyl chloride was added dropwise to an eight-fold excess of ethereal diazomethane[12] at −10 to −5°. After being sixteen hours at 4°, crude diazoacetophenone, recovered by evaporation of the solvent *in vacuo*, was dissolved in 50 cc. of anhydrous ether and treated with a dilute ethereal solution of bromine.[13] After the initially vigorous evolution of nitrogen and the development of a persistent red color, the reaction mixture was washed with sodium bisulfite and water. Crude ω,ω-dibromoacetophenone (V) obtained as a yellowish-amber oil by evaporation of solvent *in vacuo*, was converted to VII by refluxing for twenty-five minutes in 5% aqueous potassium hydroxide.[14] The filtered reaction mixture was clarified with Norit-A, acidified with concentrated hydrochloric acid and extracted with four portions of ether. Evaporation of the dried ether solution gave crude mandelic acid which was recrystallized from benzene; 0.09 g. of light tan crystals; m. p. 112–114° (24% of the theoretical yield based on I). Two more recrystallizations afforded 0.0641 g. of purer VI, m. p. 117–118.5°, showing no depression on admixture with an authentic sample.

Determination of C^{13} in Mandelic Acid (VII). (a) Oxidation with Acidic Permanganate.—A solution of 0.0627 g. of the mandelic acid obtained above (m. p. 117–118.5°) in 1.75 cc. of 10% sulfuric acid was oxidized[15] by 0.14 g. of potassium permanganate in the same apparatus used above for the Schmidt reaction, the nitrogen being purified by passing through two solutions of barium hydroxide. After the reaction mixture had been heated for ten minutes at 80–95°, the barium carbonate was collected as described above (0.1138 g., 140% yield).

Anal. Abundance ratio $C^{12}O_2/C^{13}O_2$: 78.3, 78.8, 78.5, 78.8, 78.6 ± 0.2. Corrected for resolution: 82.5 ± 0.2, corresponding to 1.20% $C^{13}O_2$.

From the reaction mixture 0.0365 g. (72.5% yield) of benzoic acid (IX), m. p. 122–123°, was isolated.[16]

(b) Oxidation with Neutral Permanganate.—The sublimed residues from the recrystallization of the mandelic acid (11.1 mg., m. p. 80–103°[17]) were dissolved in 0.36 cc. of water and oxidized with 0.05 g. of potassium permanganate, 8.3 mg. of barium carbonate being collected in the usual manner (57.5% yield).

Anal. Abundance ratio $C^{12}O_2/C^{13}O_2$: 81.0, 77.5, 78.5, 77.5, 76.6, 77.4: 78.1 ± 1.1. Corrected for resolution 82.0 ± 1.1, corresponding to 1.21% $C^{13}O_2$.

Pure benzoic acid, m. p. 121.6–122°, was isolated from the reaction mixture by extraction and sublimation.

(c) Determination of C^{13} in Benzoic Acid (IX).—As in the previously described Schmidt procedure, 0.0350 g. of benzoic acid was decarboxylated to 18.2 mg. of barium carbonate (32.2% yield).

Anal. Abundance ratio $C^{12}O_2/C^{13}O_2$: 41.6, 41.5, 42.8, 41.6, 42.1, 40.7, 40.8: 41.6 ± 0.5. Corrected for resolution: 43.7 ± 0.5, corresponding to 2.24% $C^{13}O_2$.

Determination of Deuterium.—Essentially the procedure described by Cohn[18] was employed with minor modifications. For the extended procedure recommended for the purification of the water of combustion, we have substituted a single sublimation in order to permit analysis of smaller samples of organic material. This simplification has resulted in an increased error, deuterium-free compounds giving water apparently containing 0.02–0.04% deuterium oxide.

Rearrangement of Phenylglyoxal Hydrate to Mandelic Acid (X).—Phenylglyoxal was obtained as its hydrate, m. p. 74–77°, by the oxidation of acetophenone with selenium dioxide[19]; phenylosazone, m. p. 150.6–151.4°; reported[20] m. p. 151–2°.

Anal. Calcd. for $C_8H_6O_2{\cdot}H_2O$: C, 63.10; H, 5.30. Found: C, 63.61; H, 5.76.

A cooled mixture (incompletely dissolved) of 0.587 g. of phenylglyoxal hydrate in 9.085 g. of water containing 7.25 weight per cent. of deuterium oxide (corrected for water of hydration) was shaken vigorously with 0.59 g.

---

(9) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940; p. 319, 351.

(10) Wilson, Nier and Reimann, "Preparation and Measurement of Isotopic Tracers," J. W. Edwards, Ann Arbor, Michigan, 1946, pp. 31–42 (Rittenberg).

(11) *Ibid.*, pp. 11–30 (Nier).

(12) Bradley and Robinson, *J. Chem. Soc.*, 1317 (1928).

(13) Houben-Weyl, "Die Methoden der organischen Chemie," Georg Thieme, Leipzig, 1941, Vol. IV, p. 883.

(14) Engler and Wöhrle, *Ber.*, **20**, 2202 (1887).

(15) Fieser, "Experiments in Organic Chemistry," D. C. Heath Co., Boston, Mass., 1944, 2nd ed., p. 219.

(16) The 140% yield of carbon dioxide may be explained by assuming the complete oxidation of only 5% of the mandelic acid. This amount of destructive oxidation would cause an error of +0.04% in the C^{13} content of recovered carbon dioxide.

(17) Presumably contaminated by benzoic acid.

(18) Ref. 10, pp. 51–59.

(19) Blatt, "Organic Syntheses," John Wiley, New York, N. Y., 1939, Coll. Vol. II, p. 509.

(20) Müller and von Pechmann, *Ber.*, **22**, 2558 (1889).

of barium oxide. After twenty hours at 28°, the reaction mixture was acidified with concentrated hydrochloric acid and extracted with six 10-cc. portions of ether. Evaporation gave 0.425 g. (72.5%) of crystalline mandelic acid which was dissolved in 10 cc. of 0.5 *N* barium hydroxide. The solution was filtered, allowed to stand one hour, acidified, and extracted with ether. After repetition of the equilibration and sublimation, 0.317 g. (54.2%) of mandelic acid was obtained. Recrystallized from benzene, pure X was obtained, m. p. 118.5–119.3°, showing no depression on admixture with an authentic sample.

Anal. Calcd. for $C_8H_7D_{(7.25\%)}O_3$: D_2O, 0.906. Found: D_2O, 0.036.

The above procedure was repeated using 10.24 g. of water containing 27.6 weight per cent. (corrected for water of hydration) of deuterium oxide and 0.61 g. of phenylglyoxal hydrate. There was obtained 0.360 g. (59%) of crude mandelic acid. Recrystallization afforded 0.296 g., m. p. 118–119°.

Anal. Calcd. for $C_8H_7D_{(27.6\%)}O_3$: D_2O, 3.45. Found: D_2O, 0.039.

α-Hydroxyphenylacetic-*d* Acid.—Mandelic acid (1.470 g.) was refluxed under nitrogen for one week with 13.52 g. of 29.56% deuterium oxide and 1.23 g. of barium oxide. The deuterated mandelic acid, recovered by acidification with concentrated hydrochloric acid, extraction with ether and evaporation *in vacuo*, was equilibrated twice by refluxing for eighteen hours with 17 cc. of water under nitrogen. The recovered equilibrated acid was recrystallized from benzene giving a first crop (A) weighing 0.876 g.

Anal. Calcd. for $C_8H_7D_{(29.56\%)}O_3$: D_2O, 3.70. Found: D_2O, 3.57.

Sample A was twice reëquilibrated by treating with 23 cc. of 0.5 *N* baryta for seventy-five minutes at room temperature.

Anal. Found: D_2O, 3.57, 3.57, 3.57.

Summary

Using phenylglyoxal in which the ketone carbon is marked with C^{13}, it has been proved that there is no rearrangement of the carbon skeleton in the alkali-catalyzed conversion to mandelic acid. The failure of solvent deuterium to become attached to the alcohol carbon atom of mandelic acid prepared from phenylglyoxal in heavy water has allowed exclusion of a proton-removal mechanism and has substantiated a mechanism involving intramolecular transfer of hydrogen. The present status of the mechanism is discussed.

NEW YORK 27, N. Y. RECEIVED AUGUST 25, 1947

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF CALIFORNIA]

Configuration and Adsorption. A Comparison of the Adsorption of the *cis* and *trans* Isomers of Dichloroethylene on Activated Carbon

BY DAVID H. VOLMAN AND LAWRENCE J. ANDREWS

In an attempt to account for the data of adsorption from the vapor phase on activated carbon adsorbates may be separated into three classifications: first, molecules which can undergo hydrogen bonding; second, molecules which do not form hydrogen bonds but which possess permanent dipole moments; third, molecules which do not form hydrogen bonds and do not have permanent dipole moments.

Only the first classification is known definitely to behave abnormally in adsorption on carbon. For this type of compound the correlation of adsorbability and condensation properties of the gas has been pointed out recently by Volman and Klotz.[1] It was proposed that the initial adsorption does not reflect the hydrogen bonding properties of the molecule even though the relative pressures do, and the apparent anomalies in adsorption are to be explained by the values assigned to the relative pressure axis for the isotherms. For both of the other classifications no anomalies comparable to those found with a compound of the first classification such as water are known. However, it seemed of interest to determine the effect of the existence of a permanent dipole moment on van der Waals adsorption on carbon. A near approach to a comparison of this nature should be obtained by studying the adsorption of molecules differing only in geometric configuration. Thus by choosing *cis*- and *trans*-dichloroethylene the principal difference in interaction effects would seem to be the large difference in dipole moment, zero for the *trans* and 1.8 debyes for the *cis* compound.[2] In addition the isomers are easily obtained in a pure state and have convenient physical properties for adsorption studies.

Further interest in the problem derives from the fact that no comparisons of the adsorption of *cis–trans* isomers from the vapor phase have been made. However, in recent years extensive studies directed toward the separation of *cis–trans* isomers by chromatographic adsorption have been carried out.[3] These studies have all been made from solution and primarily with stereoisomers of carotenoids. In addition the adsorption of maleic and fumaric acids from aqueous solution on activated carbon has been carried out.[4] Here the adsorption is mainly dependent on the degree of ionization of the acids in solution. It was expected that a study of gas phase adsorption of *cis-trans* isomers would yield information on the possibility of separation of such isomers by adsorption techniques.

Experimental

Preparation of Materials.—The *trans* compound was obtained by fractionation of Eastman Kodak Co. *trans*-

---

[1] Volman and Klotz, *J. Phys. Chem.*, **14**, 642 (1946).

[2] *Trans. Faraday Soc.*, **30**, Appendix (1934).

[3] Zechmeister, *Chem. Rev.*, **34**, 267 (1944).

[4] Phelps, *J. Chem. Soc.*, 1724 (1929).

dichloroethylene through a four-foot column packed with glass helices. The fraction retained boiled at 48.1° at 756 mm. The *cis* compound was obtained from the *trans* by isomerization according to the method of Jones and Taylor.[5] The *cis* isomer (b. p. 60.5° at 766 mm.) was isolated from the resulting mixture by fractionation on the four foot column.

The activated carbon was obtained from the Pittsburgh Coke and Chemical Company. It was screened to 20–30 mesh, dried at 140° for twenty-four hours and stored in dry air.

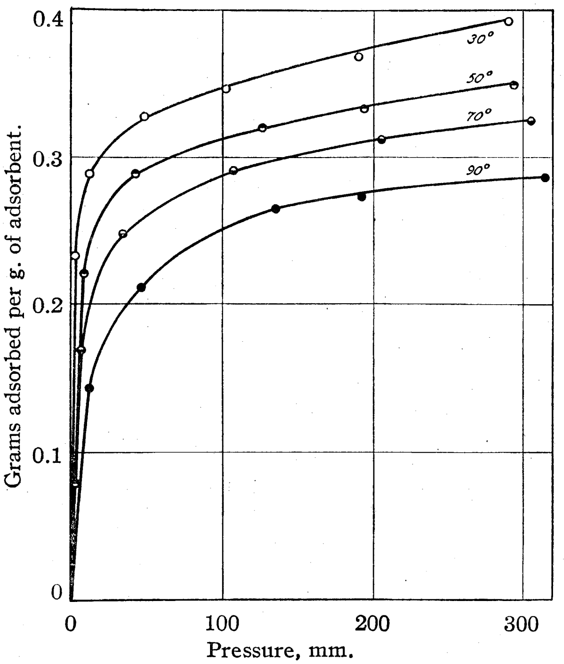


Fig. 1.—*trans*-Dichloroethylene adsorption isotherms.

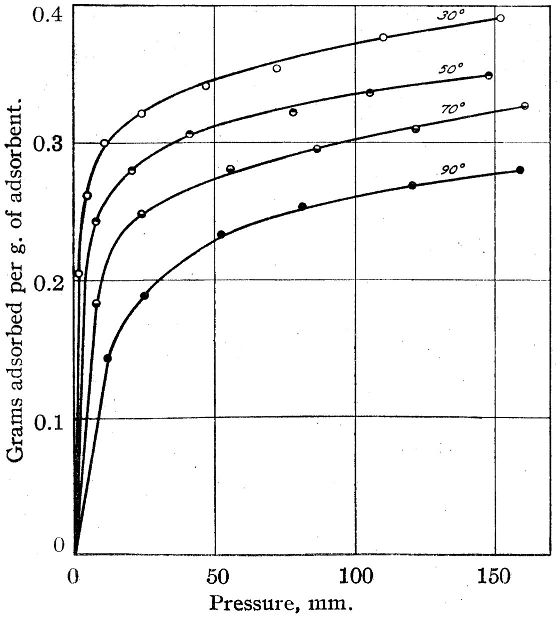


Fig. 2.—*cis*-Dichloroethylene adsorption isotherms.

Adsorption Method.—Adsorptions were determined by a simple gravimetric apparatus. Two grams of the activated carbon was weighed directly into an adsorption chamber. The sample was then outgassed at 100° for twenty-four hours. With proper manipulation of the stopcocks the adsorption chamber may be removed and weighed without breaking the vacuum over the carbon. The adsorption chamber is then replaced in a thermostat at the isothermal temperature, and after evacuation of the air contaminated region the carbon is allowed to come to equilibrium with enough adsorbate to give the desired pressure. The adsorption chamber may then be removed and weighed and the procedure repeated for the full range of pressures used. Although this simplified apparatus is of limited accuracy, the data are sufficiently reliable for the purposes of this experiment.

Results and Discussion

Comparison of Isotherms.—Figures 1 and 2 show the adsorption isotherms obtained for the *trans* and *cis* configurations, respectively, at temperatures 30, 50, 70 and 90°. In order to compare the area of surface covered by the two adsorbates at the same relative pressures it is necessary to determine the areas covered in adsorption. This may be calculated from a knowledge of the weight adsorbed provided the area occupied per molecule is known. A reasonable assumption is that the area occupied by an adsorbed molecule on the surface is the same as the cross section obtained by considering the molecules to be hexagonally close packed in the liquid. Then the average area per molecule is given by

$$A = 4(0.866)\left[\frac{M}{4\sqrt{2}N\rho}\right]^{2/3} \qquad (1)$$

where M is the molecular weight of the gas, N is Avogadro's number and ρ is the density of the liquefied gas.[6] Even if this is not an exact expression for the area of an adsorbed molecule, the assumption of the dependence of A on $1/\rho^{2/3}$ appears to be the significant one for comparative purposes since the exact area is not important.

The densities of the isomers were determined over a range of temperatures from 25 to 48° by means of a Westphal balance and agreed well with already published data.[7] Since the coefficient of thermal expansion is

$$\alpha = \frac{1}{V}\left(\frac{\partial T}{\partial V}\right)_p \qquad (2)$$

a plot of log density *vs.* T should yield a straight line if α is sufficiently constant in the region used. From such a linear plot, Fig. 3, the density at temperatures greater than 48° may be obtained.

To obtain the relative pressures for a comparison of adsorption it was necessary to know the saturation vapor pressures. In the region below the boiling point these values may be obtained from the data of Herz and Rathmann.[7] At higher temperatures the saturation pressures were calculated by use of the Clausius–Clapeyron equation assuming a constant heat of vaporization. The values used are shown in Table I. In Table II a

---

[5] Jones and Taylor, THIS JOURNAL, **62**, 3480 (1940).

[6] Emmett and Brunauer, THIS JOURNAL, **59**, 1553 (1937).

[7] Herz and Rathmann, *Chem. Ztg.*, **37**, 621 (1913).

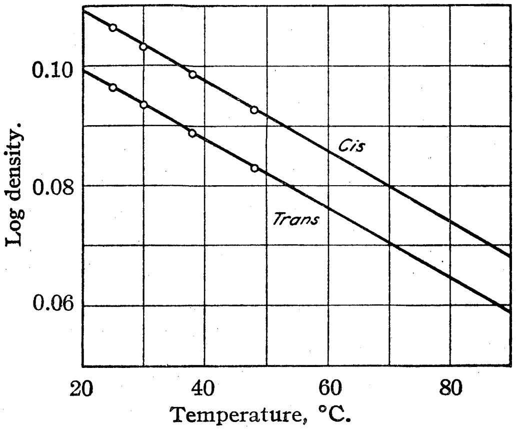


Fig. 3.—Density of *cis*- and *trans*-dichloroethylene.

comparison of the areas covered at the same relative pressures for the *cis* and *trans* isomers is given. The values are seen to be in very good agreement, especially since the P_0 values above the boiling point are of limited accuracy.

TABLE I

SATURATION VAPOR PRESSURES AND AVERAGE ADSORBED MOLECULAR AREAS OF *cis*- AND *trans*-DICHLOROETHYLENE

Temp., °C.	Saturation vapor pressure, mm.		Molecular areas, sq. Å.	
	Cis	*Trans*	*Cis*	*Trans*
30	251	380	27.5	27.9
50	537	776	28.0	28.4
70	1050	1440	28.5	28.9
90	1900	2570	29.0	29.4

TABLE II

COMPARISON OF ADSORPTION OF *cis*- AND *trans*-DICHLOROETHYLENE AT THE SAME VALUES OF RELATIVE PRESSURE

Temp., °C.	Relative pressure, P/P_0	Area of surface covered, sq. m./g.	
		cis	*trans*
30	0.1	561	567
	.2	603	602
	.3	632	626
	.4	653	647
	.5	667	663
	.6	680	678
50	.1	543	532
	.2	587	580
	.3	613	608
70	.1	532	532

The close correspondence for area covered at the same relative pressures in the above data indicates that the forces important in adsorption are the same as those which account for condensation even at low relative pleasure values. Brunauer, Emmett and Teller[8] have derived a theory of adsorption isotherms on the assumption that the same forces that produce condensation are also responsible for adsorption. Our findings indicate that this is valid where the principal intermolecular forces are van der Waals with or without a contribution due to the existence of a permanent dipole moment. On the basis of the discussion of Volman and Klotz,[1] molecules which form hydrogen bonds in the liquid but not in the vapor state are excluded from the above generalization.

Surface Area and Heat of Adsorption.—The shape of the adsorption isotherms and the exten-

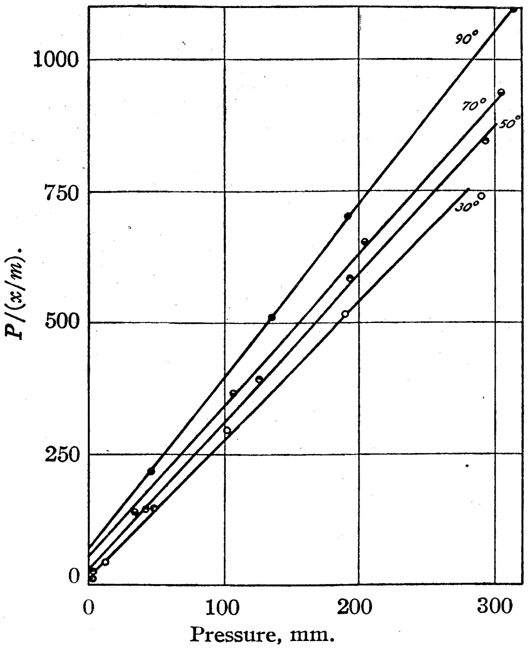


Fig. 4.—Adsorption isotherms of *trans*-dichloroethylene, plotted according to the Langmuir equation x/m in grams per g. of adsorbent.

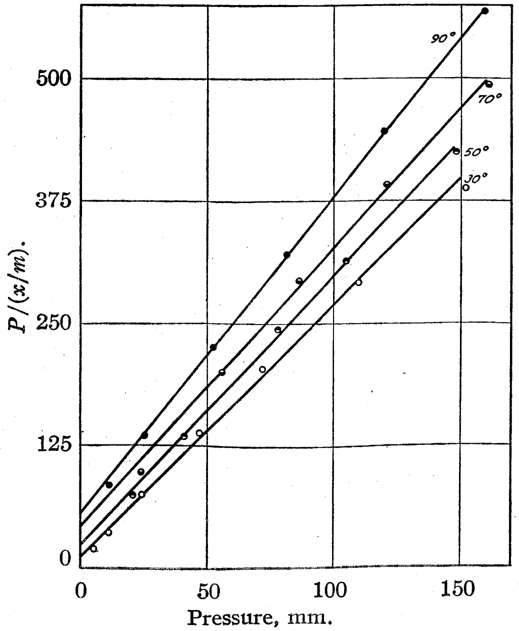


Fig. 5.—Adsorption isotherms of *cis*-dichloroethylene, plotted according to the Langmuir equation x/m in grams per g. of adsorbent.

---

(8) Brunauer, Emmett and Teller, THIS JOURNAL, **60**, 309 (1938).

sive evidence of Brunauer and Emmett[9] for unimolecular adsorption on activated carbon suggested the advisability of Langmuir equation plots of the adsorption data. Figures 4 and 5 show the results obtained.

Using the B.E.T.[8] equation for unimolecular adsorption in the form

$$\frac{p}{(x/m)} = \frac{p_0}{c(x/m)_M} + \frac{p}{(x/m)_M} \qquad (3)$$

where $(x/m)_M$ is the weight adsorbed per g. of adsorbent equivalent to a monolayer, the area corresponding to a monolayer may be determined from the slopes of the plots in Figs. 4 and 5. Since c in the above equation is defined by

$$c = \frac{a_1b_2}{b_1a_2}e^{(E_1 - E_L)/RT} \qquad (4)$$

where $E_1 - E_L$ is the difference between the heat of adsorption and the heat of liquefaction, $E_1 - E_L$ may be determined from the intercepts of the curves if a_1b_2/b_1a_2 is assumed unity as is customary.

Although it has been common to use the unimolecular adsorption equation for isotherms which are not approximated by the $n = \infty$ form of the B.E.T. equation, it has been pointed out[10] that the limiting B.E.T. equation for $n = 1$ is not valid except for isotherms which have an n value very close to unity. Joyner, Weinberger and Montgomery[10] have shown that the B.E.T. equation may be written

$$\frac{\Phi(n,X)}{(x/m)} = \frac{1}{c(/x/m)_M} + \frac{\theta(n,X)}{(x/m)_M} \qquad (5)$$

where

$$\Phi(n,X) = \frac{X(1 - X^n) - nX^n(1 - X)}{(1 - X)^2}$$

and

$$\theta(n,X) = \frac{X(1 - X^n)}{1 - X}$$

X is the relative pressure and n is the number of layers to which the gas is limited.

For the proper choice of n, a plot of $\Phi(n,X)/(x/m)$ *vs.* $\theta(n,X)$ should yield a straight line. Figures 6 and 7 show the results obtained when $n = 1.60$ is used. The plots are seen to be linear and are superior to the $n = 1$ plots, especially for the 30° data which cover the greatest relative pressure region. The area and $E_1 - E_L$ values obtained for $n = 1$ and $n = 1.60$ are presented in Table III. The use of the more correct $n = 1.60$ in place of $n = 1$ results in considerably lower and more constant monolayer areas. However, the $E_1 - E_L$ values are not appreciably altered.

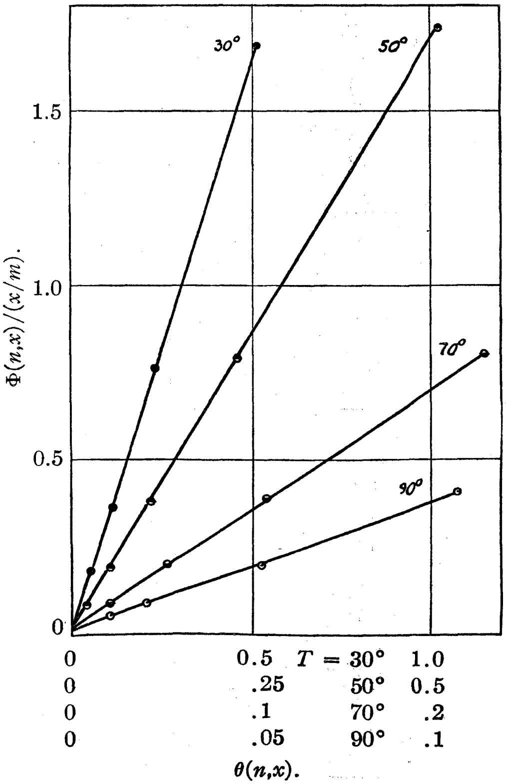


Fig. 6.—Adsorption isotherms of *trans*-dichloroethylene according to B. E. T. theory for $n = 1.60$.

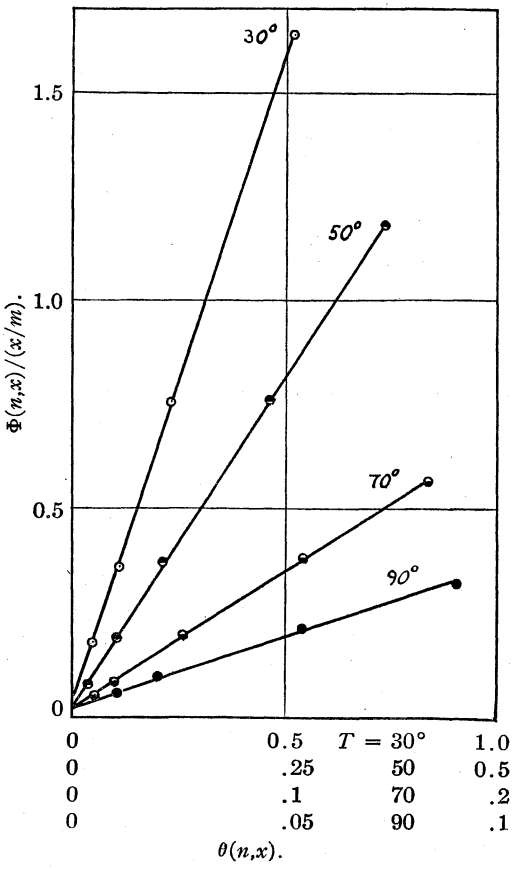


Fig. 7.—Adsorption isotherms of *cis*-dichloroethylene according to B.E.T. theory for $n = 1.60$.

---

[9] Brunauer and Emmett, THIS JOURNAL, **59**, 2682 (1937).

[10] Joyner, Weinberger and Montgomery, *ibid.*, **67**, 2182 (1945).

TABLE III

COMPARISON OF MONOLAYER AREAS AND DIFFERENCE BETWEEN HEAT OF ADSORPTION AND VAPORIZATION FOR *cis* AND *trans*-DICHLOROETHYLENE.

Temp., °C.	Area of monolayer, sq. m./g.				$E_1 - E_L$ kcal./mole			
	cis		*trans*		*cis*		*trans*	
	$n = 1$	$n = 1.6$	$n = 1$	$n = 1.6$	$n = 1$	$n = 1.6$	$n = 1$	$n = 1.6$
30	6.8×10^2	5.6×10^2	6.9×10^2	5.6×10^2	2.5	2.7	2.7	2.7
50	6.4	5.6	6.6	5.6	2.7	2.7	2.8	3.0
70	6.4	5.6	6.4	5.4	2.9	3.3	3.0	3.3
90	5.7	5.6	5.7	5.2	3.4	3.2	3.5	3.3

The differential heat of adsorption is ordinarily considered to be given by the Clausius–Clapeyron type equation

$$\frac{q}{R} = \left(\frac{\partial \ln p}{\partial(1/T)}\right)_a \qquad (6)$$

where the amount of adsorbate on the surface is the same. Then the heat of adsorption may be calculated from isosteres constructed on the basis of constant amount adsorbed. However, Wilkins[11] has correctly pointed out that the above equation should be applied to isosteres based on a constant area of surface covered rather than constant weight adsorbed.

In Fig. 8 plots of log p *vs.* $1/T$ are shown for equal areas covered in the temperature range 30–70°. The q values found are 8.5 kcal./mole for the *trans* and 9.0 kcal./mole for the *cis* compound. Using 7.0 and 7.4 kcal./mole as the heats of vaporization for the *trans* and *cis* compounds, respectively,[7] these differences are seen to be about the same as for the heats of vaporization. The values of $q - E_L$ obtained are correspondingly 1.5 and 1.6 kcal./mole. If the calculation is made on the basis of constant amount adsorbed, one obtains values of 3.9 and 3.8 kcal./mole, respectively. Wilkins[11] has predicted that the values based on constant weight should be lower than those based on constant area covered. However, it may be readily seen that the slope of curves constructed on the basis of constant weight adsorbed would be steeper than the ones shown in Fig. 8. For example if the point corresponding to the highest temperature were the same for both methods of calculation, then at a common lower temperature the pressure corresponding to an equal area covered must be greater than the pressure corresponding to an equal weight absorbed if the density of the adsorbate decreases with increasing temperature.

The above values are to be compared with the $E_1 - E_L$ values reported in Table III, approximately 3.0 kcal./mole. The discrepancy is not unexpected since the E_1 values are integral values while the isosteric values are differential ones. Actually the isosteres were taken near a monolayer where the differential heat of adsorption would be expected to be lower than the integral heat of adsorption since the differential heat of adsorption generally decreases with increasing adsorption even within a monolayer.[12]

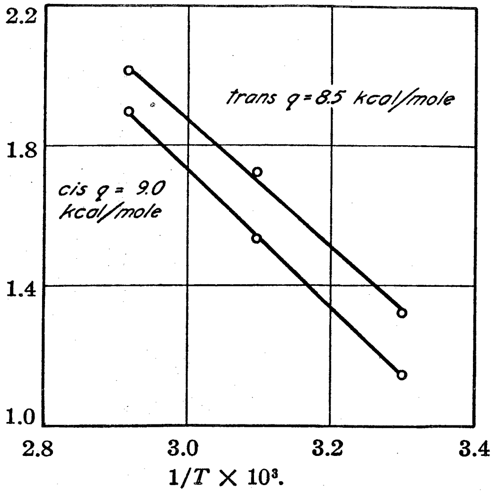


Fig. 8.—Isosteric heat of adsorption of the dichloroethylenes: area covered equal to 531 sq. m./g.

Note on the Separation of *cis–trans* Isomers by Adsorption.—It is of interest to speculate on the possibilities of separation of the *cis–trans* isomers by adsorption on activated carbon from the gas phase. A separation factor for a single stage in adsorption may be defined by

$$\gamma = (x_c/X_t)/(p_c/p_t) \qquad (7)$$

where x_c/x_t is the ratio of weights of *cis* and *trans* isomers on the adsorbent and p_c/p_t is the ratio of partial pressures of *cis* and *trans* isomers in the gas phase in equilibrium with the adsorbent. This equation is analogous to the separation factor usually defined for isotopic separation.

Let us now consider the separation factor obtained for an equimolar gas phase mixture of *cis* and *trans*-dichloroethylenes. Assume that in the mixed adsorption the individual adsorptions are in the same ratio what would obtain if they were adsorbed singly at a pressure equal to the total. For a pressure of 5.0 mm. for each isomer this leads to a value of $\gamma = 1.07$ for data from the 30° isotherms. This value is in the same general range usually obtainable in single stage separations of isotopic mixtures and implies that separation of most *cis–trans* isomers by gas phase adsorption would be a multi-stage process. The recent results of Isom and Hunt[13] obtained in an attempt to separate diastereoisomers by gas phase adsorption on activated carbon confirm this conclusion. However, it may be observed that Claesson,[14] has obtained considerable success in gas phase separations by using the displacement development techniques of chromatography.

---

[11] Wilkins, *Proc. Roy. Soc.* (*London*), **A164**, 496 (1938).

[12] Beebe, Biscoe, Smith and Wendell, THIS JOURNAL, **69**, 95 (1947).

[13] Isom and Hunt, *J. Phys. Chem.*, **50**, 28 (1946).

[14] Claesson, *Arkiv Kemi, Mineral Geol.*, **23A**, 1 (1946).

Summary

1. Adsorption isotherms on activated carbon were determined for *cis* and *trans*-dichloroethylene over a range of temperatures in the gas phase.

2. The adsorption for both isomers followed the B.E.T. theory if the number of layers possible in adsorption was taken as 1.6. The surface areas and heats of adsorption based on the theory were determined.

3. Isosteric heats of adsorption based on a constant fraction of the surface covered rather than constant weight adsorbed were calculated.

4. The adsorption of the *cis* and *trans* isomers were found to be the same when a comparison of surface area covered at fixed relative pressures was made.

5. It was concluded that the condensation properties of molecules adequately determine the adsorption where the only intermolecular forces are van der Waals with or without permanent dipole interaction.

6. It was shown that the separation of *cis–trans* isomers by adsorption on charcoal from the gas phase could be effected only in a multi-stage apparatus.

DAVIS, CALIFORNIA RECEIVED MAY 14, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

The Partial Molal Volume of Acetic Acid in Sodium Acetate and in Sodium Chloride Solutions[1]

BY HENRY E. WIRTH

It has been shown[2] that the partial molal volumes of certain electrolytes depend on the total (volume) ionic strength of the solution as predicted by the Debye–Hückel theory. Redlich and Klinger[3] and Gucker[4] have shown experimentally that the apparent molal volumes of certain non-electrolytes are linear functions of the volume concentration. Redlich and Nielsen[5] found that the apparent molal volume of acetic acid (Φ_3)[6] could be represented by the equation

$$\Phi_3 = 51.8397 + 0.14184m_3 \qquad (1)$$

in the range 0.2–5 *m*, where *m* is the molality. Since the partial molal volume ($\overline{V}_3$) can be obtained from the apparent molal volume by the relation

$$\overline{V}_3 = \Phi_3 + m_3\partial\Phi_3/\partial m_3 \qquad (2)$$

$\overline{V}_3$ is also a linear function of the molality in this concentration range. In this paper the effects of electrolytes on the partial molal volume of acetic acid are reported.

Methods.—Densities at 25° were determined by the sinker method using apparatus described previously.[2] A stock solution of acetic acid was analyzed by adding a weighed excess of standard carbonate-free sodium hydroxide solution and titrating the excess base with dilute hydrochloric acid solution using phenolphthalein as the indicator. The stock solution contained 0.37584 ± 0.00004 g. of acetic acid per gram of solution.

Solutions for the density determination were prepared by weight from the stock acetic acid. Sufficient anhydrous salt (sodium chloride or sodium acetate, previously dried at 200° for six hours) was added to give the required concentration of electrolyte.

The observed density differences were used to calculate the volume of solution containing 1000 grams of water (V) and the apparent molal volume of acetic acid in each of the solutions investigated. The partial molal volumes were obtained from the apparent molal volumes by use of equation 2.

Results

The equation

$$V = 1002.935 + 51.832m_3 + 0.1394m_3^2 \qquad (3)$$

which represents the experimental values of V in an aqueous acetic acid solution (Table I) with an average deviation of ±0.004 ml. can be arranged to give $\Phi_3 = 51.832 + 0.1394m_3$. The values of Φ_3 reported here average 0.013 ml. per mole less than those reported by Redlich and Nielsen.[5] This compares to the probable experimental error of 0.008 ml. per mole due to errors in concentration alone quoted by these authors.

Differentiation of equation 3 gives

$$\overline{V}_3 = 51.832 + 0.2788m_3 \qquad (4)$$

which agrees with the values of $\overline{V}_3$ calculated directly from the data with an average deviation of ±0.008 ml. per mole. Equations 2, 3 and 4 are valid only in the concentration range 0.16–2.5 molal, since in solutions less than 0.16 *m* the increased ionization of acetic acid causes Φ_3 and $\overline{V}_3$ to decrease toward the limiting value (40.68) characteristic of H^+ and $C_2H_3O_2^-$ at infinite dilution.

For aqueous sodium chloride solutions the equation

$$V = 1002.935 + 16.670m_2 + 1.636_3m_2^{3/2} + 0.170_5m_2^2 \qquad (5)$$

represents the experimental results with an aver-

---

[1] Presented at the Chicago meeting of the American Chemical Society, September, 1946.

[2] Wirth, THIS JOURNAL, **59**, 2549 (1937).

[3] Redlich and Klinger, *Sitzb. Akad. Wiss. Wien, Abt. IIb*, **143**, 489 (1934).

[4] Gucker, Gage and Moser, THIS JOURNAL, **60**, 2582 (1938).

[5] Redlich and Nielsen, *ibid.*, **64**, 761 (1942).

[6] In this paper the subscript 3 refers to acetic acid, the subscript 2 to sodium chloride or sodium acetate.

TABLE I

PARTIAL MOLAL VOLUME OF ACETIC ACID (MOL. WT. 60.052) IN WATER SOLUTION AT 25°

m_3	$\frac{(d_3 - d_1)}{1000}$	V, ml.	$\Delta V \times 10^3$ (Eq. 3)	Φ_3	$\overline{V}_3$	$\Delta \overline{V}_3 \times 10^3$ (Eq. 4)
0.04269	0.360	1005.143	−5	51.72	51.8	
.04129	0.353	1005.066	−9	51.62	51.7	
.16317	1.351	1011.390	−6	51.829	51.90	20
.16889	1.399	1011.687	−6	51.824	51.90	20
.38251	3.110	1022.782	1	51.887	51.942	3
.36874	3.003	1022.065	−2	51.881	51.934	−1
1.0724	8.327	1058.688	3	51.983	52.137	5
1.0015	7.814	1054.985	1	51.972	52.115	3
2.4360	17.319	1130.028	2	52.171	52.520	8
2.5225	17.837	1134.569	3	52.182	52.544	7

age deviation of ±0.001 ml. In addition to those terms involved in equations 3 and 5, only two additional terms are required to represent all the data on mixed solutions of acetic acid and sodium chloride with an average deviation of $\pm 0.005_6$ ml. (Table II). The complete equation is

$$V = 1002.935 + 16.670m_2 + 1.636_3 m_2^{3/2} + 0.170_5 m_2^2 + 51.832m_3 + 0.1394m_3^2 + 0.3070m_2m_3 - 0.1212m_2^{3/2}m_3 \quad (6)$$

The addition of another term involving either $m_2m_3^2$ or $m_2^2m_3$ does not improve the fit. Differentiation of equation 6 gives

$$\overline{V}_3 = 51.832 + 0.2788m_3 + 0.3070m_2 - 0.1212m_2^{3/2} \quad (7)$$

The average deviation between the partial molal volumes of acetic acid calculated directly from the data and calculated from equation 7 is ±0.012 ml. per mole.

TABLE II

PARTIAL MOLAL VOLUMES OF ACETIC ACID IN SODIUM CHLORIDE (MOL. WT. 58.454) SOLUTIONS AT 25°

m_3	$\frac{(d_3 - d_2)}{1000}$	V, ml.	$\Delta V \times 10^3$ eq. 6	Φ_3	$\overline{V}_3$	$\Delta \overline{V}_3 \times 10^3$ eq. 7
$m_2 = 0.04000_5$, $d_2 = 0.998729$						
0.1215_2	1.000	1009.910	−6	51.806	51.910	33
0.3172_4	2.561	1020.073	−2	51.884	51.930	−1
0.6350_8	5.017	1036.593	−1	51.929	52.023	−8
1.038_9	7.986	1057.625	1	51.989	52.141	7
$m_2 = 0.1600_3$, $d_2 = 1.003620$						
0.2105_3	1.645	1016.645	8	51.920	51.947	15
0.5070_2	3.899	1032.042	−5	51.927	51.995	−19
0.8600_0	6.449	1050.422	−3	51.987	52.102	−14
1.382_2	10.017	1077.659	−14	52.054	52.238	−21
$m_2 = 0.3590_3$, $d_2 = 1.011587$						
0.2943_3	2.159	1024.578	−8	51.934	51.979	−21
0.7116_8	5.058	1046.309	−3	52.013	52.121	5
1.199_1	8.249	1071.734	−10	52.075	52.256	3
2.126_3	13.715	1120.328	16	52.216	52.538	26
$m_2 = 1.000_2$, $d_2 = 1.036276$						
0.2100_5	1.242	1032.346	3	52.059	52.087	10
0.4401_3	2.565	1044.332	−1	52.074	52.133	−8
1.007_0	5.622	1073.940	6	52.164	52.299	0
1.584_0	8.496	1104.150	−6	52.235	52.448	−12
$m_2 = 2.188_4$, $d_2 = 1.078813$						
0.3110_4	1.112	1061.739	−4	52.147	52.189	−10
0.6694_7	2.307	1080.476	6	52.213	52.305	−2
1.437_8	4.644	1120.733	−2	52.309	52.506	−7

Figure 1 shows that in dilute sodium chloride solutions (0.04–0.36 molal) the partial molal volume of acetic acid in a solution of given total molality ($m_2 + m_3$) is the same as in an aqueous solution of the same molality. At higher sodium chloride concentrations (1.0 and 2.2 molal) $\overline{V}_3$ is less than in solutions of equal molality containing only acetic acid.

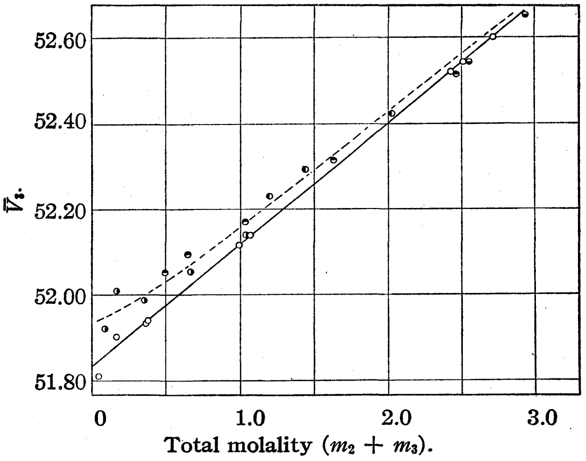


Fig. 1.—Partial molal volume of acetic acid in sodium chloride solution: ○, m_2 = 0.04; ◐, m_2 = 0.16; ⊖, m_2 = 0.36; ◑, m_2 = 1.0; ◓, m_2 = 2.19. The solid line represents the partial molal volume of acetic acid in aqueous solution.

In aqueous solutions containing only sodium acetate the equation

$$V = 1002.935 + 39.274m_2 + 1.881m_2^{3/2} + 0.114m_2^2 \quad (8)$$

represents the experimental values with an average deviation of ±0.0016 ml. Values of Φ_3 calculated from the derived relation $\Phi_3 = 39.274 + 1.881m_2^{1/2} + 0.114m_2$ deviate from the values reported by Redlich and Nielsen[5] by ±0.040 ml. per mole as compared to a deviation of ±0.029 ml. per mole found for their equation: $\Phi_3 = 39.244 + 1.86c_3^{1/2} + 0.209c_3$.

An equation similar to equation 6 was found to

$$V = 1002.935 + 39.274m_2 + 1.881m_2^{3/2} + 0.114m_2^2 + 51.832m_3 + 0.1394m_3^2 + \alpha m_2m_3 + \beta(m_2m_3)^{3/2} \quad (9)$$

represent the experimental values for a given sodium acetate concentration but was not valid for all sodium acetate concentrations. Values of α and β are: 3.464, −10.13 (m_2 = 0.04); 0.9968, −0.920 (m_2 = 0.16); 0.5855, −0.2255(m_2 = 0.365); 0.3733, −0.0461 (m_2 = 1.0); and 0.3094, −0.0193 (m_2 = 2.25), respectively.

TABLE III

PARTIAL MOLAL VOLUMES OF ACETIC ACID IN SODIUM ACETATE (MOL. WT. 82.041) SOLUTIONS AT 25°

m_3	$\frac{(d_3 - d_2)}{1000}$	V, ml.	$\Delta V \times 10^3$ Eq. 9	$\Delta V \times 10^3$ Eq. 10	Φ_3	$\bar{V}_3$	$\Delta\bar{V}_3 \times 10_3$ Eq. 11	$\Delta\bar{V}_3 \times 10_3$ Eq. 12
			$m_2 = 0.039966$, $d_2 = 0.998761$					
0.04897	0.401	1007.064	−1	1	51.86	51.92	−40	−50
.12234	0.989	1010.878	1	1	51.94	52.01	50	30
.31453	2.515	1020.864	−2	8	51.954	51.988	− 3	−17
.63121	4.948	1037.337	−2	− 1	51.985	52.055	4	15
1.0037	7.682	1056.746	3	− 8	52.029	52.138	8	57
			$m_2 = 0.15960$, $d_2 = 1.003730$					
0.09512	0.741	1014.270	−2	0	51.96	52.01	20	40
.20270	1.562	1019.868	2	− 6	52.00	52.02	−10	20
.49001	3.716	1034.814	−2	− 2	52.011	52.062	− 3	− 5
.82430	6.113	1052.236	2	− 6	52.054	52.140	0	− 6
1.3487	9.697	1079.608	−1	0	52.110	52.250	−15	−20
			$m_2 = 0.36553$, $d_2 = 1.012050$					
0.13415	0.968	1024.705	3	− 7	52.04	52.05	0	20
.28443	2.029	1032.531	2	− 8	52.061	52.094	9	22
.67014	4.668	1052.634	−1	− 7	52.093	52.172	0	− 1
1.2652	8.476	1083.722	−2	− 1	52.163	52.313	− 1	−15
2.1066	13.363	1127.832	3	10	52.268	52.516	− 8	−31
			$m_2 = 0.99911$, $d_2 = 1.036202$					
0.20864	1.178	1055.058	−1	− 5	52.20	52.23	0	20
0.44858	2.488	1067.600	2	−11	52.239	52.294	10	17
1.0387	5.543	1098.488	−6	− 4	52.297	52.424	0	−12
1.7214	8.750	1134.346	8	0	52.390	52.601	7	−22
			$m_2 = 2.2541$, $d_2 = 1.078767$					
0.30881	0.944	1114.625	−5	− 6	52.51	52.55	− 10	0
0.68920	2.028	1134.642	4	−16	52.573	52.653	13	4
1.5026	4.144	1177.530	0	10	52.657	52.832	4	42

The simplest equation that would represent all the data was found to be

$$V = 1002.935 + 39.274m_2 + 1.881m_2^{3/2} + 0.114m_2^2 + 51.931m_3 + 0.1394m_3^2 + 0.2391m_2m_3 + 0.005187m_2^{-1}m_3 - 0.02000m_2^{-1/2}m_3 - 0.00338m_2^{-1}m_3^2 \quad (10)$$

The average deviation between observed and calculated values is ±0.005 ml. This equation is adequate for interpolation but cannot be used for extrapolation to solutions more dilute in acetic acid and sodium acetate than those used in this work.

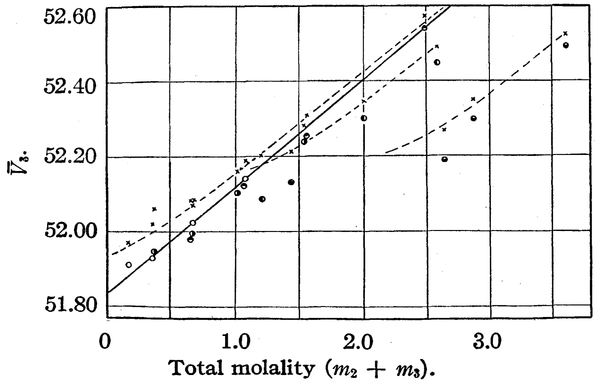


Fig. 2.—Partial molal volume of acetic acid in sodium acetate solution: ○, m_2 = 0.04; ◐, m_2 = 0.16; ◒, m_2 = 0.365; ◑, m_2 = 1.0; ◓, m_2 = 2.25. The solid line represents the partial molal volume of acetic acid in aqueous solution.

By differentiation of equations 9 and 10 the following equations for the partial molal volume were obtained:

$$\bar{V}_3 = 51.832 + 0.2788m_3 + \alpha m_2 + 3/2\beta m_2^{3/2}m_3^{1/2} \quad (11)$$

(average deviation ±0.010 ml. per mole) and

$$\bar{V}_3 = 51.931 + 0.2788m_3 + 0.2391m_2 + 0.005187m_3^{-1} - 0.02000m_2^{-1/2} - 0.00676m_2^{-1}m_3 \quad (12)$$

(average deviation ±0.021 ml. per mole) (Table III).

The observed values of $\bar{V}_3$ in sodium acetate solutions are greater than in aqueous acetic acid solutions of equal molality (Fig. 2). The greatest differences are found in the more dilute solutions. This is to be expected from the decreased ionization of acetic acid in the sodium acetate solutions.

Summary

The volume of solution containing 1000 g. of water, the apparent molal volume of acetic acid, and the partial molal volume of acetic acid are reported for solutions containing acetic acid and

either sodium chloride or sodium acetate. Empirical equations representing the data are developed.

As a rough approximation the partial molal volume of acetic acid in a solution containing electrolyte is the same as in an aqueous solution of the same total molality. This approximation does not hold in solutions of sodium chloride with molalities greater than 0.4.

COLUMBUS 10, OHIO RECEIVED OCTOBER 4, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICS OF COLUMBIA UNIVERSITY]

Long Life Zirconium from Uranium 235 Fission

BY A. V. GROSSE[1] AND E. T. BOOTH

In our first paper on radioactive zirconium and columbium from uranium fission[1a] we described, outside of the 17.0-hour zirconium, also a long life zirconium, with a period of more than twenty days. In the following few months additional evidence was obtained, but publication was postponed due to other urgent atomic energy investigations. In the intervening years this fission product was investigated as part of the Plutonium Project,[2] but no details have appeared as yet. In 1940 Hahn and Strassmann[3] claimed to have discovered a 26-day zirconium. This they cancelled, however, in a short note in 1943[4] and simultaneously announced the long life zirconium to be described below. In the recently published Nuclear Physics Tables[5] the properties of our isotope have been inadvertently mixed with those of Hahn and Strassmann's 26-day zirconium. It thus seems worthwhile to publish our original findings.

Our zirconium proved to have a half-period of sixty-six days; this was followed for nearly three hundred days. As mentioned previously, it emitted electrons of about 0.25 MEV. energy. Chemical evidence proved unambiguously that the carrier of β-activity was the element zirconium. It produced a long life columbium isotope with very soft radiation, whose period was not determined.

Experimental Part

A typical experiment was carried out as follows: A 100-cc. solution of 70 g. of uranyl nitrate was bombarded by slow neutrons from the Columbia cyclotron on and off for a number of days. This was diluted to 1000 cc. of a 25% hydrochloric acid solution (by adding 588 cc. of 36% hydrochloric acid). Ten cc. of zirconium oxychloride solution, containing 135 mg. of zirconium dioxide, was added as carrier, together with various solutions containing a few milligrams each of stable isotopes to act as carriers for the radioactive fission products (*i. e.*, Rb, Cs, Sr, Ba, Y, La, Mo, Sb, Te, Ce, Cb, Br and I). On addition of 10-fold molar excess of phosphoric acid a fine, nicely settling precipitate of *zirconium phosphate* (ZrP_2O_7) was obtained, containing some insoluble columbic acid ($HCbO_3$).

This precipitate was washed with 25% hydrochloric acid and then purified twice from possible *natural* radioactive contaminations by addition of a few milligrams of Th, Bi, Pb, La + Ba and Fe as carriers. The radio-pure zirconium phosphate, still containing the added columbic acid and some iron oxide, was converted to zirconium dioxide by melting with a 10-fold quantity of sodium potassium carbonate in a platinum–gold dish; 143 mg. of zirconium dioxide and a trace of ferric oxide were obtained. These were further purified and fractionated as shown in Fig. 1; 19.0 mg. was painted on an aluminum disc (Al, 45) and measured. The rest was converted into acid soluble zirconium hydroxide (by sodium bisulfate melt and ammonia precipitation) and fractionally crystallized as $ZrOCl_2 \cdot 8H_2O$ from concentrated hydrochloric acid. The head or purest fraction of oxychloride was converted to oxide (56.5 mg. of snow white zirconium dioxide) and all of it painted on Al 47. Intermediate fractions were discarded. The residual zirconium was precipitated from the mother liquor, after diluting with hydrochloric acid, as a pure zirconium phosphate; all of it, equivalent to 16.7 mg. of zirconium dioxide, was painted on Al 48. The columbium was precipitated, from the sodium potassium carbonate-melt solution, with dilute acid; 51 mg. of columbium pentoxide, containing small amounts of zirconium dioxide, was obtained and painted on Al 46 for measurement.[5a] The scheme of the chemical separation is illustrated in Fig. 1. All measurements were made using an F. P. 54 amplifier and through 1 or 5 mil Al foil. The results of our measurements through 1 mil aluminum are plotted in Fig. 2. We see that all three zirconium preparations decay with the same period, namely, sixty-six days.

The specific activity *per 1.0 mg. of zirconium dioxide* of all three preparations, after correcting to *zero time*, was as follows:

Al 45, initial material = 4.9×10^{-3} div./sec.
Al 47, head fraction = 4.9×10^{-3} div./sec.
Al 48, tail end = 5.2×10^{-3} div./sec.

Thus, they are, within experimental error, identical. Zirconium is the only element, except ekatantalum (no. 91) and hafnium, which is precipitated from concentrated hydrochloric acid by phosphoric acid. Ekatantalum can be carefully separated from zirconium by the procedure we originally used to separate protactinium[6] and as was also subsequently demonstrated by the separation of ekatantalum^{233} from thorium + *n* products.[7] Hafnium is only separated slowly from zirconium by tedious fractionation.[8] Thus the constancy of the specific activity, together with the other chemical evidence, is strong proof

---

(1) Present address: Houdry Process Corp., Marcus Hook, Pa.

(1a) A. V. Grosse and E. T. Booth, *Phys. Rev.*, **57**, 664–665 (1940).

(2) "Nuclei Formed in Fission," issued by the Plutonium Project, THIS JOURNAL, **68**, 2411–2442 (1946).

(3) O. Hahn and F. Strassmann, *Naturwissenschaften*, **28**, 548 (1940).

(4) O. Hahn and F. Strassmann, *ibid.*, **31**, 499–501 (1943).

(5) J. Mattauch, "Nuclear Physics Tables," Interscience Publishers, Inc., New York City, N. Y., 1946, p. 140.

(5a) Data on this columbium isotope will be published later. Hahn and Strassmann[4] give it a half life of fifty-five days.

(6) A. V. Grosse, *Ber.*, **61**, 233 (1928).

(7) A. V. Grosse, E. T. Booth and J. R. Dunning, *Phys. Rev.*, **59**, 322–323 (1941).

(8) G. v. Hevesy, "Recherches sur les propriétés du hafnium," Kopenhagen, 1925, p. 105.

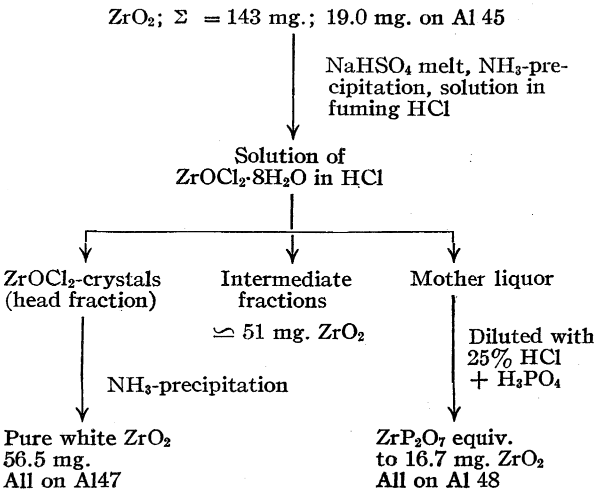


Fig. 1.—Purification and Fractionation of ZrO_2.

that the sixty-six-day activity is due to zirconium; hafnium is excluded both because of its high atomic mass and the relatively high intensity of our activity.

A blank run was made on the uranium solution we used in order to exclude any contamination from various possible cyclotron sources and targets; any possible contamination of the zirconium preparation was found to be below 1% of our activity.

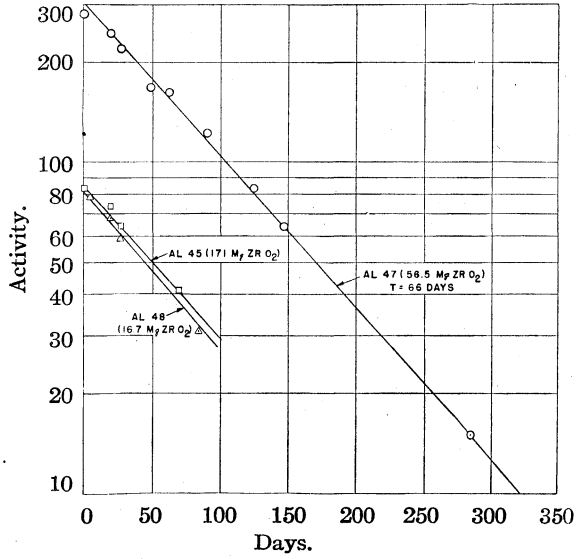


Fig. 2.—Zirconium of sixty-six days half period.

Discussion

Thus the existence of two zirconium isotopes of 17.0 hours and 66 days half-time seems assured. The fission yield of the first isotope was found to equal 6.1% in a joint investigation with H. Anderson and E. Fermi.[9]

Subsequently, these two isotopes have been confirmed by workers on the Plutonium Project.[2] Furthermore, their mass numbers have been established and the fission series determined as follows[10]:

$$(1)\quad Kr^{97} \xrightarrow[\text{short}]{\beta^-} Rb^{97} \xrightarrow[\text{short}]{\beta^-} Sr^{97} \xrightarrow[\text{short}]{\beta^-} Y^{97} \xrightarrow[\text{short}]{\beta^-} Zr^{97}_{17.0h} \xrightarrow{\beta^-} Cb^{97}_{75min.} \xrightarrow{\beta^-} Mo^{97}_{stable}$$

Fission yield = 6.1% (A. F. and G.[9])

$$\begin{tikzcd} & & Cb^{95}_{90h} \arrow[d] & \\ (2)\quad Y^{95}_{<1.5h} \arrow[r, "\beta^-"] & Zr^{95}_{66d} \arrow[ur, "2\%"] \arrow[r, "\beta^-", "98\%"'] & Cb^{95}_{63d} \arrow[r, "\beta^-"] & Mo^{95}_{stable} \end{tikzcd}$$

Fission yield = 6.4% (P. P.[2])

Both in G. Seaborg's 1940 report[11] and the Nuclear Physics Tables[5] of 1946, the mass assignments are erroneous, namely, 95 for 17.0 hr. Zr and 75 min. Cb and 93 for the 66 day zirconium.

Hahn and Strassmann have withdrawn their claims[1] to a twenty-six day zirconium[4]; as we suspected earlier, it was very likely due to a contamination of their very weak preparation with UX.

Other radioactive zirconium isotopes from uranium fission are to be expected, since the 93 mass series ending in the stable Cb^{93} and the 97, 98 and 100 series, ending in the corresponding stable molybdenum isotopes, *should pass through* such radioactive bodies. Furthermore, all series from masses 90 to 100 should have high fission yield from 5.0% to a maximum of about 6.4% since they all lie on the light group *hump* of the fission curve.

However, no reliable information is available on such isotopes. The Plutonium Project (p. 2421) lists a Zr^{93} with a half time of 2.5 minutes as questionable and is left out of the otherwise well-known mass 93 series. It will be the object of future research to find these isotopes.

This work was carried out from February to August, 1940, in the Department of Physics of Columbia University. Pressure of National Defense Work prevented earlier publication.

Acknowledgments.—We wish to acknowledge the continued interest of Dean G. Pegram and Dr. John Dunning in this investigation.

Summary

A long life zirconium of 66-day half period is described as a product of uranium 235 fission.

Other zirconium isotopes from U-fission are critically reviewed.

RECEIVED JUNE 25, 1947

---

[9] H. Anderson, E. Fermi and A. V. Grosse, *Phys. Rev.*, **59**, 52–56 (1941).

[10] See ref. 2, p. 2439.

[11] G. Seaborg, *Chem. Rev.*, **27**, 239 (1940).

[Contribution from the Department of Chemistry of the University of Rochester]

Photochemical Studies. XXXIX. A Further Study of the Fluorescence of Acetone

By Roy E. Hunt[1] and W. Albert Noyes, Jr.[2]

The problem of energy exchange between polyatomic molecules is one about which relatively little is known experimentally and for which the theory can be stated only in general, and somewhat unsatisfactory, terms. There is, perhaps, no more fundamental problem in the field of reaction kinetics, and studies of fluorescence offer one means of obtaining data essential to a more satisfactory statement of the theory. Interpretations of this type of data are difficult and are usually based on classical assumptions which do not add materially to the field.

Studies of the fluorescences of acetone and of biacetyl have been numerous and yet there are still many points of ambiguity. The present study was started with a view to obtaining a better insight into the behavior of these fluorescences. While certain points have been clarified, much remains to be done before a final understanding of all of the data will be possible.

Summary of Previous Work

The fluorescence of acetone vapor seems to have been described first by Damon and Daniels[3] who observed both green and blue parts, the former at least six times as intense as the latter. Damon[4] and Fugassi[5] extended the study to acetone–oxygen mixtures, the change in visual color from blue to green being an indication of the disappearance of oxygen. Fugassi[5] showed the quantum yield of oxygen disappearance to be equal to that of acetone disappearance in an oxygen-free system.

The existence of fluorescence might normally indicate a discrete absorption spectrum. Such an absorption was found by Norrish, Crone and Saltmarsh[6] and further studied by other authors.[7] However, the existence of a threshold[8] for exciting the fluorescence has not been confirmed, and it is now generally agreed that acetone fluoresces at both 3130 Å. and 2537 Å. although more weakly at the latter wave length. A complete description of the absorption spectrum is not possible at the present time. There may be a continuum underlying the whole absorption region from about 2400 Å. to about 3200 Å. The bands may have a diffuse character, indicating the possibility of predissociation, but with a complex molecule of this type any definite conclusions in this connection are unwarranted. In any case there seems to be no fundamental difference (other than magnitude of certain quantum yields) between the photochemical behaviors of acetone at 3130 Å. and at 2537 Å.[9] Acetone shows many sharp bands in the region below 2000 Å.,[10] but no fluorescence could be observed by excitation with wave lengths between 1800 and 2000 Å.[11]

The first attempt at a quantitative study of the fluorescence of acetone with 3130 Å. radiation showed that plots of I_a/I_f *vs.* pressure gave reasonably straight lines (I_a = intensity loss due to absorption of radiation, I_f = intensity of fluorescence.)[12] Due to the experimental method long exposures were used, and while the total fluorescence (green plus blue) was measured, the major portion of the fluorescence was undoubtedly in the green.[3] Moreover, only relatively high pressures (over 30 mm.) could be studied and the true effect of collisions could not be ascertained. An attempt to repeat this work[13] by a different method indicated that the fluorescent intensity was a function of time. The green parts of the fluorescences of biacetyl and of acetone were shown to be identical. This led Matheson and Zabor[14] to examine the fluorescences of other compounds containing the CH_3CO- group, thus showing the same fluorescence to be found in acetaldehyde and methyl ethyl ketone. The emitter seems to be the same (for the green) for all of these compounds and is probably biacetyl.

The most precise work on the fluorescences of acetone and of biacetyl is due to Almy and his co-

---

(1) National Research Council Predoctoral Fellow, December, 1945 to April, 1947.

(2) This work was supported in part under Contract N6onr-241, Task I, with the United States Navy.

(3) G. H. Damon and F. Daniels, This Journal, **55**, 2363 (1933).

(4 G. H. Damon, *Ind. Eng. Chem., Anal. Ed.*, **7**, 133 (1935).

(5) P. Fugassi, This Journal, **59**, 2092 (1937).

(6) R. G. W. Norrish, H. G. Crone and O. D. Saltmarsh, *J. Chem. Soc.*, 1456 (1934).

(7) W. A. Noyes, Jr., A. B. F. Duncan and W. M. Manning, *J. Chem. Phys.*, **2**, 717 (1934); W. A. Noyes, Jr., *Trans. Faraday Soc.*, **33**, 1495 (1937).

(8) R. G. W. Norrish and M. Appleyard, *J. Chem. Soc.*, 874 (1934).

(9) A disagreement is indicated from the ratios of ethane to carbon monoxide found by R. Spence and W. Wild, *J. Chem. Soc.*, 352 (1937); 590 (1941), and by D. S. Herr and W. A. Noyes, Jr., This Journal, **62**, 2052 (1940), respectively. The ratios obtained by the former authors would indicate little or no biacetyl to be formed at 3130 Å. The probable explanation of this discrepancy is found in the work of Damon and Daniels[3] and of G. M. Almy and S. Anderson, *J. Chem. Phys.*, **8**, 813 (1940), which showed that biacetyl (probably mistaken for diacetone alcohol by Damon and Daniels) does not accumulate indefinitely in the system, particularly when polychromatic light is used. The work of J. G. Roof and F. E. Blacet, This Journal, **63**, 1126 (1941), showed that the photochemical decomposition of biacetyl is a chain reaction under some conditions and the reaction should be initiated, therefore, by free radicals from acetone. For a review, see W. Davis, Jr., *Chem. Rev.*, **40**, 201 (1947).

(10) See W. A. Noyes, Jr., A. B. F. Duncan and W. M. Manning, ref. 7.

(11) J. P. Howe and W. A. Noyes, Jr., This Journal, **58**, 1404 (1936).

(12) C. F. Fisk and W. A. Noyes, Jr., *J. Chem. Phys.*, **2**, 654 (1934).

(13) M. S. Matheson and W. A. Noyes, Jr., This Journal, **60**, 1862 (1938).

(14) M. S. Matheson and J. W. Zabor, *J. Chem. Phys.*, **7**, 536 (1939).

workers.[15] This work confirms and extends earlier work. The main conclusions from all work thus far may be summarized briefly as follows: (1) The green fluorescence is associated with the presence of biacetyl and the biacetyl molecule is probably the emitter.[13,14,15] (2) The weak blue fluorescence is found in carefully purified acetone and also in acetone with oxygen present and is probably due to the acetone molecule.[3,4,5,15,19] (3) The quantum yield of fluorescence is low for both acetone and biacetyl, not over 2 or 3% in the most favorable case in acetone and probably much less for the blue alone; in biacetyl an efficiency of 14 per cent. is found.[15] (4) The lifetime of the excited state in biacetyl is quite long, of the order of 1.5×10^{-3} sec.[15,16] (5) At temperatures over about 100° there is very little green fluorescence,[14] indicating that biacetyl is not produced from acetone at such temperatures.[17] (6) Either the emission process in biacetyl is not the direct reverse of the absorption process or only a small fraction of the absorbing molecules reach the state which can fluoresce. Lewis and Kasha[18] designate the upper state as triplet and describe the fluorescence as phosphorescence due to the long life. (7) While the fluorescences of biacetyl excited by 4358 Å. and 4047 Å. are normal in the sense that they are quenched by collisions,[15] that excited by 3660 Å. shows the reverse effect.[19,15] This can be explained by assuming that molecules excited by 3660 Å. are capable of dissociating unless stabilized by collisions, whereas those produced by the other two wave lengths are not. (8) As acetone is irradiated, the blue fluorescence grows weaker as the green grows stronger.[15] (9) The green fluorescence reaches nearly full intensity when the biacetyl pressure is very low[13,19,15] (not over a few tenths of a millimeter) compared to the acetone pressure (100 mm. or more), thus indicating some mechanism which is quite specific and which is not inhibited markedly by the acetone. (10) Experiments with deutero-biacetyl indicate that there is probably little reaction of the type $CH_3 + CD_3COCOCD_3 = CH_3COCD_3 + COCD_3$[20] at temperatures up to 62°. (11) The blue fluorescence is observed in solid acetone and possibly also in other solid ketones.[21]

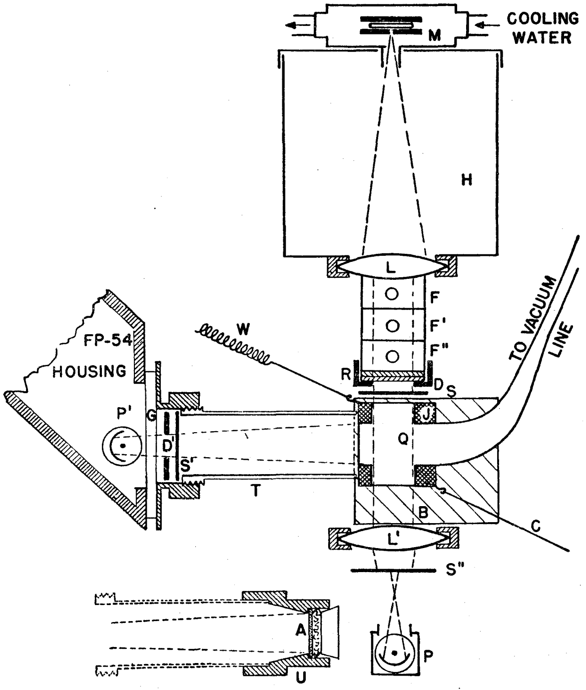


Fig. 1.—Diagram of optical set-up, including fluorescence cell, light source and filters, and transmission and fluorescence photocells: A, radium-activated phosphor disc; B, bench on which cell can move; C, cord removing cell from beam; D,D', diaphragms; F,F',F", filter solutions; G, glass filter, Corning no. 738; H, housing to enclose light; J, jacket of copper around cell; L,L', lenses (quartz 14-cm. focus); M, mercury arc (H-6 shown); P,P', photocells, GL-929; Q, quartz fluorescence T-cell; R, red-purple Corex glass filter; S,S',S", shutters; T, tube for constant light path; U, unit for calibrating fluorescence photocell circuit; W, wire spring to return cell.

From the above it may be stated that two points, among others, need clarification: (a) the mechanism of excitation of the fluorescence ascribed to biacetyl when acetone is the absorbing molecule; (b) the relationship of the blue fluorescence to the green. The present work was performed with the object of clarifying some of the steps in the mechanism of these fluorescences.

Experimental

The acetone (J. T. Baker C. P.) was fractionally distilled after standing for two days in the dark over anhydrous calcium chloride. The middle half was collected and the distillation repeated. The middle half from this second distillation was stored under vacuum over anhydrous calcium sulfate and fractionally distilled from a temperature of 0° to one of −7°. The middle half from this final step, amounting to about 4 cc., was kept in a blackened storage reservoir separated from the line by a mercury cut-off.

Oxygen was prepared by heating C. P. potassium permanganate, passed through glass wool and a trap immersed in liquid nitrogen. It was stored in a one-liter bulb separated from the line by a mercury cut-off.

For most of the experiments a General Electric AH-6 high pressure mercury arc was used. The optical system, including the color filters, is shown schematically in Fig. 1. The color filter combination consisted of a 5-cm. length of 0.0005 *m* potassium chromate, 5 cm. of 0.356 *m* nickel chloride, and 1.0 cm. of 0.0245 *m* potassium biphthalate. The emission lines from this type of arc are

---

[15] G. M. Almy, H. Q. Fuller and G. D. Kinzer, *J. Chem. Phys.*, **8**, 37 (1940); G. M. Almy and S. Anderson, *ibid.*, **8**, 805 (1940); H. Q. Fuller, L. W. Phillips and G. M. Almy, *ibid.*, **7**, 973 (1939); G. M. Almy and P. R. Gillette, *ibid.*, **11**, 188 (1943).

[16] R. D. Rawcliffe, *Phys. Rev.*, **59**, 915 (1941).

[17] See D. S. Herr and W. A. Noyes, Jr., ref. 9.

[18] G. N. Lewis and M. Kasha, THIS JOURNAL, **67**, 1001 (1945).

[19] F. C. Henriques, Jr., and W. A. Noyes, Jr., *ibid.*, **62**, 1038 (1940).

[20] D. S. Herr, M. S. Matheson and W. D. Walters, *ibid.*, **63**, 1464 (1941).

[21] Unpublished results kindly shown to us by Dr. A. B. F. Duncan of this Laboratory.

very broad, and hence the radiation is not strictly monochromatic, although at least 95% lies in the region of 3075–3250 Å.[21a]

A Hanovia 150-watt Uviarc was used for part of the work. This arc operates at a much lower pressure than the AH-6 and with the color filter combination at least 95% of the radiation lay in the group of lines at 3130 Å.

The beam incident on the fluorescence cell was parallel and practically homogeneous. It filled 90% of the transmission arm with little or no radiation hitting the walls. Scattered radiation reaching the photoelectric cell used to measure the fluorescent intensity amounted to less than 0.1% of the fluorescent intensity in most cases. Even in the most unfavorable case (determination of the fluorescence at very low pressures) scattered radiation was not over 20% of the total.

Incident intensity was varied by means of fine mesh screens oxidized in a flame and used singly or in pairs. The meshes varied from 20 to 150 per inch with transmissions from 30 to 60%. The intensity was calculated from the measured transmissions of the screens in each case.[22]

The fluorescence cell, which had the form indicated in Fig. 1, was made of fused quartz with windows about 1.5 mm. in thickness. All portions of the cell except the windows were painted black. It was attached to the rest of the vacuum system by 6 feet of 8 mm. tubing, thus permitting it to be moved into and out of the light beam. For experiments at higher temperatures the cell was enclosed in a copper block cut in two sections and surrounded with a layer of asbestos, a winding of resistance wire and a second layer of asbestos. Temperatures were measured with a thermocouple inserted in a well drilled in the copper block.

Transmitted radiation was condensed with a quartz lens on a GL-929 photocell with a S-4 surface and the current measured with a galvanometer using an Ayrton shunt to vary the sensitivity.[23]

The fluorescent radiation was measured with a GL-929 photocell and d. c. amplifier employing an FP-54 electrometer tube and a modified DuBridge circuit.[24] The stability of the circuit was excellent except in very humid weather. The fluorescent radiation passed through a Corning glass filter no. 738, 2 mm. in thickness, which removed more than 99% of the ultraviolet radiation incident upon it.

The fluorescence amplifier circuit was calibrated by applying a fixed voltage to the control grid of the FP-54 tube and recording the resulting scale deflection. A one inch radium activated phosphor disc, emitting blue radiation at a brightness of 0.25 microlambert, was used as an absolute source of calibration.[25]

The circuit for measuring the transmitted intensity was calibrated with a small automobile light operating at exactly 5.55 volts from a storage battery. This circuit was checked before and after (and occasionally during) each run. This was necessary because of the extreme sensitivity of the galvanometer used. The reproducibility of the sensitivity left something to be desired.

At low acetone pressures the largest error lies in the experimental determination of the absorption by the acetone since this is determined as the small difference in two large quantities. Neither the constancy of the light source nor the constancy of the galvanometer sensitivity were adequate for this purpose. Especially after the accumulation of photochemical decomposition products and after the addition of other gases such as oxygen, the complete removal of the acetone by condensation with liquid air through the long tubing connecting the cell with the trap proved to be slow and unreliable. Hence, the procedure was adopted of removing the cell from the light path and determining the intensity of the beam directly. This coupled with a determination of the mean transmission of the two windows of the cell permitted a calculation of the intensity incident on the ketone if it is assumed that the two windows absorb and reflect to equal extents. The assumption of Beer's law for these very low absorptions is valid even if the light is not strictly monochromatic.

The procedure used may be described in the following steps: (1) measurements were made of I_t^0, I_0, and again of I_t^0 where I_t^0 is the light transmitted by the cell when the ketone is condensed by liquid nitrogen (but foreign gas, if any, is present) and I_0 is the intensity of the beam when the cell is removed from the light path; (2) the measurement of I_s^0, *i. e.*, the intensity of the scattered light; (3) remeasurement of I_0 and I_t^0 and a check of the zero reading of the transmission photocell with the shutter at S″ (Fig. 1) closed; (4) vaporization of the ketone into the cell, measurement of I_0, I_t (the light transmitted by the filled cell), and again of I_0; (5) measurement of I_f (the intensity of the fluorescence) and of I_t; (6) remeasurement of I_0 and I_t and a recheck of the zero readings of the transmission and fluorescent photocell circuits; (7) repetition of the empty cell readings after freezing down or pumping out the ketone.

The value of T (the fraction of total radiation transmitted through the first window) was obtained from an average of the empty cell readings before and after each run. Corrections were applied on the basis of calibrations made each day and for changes in shunt readings. The value of I_a was obtained from a corrected value of I_t. Dividing I_f and I_t by I_0 corrected for small changes in lamp intensity.

The value of $1/Q$ used in this article is the ratio I_a/I_f, where I_a is the actual loss in intensity in passing through the absorbing gas expressed in arbitrary units, where each unit is 1.6×10^9 quanta/second/cc. and I_f is the intensity of the fluorescence in arbitrary units.

The line for handling the gases and measuring pressures need not be described in detail. No stopcocks using grease were present in the line. Low pressures of gases not condensed by liquid nitrogen were measured with the McLeod gage. Foreign gases, such as oxygen, could be admitted from storage bulbs by the use of a Toepler pump. Pressures of the ketone were read directly on a manometer. The main disadvantage in the entire system resided in the long tubing between the cell and the trap, made necessary by the need of moving the cell into and out of the light path. This resulted in slow condensation of the ketone in the presence of non-condensable gases and also in slowness of diffusion back into the cell of biacetyl. The latter would vaporize more slowly than acetone after condensation by liquid nitrogen.

The transmitted light was photographed with a small Bausch and Lomb Littrow-type spectrograph and the fluorescence was photographed with a wide aperture glass prism spectrograph. Eastman I-F and I-G plates were used. Due to the low intensity of the fluorescence, particularly in the blue, a wide slit was necessary, thus render-

---

(21a) W. Davis, Jr. and R. E. Hunt, THIS JOURNAL, **69**, 1415 (1947).

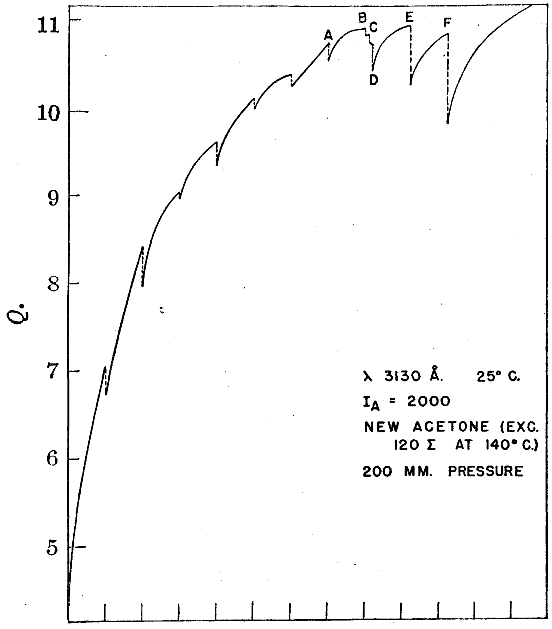
(22) The validity of varying light intensity in this way has been discussed by R. G. Dickinson (see W. A. Noyes, Jr., and P. A. Leighton, "The Photochemistry of Gases," The Reinhold Publishing Company, New York, 1941, p. 202.) The screens were placed just in front of the window through which radiation was incident on the ketone. This method reduces the total radiation but does not decrease the intensity per unit area for the portions illuminated. Other methods which might have been used to vary the light intensity would not have been valid unless the radiation were highly monochromatic. Comparison of results with the Uviarc and the AH-6 arc, while not extensive enough to warrant definite conclusions, did not show any striking differences in behavior. The latter arc was about 25 times as intense as the former.

(23) The light intensities absorbed by the ketones in the fluorescence cell were calculated from the values of the intensities of the transmitted light using the method of R. E. Hunt and T. L. Hill, *J. Chem. Phys.*, **15**, 111 (1947).

(24) The d. c. amplifier was designed and constructed by Dr. J. B. Platt of the Department of Physics and loaned for this work by Prof. Brian O'Brien of the Institute of Optics, University of Rochester.

(25) The disc was obtained from the United States Radium Corporation, which also furnished the brightness calibration. The brightness of this disc was of the same order of magnitude as that of the blue fluorescence.

ing uncertain any conclusions about the discrete character of the fluorescence. Microphotometer tracings were obtained in the recording microphotometer in the Institute of Optics.



Exposure: 1 division = 10 min. (20Σ).

Fig. 2.—Variation of total fluorescent efficiency (Q) with exposure as a function of intermittent dark periods. Unlettered breaks in curve are 5-min. dark periods; points A-C, 10-min. periods; D, 40 min.; E, 240 min.; F, 2 days.

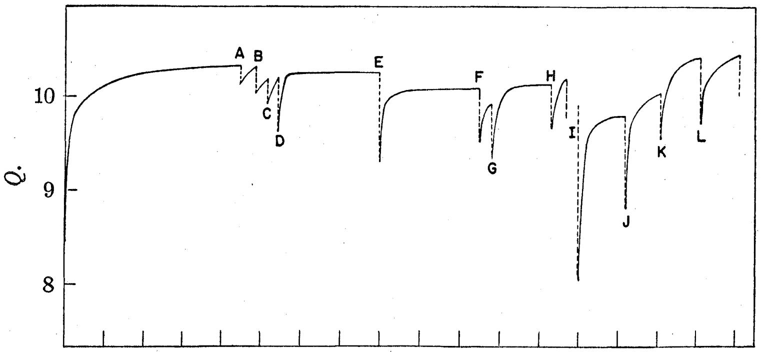
Discussion of Results

The trend of $1/Q$ (or of Q) as a function of several variables is more important than actual numerical values, and hence the results are presented graphically in Figs. 2–9, inclusive. The variables employed were absorbed intensity at constant pressure, pressure at constant absorbed intensity, and temperature.

At the start of a run with carefully purified acetone, the green fluorescence is weak or entirely absent but increases with time quite rapidly at room temperature. The blue fluorescence simultaneously decreases. Therefore, the radiation measured by the photoelectric cell consists mainly of green after the first few minutes except at elevated temperatures. Determination of the behavior of the blue as a function of various variables was accomplished satisfactorily only at temperatures above about 120° where the green was absent. Oxygen may eliminate the green entirely, but it also strongly decreases the intensity of the blue. At 0.4 mm. pressure of oxygen the green was absent and the blue decreased by a factor of ten.

Figures 2 and 3 indicate some of the reasons for difficulties in reproducing results. In Fig. 2 the quantity of Q (defined as the ratio I_f/I_a where I_f is the intensity of the fluorescence and I_a is the decrease in intensity due to absorption by the vapor) is shown as a function of time. Since these measurements were made with a photoelectric cell, they include both the green and the blue, although the green is at least three-quarters of the total intensity after the curve has ceased its rapid rise. The breaks in the curve are brought about by various dark periods as indicated in the caption. The decrease in Q after a dark period may be due either to a slow diffusion of some substance, presumably biacetyl, from the fluorescence cell into the rest of the apparatus or to a disappearance of this substance either due to a chemical reaction or perhaps due to polymerization. That it invariably occurred even after long periods of illumination would indicate that it is not entirely due to diffusion because eventually biacetyl would be expected to attain a more or less uniform concentration throughout the entire system. Earlier work[26] has given some indication of removal of biacetyl from the gas phase by a process which does not depend on illumination.

In Fig. 3 somewhat similar data are shown except that the acetone at the beginning of the curve had already been exposed to radiation for an appreciable length of time. Although in this instance the curves had reached approximate constancy during illumination, the value of Q was always found to be low after a dark period. The



Exposure: 1 division = 10 min. (20 Σ).

Fig. 3.—Variation of total fluorescent efficiency (Q) with exposure as a function of dark period duration and liquid nitrogen cooling: acetone sample had been used for two weeks under wide variety of conditions of intensity and temperature; pressure 163.7 mm.; temperature 24°; wave length 3130 Å.; $I_a = 2000$. Points A-E are dark periods of 5, 10, 20, 40, 80 min.; F-H, periods of 40, 40, 80 min. At point I, ketone was cooled with liquid nitrogen to −196° for 10 min., 20 mm. remaining unfrozen in the line due to slow diffusion through non-condensable products. After vapor had warmed to room temperature, fluorescence readings were begun at once. At J, after 10 min. at −196°, vapor stood 45 min. at 24° before readings were begun; at K, only 4.5 min. was allowed for diffusion. At L, liquid nitrogen was kept on ketone trap 3 min. only, with 4.5 min. allowed subsequently for diffusion.

---

[26] Unpublished results obtained by Dr. V. R. Ells.

effect of freezing out the acetone and any condensible reaction products with liquid nitrogen for varying periods of time is shown by points I, J, K and L. In this instance the lower rate of evaporation of biacetyl as compared to acetone almost certainly leads to a temporary deficiency of biacetyl in the fluorescent cell and Q is low until the concentration of this compound has been replenished through irradiation.

It has been shown[13] that the amount of biacetyl does not determine the intensity of the fluorescence providing it has reached a certain value, probably not over a fraction of a millimeter. There are also indications[15] that biacetyl reaches a steady state when acetone is illuminated. Data on this point are difficult to obtain and especially since it is not known whether the steady state concentration, if there is one, is the same when approached from both directions. The only clue to this point would be obtained from the data of Roof and Blacet[9] which indicate that under some conditions the photochemical decomposition of biacetyl is a chain reaction. It might, therefore, be initiated by free radicals from acetone.

The data in Figs. 2 and 3 do indicate, however, that Q for total fluorescence attains an approximately constant value after long periods of illumination. The blue intensity goes down about 50% during the period when the green builds up to its maximum. This is in agreement with the work of Almy and Anderson.[15]

The so-called green fluorescence consists of several "bands" whose wave lengths have been measured by other authors.[6,13,14,27] The blue fluorescence extends from about 3850 Å. to about 5000 Å. This fluorescence has one weak maximum which occurs near the long wave end of this region (see Fig. 4). This weak maximum may possibly be associated with the so-called green bands commonly ascribed to biacetyl. Evidence for this is uncertain, but the separation in wave numbers between the various maxima indicate that this conclusion has some merit. If the fluorescence due to the biacetyl occurs mainly from low vibration levels in an upper electronic state,[28] the transition corresponding to the maximum around 4650 Å. would have to be either to a lower vibration level in the ground state or from a higher vibration level of the upper state than the transitions ascribed to the other bands.

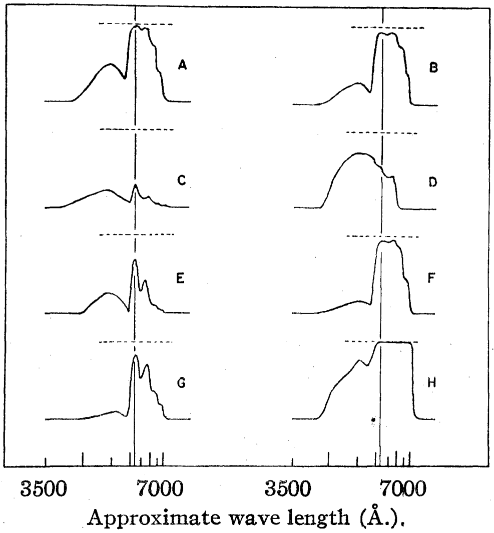


Fig. 4.—Representative microdensitometer tracings showing spectral distribution of acetone fluorescence under various conditions of excitation and exposure. Eastman I-F plates were used sensitized to 7000 Å. except for curve D for an I-G plate with the limit of 5800 Å. was used. A small glass spectrograph with 0.9 mm. slit was used. Acetone at a pressure of 170 mm. was irradiated by monochromatic 3130 Å. ultraviolet light except for curve H (see below). Exposure times with ten minutes except C and D. A New acetone 25°, irradiated 21 minutes, integrated intensity 90 Arbitrary Units. B. Same as A except time of irradiation 128 minutes, integrated intensity 550 Arbitrary Units. C. Old acetone irradiated at 120° with an integrated intensity of 820 Arbitrary Units plus irradiation at 25° for 1600 Arbitrary Units (30 min. exposure.) D. Solid acetone at −196°. Identical curve obtained after two hours of irradiation (5 min. exposure). E. Old acetone previously irradiated for 1200 Arbitrary Units at 25°, 0.01 to 0.04 mm. oxygen initially present. F. Old acetone previously irradiated for 2300 Arbitrary Units at 2500–3600 Å. at 25°, after which products non-condensable with liquid nitrogen were removed. Identical curve after 74 minutes additional irradiation. G. Old acetone exposed over a period of several minutes at 25°, slit width 0.5 mm. H. Old acetone irradiated at 2500–3600 Å. with two day intermediate dark period prior to photographing fluorescence. Exposure taken during irradiation with 2500–3600 Å.

The effect of temperature on the green and blue fluorescences is indicated in Fig. 5. It is to be noted that the intensity of the green fluorescence decreases markedly with increase in temperature whereas the blue shows only a very gradual change and its value at 200° is still 20% of its value at 25°. The fact that the curve obtained with decreasing temperature lies lower than the curve obtained as the temperature increases may indicate a small decomposition of biacetyl at high temperature. This must be due to a photochemical reaction (perhaps with a high quantum yield) rather than a pure thermal reaction. On the other hand, even when biacetyl is known to be present the green is absent at temperatures of about 125° and above. Thus the increase in temperature has two effects: (1) it prevents formation of biacetyl, probably due to the instability of the acetyl radical and (2) it inhibits in some way the mechanism for exciting the green fluorescence.

Figures 6 and 7 show the effect of absorbed intensity on the fluorescence. In Fig. 6 the total fluorescence, blue plus green, is shown as a function of intensity, the intensity being varied by a

---

(27) Padmanabhan, *Proc. Ind. Acad. Sci.*, **5A**, 594 (1937).

(28) W. A. Noyes, Jr., and F. C. Henriques, Jr., *J. Chem. Phys.*, **7**, 767 (1939).

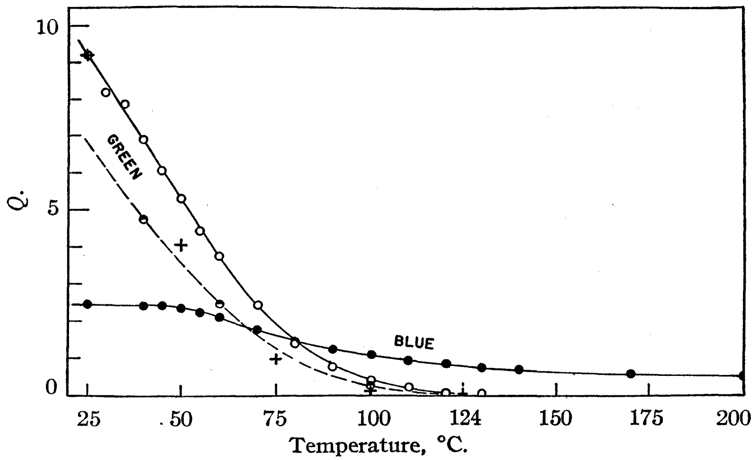


Fig. 5.—Fluorescent efficiency ($I_f/I_a = Q$) as a function of temperature for blue and green acetone fluorescence: pressure 165 mm.; wave length 3130 Å.: ●, blue, obtained spectrographically 25–140°, photometrically 140–200° (not corrected for varying spectral sensitivity of photocell)*; temperature increasing between points. ○, green, obtained photometrically, correcting total deflections for presence of blue; increasing temperatures. ◓, green, same; decreasing temperatures. +, green, obtained spectrographically; increasing temperatures.

factor of about 50. This particular sample had previously been exposed for some minutes at room temperature, part of the time with oxygen present. The variation with intensity is so slight as to be well within experimental error. In Fig. 7 the curve labeled "green" is obtained at room temperature and is really total fluorescence, mainly "green." Again there is no variation in intensity greater than experimental error. The measurements of the blue in Fig. 7 were made at 145° where the green is absent, and show at most an extremely small variation with intensity, certainly not much larger than experimental error.

In Figs. 8 and 9, $1/Q$ is shown as a function of pressure. In this instance the data are not so reliable as might be desired due to the difficulties of measuring percentage absorption at low pressures. It is believed that the values for the blue fluorescence in Fig. 8 for which the absorbed intensity is calculated from Beer's law at low pressures are most reliable.

$1/Q$ for the green, in contrast to the blue, shows some tendency to increase at low pressures. The curve in Fig. 9 is for total fluorescence; correction for the presence of the blue would cause a somewhat greater rise for the green alone at low pressures.

The detailed mechanisms for the blue and the green fluorescences can be discussed only in general terms. The interpretations given by Almy and his co-workers[15] are supported in broad outline, although some differences seem to be necessary.

A Stern–Volmer mechanism is not obeyed for either the blue or the green, although $1/Q$ *vs.* pressure at high pressures is a straight line in agreement with earlier data.[12] The relative insensitivity of $1/Q$ to large changes in pressure when the pressure is above about 50 mm. may indicate one of two things: (1) the molecule or radical responsible for the fluorescence has such an extremely short life in the activated state that it does not have time to be deactivated; or (2) the molecule or radical is extremely insensitive to collisions with acetone molecules. With the former assumption lifetimes perhaps as short as 10^{-8} second would be required, whereas Almy has shown that the lifetime of the active molecule responsible for the green is about 10^{-3} second.

A better estimate of the probable lifetime of the species responsible for blue emission can be obtained from the effect of oxygen which, as already stated, decreases the intensity of the blue when it is present at a pressure of 0.1 mm. Using the assumption that collisions of excited molecules with acetone have no effect and that collisions with oxygen are 100% efficient, one calculates a mean life for the excited species of about 10^{-5} second. This may be considered to be a lower limit. If the mechanism proposed by Almy and co-workers[15] whereby the biacetyl molecules are excited by collision of the second kind with excited ace-

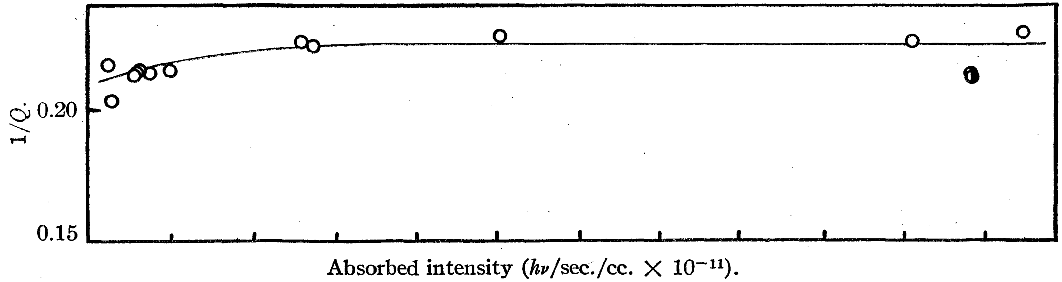


Fig. 6.—Quenching of total acetone fluorescence as a function of (low) absorbed intensity at constant pressure and temperature; sample pre-exposed 30Σ (8Σ with O_2); uviarc, λ3130 Å. 29°; pressure, 208 mm.: ○, at decreasing intensity (adding resistance in circuit to cool arc); ◑, following day with hot arc.

---

* Corrected quantum efficiencies of blue are about half that shown on graph.

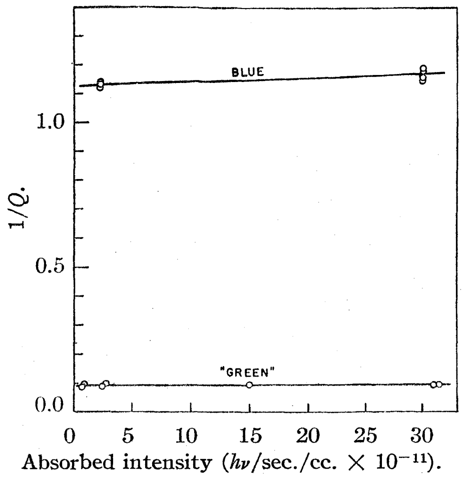


Fig. 7.—Quenching of blue and "green" acetone fluorescence as a function of absorbed intensity at constant pressure and temperature, high intensity: blue measured at 145° and 209 mm. pressure (not corrected for variable spectral sensitivity of photocell); "green" is total fluorescence at 25° and 164 mm., as measured; *ca.* 25% of observed deflection is due to blue.

tone molecules is accepted, the lifetime might be even longer.

The most significant aspect of the data concerning the green fluorescence is its decrease in intensity with increase in temperature even when biacetyl is known to be present. The decrease in intensity parallels semi-quantitatively the decrease in stability of the acetyl radical. This might indicate that the mechanism of excitation involves, in some way, the acetyl radical. The further fact that in starting with carefully purified acetone the blue decreases only 50% while the green increases from practically zero to a large value during continued exposure, indicates that the mechanism for the blue and the mechanism for the green are not identical and may possibly not be related.

The variation of $1/Q$ with pressure for the blue at 140° necessitates a marked sensitivity to collision at low pressures and the attainment of a statistical distribution among various energy levels, largely independent of pressure once the pressure reaches about 50 mm.

The principal data concerning the blue fluorescence may be described adequately by a series of simple steps resembling those used previously to describe other fluorescences[29,28] in which molecules are transferred from one state to another by collisions. This mechanism may be written

$$\mathrm{A} + h\nu = \mathrm{A}'; \; k_1'I_a \qquad (1)$$

$$\mathrm{A}' = \mathrm{CH_3COCH_3} + h\nu; \; k_2(\mathrm{A}') = I_b' \qquad (2)$$

$$\mathrm{A}' + \mathrm{A} = 2\mathrm{A}(\text{or } \mathrm{A} + \text{dissociation products}); \; k_3(\mathrm{A}')(\mathrm{A}) \qquad (3)$$

$$\mathrm{A}' + \mathrm{A} = \mathrm{A}'' + \mathrm{A}; \; k_4(\mathrm{A}')(\mathrm{A}) \qquad (4)$$

$$\mathrm{A}'' = \mathrm{CH_3COCH_3} + h\nu; \; k_5(\mathrm{A}'') = I_b'' \qquad (5)$$

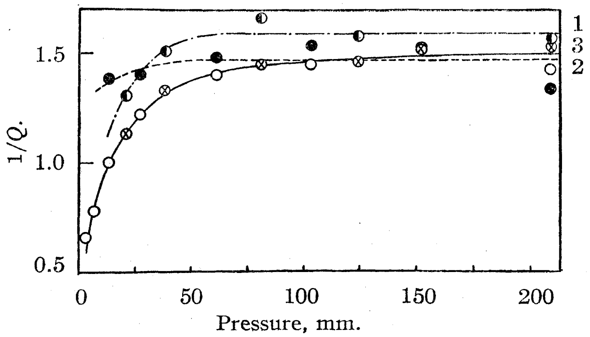


Fig. 8.—Quenching of blue fluorescence as a function of acetone pressure at 140°, wave length 3130 Å.: ◐, constant absorbed intensity (I_a = 2.5 ± 0.5 × 10^{11} hν/sec./cc.), values of I_a measured experimentally; ⊗, constant absorbed intensity; I_a calculated, assuming Beer's law; ●, constant incident intensity (I_0 = 4.9 × 10^{13} hν/sec./sq. cm.); I_a measured experimentally; ○, constant incident intensity; I_a calculated. Curve 3 (solid) is drawn through both sets of points for which calculated values of I_a were used. The broken curves are for points using I_a measured experimentally, at constant I_a (curve 1) and constant I_0 (curve 2).

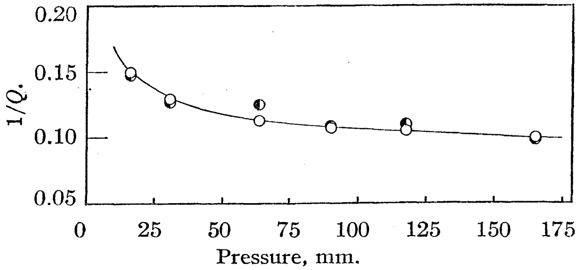


Fig. 9.—Quenching of total fluorescence (predominantly green) as a function of acetone pressure at 25° and constant absorbed intensity; I_a = 4 ± 1 hν/sec./cc.; wave length 3130 Å.

The constant k_1' indicates that only part of the molecules which undergo the act of absorption form excited molecules, or at least form excited molecules capable of the following reactions. From considerations of the photochemistry of acetone the vast majority must undergo a dissociation into CH_3CO and CH_3. From this series of equations one obtains the relationships

$$\frac{I_b' + I_b''}{I_a} = Q_b = \frac{k_1(k_2 + k_4(\mathrm{A}))}{k_2 + k_3(\mathrm{A})} = \frac{k_1(1 + k_4(\mathrm{A})/k_2))}{1 + k_3(\mathrm{A})/k_2 + k_4(\mathrm{A})/k_2} \qquad (6)$$

where $I_b' + I_b''$ = total quanta of blue radiation emitted per cubic centimeter per second and I_a is the number of quanta of incident radiation absorbed per cubic centimeter per second. If more states are used, equation (6) takes the form of a ratio of polynomials. When the pressure is very high, Q_b should be independent of pressure thus agreeing with the data in Fig. 8. If the pressure is extremely low Q_b should again be independent of pressure, but this levelling off will be important

---

(29) J. P. Howe and W. A. Noyes, Jr., THIS JOURNAL, **57**, 1262 (1935).

only below 0.1 mm., a pressure lower than could be studied. With $k_3/k_2 = 0.24$, $k_4/k_2 = 0.088$, $k_4/k_3 = 0.37$, and $k_1 = 2.36$ (pressures in millimeters are used), equation (6) reproduces the experimental data well within experimental error. Since k_1 includes several factors it has no simple theoretical meaning, but the ratio of k_4 to k_3 means that the initially formed state is converted into the metastable state at about one third the rate it is deactivated. The metastable state must be very insensitive to collisions to explain the flat portion of the curve at high pressures, and hence no deactivation step is included for A″.

The absolute values of these constants cannot be calculated without making some assumptions. If every collision is assumed to cause the initially formed state to undergo either (3) or (4) and if the collision diameter is assumed to be 4×10^{-8} cm., $(k_3 + k_4)$ has the value 8×10^6 if the pressure in millimeters is used. Thus k_2 would be about 3×10^7 sec.$^{-1}$ and the mean life of the initially formed state would be about 3×10^{-8} sec. There is no way of estimating the mean life of the metastable state A″ due to the very small deactivating effect of collisions at high pressures.

The data on the quenching of the blue fluorescence by oxygen are not very extensive and, for various reasons, could not be made very precise. However, when the acetone pressure was 200 mm., 0.4 mm. of oxygen reduced the intensity by a factor of approximately 10. The following equations may now be added

$$A'' + O_2 = A + O_2;\ k_6(A'')(O_2) \qquad (7)$$

$$A' + O_2 = A + O_2;\ k_7(A')(O_2) \qquad (8)$$

and equation (6) becomes

$$Q_b = \left[\frac{k_1}{1 + (k_3/k_2 + k_4/k_2)(A) + k_7(O_2)/k_2}\right] \left[1 + \frac{k_4(A)/k_2}{1 + k_6(O_2)/k_5}\right] \qquad (9)$$

The term in k_7 should be negligible at the low pressure of oxygen used and hence from the data one can estimate k_6/k_5 to be 49 if the concentration of oxygen is replaced by millimeters pressure. If a collision diameter of 3×10^{-8} cm. is taken for collisions between metastable acetone molecules and oxygen, one can estimate k_6 and hence k_5. The latter is 10^5 sec.$^{-1}$ giving a mean life of the metastable acetone molecules of 10^{-5} second. This may be taken as a lower limit, and the actual value may be much larger if this state shows a low efficiency for quenching by oxygen molecules.

These lives of 10^{-8} and 10^{-5} second for the active and for the metastable molecules, respectively, are only orders of magnitude, but they do indicate that the picture of the blue fluorescence embodied in equations (1) to (5) is adequate to explain all of the known facts at constant temperature. The value of $1/Q$ is independent of intensity and independent of pressure at high pressures.

The mechanism embodied in equations (1) through (8) indicates that the ratio $(A'')/A$ is given by $k_4(A)/k_5 = 22\ P_{\text{mm.}}$ (in the absence of O_2). k_4 is probably more temperature dependent than k_5, and hence the fraction of A″ would increase with temperature. Since A″ is not appreciably deactivated by collisions, this would cause an increase in blue with temperature. This is contrary to the facts and hence the temperature effect must be explained in some other way. Equation (3) is the most logical step to use, particularly in view of the increase in quantum yields of decomposition with temperature. An activation energy of 2500 to 3000 cal. for reaction (3) would be adequate to explain the decrease in blue fluorescence with increase in temperature.

Finally it is necessary to include some deactivation of A″ by biacetyl since the blue does decrease slightly as the green increases in intensity. Due to its short life A′ would not be deactivated at low biacetyl pressures. If A″ is the only form deactivated in this way, the decrease in the blue is semiquantitatively explained.

Later work has shown structure to exist in the blue fluoresence. Thus dissociation accompanying the fluorescent act need not be postulated.

These general conclusions are the only ones warranted concerning the character of the blue fluorescence. Two types of information would still be desirable: (1) a study of the quenching down to very low pressures, *i. e.*, below 0.1 mm.; (2) a spectrographic study of the fluorescence at all pressures with high dispersion and high resolution. Both types of data would be exceedingly difficult to obtain due to the weakness of the blue fluorescence.

The interpretation of the green fluorescence must also be given in general terms. Two facts seem to be of paramount importance in this connection: (1) the intensity of the green is not dependent to any marked extent on the quantity of biacetyl once the latter has reached a value in the neighborhood of 0.1 mm.; (2) the intensity of the green decreases with increase in temperature even when biacetyl is known to be present and parallels at least qualitatively the decrease in stability of the acetyl radical.

Two general methods of exciting biacetyl to fluorescence when acetone is the absorbing molecule may be imagined; (1) inelastic collision of the second kind; (2) a recombination of two free radicals using biacetyl as the third body.

The very gradual decrease in intensity of the blue and the rapid decrease in the green with rise in temperature indicate that the two processes are not completely dependent on each other. The effect of pressure on $1/Q$ (Fig. 9) is also not at all similar to the effect on the blue fluorescence and indicates that collisions tend to enhance the fluorescence. This resembles the behavior of the fluorescence of pure biacetyl when excited by radiation of wave length 3660 Å.[15,19] and is best explained by assuming that the level initially formed is capable of predissociation and that fluorescence only occurs after loss of some energy through collisions.

If the absence of green fluorescence at 140° is due directly or indirectly to the instability of the acetyl radical, the three body process

$$CH_3 + CH_3CO + B = B' + CH_3COCH_3; \quad k_8(CH_3)(CH_3CO)(B) \qquad (10)$$

must be responsible, where B is a molecule of biacetyl. The effect of oxygen in quenching the green would be due, in that event, to reaction with free radicals.

A complete set of equations satisfying the photochemical as well as the fluorescence data can be written down using equation (10) as the means of producing excited biacetyl. The resulting equation for $1/Q$ is, however, very complex and while it has the correct form there is no means of showing that it is a unique solution to the problem. Since $1/Q$ decreases slightly with increase in pressure, it is necessary to postulate that the active molecule B′ can dissociate unless it is stabilized by collisions. At higher pressures $1/Q$ is practically independent of pressure so that an additional state B″ (or perhaps several additional states) must be postulated. Some of these would be metastable and incapable of fluorescence. The fluorescing states would be converted into the other and vice versa by collisions. These suggestions agree with those made by Almy and coworkers.[15]

If a mechanism for exciting biacetyl based on collisions of the second kind is used, the decrease in green intensity with increase in temperature would be ascribed to two effects: (1) a decrease in the concentration of activated and metastable acetone molecules (A′ and A″, respectively); (2) an increased tendency for the activated or metastable biacetyl molecules to decompose. The first of these effects is insufficient in itself to provide an adequate explanation since the decrease in intensity of the blue fluorescence is explained by some inhibiting step with an activation energy of 2500–3000 cal., while the green demands a step with an activation energy of 4500–5000 cal.

Since it has been shown that biacetyl fluorescence is normally quenched when excited by 4060 and 4370 Å. radiation,[15] whereas collisions enhance the fluorescence when it is excited by 3660 Å. radiation,[15,19] one can estimate a maximum activation energy required to raise the fluorescing molecules to such a state that they can predissociate. Taking the difference in calories per gram molecule corresponding to 4060 and 3660 Å. quanta, respectively, one finds 7600 calories. The correct figure may be less. Another guess can be made from the absorption spectrum of biacetyl described by Henri[30] who gives the longest wave absorption band as 4670 Å. and the onset of predissociation as 4400 Å. The difference corresponds to 3900 cal. per molecule, and this, if the spectrum has been correctly interpreted, should correspond to the minimum activation energy required to bring an excited non-vibrating molecule to the predissociating state. These figures, while probably inaccurate, lend some small support to the interpretation of the temperature effect on the fluorescence.

Several authors have studied the photochemistry of biacetyl.[31,32,33] A detailed interpretation of the data is not possible because many processes must be involved. The low yield at room temperature may be due to a recombination reaction and part of the increase with temperature due to the instability of the acetyl radical. However, at long wave lengths (>3660 Å.) where fluorescence occurs, the effect of temperature on activated molecules must be considered.

The effect of oxygen on green fluorescence is to be ascribed to two effects: (1) inhibition of biacetyl synthesis through reaction with acetyl radicals; (2) inhibition of the fluorescence even when biacetyl is present. The latter effect, in turn, must be due to two causes: (1) decrease in the number of excited or metastable acetone molecules if the energy transfer is by collisions of the second kind or reaction with radicals if excitation is by some process, such as equation (10); (2) quenching of excited or metastable biacetyl molecules. There is ample evidence for both of these steps in the effect of oxygen on the blue and on the fluorescence of pure biacetyl.[15] Undoubtedly both effects are important.

It should be emphasized finally that while these fluorescence studies throw much light on the photochemistry of acetone, particularly with long exposures, they do not affect in any essential way the mechanism previously presented for the photochemistry of acetone.[9] No precise estimate of absolute fluorescence efficiency can be given, but that of the blue does not exceed one or two per cent. and may be much less.

Summary

1. The quenching of the "blue" and "green" fluorescences of acetone has been studied as a function of intensity, pressure, added oxygen, and temperature.

2. Since screens were used to vary intensity, the variation with intensity is valid only if the excited molecules or radicals involved have long lives. This is probably true for the "green" but may not be true for the "blue." No variations of quenching with intensity were observed.

3. The fluorescent efficiency of the "blue" decreases as the pressure increases and approaches a constant value. That of the green increases as the pressure increases and also approaches a constant value.

4. The efficiency of the "blue" decreases gradually with increase in temperature and is still

---

[30] V. Henri, "La Structure des Molecules," Gauthier-Villars et Cie., Paris, 1925.

[31] J. G. Roof and F. E. Blacet, THIS JOURNAL, **63**, 1126 (1941).

[32] R. G. W. Norrish and F. W. Kirkbride, *Trans. Faraday Soc.*, **27**, 404 (1931).

[33] H. W. Anderson and G. K. Rollefson, THIS JOURNAL, **63**, 816 (1941).

20% of its room temperature value at 200°. The green decreases much more rapidly and is practically absent at 135°.

5. Alternative explanations of the various phenomena are discussed, and several suggestions concerning mechanism are made. There must be two states of acetone, one with a much shorter life than the other. The biacetyl may be excited by either of two processes: (a) collision of the second kind; (b) radical recombination using biacetyl as the third body. In either case the "active" biacetyl molecules must have a greater probability of decomposition at high temperatures than at low.

ROCHESTER, NEW YORK RECEIVED JUNE 23, 1947

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, COLLEGE OF AGRICULUTRE, UNIVERSITY OF CALIFORNIA]

Interaction of Ions and Dipolar Ions. IV. The Solubility of Cupric Iodate in Glycine and in Alanine Solutions

BY R. M. KEEFER

In previous communications[1,2] it was shown that the solubility of certain 1–1 and 2–1 type salts in dipolar ion solutions could be expressed by equations of the type

$$\frac{1}{Z_1Z_2}\log\frac{S}{S_\infty} = 0.506\left(\frac{78.54}{D_s}\right)^{3/2}\frac{\sqrt{\mu}}{1 + A\left(\frac{78.54}{D_s}\right)^{1/2}\sqrt{\mu}} + 0.0625\,\frac{R^2}{a_{id}}[\mathrm{HR}^{\pm}] \quad (1)$$

where Z_1 and Z_2 are the valences of the ions; S_∞ is the theoretical solubility at $\mu = 0$ and $[\mathrm{HR}^{\pm}] = 0$; D_s is the dielectric constant of the solution; A is $0.3288a_i$ where a_i is the distance of closest approach of the ions; R is the dipole distance in the dipolar ion; a_{id} is the distance of closest approach of an ion to a dipolar ion; and $[\mathrm{HR}^{\pm}]$ is the concentration of the dipolar ion. The solubility of silver iodate and lead iodate in glycine and alanine solutions[3] is much higher than would be predicted by eq. (1). The increased solubility was accounted for by assuming complex ions consisting of one negative ion of the amino acid to one silver or lead ion. This investigation was undertaken to obtain information on the stability of a complex between one negative ion of the amino acid[4] and cupric ion.

Experimental

Cupric Iodate.—Equal volumes of 0.2 *M* potassium iodate and 0.1 *M* cupric nitrate were added dropwise with constant stirring to 3 liters of water at 60°. After six hours the precipitate was filtered off and allowed to equilibrate with water overnight. The precipitate was sedimented several times and the smaller particles were discarded. The preparation was air dried before using. After drying for two hours at 250–270° the dried cupric iodate when analyzed iodometrically was 100.1% cupric iodate.

The solubility determinations and general technique have been described in a previous communication.[1] The iodometric determinations were modified for the presence of cupric ion using the method of Foote and Vance.[5] Duplicate solubility determinations agreed to 2 parts in 1000.

The *p*H of the solutions was determined using a Model G Beckman *p*H meter and is accurate to ±0.01 *p*H unit. The definition of *p*H used in this work is the negative logarithm of the hydrogen ion activity.

Results

The solubility (moles/1000 g. H_2O) of cupric iodate in potassium chloride solutions at 25.00° is given in Table I. The solubility of cupric iodate in water is much lower than the value (3.693×10^{-3} *M*) reported by Peterson and Meyers.[6] Column 3 of Table I gives the solubility of cupric iodate calculated by means of equation (2).

$$\log[\mathrm{Cu}^{++}][\mathrm{IO}_3^-]^2 = -7.1353 + \frac{3.036\sqrt{\mu}}{1 + 1.08\sqrt{\mu}} \quad (2)$$

The distance of closest approach of the ions is then 1.08/0.3288 or 3.28 Å.

TABLE I

SOLUBILITY OF CUPRIC IODATE IN POTASSIUM CHLORIDE SOLUTIONS AT 25°

(*M* is Moles/1000 g. H_2O and *S* is *M* of Cupric Iodate)

KCl, *M*	$Cu(IO_3)_2$, $M \times 10^3$	Calcd. $Cu(IO_3)_2$, $M \times 10^3$
0	3.245	3.243
0.00501	3.398	3.396
.01002	3.517	3.521
.02005	3.730	3.730
.03511	3.975	3.969
.05017	4.166	4.166
.07529	4.453	4.454
.1005	4.694	4.697

Table II gives the solubility of cupric iodate in glycine and in alanine solutions together with the *p*H of the resulting solution. Since the *p*H values are all less than the isoelectric point of the amino acids (6.1), it is evident that reactions are taking place which produce hydrogen ion. Assuming

---

(1) Keefer, Reiber and Bisson, THIS JOURNAL, **62**, 2951 (1940).

(2) Keefer and Reiber, *ibid.*, **63**, 3504 (1941).

(3) Keefer and Reiber, *ibid.*, **63**, 689 (1941).

(4) Gould and Vosburgh, *ibid.*, **64**, 1630 (1942).

(5) Foote and Vance, *Ind. Eng. Chem.*, *Anal. Ed.*, **8**, 119 (1936).

(6) Peterson and Meyers, *ibid.*, **52**, 4853 (1930).

complex ion formation similar to the case of silver iodate and lead iodate,[3] then

$$\mathrm{Cu^{++} + HR^{\pm} \rightleftarrows CuR^{+} + H^{+}} \quad K_1 = \frac{\mathrm{(CuR^{+})(H^{+})}}{\mathrm{(Cu^{++})(HR^{\pm})}} \qquad (3)$$

$$\mathrm{HR^{\pm} + H^{+} \rightleftarrows H_2R^{+}} \qquad (4)$$

In Fig. 1 the concentration of combined copper (eq. 7) is plotted against the amount of hydrogen ion produced including the hydrogen ion used up in eq. 4. Below 5×10^{-3} M combined cupric ion there is more combined cupric ion than there is hydrogen ion produced. This indicates the formation of a complex not liberating hydrogen ion as indicated in the equation.

$$\mathrm{Cu^{++} + HR^{\pm} \rightleftarrows CuHR^{++}} \qquad K_\alpha = \frac{\mathrm{[CuHR^{++}]}}{\mathrm{[Cu^{++}][HR^{\pm}]}} \qquad (5)$$

Pedersen[7] has shown that cupric ion tends to form complexes with acetate ion. The replacement of a hydrogen by the positively charged NH_3^+ group would tend to decrease the possibility of formation of such a complex.

TABLE II

SOLUBILITY OF CUPRIC IODATE IN GLYCINE AND ALANINE SOLUTIONS AT 25°

(Moles/1000 g. H_2O).

Glycine, M	$Cu(IO_3)_2$, $M \times 10^3$	pH	Cor. pH
0.01253	4.096	3.32	
.02509	4.805	3.31	
.05023	6.17	3.32	3.35
.07542	7.46	3.37	
.1008	8.72	3.38	
.1515	11.16	3.39	
.2025	13.52	3.41	
Alanine			
0.01252	3.98	3.40	
.02508	4.60	3.37	
.05019	5.84	3.40	3.405
.07541	6.98	3.42	3.43
.1008	8.06	3.44	
.1516	10.22	3.48	3.47
.2027	12.30	3.49	

Above 5×10^{-3} M combined cupric ion there is more hydrogen ion produced than cupric ion combined, indicating the probable reaction

$$\mathrm{Cu^{++} + 2HR^{\pm} \rightleftarrows CuR_2 + 2H^{+}}$$

$$K_2 = \frac{\mathrm{(CuR_2)(H^{+})^2}}{\mathrm{(Cu^{++})(HR^{\pm})^2}} \qquad (6)$$

Attempts to explain the results assuming CuR_2 and $CuHR^{++}$ or CuR_2 and CuR^+ to be the only complex ions failed to give constant equilibrium constants. The following method was used to evaluate the three equilibrium constants.

The amount of combined cupric ion is given by

$$S - \mathrm{[Cu^{++}]} = \mathrm{[CuR_2] + [CuR^{+}] + [CuHR^{++}]} \qquad (7)$$

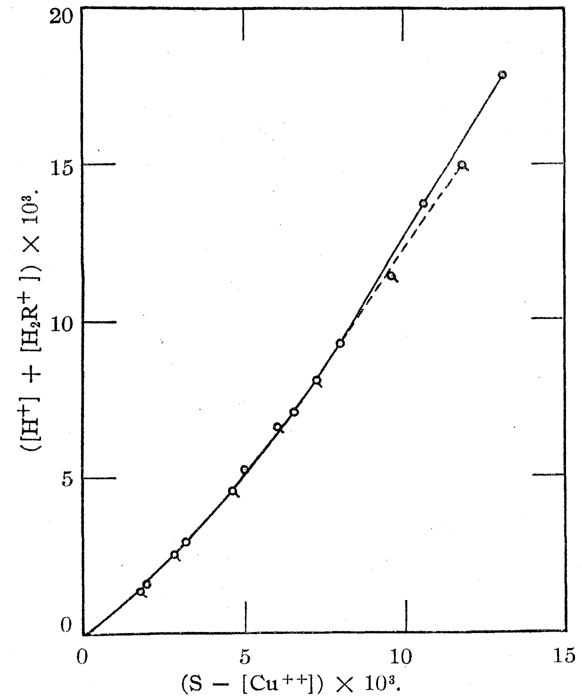


Fig. 1.—Hydrogen ion produced *versus* cupric ion complex formed in glycine and alanine solutions saturated with cupric iodate: ○, glycine solutions; ♂, alanine solutions.

The concentration of hydrogen ion produced will be equal to

$$\mathrm{[H^{+}] + [H_2R^{+}] = 2[CuR_2] + [CuR^{+}]} \qquad (8)$$

$$\mathrm{[HR^{\pm}]_i = [HR^{\pm}] + [H_2R^{+}] + 2[CuR_2] + [CuR^{+}] + [CuHR^{++}]} \qquad (9)$$

where $\mathrm{[HR^{\pm}]_i}$ is the total concentration of dipolar ion used. The ionic strength of the solution is given by

$$\mu = 2(\mathrm{[Cu^{++}] + [CuHR^{++}]}) + {}^1/_2(\mathrm{[CuR^{+}] + [H^{+}] + [H_2R^{+}] + [IO_3^{-}]}) \qquad (10)$$

or by substituting (7) and (8) in (10)

$$\mu = 2S - \mathrm{[CuR^{+}] - [CuR_2]} \qquad (11)$$

In the amino acid solutions saturated with cupric iodate there are eight unknowns (exclusive of activity coefficients) as follows: $\mathrm{[Cu^{++}]}$, $\mathrm{[CuR^{+}]}$, $\mathrm{[CuHR^{++}]}$, $\mathrm{[CuR_2]}$, $\mathrm{[H_2R^{+}]}$, $\mathrm{[HR^{\pm}]}$, $\mathrm{[H^{+}]}$ and μ. Although individual ion activity coefficients may not be determined, the general calculations are somewhat simplified if they are assumed to be given by equation 1 after substitution of $-1/Z_i^2 \log \gamma_i$ for $1/Z_1Z_2 \log S/S_\infty$. R was assumed to be 3.89 Å. for glycine[2] and 3.60 for alanine[2]. For cupric ion a_i was assumed to be the same in solutions containing glycine as in potassium chloride solutions. For CuR^+ and H_2R^+ a_i was assumed to be the radius of the dipolar ion plus one-half the distance of closest approach of cupric ion and iodate ion. At the ionic strengths involved an error of 0.1 Å. in a_i introduces a 1% error in the activity coefficient. The activity coefficients of CuR_2 and

---

[7] Pedersen, *Det. Kgl. Danske Videnskab Selskab, Math.-fys. Medd.*, **22**, 1 (1945).

TABLE III

CALCULATED COMPOSITION OF GLYCINE AND ALANINE SOLUTIONS SATURATED WITH CUPRIC IODATE AND THE EQUILIBRIUM CONSTANTS INVOLVED

$K_1 = 0.032$

$[Cu^{++}]$ $M \times 10^3$	γCu^{++}	$[HG^{\pm}]$	$[CuG^+]$ $M \times 10^3$	γCuG^+	$[CuG_2]$ $M \times 10^3$	$[CuHG^{++}]$ $M \times 10^3$	$K_2 \times 10^4$	$K\alpha$
2.160	0.634	0.00919	0.940	0.896	0.38	0.87[a]		44
1.670	.608	.01896	1.420	.889	0.72	1.31[a]		41
1.137	.564	.03929	2.06	.874	1.47	1.66[a]	2.97	37
0.867	.524	.05999	2.38	.861	2.34	1.87	2.62	36
.701	.490	.08017	2.50	.849	3.36	2.15	2.66	38
.518	.431	.1222	2.60	.827	5.56	2.46	2.76	39
.423	.383	.1645	2.72	.807	7.58	2.80	2.63	40

$K_1 = 0.034$

Alanine		$[HA^{\pm}]$	$[CuA^+]$	γCuA^+	$[CuA_2]$	$[CuHA^{++}]$		
2.265	0.639	0.00967	1.15	0.904	0.18	0.38	..	..
1.800	.614	.01989	1.96	.902	.28	0.56	..	..
1.231	.575	.04065	2.83	.879	.85	1.58	1.12	31
0.945	.541	.06178	3.32	.868	1.51	1.61	1.07	28
.771	.512	.0835	3.64	.858	2.22	1.69	1.04	26
.568	.458	.1272	3.96	.840	3.87	1.93	1.06	27
.455	.414	.1707	4.09	.823	5.46	2.41	1.05	31

[a] Calculated using CuG_2 calculated by assuming $K_2 = 2.65 \times 10^{-4}$.

HR^+ were assumed to be unity. To solve for the above 8 unknowns there are seven equations (1, 4, 7, 8, 9, 11) including the definition of pH. To obtain the eighth equation a value of K_1 was assumed and the equations solved. Then K_2 was calculated. By successive trials a value of K_1 was chosen so that K_2 would be constant for the series of runs. First a value of μ was selected using eq. 11 and then the concentration of cupric ion was calculated using eq. 1. $[H^+]$ and $[H_2R^+]$ were calculated using activity coefficients from eq. 1 and the pK_A of the amino acid (glycine[8] 2.350, alanine[9] 2.348). A value of K_1 was chosen and $[CuR^+]$ calculated. Using eq. 8 $[CuR_2]$ was evaluated. In the final calculations errors in pH measurement were smoothed out by using values from Fig. 1 for the total amount of hydrogen ion produced. The corrections involved are given in column 4 of Table II. With $[CuR_2]$ known, values of K_2 were calculated. The series of calculations was repeated until constant values of K_2 were obtained. Table III gives the concentrations of the ions and the equilibrium constants. Column 7 gives the concentration of $[CuHG^{++}]$ determined from eq. 7 after K_1 and K_2 were evaluated. The concentration equilibrium constant, K_α, for eq. 5 was calculated and appears in column 9 of Table III. $K\alpha$ should show little variation with ionic strength since the effect on Cu^{++} should be practically the same as the effect on $CuHR^{++}$. Equilibrium constants are not included for any case in which the concentration of complex ion falls much below $1 \times 10^{-3}M$.

Pedersen[6] has studied the equilibrium

$$Cu^{++} + Ac^- \rightleftarrows CuAc^+ \quad K_\beta = 146 \qquad (12)$$

The strength of monocarboxylic acids[10] may be calculated from the known constant of acetic acid by introducing corrections for each group replacing a hydrogen as in the equation

$$\log K = \log K_{HAc} + \frac{A_\alpha \Sigma I \alpha^{i_\alpha}}{1 + B|\Sigma I \alpha^{i_\alpha}|} \qquad (13)$$

K is the dissociation constant of the substituted acid. A_α is a constant equal to 0.3. I is the inductive effect for each group replacing a hydrogen. α is the fractional decrease in the inductive effect for each transmission across an atom and is equal to 1/2.8. The number of atoms between the group added and the α carbon atom of the carboxylic acid is i_α. If the complex ion $CuHR^{++}$ involves a linkage between the carboxylate group and the cupric ion, K_α should be given by equation 13 by replacing K by $1/K_\alpha$, K_{HAc} by $1/K_\beta$, and including the inductive effect of the NH_3^+ group (12.3 for the + charge and 1.3 for the N atom). Solving the equation with the above substitutions gives $K_\alpha = 0.2$ which would indicate that the ion would be much less stable than the experimental value of 39 indicates. Thus the linkage is probably between cupric ion and the amine group rather than between cupric ion and the carboxylate group. Values of the concentration dissociation constant[11] for CuG_2 and CuA_2 have been reported. By using the second ionization constants of glycine[8] and alanine[9] (1.67×10^{-11} and 1.36×10^{-10}) and estimating the activity coefficients involved, values of K_2 (eq. 6) may be approximated. The values are 2.2×10^{-4} for glycine and 1.1×10^{-4} for alanine. The agreement is good considering the approximations

---

[8] Owen, THIS JOURNAL, **56**, 24 (1934).

[9] Smith, Taylor and Smith, *J. Biol. Chem.*, **122**, 109 (1937).

[10] Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall, New York, N. Y., 1941, p. 221.

[11] Keefer, THIS JOURNAL, **68**, 2329 (1946).

involved in estimating the activity coefficients.

Summary

The solubility of cupric iodate in glycine and in alanine solutions has been determined. The solubility results may be explained by assuming three complex ions, namely, $CuHR^{++}$, CuR^{+} and CuR_2. The equilibrium constants for the reaction of cupric ion and the amino acids to form the above complex ions have been evaluated.

DAVIS, CALIFORNIA RECEIVED JUNE 30, 1947

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF EMORY UNIVERSITY]

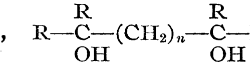
A Study of Organic Parachors. IX. The Additive Nature of Structural Units in the Parachors of Ditertiary Glycols and Chlorides[1,2]

BY THOMAS P. JOHNSTON[3] AND OSBORNE R. QUAYLE

Parachor, first considered primarily an additive property, has been shown to be highly susceptible to minor differences in structure, as, for example, those existing between two isomeric tertiary alcohols. This sensitivity would at first seem to decrease its usefulness as a method of correlating the physical properties of organic compounds with their structure. If such differences are capable of evaluation, however, the parachor immediately becomes a more delicate tool. Results have been obtained with series of tertiary alcohols[4,5] and chlorides[6,7] evaluating the inherent constitutive variations so that the parachor of any tertiary alcohol or chloride having normal alkyl groups may be predicted with reasonable accuracy. These results have been published in the form of tables[5,7] from which reliable theoretical values for such types may be conveniently calculated. It is to be emphasized that the actual value of CH_2 in all cases is considered essentially a constant, 40.0,[8,9] and that constitutive variations are attributed to the alteration of valence forces around the tertiary carbon atom and the attached chlorine or hydroxyl.

The neglect of minor structural effects in the calculation of parachor values is a common cause of considerable deviation between theoretical and calculated values. If structural groups exhibiting constitutive variations can be evaluated, they should in turn be primarily additive in more complex molecules. To test this assumption the parachors of a number of symmetrical ditertiary glycols and chlorides were measured and compared with calculated theoretical values. Parachors for the structural units of each molecule, divided as nearly as possible at the center of symmetry, were calculated and added to obtain the theoretical parachor for the whole molecule. The validity of treating structural units of a complex molecule in an additive manner once the constitutive divergence has been evaluated is upheld by the experimental data presented in this paper.

Ditertiary glycols (Table I) of the general formula,



$$\mathrm{R{-}\overset{R}{\underset{OH}{C}}{-}(CH_2)_{\mathit{n}}{-}\overset{R}{\underset{OH}{C}}{-}R}$$

in which R is methyl, ethyl and propyl and *n* is 2, 4, 7 and 8, were prepared by the standard method of adding the appropriate dibasic ester to the Grignard reagent.[10] The 2,10-, 3,11- and 4,13-diols have not been previously reported in the literature. The yield in the preparation of the 4,13-diol from dimethyl sebacate was least satisfactory; a yield of less than 5% of purified crystals was separated from the predominant viscous non-crystallizable oil. The Grignard addition complexes were hydrolyzed with either saturated aqueous ammonium chloride or cold dilute sulfuric acid, preferably the former. Toluene was the usual solvent for crystallization. These glycols are somewhat more stable than the simple tertiary alcohols in that they all withstand the temperature of boiling toluene and subjection to temperature up to 80° *in vacuo* and at least one, the 3,11-diol, may be distilled without decomposition at a relatively high temperature, about 140° at less than 1 mm. Parachors of only the lower melting glycols were measured, since solid compounds do not lend themselves to ready parachor measurement with the apparatus presently installed in this Laboratory.

The dichlorides (Table I) corresponding to the above ditertiary glycols were in general made by passing dry hydrogen chloride into an anhydrous ether solution of the glycol at a low temperature. A small amount of methanol was added to increase the solubility. After standing twenty-four hours the solvent was removed under reduced pressure

---

[1] Presented in part before the Division of Organic Chemistry of the American Chemical Society at the Atlantic City meeting, April 17, 1947.

[2] The authors wish to express their gratitude to Prof. E. Emmet Reid, research consultant to the department, for his continued interest in the problem and for his several suggestions.

[3] From material to be presented by Thomas P. Johnston to the graduate faculty of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[4] Owen, Quayle and Beavers, THIS JOURNAL, **61**, 900 (1939).

[5] Quayle and Smart, *ibid.*, **66**, 935 (1944).

[6] Quayle, Owen and Beavers, *ibid.*, **61**, 3107 (1939).

[7] Smart and Quayle, *ibid.*, **67**, 21 (1945).

[8] Mumford and Phillips, *J. Chem. Soc.*, 2112 (1929).

[9] Quayle, Day and Brown, THIS JOURNAL, **66**, 938 (1944).

[10] The glycol in which R is propyl and *n* is 7 was not isolated; the only attempt to prepare it from dimethyl azelate gave a non-crystallizable oil.

TABLE I

DITERTIARY GLYCOLS AND CHLORIDES

Glycol	M. p., °C. Found[a]	M. p., °C. Lit.	Empirical formula	Analyses, % Carbon Calcd.	Analyses, % Carbon Found	Analyses, % Hydrogen Calcd.	Analyses, % Hydrogen Found	Corresponding dichlorides M. p. of solids, °C.	Corresponding dichlorides Refractive index t°	Corresponding dichlorides Refractive index n^t_D	Corresponding dichlorides Analyses, % Cl[b] Calcd.	Corresponding dichlorides Analyses, % Cl[b] Found
2,5-Dimethyl-2,5-hexanediol[c]	88–89	*d, e, f, g*	$C_8H_{18}O_2$	65.71	65.47	12.41	12.58	64–65[h]				
3,6-Diethyl-3,6-octanediol	66.5–67	66–67.5[i]	$C_{12}H_{26}O_2$	71.23	71.08	12.95	12.88		20	1.4722	29.64	29.69
4,7-Dipropyl-4,7-decanediol	86.5–87	43[j]	$C_{16}H_{34}O_2$	74.36	74.07	13.26	13.35		20	1.4693	24.01	24.18
2,7-Dimethyl-2,7-octanediol[k]	90–90.5	*l, m, n*	$C_{10}H_{22}O_2$	68.91	69.02	12.73	12.71	50–50.5[o]			33.58	33.55
3,8-Diethyl-3,8-decanediol	71–72	72–73[m]	$C_{14}H_{30}O_2$	72.99	72.85	13.13	13.15		20	1.4720	26.53	26.34
4,9-Dipropyl-4,9-dodecanediol	86–86.5	93[m]	$C_{18}H_{38}O_2$	75.46	75.33	13.37	13.37	29.5–30	30	1.4676	21.93	21.93
2,10-Dimethyl-2,10-undecanediol	67–67.5		$C_{13}H_{28}O_2$	72.16	72.16	13.04	13.10		20	1.4580	28.00	28.06
3,11-Diethyl-3,11-tridecanediol[p]	59.5–60		$C_{17}H_{36}O_2$	74.93	74.91	13.32	13.20		20	1.4726	22.92	22.85
2,11-Dimethyl-2,11-dodecanediol[q]	60.5–61	*r, s*	$C_{14}H_{30}O_2$	72.99	72.80	13.13	13.20	28–29	30	1.4550	26.53	26.34
3,12-Diethyl-3,12-tetradecanediol	60–61	*t, u*	$C_{18}H_{38}O_2$	75.46	75.39	13.37	13.35		20	1.4722	21.93	21.97
4,13-Dipropyl-4,13-hexadecanediol[v]	47.5–48		$C_{22}H_{46}O_2$	77.12	76.83	13.54	13.60		20	1.4709	18.69	18.80

[a] All m. p.'s reported in this paper uncorrected. [b] Empirical formula same as that of glycol except replacement of 2 OH by 2 Cl. [c] Only appreciably water-soluble member of series. Anhydrous ethyl acetate was solvent for final crystallization. Corresponding di-chloride can be purified by sublimation by warming under reduced pressure and/or crystallization from methanol. Pleasant odor. [d] 92–93°, Zelinsky, *Ber.*, **35**, 2139 (1902), and Pace, *C. A.*, **22**, 3890 (1928). [e] 88.5–89°, Pogorzelski, *Chem. Zentr.*, **75**, I, 578 (1904). [f] 89°, Harries and Turk, *Ann.*, **343**, 364 (1905). [g] 92°, Bruylants, *Chem. Zentr.*, **80**, II, 797 (1909). [h] Pogorzelski, *Chem. Zentr.*, **70**, I, 773 (1899) reported m. p. 64°; Henry, *Compt. rend.*, **143**, 497 (1906), 66–67°. [i] Zal'kind and Buistryakov, *C. A.*, **9**, 2511 (1915). [j] Dupont, *Compt. rend.*, **156**, 1623 (1913). [k] Few drops of methanol added to toluene as solvent for crystallization to increase solubility. Corresponding dichloride was crystallized from methanol. Slight odor. [l] 88–89°, Michiels, *C. A.*, **7**, 3602 (1913), and Zal'kind and Aizikovich, *ibid.*, **31**, 4283 (1937). [m] 92°, Bouvet, *Bull. soc. chim.*, **17**, 202 (1915). [n] 94°, Zelinski, see *C. A.*, **9**, 2639 (1915). [o] Reference[m] reported m. p. 49°. [p] B. p. about 139–142° at < 1 mm. [q] Crystallized from toluene to which pyridine in ratio of 1 drop per 10 cc. was added. [r] 62°, Petrov and Sanin, *C. A.*, **34** 4054 (1940). [s] 57.5–58°, Kislovskaya, *ibid.*, **8**, 1422 (1914). [t] 72.5°, reference [r]. [u] 59°, Landa and Habada, *C. A.*, **31**, 1757 (1937). [v] Crystallized from pet. ether.

and the dichloride or its chloroform solution dried over sodium sulfate and sodium carbonate. Further purification can be effected by a modification of the method of Whitmore and Williams.[11] The following dichlorides were prepared: 2,5-dichloro-2,5-dimethylhexane, 3,6-dichloro-3,6-diethyloctane, 4,7-dichloro-4,7-dipropyldecane, 2,7-dichloro-2,7-dimethyloctane, 3,8-dichloro-3,8-diethyldecane, 4,9-dichloro-4,9-dipropyldodecane, 2,10-dichloro-2,10-dimethylundecane, 3,11-dichloro-3,11-diethyltridecane, 2,11-dichloro-2,11-dimethyldodecane, 3,12-dichloro-3,12-diethyltetradecane, 4,13-dichloro-4,13-dipropylhexadecane.

Average over-all yields were about 75%; the average yield exclusive of those purified by sulfuric acid was about 85%. Only the 2,5- and 2,7-dichlorides have been previously reported.[12] These dichlorides should be kept anhydrous and cold to prevent decomposition over an extended period of time.

The parachors of all the above dichlorides and five of the glycols have been measured (Table II). Surface tensions were determined by the maximum bubble pressure method, the apparatus used being a modification of that of Sugden.[5] The type of pycnometer employed in the determination of density was designed for volatile liquids[13] but has been found satisfactory for the rather viscous dichlorides and even for the melts of the low-melting solids. The experimental precision in the measurement of surface tension was estimated to be not less than one part in five hundred, the more precise values being attainable at the lower temperatures. The over-all precision in the determination of the parachor was approximately one part in two thousand. It is recognized that the lack of direct methods of purification, the measurement of surface tension and density at relatively high temperatures and the inherent instability of tertiary chlorides especially at elevated temperatures have undoubtedly tended to increase the experimental error. It is felt, however, that definite conclusions concerning the problem as stated above may be derived from the experimental data obtained.

A sample calculation of the theoretical value for a parachor, that of 3,8-dichloro-3,8-diethyldecane, follows in which values for the structural units (tertiary chlorides) are taken from the table published by Smart and Quayle[7]; the atomic parachor of hydrogen used (15.5) is that reported by Quayle, Day and Brown[9]: (2 × ethylethylethylchloromethane) − (2 × hydrogen) = parachor of 3,8-dichloro-3,8-diethyldecane. (2 × 338.8) − (2 × 15.5) = 646.6. This method is based upon the assumption that, once evaluated, the parachors of the component groups may be added to ascertain the parachor for the larger molecule. In the compounds in which functional groups are separated by a small number of carbon atoms, a new constitutive factor involving the influence of one functional group on the other was recognized as a possibility. Thus in cases where n is 2, deviations from the calculated parachor were anticipated since no appraisal of this new constitutive effect has been included. It would be expected that the observed parachor would be less than the calculated value. This is evident in the data of Table III.

---

(11) Whitmore and Williams, THIS JOURNAL, **55**, 406 (1933).

(12) See references under Table I.

(13) Lipkin, Davison, Harvey and Kurtz, *Ind. Eng. Chem., Anal. Ed.*, **16**, 55 (1944).

TABLE II

PARACHOR DATA OF DITERTIARY GLYCOLS AND CHLORIDES

Compound	Temp., °C.	Density, g./ml.	Surface tension,[a] dynes/cm.	Parachor
3,6-Diol	70	0.8985	27.12	513.9
	75	.8946	26.73	514.2
	80	.8904	26.20	514.1
3,11-Diol	65	.8796	29.61	722.5
	70	.8755	29.31	724.1
	75	.8713	28.89	725.0
2,11-Diol	65	.8676	29.79	620.3
	70	.8641	29.39	620.7
	75	.8602	28.99	621.4
3,12-Diol	65	.8767	30.05	765.0
	70	.8725	29.63	766.0
	75	.8684	29.24	767.1
4,13-Diol	60	.8643	28.32	914.5
	65	.8602	27.98	916.0
	70	.8566	27.62	916.9
2,5-Di-Cl	70	.9543	24.13	425.3
	75	.9496	23.59	425.1
3,6-DiCl	25	.9995	31.32	566.2
	35	.9917	30.40	566.5
	50	.9799	29.03	566.7
4,7-Di-Cl	25	.9580	29.85	720.6
	35	.9505	28.95	720.7
	50	.9391	27.63	721.0
2,7-Di-Cl	55	.9496	26.39	504.0
	60	.9448	26.08	505.1
	65	.9407	25.63	505.1
	70	.9362	25.19	505.3
3,8-Di-Cl	25	.9799	32.16	649.5
	35	.9723	31.21	649.8
	50	.9614	29.84	649.8
4,9-Di-Cl	25	.9488	30.72	802.4
	35	.9417	29.82	802.5
	45	.9342	28.90	802.6
	55	.9269	28.03	802.7
2,10-Di-Cl	25	.9519	30.32	624.3
	35	.9439	29.44	625.0
	50	.9322	28.11	625.5
3,11-Di-Cl	25	.9599	32.59	770.0
	35	.9530	31.75	770.2
	50	.9424	30.44	771.1
2,11-Di-Cl	25	.9451	30.76	666.0
	35	.9370	29.86	666.8
	45	.9296	28.99	667.2
	55	.9220	28.11	667.5
3,12-Di-Cl	25	.9540	32.89	811.7
	35	.9467	31.99	812.4
	50	.9364	30.70	812.9
4,13-Di-Cl	25	.9318	31.51	964.9
	35	.9248	30.69	965.8
	50	.9146	29.40	966.2

[a] Mean probable error not over ±0.03.

The parachor of the compound cited above calculated from values of Mumford and Phillips[8] for the individual atoms includes a strain constant (−3.0) for secondary branching of the carbon chain, which was not considered to vary with the length of the chain involved: Parachor of $C_{14}H_{28}Cl_2$ = (14 × 9.2) + (28 × 15.4) + (2 × 55.0) + (2 × −3.0) = 664.0.

TABLE III

COMPARISON OF EXPERIMENTAL AND CALCULATED PARACHORS

The experimental parachor at 25° is given in all cases in which such measurement was possible. Experimental values listed for glycols were obtained by extrapolation to 25°.

Compound	Parachor Exp.	Parachor Calcd.	JQ[a] % dev.	Previous calcd. values % Dev. (uncor.)[b] %	Previous calcd. values Dev. (cor.)[c]
3,6-Diol	511.2[d]	519.8	1.7	5.6	4.5
3,11-Diol	712.1	708.9	−0.45	3.9	3.1
2,11-Diol	615.9	603.0	−2.1	0.67	−0.31
3,12-Diol	756.6	748.0	−1.1	3.1	2.3
4,13-Diol	906.1	903.2	−0.32	3.7	3.1
2,5-Di-Cl	425.2[e]	427.8	0.61	1.1	−0.28
3,6-Di-Cl	566.2	575.2	1.6	4.2	3.1
4,7-Di-Cl	720.6	731.4	1.5	4.0	3.2
2,7-Di-Cl	505.2[f]	502.8	−0.48	0.95	−0.24
3,8-Di-Cl	649.5	646.6	−0.48	3.1	2.4
4,9-Di-Cl	802.4	802.8	0.05	3.4	2.7
2,10-Di-Cl	624.3	620.7	−0.58	0.91	−0.05
3,11-Di-Cl	770.0	764.5	−0.71	2.6	1.8
2,11-Di-Cl	666.0	660.2	−0.87	0.60	−0.30
3,12-Di-Cl	811.7	804.0	−0.95	2.3	1.5
4,13-Di-Cl	964.9	961.6	−0.34	2.6	2.0
Average % deviation,					
glycols			1.1	3.4	2.7
chlorides			0.74	2.3	1.6
omitting n = 2, glycols			1.0	2.8	2.2
chlorides			0.56	2.1	1.4
Algebraic sum % dev.					
glycols			−2.3	17.0	12.7
chlorides			−0.65	25.8	15.8
omitting n = 2, glycols			−4.0	11.4	8.2
chlorides			−4.4	16.5	9.8

[a] Based on tables of references (5) and (7). Fourth CH_2 in longest alkyl group of dichlorides taken as 39.5 instead of devious 38.6. [b] Derived from atomic constants only with no correction for branching of chain. [c] Mumford and Phillips' correction for branching of chain used. [d] 5° increment taken as 0.3. [e] Average of 70 and 75°. [f] Average of 60, 65 and 70°.

In Table III the experimental parachors are compared with values calculated as in the above examples and also with values based simply on Mumford and Phillips' atomic parachors with no correction for branching.

It should be pointed out that while the use of an average correction value or strain constant greatly reduces the total deviation in a series, it does not distinguish between two isomers both with the same type of branching. Such isomers always differ from each other. It is seen from Table III that for the five glycols reported the average deviation between calculated and observed values is 1.1%; the minimum, 0.3%; the maximum, 2.1%. Strictly additive values give an average deviation of 3.4%, a minimum of 0.7% and a maximum of 5.6%. The application of an average correction for secondary branching gives an average deviation of 2.7%, a minimum of 0.3% and a maximum of 4.5%. For the eleven dichlorides reported the average deviation between the observed and predicted values is 0.7%; the minimum, 0.05%; the maximum, 1.6%. Strictly additive values give an average deviation of 2.3%, a minimum of 0.6% and a maximum of 4.2%. The application of an average correction for branching gives an average deviation of 1.6%, a minimum of 0.05% and a maximum of 3.2%. Exclusive of dichlorides in which the number of separating methylene groups is two, the average deviation is 0.6% for the parachors in which individual constitutive values are included, whereas the average deviation is 1.4% for parachors in which an average correction is applied.

Experimental

The ditertiary glycols and chlorides were all prepared by standard methods. Detailed procedures are given below for two typical examples.

2,10-Dimethyl-2,10-undecanediol.—Thirty-two grams of dimethyl azelate (0.15 mole) in 170 cc. of dry ether was added dropwise under moderate reflux to methylmagnesium iodide prepared by the addition of 46 cc. of methyl iodide in 60 cc. of dry ether to 17.4 g. of magnesium in 170 cc. of dry ether.[14] The addition mixture was warmed under gentle reflux over a water-bath for two hours (with agitation if possible) after all the ester had been added. It was then allowed to cool and was hydrolyzed by working into the mass saturated aqueous ammonium chloride solution until separation of a supernatant ether layer occurred.[15] The ether layer was decanted and the hydrolysis mass washed several times with small portions of ether. (If a red color due to iodine develops, it may be removed by washing with 5% aqueous thiosulfate solution.) The combined ether extracts were dried over Drierite. Most of the ether was removed from the extract by distillation. Final traces of ether and other volatiles were removed by heating up to 70° under reduced pressure. On cooling the residue readily crystallized to a red-brown solid. The first series of crystallizations from toluene gave 29 g. of slightly brown solid (91% crude). After four recrystallizations 24 g. (75%) of colorless, odorless crystals, m. p. 67–67.5°, was obtained.

2,10-Dichloro-2,10-dimethylundecane.—Ten grams of 2,10-dimethyl-2,10-undecanediol was dissolved in 162 cc. of anhydrous ether (8% solution) to which was added 30 cc. of methanol.[16] The temperature was maintained between −10 and −20° by an ice–salt-bath. Anhydrous hydrogen chloride was bubbled through with mechanical agitation until the solution was saturated or nearly so (twenty hours). After standing overnight in an ice–salt mixture the reaction mixture was concentrated by drawing dry air through under reduced pressure. Evaporation was continued in a large test-tube until the mixture became cloudy, at which point it was allowed to settle into two layers. The top ether layer was pipetted into a cold glass-stoppered bottle. The above extraction was repeated twice with small volumes of cold ether. The combined ether extracts were aerated further to remove as much of the remaining hydrogen chloride as possible, a small volume of chloroform was added and the solution was dried in the cold over 1:1 sodium sulfate and carbonate for twenty-four hours. Nine and six-tenths grams of oil with slight odor and color was recovered from the filtered chloroform solution by aeration as described above. Further evaporation and extraction of the original reaction residue gave 1.3 g. of brown oil for a total yield of 11.2 g. of crude dichloride (96%). The first fraction was further purified by the following general procedure. Ten cc. (9.6 g.) of the 2,10-dichloride was dissolved in 15 cc. of chloroform. The chloroform solution and 5 cc. of concentrated sulfuric acid were cooled to −15° in separate small glass-stoppered bottles, mixed and shaken thoroughly at intervals in the cold for twenty minutes. The mixture was allowed to stand in an ice–salt-bath for twenty-five minutes before the chloroform layer was pipetted off, centrifuged five to ten minutes, dried twenty-four hours in the cold over sodium sulfate–carbonate mixture and concentrated by aeration under reduced pressure as above. This final evaporation of solvent required about four hours toward the end of which a water-bath at 45° was applied. The yield of dried and filtered, colorless and odorless oil was 8.6 g. (74% over-all).

Summary

Three new ditertiary glycols and nine new ditertiary chlorides have been prepared.

The parachors of a number of ditertiary glycols and chlorides have been measured and shown to compare satisfactorily with predicted values.

These results indicate that large structural units after evaluation may be treated in general in an additive manner in predicting the parachor of a large molecule. As expected the agreement is closer when the functional groups are separated by four or more carbon atoms.

EMORY UNIVERSITY, GA. RECEIVED JULY 31, 1947

---

[14] Good mechanical agitation is essential since the Grignard addition products of dibasic esters of high molecular weight tend to separate as tough solid masses and stop the stirrer.

[15] Hydrolysis procedure outlined by Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., New York, N. Y., 1941, p. 410.

[16] Concentration of solution and volume of methanol added was varied according to the solubility of a particular glycol at low temperatures.

[CONTRIBUTION FROM RESINOUS PRODUCTS & CHEMICAL CO., INC.]

Condensation of Cyclohexanone with Nitriles

BY HERMAN A. BRUSON, EDWARD RIENER AND THOMAS RIENER

The reaction of phenols with nitriles in the presence of aluminum chloride (Houben–Hoesch method) to yield ketimines and ultimately ketones suggested the possibility that cyclohexanone might react in its enolic form with acetonitrile and aluminum chloride to yield 2-acetylcyclohexanone.

Upon addition of a mixture of acetonitrile and cyclohexanone to a cooled, stirred suspension of anhydrous aluminum chloride in carbon disulfide a semisolid reaction mass forms which soon prevents further stirring. After decomposition of the product with ice water the mixture yields a crystalline solid (I) melting at 140° and having the formula $C_{14}H_{23}O_2N$. This product corresponds to a composition of two moles cyclohexanone and one mole acetonitrile. It may be more readily obtained by using ethylene dichloride instead of carbon disulfide as a solvent, since the reaction mixture then remains fluid and homogeneous, and can be continuously stirred during the reaction period.

The chemical properties of (I) are as follows:

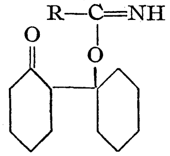
It is a ketone since it yields a crystalline monoxime and a crystalline mono-semicarbazone. It is a base since it dissolves readily in concentrated hydrochloric acid but not in water at room temperature and is reprecipitated unchanged from the acid solution by the addition of excess sodium hydroxide solution.

When the product is steam distilled from an admixture with dilute sulfuric acid the nitrogen is split off as ammonia and an oil steam distills over. The oil was found to be 2-cyclohexenylcyclohexanone. Acetic acid is found in the aqueous steam distillate layer. Since cyclohexanone upon steam distillation from dilute sulfuric acid under the same conditions gave no detectable amount of cyclohexenylcyclohexanone it may safely be concluded that (I) is derived from 2-cyclohexenylcyclohexanone or 2-cyclohexylidenecyclohexanone and not from cyclohexanone itself.

To test this hypothesis, acetonitrile was treated with 2-cyclohexenylcyclohexanone in the presence of an aluminum chloride suspension in ethylene dichloride and the same crystalline product (I) melting at 140° was obtained, although in poorer yield.

That the methyl group of the acetonitrile is not involved in the reaction is shown by the fact that benzonitrile reacts in an analogous manner with cyclohexanone and aluminum chloride to yield a crystalline product (II) melting at 120–121° and having the formula $C_{19}H_{25}O_2N$ corresponding to a molar ratio of cyclohexanone to nitrile of 2:1. Propionitrile likewise reacted with cyclohexanone to yield a crystalline product (III) melting at 92–93° and having the formula $C_{15}H_{25}O_2N$ corresponding to a molar ratio of cyclohexanone to nitrile of 2:1.

A consideration of the above data makes it highly probable that these products are all derived from the aldol of cyclohexanone by the addition of the hydroxyl group thereof to the cyano group to form an iminoether[1] containing a free ketonic group as shown in formula (A).



(I) R = CH_3
(II) R = C_6H_5
(III) R = C_2H_5

(A)

This structure is consistent with all of the above-mentioned facts and reactions except for the possibility that such a formula might *a priori* be suggestive of a rather unstable molecule. The crystalline products obtained by us are however remarkably stable. The product $C_{14}H_{23}O_2N$ (I) obtained from acetonitrile and cyclohexanone or 2-cyclohexenylcyclohexanone is, for example, distillable *in vacuo*. It is also steam distillable from neutral solution and can be boiled for short periods of time with aqueous 10% sodium hydroxide solution without evolution of ammonia or any noticeable change. Only in acid solution does it undergo the complete breakdown upon prolonged standing or upon short boiling which is so characteristic of iminoethers in general.

Experimental

(I) Condensation of Cyclohexanone with Acetonitrile.—To a stirred suspension of 133.5 g. anhydrous, powdered, sublimed aluminum chloride in 300 cc. of carbon disulfide there was added dropwise with cooling to 30–35°, a mixture of 41 g. of acetonitrile and 196 g. of cyclohexanone during the course of forty-five minutes. After about half of this mixture had been added the solid nature of the product prevented further stirring. On standing for about three hours the mixture became a little more fluid and was stirred for eighteen hours at room temperature. It was then poured into 1 liter of chipped ice. After the ice had melted the oil layer was separated and the aqueous layer was extracted with benzene. The combined oil and extract was washed several times with water and the solvent was removed by evaporation in vacuum on a steam-bath. The residue (155 g.) partially solidified on cooling and scratching to a chocolate-colored crystalline magma. For purification it may be recrystallized from diisobutylene or methylcyclohexane with the help of Norite to remove the color; yield 55–75 g. of white crystals, m. p. 140–141°.

Anal. Calcd. for $C_{14}H_{23}O_2N$: C, 70.89; H, 9.70; N, 5.90; mol. wt., 237. Found: C, 71.20; H, 9.72; N, 5.86; mol. wt. (ebullioscopic in acetone), 241.

It is soluble in alcohol, benzene, ether, but insoluble in cold petroleum ether. It is somewhat soluble in boiling water and crystallizes out on cooling.

---

[1] A. Pinner, "Die Imidoäther und ihre Derivate," Berlin, 1892; Pinner and Klein, *Ber.*, **10**, 1889 (1877).

The use of 200 cc. of ethylene dichloride instead of the carbon disulfide in the above preparation allows better stirring. The yield of product in this case was 44 g.

Semicarbazone of (I).—This was prepared by heating on a steam-bath under reflux for three hours a mixture of 4.7 g. of (I), 25 cc. of ethanol, 15 cc. of water, 7 g. of sodium acetate and 5.5 g. of semicarbazide hydrochloride. The product was allowed to stand several days at 5° and the white crystalline deposit filtered off. It was recrystallized three times from water to a constant melting point of 194–195° and dried *in vacuo* at 100° for analysis.

Anal. Calcd. for $C_{15}H_{26}O_2N_4$: C, 61.22; H, 8.84; N, 19.04. Found: C, 61.55; H, 9.27; N, 19.00.

A mixed melting point with the semicarbazone of 2-cyclohexenylcyclohexanone of m. p. 195–196° showed a 15° depression.

Oxime of (I).—This was prepared by heating on a steam-bath under reflux for three hours a mixture of 2 g. of (I), 30 cc. of ethanol, 30 cc. of water, 3.3 g. of sodium acetate and 1.7 g. of hydroxylamine sulfate. Since the product did not crystalline on cooling, the solution was evaporated to dryness *in vacuo* and extracted with ether. Upon evaporation of the ether extract a soft mass was obtained which solidified when rubbed with 20 cc. of petroleum ether. The solid material was recrystallized from nitromethane and then from petroleum ether (b. p. 90–100°) to form white crystals, m. p. 163–164°.

Anal. Calcd. for $C_{14}H_{24}O_2N_2$: C, 66.66; H, 9.52; N, 11.11. Found: C, 66.53; H, 9.66; N, 10.85.

(I) **Condensation of Acetonitrile with 2-Cyclohexenylcyclohexanone.**—To a stirred suspension of 89.5 g. of powdered, sublimed, anhydrous aluminum chloride in 150 g. of ethylene dichloride, there was added dropwise a mixture of 27.5 g. of acetonitrile and 118 g. of 2-cyclohexenylcyclohexanone[2] while cooling the reaction mixture to 20–30°. After stirring for twenty-one hours at room temperature the mixture was added to chipped ice and the oil layer separated, washed with water and dried *in vacuo*. The residual oil (109 g.) was distilled under reduced pressure and the fraction boiling at 175–225° (0.5–1 mm.) was collected; yield 17 g. It was recrystallized from petroleum ether (b. p. 90–100°) and formed white crystals, m. p. 140–141°, which gave no depression in melting point with the product (I) obtained from cyclohexanone and acetonitrile.

Hydrolysis of (I).—A mixture of 1000 g. of 10% sulfuric acid and 179 g. (I), prepared from cyclohexanone and acetonitrile was blown with steam for five hours and the distillate (3500 cc.) collected. The oil layer was separated from the distillate and the aqueous layer extracted with ether. The combined oil and ether extract upon distillation *in vacuo* at 10 mm. yielded 52 g. of 2-cyclohexenylcyclohexanone, b. p. 133–136° (10 mm.), identified by its semicarbazone, m. p. 194–195°, and by its mixed melting point with an authentic sample of the semicarbazone of 2-cyclohexenylcyclohexanone of m. p. 195–196° with which it gave no significant depression.

(II) **Condensation of Cyclohexanone with Benzonitrile.**—The procedure given for (I) above was followed, using 133.5 g. of anhydrous aluminum chloride, 300 cc. of ethylene dichloride, 103 g. of benzonitrile and 196 g. of cyclohexanone. The crude product was a brown oil weighing 264 g. Upon extraction with hot petroleum ether (b. p. 90–100°) a light brown powder (82 g.) was left behind as a residue. This was recrystallized several times with considerable loss from petroleum ether and finally from ethylcyclohexane to a constant m. p. 120–121°.

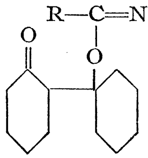
Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 76.25; H, 8.36; N, 4.68. Found: C, 76.74; H, 8.58; N, 4.66.

(III) **Condensation of Propionitrile with Cyclohexanone.**—The procedure given for (I) above was applied to a mixture of 133.5 g. of anhydrous aluminum chloride, 200 cc. of ethylene dichloride, 55 g. of propionitrile and 196 g. of cyclohexanone. The crude product was a brown oil (154 g.) which gradually crystallized in part after several days standing. The sticky crystalline product was spread out on porous tile which absorbed the oily impurity leaving about 80 g. of pinkish crystals. This material was recrystallized from petroleum ether (b. p. 90–100°) to a constant m. p. 92–93°; yield 60 g.

Anal. Calcd. for $C_{15}H_{25}O_2N$: C, 71.71; H, 9.96; N, 5.68. Found: C, 71.88; H, 10.18; N, 5.55.

Summary

Cyclohexanone condenses in the presence of aluminum chloride with nitriles R–CN to yield crystalline compounds which appear to be iminoethers of the aldol of cyclohexanone having the general formula



PHILADELPHIA, PA. RECEIVED SEPTEMBER 11, 1947

---

[2] Hückel, Neunhoffer, Gerche and Frank, *Ann.*, **477**, 119 (1930).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

A New Synthesis of Organosilicon Compounds[1]

BY E. W. PIETRUSZA,[2] L. H. SOMMER AND F. C. WHITMORE

In a previous communication[3] we reported the preparation of *n*-octyltrichlorosilane in almost quantitative yield from the reaction of 1-octene with trichlorosilane in the presence of a small amount (7 mole %) of diacetyl peroxide. The use of a weak ultraviolet source as the catalyst gave a 24% yield.

$$\mathrm{RCH{=}CH_2 + SiHCl \xrightarrow[\text{or U. V. L.}]{(CH_3COO)_2} RCH_2CH_2SiCl_3} \quad (1)$$

In extension of these results, the present paper reports that this new synthesis[4] is generally applicable to the addition of $SiHCl_3$ to olefins of varied structure, *i. e.*, $RCH{=}CH_2$, $RCH{=}CHR$, $R_2C{=}$

---

[1] Paper XV in a series on organosilicon compounds. See THIS JOURNAL, **70**, 445 (1948), for XIV.

[2] This paper comprises part of the subject matter of a thesis submitted by E. W. Pietrusza in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of The Pennsylvania State College. Allied Chemical and Dye Corporation Fellow 1945–1947.

[3] Sommer, Pietrusza and Whitmore, THIS JOURNAL, **69**, 188 (1947).

[4] An excellent treatment of other syntheses of organosilicon compounds is given in Rochow, "Introduction to the Chemistry of the Silicones," John Wiley and Sons, New York, N. Y., 1946, pp. 18–30.

TABLE I

ADDITION OF TRICHLOROSILANE TO OLEFINS

Olefin[k]	Cat.	Reaction Temp., °C.	Reaction Time, hr.	Product[h]	B. p. °C. Mm.	$n^{20}D$	Anal. % Cl[f] Calcd.	Anal. % Cl[f] Found	Yield, %
1-Octene	A[a]	50–63	9	$CH_3(CH_2)_5CH_2CH_2SiCl_3$	231–232 (731)	1.4480	43.0	43.0	99.0
1-Octene[j]	L[b]	44–74	40	$CH_3(CH_2)_5CH_2CH_2SiCl_3$	232 (727)	1.4480	43.0	42.8	47.0
2-Octene	A	50–62	18	$C_8H_{17}SiCl_3$	222–223 (721)	1.4532	43.0	42.8	99.0
2-Methyl-1-heptene	A	49–58	25	$CH_3(CH_2)_5CH(CH_3)CH_2SiCl_3$	221–222 (736)	1.4500	43.0	42.8	70.0
2-Methyl-2-butene	A	41–45	20	$C_5H_{11}SiCl_3$	163–167 (729)	1.445	51.9	51.8	24.6
2-Methyl-2-butene[j]	L	42–52	45	$C_5H_{11}SiCl_3$	164–165 (736)	1.4503	51.9	52.1	64.0
2-Methyl-1-propene[j]	L	25–30	135	$CH_3CH(CH_3)CH_2SiCl_3$	145–146 (730)	....	55.6	53.3	5.0
2,3-Dimethyl-2-butene	A	45–53	23	$CH_3CH(CH_3)C(CH_3)_2SiCl_3$[i]	186–187 (728)	1.4631	48.6	48.3	59.3
2,4,4-Trimethyl-1-pentene	A	49–50	15	$C_8H_{17}SiCl_3$	207–208 (721)	1.4478	43.0	42.8	9.1
2,4,4-Trimethyl-2-pentene	A	49–52	42	$C_8H_{17}SiCl_3$	219–220 (731)	1.4667	43.0	42.7	9.3
1,1-Dineopentylethylene	A	50–60	27	$C_{12}H_{25}SiCl_3$	260–275 (739)	1.4581	35.2	31.2	1.6
Allyl chloride	A	43–47	27	$C_3H_6SiCl_4$	165–166 (721)	1.451	50.2[g]	50.5	20.4
Allyl chloride	L	41–43[d]	45	$C_3H_6SiCl_4$	165–180 (726)	....	50.2	51.3	8.4

[a] Diacetyl peroxide, 3.8 mole%, based on olefin used. [b] Ultraviolet light applied externally. [c] Reaction was performed in a Vycor flask. (1-Octene when placed in a Pyrex flask and exposed to ultraviolet light for seventy-two hours gave a 24.3% yield of product, and when placed in a quartz flask and exposed to ultraviolet light for twenty-four hours gave a 31% yield of product.) [d] Quartz flask. [e] Pyrex glass, sealed ampule. [f] Values were obtained by treating a weighed sample with excess standard base and back-titrating with standard acid. [g] In this case, only the chlorines attached to silicon are neutralized by 0.1 *N* base. See Sommer, Dorfman, Goldberg and Whitmore, THIS JOURNAL, 68, 488 (1946). [h] Empirical formulas are given when the mode of addition of $SiHCl_3$ is uncertain. [i] F. p. 15–16°. [j] 0.2 mole. [k] 0.33 mole.

CH_2, $R_2C{=}CHR$, $R_2C{=}CR_2$, where R is alkyl, and to allyl chloride.

Olefins having these structures give excellent yields of the alkyltrichlorosilane when R is a straight-chain group such as methyl, *n*-amyl, or *n*-hexyl. However, if R is a highly-branched group, such as *t*-butyl or neopentyl, with the branching close to the olefinic linkage, the yield is considerably reduced. The low yield of isobutyltrichlorosilane may possibly be due to the volatile nature of the olefin which in our case necessitated the use of a low reaction temperature.

Comparison experiments using peroxide and ultraviolet light as catalysts indicate that the former generally gives faster reaction. However, use of the latter with 2-methyl-2-butene gave a better yield of product.

It is of interest that the alkyltrichlorosilanes formed in these reactions are incapable of undergoing further reaction with olefins under the conditions used. This leads in most cases to a product of high purity. In this respect the present method compares favorably with the Grignard method and the direct method which generally give mixtures of alkylchlorosilanes.[4]

The synthesis of 1,1,2-trimethylpropyltrichlorosilane from 2,3-dimethyl-2-butene and trichlorosilane is of interest, since reported preparations of tertiary alkyl silicon compounds have previously been limited to the use of tertiary alkyl lithium compounds[5] which are somewhat difficult to prepare in good yield.

The results of a preliminary study of the reactions of 1-octene with silicon hydrides other than trichlorosilane indicate that the latter reacts far more readily. *n*-Propyldichlorosilane gave a low yield (6%) of impure product when diacetyl peroxide was used. Triethoxysilane gave no reaction using either catalyst. Triethylsilane gave no reaction using peroxide, and a low yield of impure product (3%) when light was used. Diethylsilane gave a fair yield of a product which appeared to be mainly the mono addition product, but which could not be purified because of the small amount of starting material used.

Silicon tetrachloride failed to react with 1-octene using either catalyst.

While no detailed proof is available for the formulation of the addition of trichlorosilane to olefins as a free-radical chain reaction,[3] such an assumption seems reasonable on the basis of the following points: (1) Extensive evidence for the decomposition of diacetyl peroxide and other peroxides into free radicals on heating is beyond question. (2) Catalysis by ultraviolet light is evidence for a free-radical mechanism. (3) The small amounts (3.8 mole %) of diacetyl peroxide used in the present syntheses leave little doubt that these are chain reactions.

Experimental

Trichlorosilane was prepared in excellent yield by passing dry hydrogen chloride over ferrosilicon.[6] The olefins used were synthesized and carefully purified by Dr. N. C. Cook of this laboratory, who kindly donated samples for this study. Crystalline diacetyl peroxide

---

(5) Tyler, Sommer and Whitmore, THIS JOURNAL, **69**, 981 (1947)

(6) See Whitmore, Pietrusza and Sommer, *ibid.*, **69**, 2108 (1947), for the procedure used and for references to earlier preparations.

was prepared by the method of Gambarjan as modified by Kharasch,[7] and dissolved in the olefin used. The peroxide content was determined by analysis.[8]

A detailed description of the procedure used in a typical trichlorosilane addition to an olefin is given. Essentially this same procedure was employed for the reactions given in Table I.

Olefin, Trichlorosilane and Diacetyl Peroxide.—1-Octene, 17.9 g., 0.16 mole, and trichlorosilane, b. p. 32°, 135.5 g., 1.0 mole, were placed in a three-necked flask with dropping funnel, thermometer, and a reflux condenser connected through a trap cooled in Dry Ice–acetone to a mercury seal 20 cm. in height. The system was swept with nitrogen for two hours, and the reaction mixture was heated to 45° under the slight extra pressure of the mercury. Crystalline diacetyl peroxide, 1.5 g., 0.013 mole, dissolved in 19.1 g., 0.17 mole, of 1-octene was then added during two hours. The mixture was heated at 50–63° for an additional nine hours.

After removal of excess trichlorosilane, the residue was distilled at reduced pressure and then redistilled at atmospheric pressure, giving 80.9 g. of clear colorless liquid, b. p. 231–232° at 728 mm., $n^{20}\text{D}$ 1.4480, 99% yield.

Anal. Calcd. for $C_8H_{17}SiCl_3$: Cl, 43.0. Found: Cl, 42.9, 43.0.

n-Octyltrichlorosilane from silicon tetrachloride and *n*-octylmagnesium bromide boils 233° at 731 mm.; 119° at 28 mm.[9]

Treatment of a portion of the product with ethanolic potassium hydroxide gave no hydrogen, indicating the absence of Si-H bonds.[10]

Reaction of the product, 24.8 g., 0.1 mole, with 0.35 mole of methylmagnesium bromide (using a procedure known to form the tetraalkylsilane from *n*-octyltrichlorosilane)[9] gave 13.0 g. of *n*-octyltrimethylsilane, b. p. 201.5° at 733 mm., $n^{20}\text{D}$ 1.4242, 74% yield. Constants for this compound[9] are: b. p. 202° at 760 mm., $n^{20}\text{D}$ 1.4242. All the data thus conclusively confirm equation (1).

Olefin, Trichlorosilane, and Ultraviolet Light.—1-Octene, 22.4 g., 0.2 mole, and trichlorosilane, 81.3 g., 0.6 mole, were placed in a 500 cc. quartz flask with thermometer and a reflux condenser connected through a trap cooled in Dry Ice–acetone to a mercury seal of 20 cm. height. The system was swept with nitrogen for a half hour, and the reaction mixture was heated to 46° under the slight extra pressure of the mercury. Ultraviolet light was applied from an external source and the solution was heated for twenty-four hours at a temperature range of 46–52°.

After removal of excess trichlorosilane, the residue was distilled at reduced pressure and then redistilled at atmospheric pressure, giving 15.3 g. of clear, colorless liquid, b. p. 231–232° at 728 mm., $n^{20}\text{D}$ 1.4481, 31% yield.

Anal. Calcd. for $C_8H_{17}SiCl_3$: Cl, 43.0. Found: Cl, 42.8, 42.9.

Treatment of a portion of the product with ethanolic potassium hydroxide gave no hydrogen, indicating the absence of Si-H bonds.[10]

The above product corresponds completely to the product of the peroxide catalyzed reaction. When ultraviolet light is applied for longer periods of time, better yields of the octyltrichlorosilane are obtained.

Reactions of 1-Octene with Other Silicon Hydrides.—These were carried out under essentially the same conditions as those described above.

Summary

1. A new synthesis of organosilicon compounds is described which involves the addition of trichlorosilane to olefins differing widely in structural type. These reactions are catalyzed by small amounts of diacetyl peroxide or ultraviolet light.

2. New alkyltrichlorosilanes of varying complexity were prepared by this method in good yield.

STATE COLLEGE, PA.

RECEIVED MAY 28, 1947

---

[7] (a) Gambarjan, *Ber.*, **42**, 4010 (1909); (b) Kharasch, *J. Org. Chem.*, **10**, 393 (1945).

[8] Kokatnur and Jelling, THIS JOURNAL, **63**, 1432 (1941).

[9] Whitmore, Sommer, DiGiorgio, Strong, Van Strien, Bailey, Hall, Pietrusza and Kerr, THIS JOURNAL, **68**, 475 (1946).

[10] *Cf.* Sauer, Scheiber and Brewer, *ibid.*, **68**, 962 (1946).

[CONTRIBUTION FROM THE NAVAL RESEARCH LABORATORY, WASHINGTON, D. C.]

Reaction of Lithium Aluminum Hydride with Compounds Containing Active Hydrogen

BY J. A. KRYNITSKY, J. E. JOHNSON AND H. W. CARHART

The new compound, lithium aluminum hydride, discovered by Finholt, Schlesinger, *et al.*,[1,2] has been shown to be a vigorous agent for the reduction of various types of organic compounds.[3] In addition, many compounds containing active hydrogen decompose the reagent to liberate hydrogen. The purpose of this investigation was to study the latter type of reaction and to explore the possibility of using lithium aluminum hydride as a reagent for the determination of active hydrogen.

In a previous study, it was found that ether solutions of lithium aluminum hydride could be analyzed quantitatively by decomposing with excess water at 0° and measuring the evolved hydrogen by changes in pressure.[4] In the present work, an apparatus was devised so that a known amount of material could be added to an excess of lithium aluminum hydride–ether solution at 0° and the liberated gas measured by changes in pressure. By this method, the apparent active hydrogen content of a number of organic compounds was determined.

Experimental

Apparatus.—A diagram of the apparatus used is shown in Fig. 1. The reaction flask consisted of a 500-ml. round-bottom flask bearing a 35/20 spherical socket joint. A take-off arm was attached to the neck and connected to a manometer by small bore tubing through a T-tube. The T-tube was joined to a drying tube with rubber tubing which could be closed by a pinch clamp. The reaction flask was closed by a spherical ball joint carrying a 12 × 130 mm. guide tube. A clamp with an efficient locking

---

[1] Finholt, Schlesinger and Wilzbach, Division of Physical and Inorganic Chemistry, A. C. S., Chicago Meeting, September, 1946.

[2] Finholt, Bond and Schlesinger, THIS JOURNAL, **69**, 1199 (1947).

[3] Nystrom and Brown, *ibid.*, **69**, 1197 (1947).

[4] Krynitsky, Johnson and Carhart, *Anal. Chem.*, in press.

device was used to hold the joint together in order to prevent leakage. The supporting hook was made from glass rod joined to a sealed glass tube containing an iron core. The over-all length of the supporting hook was such that its lower end almost touched the bottom of the flask when the magnet pack was in the lowered position. The magnet pack consisted of two Alnico magnets in opposition mounted so that the pack passed over the guide tube easily. The sample cup was made from 15 mm. tubing and had a capacity of approximately 2 ml. A handle was provided so that the cup could be suspended from the supporting hook.

Before using the apparatus, the volume of the system was determined. In addition to this apparatus, a second one similar in construction but using a one-liter reaction flask was used for many of the determinations.

Procedure.—The reaction flask was clamped into place, connected to the manometer and surrounded with crushed ice and ice water. Approximately 100 ml. of cold lithium aluminum hydride–ether solution (0.3 to 0.7 molar) was placed in the flask and the assembled apparatus allowed to stand with the pinch clamp closed. If a pressure change was observed in five minutes, the pinch clamp was opened momentarily and the standing process repeated until equilibrium was reached. Sometimes over one hour was required to attain this equilibrium.

The material under investigation was weighed into a sample cup which was then hung on the supporting hook. The iron core end of the hook was placed in the guide tube with the magnet pack in the raised position. This assembly was attached to the flask and the joint locked in place.

After equilibrium was re-established (usually ten to fifteen minutes), the magnet pack was lowered so that the sample was brought into the solution. Pressure readings were taken at appropriate time intervals (usually five minutes) until no further change was observed. In some cases, when reaction was slow, the mixture was agitated slightly by raising and lowering the magnet pack.

The apparatus was readied for a subsequent analysis by releasing the pressure and withdrawing the sample cup and supporting hook. The next determination was then started immediately using a fresh sample cup and supporting hook.

The apparent number of active hydrogen atoms in the molecule was calculated from the equation

$$\text{No. active H atoms} = \frac{\text{pressure (mm.)} \times \text{net free vol. (ml.)}}{\text{millimoles sample} \times 17{,}030}$$

The pressure is the observed pressure increase less the small pressure increase found by carrying out a blank determination without a sample. The net free volume is the total volume of the system less the volume of solutions added and the volume of the supporting hook. The factor 17,030 combines the constants R and T.

In general, the size of the sample was chosen so that a pressure change of approximately 100 mm. was obtained. For the apparatus described, the amount of material ordinarily used varied from 0.1 to 0.4 g. depending on its molecular weight and the number of active hydrogen atoms. Materials which were suspected of not being dry were dried using anhydrous calcium sulfate or phosphorus pentoxide.

Results and Discussion

The values found for the apparent active hydrogen content of a number of typical organic compounds are presented in Table I.

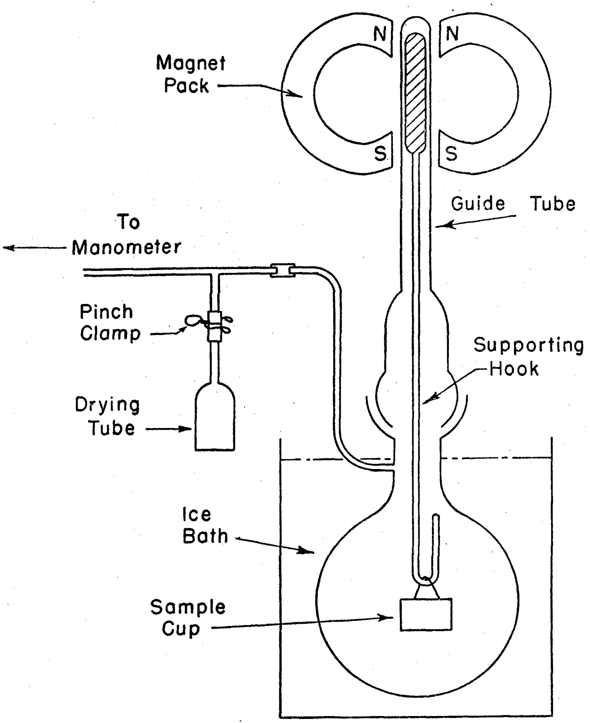


Fig. 1.—Apparatus for determining active hydrogen.

From this table, it can be seen that many of the simple alcohols, phenols and acids react with lithium aluminum hydride in ether to liberate hydrogen in the expected manner and give results which are in good agreement with the theoretical values. Although the reactions usually appeared to be complete within a few seconds, several minutes were required to reach equilibrium. The inconclusive results obtained with hydroquinone, succinic acid and terephthalic acid may be due to the formation of insoluble material which coats the crystals and inhibits further reaction. The anomalous results obtained with resorcinol may be due to the formation of an insoluble product or to partial reaction in the keto form. With the Grignard reagent, resorcinol has been reported to show from one to two atoms of active hydrogen.[5,6,7]

The amines and amides tested showed the expected number of active hydrogen atoms, and with the exception of acetanilide required prolonged reaction periods. The extreme slowness of the reaction of diamylamine was unexpected. The liberation of two hydrogens by primary amines and unsubstituted amides by this reagent at 0° is of interest since it has been reported that the Grignard reagent liberates one hydrogen from such compounds at ordinary temperatures and the second on heating.[8] Whereas the time required

---

(5) Ciusa, *Gazz. chim. ital.*, **50**, II, 53 (1920).

(6) Fuchs, Ishler and Sandhoff, *Ind. Eng. Chem., Anal. Ed.*, **12**, 507 (1940).

(7) Lehman and Basch, *ibid.*, **17**, 428 (1945).

(8) Zerewitinoff, *Ber.*, **41**, 2233 (1908).

TABLE I

Name of compounds	Time to reach equilibrium, min.	No. of active H atoms found	
Alcohols and Phenols			
n-Decanol	5–10	1.00	1.02
Benzyl alcohol	5–10	1.06	
Heptanol-2	5–10	1.02	
Cyclohexanol	5–10	0.98	1.01
t-Amyl alcohol	5–10	0.97	1.00
2-Methyl-2,4-pentanediol	5–10	2.01	2.01
α-Naphthol	10–20	1.05	1.03
β-Naphthol	5–10	1.05	1.08
Resorcinol	50–140	1.53	1.56
Hydroquinone		....[a]	
Acids			
n-Caprylic acid	5–10	1.03	1.03
2-Ethylhexoic acid	5–10	1.02	
Benzoic acid	5–10	0.99	0.99
o-Bromobenzoic acid	10–15	1.00	
Succinic acid		....[a]	
Terephthalic acid		....[a]	
Amines and Amides			
Cyclohexylamine	115	2.08	
Diamylamine	375	0.94	
Tributylamine		None[b]	
Aniline	50	1.99	2.05
β-Naphthylamine	70–80	2.04	1.99
2-Ethylhexanoamide	60	2.05	
Acetanilide	5–10	0.98	
Nitro Compounds			
Nitrobenzene	35	2.08	
o-Nitrotoluene	100	2.03	
Nitromethane	120–250	2.40	2.75
Tautomeric Compounds			
Acetyl acetone	5–10	0.94	0.95
Ethyl acetoacetate	5–10	.56	.57
Diethyl malonate	5–10	.56	.57
Diethyl methylmalonate	5–10	.25	.28
Diethyl ethylmalonate	5–10	.22	.25
Diethyl *i*-propylmalonate	5–10	.18	.21
Diethyl *n*-butylmalonate	5–10	.22	.26
Diethyl *i*-butylmalonate	5–10	.22	.25
Diethyl benzylmalonate	5–10	.19	.21
Miscellaneous			
Acetophenone	5–10	0.07	0.05
Propiophenone	5–10	0.05	0.08
Octyl mercaptan	5–10	1.00	1.01
Dioctyl thioether		None[b]	
Ethyl palmitate		None[b]	
Phenylhydrazine	70–125	Erratic[c]	

[a] Reaction with these compounds was slight and too slow to obtain significant results. [b] These compounds gave less than 0.02 atom of active hydrogen. [c] Values obtained were 3.01, 2.68, 3.47, 3.90 and 3.20.

for complete liberation of hydrogen by primary amines and unsubstituted amides was rather long, in every case the first hydrogen was liberated rapidly, usually within five minutes. This behavior was also observed for all other compounds tested showing more than one atom of apparent active hydrogen.

Nitrobenzene and nitrotoluene showed two apparent active hydrogen atoms. With the Grignard reagent nitrobenzene has been reported as showing from 1.0 to 1.9 active hydrogens depending on the reagent used.[9] In contrast to the aromatic nitro compounds, nitromethane gave erratic results showing more than two apparent active hydrogens. With the Grignard reagent, values of less than one have been reported for nitromethane.[5,10]

The reaction of lithium aluminum hydride with compounds exhibiting keto–enol tautomerism was rapid and the results indicated that the compounds tested behaved as though they were partially enolized. In this connection it is interesting to note that diethyl malonate reacted as though it were approximately 56% enolized, yet the substituted diethyl malonates gave values which ranged from 18 to 28%. With the Grignard reagent acetylacetone, ethyl acetoacetate and diethyl malonate have been reported to react as though they existed entirely in the mono-enol form.[6,8] In contrast to the Grignard reagent, it appears that lithium aluminum hydride reacts with the keto form of these compounds rapidly enough so that complete enolization cannot occur.

Definite conclusions cannot be drawn from the values obtained for acetophenone and propiophenone. However, it is indicated that these compounds reacted as though they were partially enolized. In this respect, it is of interest that acetophenone has been reported to react with the Grignard reagent as though it were approximately 12–15% enolized in isoamyl ether and 78% in pyridine or dioxane.[11,12]

Although the reaction of phenylhydrazine with lithium aluminum hydride gave erratic results, it was surprising that in three out of five determinations, more than three apparent active hydrogen atoms were found. This suggested partial cleavage of the N–N bond. Confirmation of this cleavage was obtained by detection of ammonia upon hydrolysis of such a reaction mixture. In every case, the liberation of the first two hydrogens was rapid and occurred within five minutes.

Acknowledgment.—The authors are indebted to Dr. W. E. Weaver of this Laboratory who courteously furnished the substituted malonic esters used in this work.

Summary

The apparent active hydrogen content of a number of organic compounds was determined by means of an ether solution of lithium aluminum hydride. In the majority of cases, this reagent behaved in a manner similar to that of the Grignard reagent and the expected number of hydro-

---

(9) Gilman and Fothergill, THIS JOURNAL, **49**, 2815 (1927).

(10) Zerewitinoff, *Ber.*, **43**, 3590 (1910).

(11) Kohler, Stone and Fuson, THIS JOURNAL, **49**, 3181 (1927).

(12) Lieff, Wright and Hibbert, *ibid.*, **61**, 865 (1939).

gen atoms was found. However, in some instances, the reaction was more vigorous in that it proceeded at a lower temperature and further toward completion.

With lithium aluminum hydride, the keto–enol tautomers investigated behaved as though they were only partially enolized, whereas similar compounds with the Grignard reagent act as though they exist in the enol form only.

WASHINGTON, D. C.

RECEIVED JULY 22, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, EMORY UNIVERSITY]

Claisen Condensation of Methyl Esters

BY E. EARL ROYALS

Investigations of the acetoacetic ester condensation[1] have been largely confined to the study of ethyl esters; particularly, relatively few methyl ester condensations have been reported in the literature. The present commercial availability of sodium methoxide, and observations[2] that sodium methoxide is a condensation catalyst considerably less sensitive to adverse experimental conditions than sodium ethoxide make further investigation of methyl ester condensations desirable. The present research was undertaken to determine the utility of sodium methoxide as a reagent for the condensation of the simpler methyl esters, and, more specifically, to develop methods of synthesis for certain keto-esters which have not previously been satisfactorily prepared by direct ester condensation.

McElvain and co-workers made an extensive study of the self-condensation of ethyl esters in the presence of sodium ethoxide under both equilibrium and forcing conditions.[3] Our results on the self-condensation of methyl esters, shown in Table I, are quite similar to those of McElvain in the ethyl ester series. Our forcing procedure, however, is considerably simpler and requires less of the pure ester than the one described by McElvain.

The condensation of methyl benzoate with methyl acetate has been reported to give yields of methyl benzoylacetate ranging from 45 to 85% depending on the conditions employed.[4] Dorsch and McElvain[5] condensed ethyl benzoate in the presence of sodium ethoxide with ethyl acetate, propionate, and *n*-butyrate and obtained yields of 37, 19 and 4%, respectively, of the α-benzoyl esters. We have investigated the condensation of methyl benzoate with methyl acetate, propionate and *n*-butyrate; our results are summarized in Table II. The methyl propionate condensation was chosen for pilot work. The yield of methyl α-benzoylpropionate from equivalent quantities of the two esters and sodium methoxide was found to be essentially the same whether the reactants were directly mixed, or whether the propionate was added dropwise to a mixture of methoxide and benzoate. The yield was not increased by lengthening the reaction time from four to twenty-four hours. It was found, however, that the use of excess methyl propionate and sodium methoxide greatly increased the yield of methyl α-benzoylpropionate (calculated on methyl benzoate); indeed, the second and third equivalents of propionate were utilized in inter-ester condensation with almost the same efficiency as the first. Similar results were obtained in the condensation of methyl acetate with methyl benzoate; somewhat lower yields were obtained, however, than in the corresponding methyl propionate condensations. The best conditions found for the condensation of methyl benzoate with methyl propionate were applied to the analogous methyl *n*-butyrate condensation. A negligible yield of methyl α-benzoylbutyrate was obtained. It was observed, however, that even with a reaction period of forty hours, considerable quantities of methyl *n*-butyrate were recovered unreacted, indicating that the low yield of inter-ester condensation product might be due to an unfavorable equilibrium rather than to a preference of methyl *n*-butyrate for self-condensation. Accordingly, methyl *n*-butyrate (4 moles) was condensed with methyl benzoate (1 mole) in the presence of sodium methoxide (2

TABLE I

SELF-CONDENSATIONS OF METHYL ESTERS IN THE PRESENCE OF SODIUM METHOXIDE

Methyl ester	Moles ester per mole CH_3ONa	Temp., °C.	Time, hr.	% yield β-ketoester
Acetate	6	60	8	43
Acetate (forced)[a]	6	80	8	43–50
Propionate	4	80	16	29
Propionate	6	80	16	42
Propionate (forced)	6	100	16	71
n-Butyrate (forced)	6	125	30	79
Phenylacetate (forced)	2	100[b]	6	80

[a] See text and Experimental Part for description of forcing conditions. [b] Pressure slowly reduced from atm. to final value of 10 mm.

---

[1] See Hauser and Hudson in Adams, "Organic Reactions," John Wiley and Sons, New York, N. Y., 1942, Chap. 9.

[2] Freri, *Gazz. chim. ital.*, **68**, 616 (1938); Royals, THIS JOURNAL, **67**, 1508 (1945).

[3] McElvain, THIS JOURNAL, **51**, 3124 (1929); Briese and McElvain, *ibid.*, **55**, 1697 (1933); Roberts and McElvain, *ibid.*, **69**, 2007 (1937).

[4] Ref. 1, pp. 278, 283.

[5] Dorsch and McElvain, THIS JOURNAL, **54**, 2960 (1932).

TABLE II

CONDENSATIONS OF ALIPHATIC METHYL ESTERS WITH METHYL BENZOATE IN THE PRESENCE OF SODIUM METHOXIDE

Methyl ester	Moles ester and CH_3ONa per mole benzoate	Temp., °C.	Time, hr.	Product, b. p. °C.	Product, b. p. mm.	$C_6H_5COCHRCO_2CH_3$ $n^{25}D$	$C_6H_5COCHRCO_2CH_3$ Yield, %
Acetate	1	60	4	117–122[a]	2.5	1.5355[a]	19
Acetate[b]	1	60	6	113–115	2.0	1.5361	21
Acetate[c]	3	60	6	127–130	5.0	1.5354	45
Propionate	1	80	4	130–131[d]	4.0	1.5200	24
Propionate	1	80	24	117–120	2.0	1.5206	22
Propionate[b]	1	80	6	125–127	3.0	1.5206	19
Propionate[e]	2	80	6	120	2.5	1.5206	41
Propionate[c]	3	80	6	120–123	2.0	1.5206	61
n-Butyrate[c]	3	100	6	110–129	3.0		9
n-Butyrate (forced)	2[f]	120	30	115–120[g]	1.0	1.5215	41

[a] von Auwers and Jacobsen, *Ann.*, **426**, 234 (1922), report, b. p. 151.5–151.8° (13 mm.), $n^{20}D$ 1.5394. [b] Aliphatic ester added dropwise to reaction mixture. [c] Aliphatic ester and sodium methoxide added in three equal portions to reaction mixture. [d] Characterized through 4-methyl-3-phenyl-isoxazalone-5, m. p. 121–122°. Haller and Bauer, *Compt. rend.*, **152,** 1446 (1911), report m. p. 123–124°. [e] Aliphatic ester and sodium methoxide added in two equal portions to reaction mixture. [f] Plus 2 moles excess methyl *n*-butyrate. [g] Characterized through 4-ethyl-3-phenyl-isoxazolone-5, m. p. 90.5–92.0°. Haller and Bauer, *loc. cit.*, report m. p. 91°.

moles), the methanol formed in the reaction being azeotropically distilled with the excess methyl *n*-butyrate during a reaction period of thirty hours. A yield of 41% of methyl α-benzoylbutyrate was obtained.

The results here reported for condensations of methyl benzoate with aliphatic methyl esters indicate that such inter-ester condensations, involving one ester incapable of self-condensation, may be of more general usefulness than previous investigations would indicate. Our results on inter-ester condensations are to be regarded as exploratory; further investigations along this line are in progress in our laboratory.

Experimental

Materials.—The methyl esters used were either purchased from the Eastman Kodak Company or were prepared by standard procedures. All of the esters were dried over calcium chloride, distilled, then dried over and distilled from phosphorus pentoxide through an 18-inch column packed with a nichrome spiral of the Podbielniak type. The sodium methoxide was a commercial product purchased from the Mathieson Alkali Works, Niagara Falls, N. Y.

Procedures.—The experiments described below will illustrate the general methods used. Self-condensations under non-forcing conditions were run essentially according to the procedure[3c] described by Roberts and McElvain. The forced self-condensation of methyl phenylacetate was run according to the general procedure[3b] of Briese and McElvain.

Forced Self-Condensation of Methyl Propionate.—A mixture of 317 g. (3.6 mole) of methyl propionate and 32.4 g. (0.6 mole) of sodium methoxide was placed in a 500-cc. flask under an 18-inch, nichrome spiral packed column with a Whitmore-Lux type head. The entire apparatus was protected from atmospheric moisture by suitably placed calcium chloride tubes. The reaction flask was heated in an oil-bath at 100°. The reaction mixture became homogeneous within about one hour. The column was operated at a jacket temperature of 65° with slow take-off and frequent total reflux. A total of 112 g. of distillate was collected (vapor temperature 65–68°) during a reaction period of sixteen hours. The residue on cooling to room temperature set to a solid cake. This cake was broken up, 150 cc. of ether added, and the slurry was cooled in an ice-bath. An ice-cold solution of 50 cc. of glacial acetic acid in 100 cc. of water was added in portions with stirring. Stirring was continued at ice-bath temperature until the solid material had all dissolved. The organic layer was separated, and the aqueous layer was twice extracted with 100-cc. portions of ether. The ether solutions were combined, washed once with water, and dried over sodium sulfate. Removal of the drying agent and ether, followed by distillation of the residue through the spiral-packed column referred to above gave 61 g. (70.5%) of methyl α-propionylpropionate, b. p. 74–76° (10 mm.), $n^{25}D$ 1.4211.

Condensation of Methyl Benzoate with Methyl Propionate.—A mixture of 68 g. (0.5 mole) of methyl benzoate, 44 g. (0.5 mole) of methyl propionate, and 27 g. (0.5 mole) of sodium methoxide was placed in a 500-cc., three necked flask fitted with a modified Hershberg stirrer[6] and reflux condenser protected by a calcium chloride tube. The reaction mixture was stirred in an oil-bath at 80° for six hours. After two hours, and again after four hours, additional quantities of 44 g. of methyl propionate and 27 g. of sodium methoxide were added. The reaction mixture was cooled to room temperature, and 100 cc. of ether was added to give a fluid system. This slurry was cooled in an ice-bath, then poured into an ice-cold solution of 125 cc. of glacial acetic acid in an equal volume of water. (This hydrolysis step is critical; early attempts to effect the hydrolysis by dropwise addition of the cold acetic acid solution to the reaction mixture with stirring in an ice-bath led to the formation of large amounts of benzoic acid, presumably from acid cleavage of the keto-ester.) When all of the solid material had disappeared (about five minutes), the organic layer was separated, and the aqueous layer was twice extracted with 100-cc. portions of ether. The ether solutions were combined, washed once with water, then with saturated sodium bicarbonate solution until free of acid, and again with water. The ether solution was dried over sodium sulfate, then overnight over drierite. Removal of the drying agent and ether, and distillation of the residue through the column referred to above gave 58 g. (60.5%) of methyl α-benzoylpropionate, b. p. 120–123° (2 mm.), $n^{25}D$ 1.5206. A forerun, 35 g., was obtained, b. p. 63–69° (4 mm.), $n^{25}D$ 1.4735, the physical constants indicating a mixture of methyl α-propionylpropionate and unreacted methyl benzoate.

Forced Condensation of Methyl *n*-Butyrate with Methyl Benzoate.—A mixture of 191 g. (1.88 mole) of methyl *n*-butyrate, 64 g. (0.47 mole) of methyl benzoate, and 53.5 g. (0.94 mole) of sodium methoxide was placed in

---

(6) Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8,** 313 (1936).

a 500-cc., two-necked flask under the column described above. A modified Hershberg stirrer was mounted in the second neck of the flask. The reaction mixture was stirred and heated in an oil-bath at 120–130° for thirty hours, while distillate was slowly taken off through the column jacketed at 65°. A total of 64 g. of distillate was collected. The residue was cooled in an ice-bath and worked up by the procedure described above under the condensation of methyl propionate with methyl benzoate.

Distillation of the reaction product through the spiral-packed column referred to above gave: (I) 8 g., probably methyl benzoate, b. p. 67–85° (9 mm.), (II) 47 g. methyl α-butyrylbutyrate, b. p. 85–90° (9–7 mm.), (III) 6 g. intermediate, (IV) 40 g. (41.3% on methyl benzoate) of methyl α-benzoylbutyrate, b. p. 115–120° (1 mm.), $n^{25}D$ 1.5215.

Summary

Sodium methoxide has been used to effect the acetoacetic ester type of condensation of several methyl esters. Procedures have been described for the self condensation of methyl propionate and of methyl *n*-butyrate to give good yields of β-ketoesters without the use of very large excesses of the esters. It has been found possible to effect satisfactory syntheses of methyl α-benzoylpropionate and of methyl α-benzoyl-*n*-butyrate by direct ester condensation.

EMORY UNIVERSITY, GA. RECEIVED JUNE 12, 1947

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some Dialkylaminoalkyl Sulfides and Ethers Derived from Quinoline and Acridine Heterocycles

BY R. O. CLINTON AND C. M. SUTER

Although the literature contains references to a very large number of heterocyclic nitrogen compounds substituted by basic side chains linked to the nucleus by an imino (—NH—) group, few compounds of this type in which the linkage is oxygen or sulfur have been described. It was the purpose of the present study to determine the effect of replacement of the —NH— by the —O— or —S— linkage upon the therapeutic activity of these compounds, particularly toward the malaria parasite.

The literature[1] describes several quinolines in which 2-dialkylaminoethoxy side chains are linked to the nucleus in the 2- or 4-position, and further substituents (*e. g.*, methyl, phenyl, carboxamide) appear in the quinoline ring. Bachman, *et al.*,[2] have reported the preparation of 3-amino-4-(3-diethylamino-2-hydroxypropylmercapto)-quinoline by the alkylation of the corresponding aminoquinolinethiol with 3-diethylamino-1,2-epoxypropane. In addition, several quinolyl sulfides of related types are listed by Wiselogle,[3]

TABLE I

7-CHLOROQUINOLINES

No.	4-Substituent	Max., mμ	ε × 10⁻³	Min., mμ	ε × 10⁻³
1	2-(2-Diethylaminoethylmercapto)-ethoxy[a]	231	63.00	264	1.50
		305	9.49	307	9.18
		310	9.30		
2	4-Diethylamino-1-methylbutyloxy[a]	232	32.18	264	0.85
		310	6.66		
3	2-Diethylaminoethylmercapto[a,b]	241	42.3	268	1.90
		332	17.59		
4	2-Di-*n*-hexylaminoethylamino[a,c]	221	29.60	231	24.40
		235	25.25	245	15.72
		248	15.79	278	2.10
		326	18.15	330	16.24
		339	18.20		
5	4-Diethylamino-1-methylbutylmercapto[a]	241	36.80	275	19.65
		345	16.21	347	16.15
		349	16.20		
6	4-Diethylamino-1-methylbutylmercapto[d,e]	230	30.38	280	3.77
		315	9.98	320	9.90
		322	9.94		
7	4-Diethylamino-1-methylbutylamino[a,f]	220	32.25	231	18.05
		235	18.85	243	13.80
		256	16.28	280	1.85
		330	17.83	336	15.90
		343	19.45		
8	4-Diethylamino-1-methylbutylamino[d]	218	39.40	246	15.10
		255	17.91	275	1.33
		330	11.90		
	6-CHLORO-2-METHOXYACRIDINES				
	9-Substituent				
9	2-Diethylaminoethylmercapto[a]	222	22.13	240	13.83
		275	68.97	310	1.01
		381	14.13	404	3.77
		445	5.58		
10	4-Diethylamino-1-methylbutylmercapto[a]	225	19.31	240	13.76
		276	64.26	315	0.83
		376	12.40	406	4.10
		445	5.79		
11	4-Diethylamino-1-methylbutylamino[a,g]	220 (?)	...	242	10.19
		280	55.07	318	2.69
		344	4.99	364	1.26
		424	9.40	436	8.65
		444	8.87		

[a] In 0.01 *N* hydrochloric acid. [b] Inflection at 380–385 mμ, ε = 450. [c] Huber, Bair and Laskowski, THIS JOURNAL, **67**, 1619 (1945). [d] In 0.01 *N* sodium hydroxide. [e] Inflection at 375–380 mμ, ε = 900. [f] These values agree well with those reported by Drake, *et al.*, THIS JOURNAL, **68**, 1214 (1946). [g] *Cf.* Scudi and Jelinek, *J. Biol. Chem.*, **152**, 27 (1944).

---

(1) U. S. Patents 1,572,768 (Reissue 16,394), 1,688,469, 1,841,970, 1,860,286, 1,891,980; Bachman, *et al.*, *J. Org. Chem.*, **9**, 302 (1944).

(2) Bachman, Welton, Jenkins and Christian, THIS JOURNAL, **69**, 366 (1947).

(3) Wiselogle, "Survey of Antimalarial Drugs," Vol. II, Part 2, pp. 1107–1108 (1946).

TABLE II

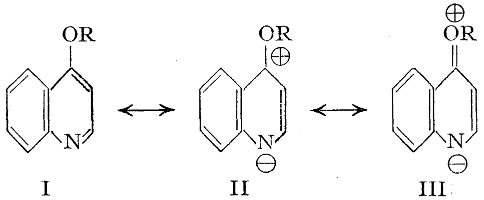
BASES AND DERIVATIVES

Compound	Base B. p., °C.	Mm.	Formula	Analyses, % Calcd.	Found
2-(2-Diethylaminoethylmercapto)-quinoline	113	0.05	$C_{15}H_{20}N_2S$	......	...
2-(3-Diethylaminopropylmercapto)-4-methylquinoline	169	0.40	$C_{17}H_{24}N_2S$	N, 9.71	9.67
4-(2-Diethylaminoethylmercapto)-3,6-dimethylquinoline[e]	150	0.06	$C_{17}H_{24}N_2S$	N, 9.71	9.73
7-Chloro-4-(2-diethylaminoethylmercapto)-quinoline[f]	140	0.34	$C_{15}H_{19}ClN_2S$	N, 9.50	9.23
4-(2-Diethylaminoethylmercapto)-3,8-dimethylquinoline	152–155[i]	0.26	....	......	...
7-Chloro-4-(3-diethylaminopropylmercapto)-quinoline[j]	140	0.04	$C_{16}H_{21}ClN_2S$	N, 9.07	8.90
7-Chloro-4-(3-N-piperidylpropylmercapto)-quinoline[l]	152	0.03	$C_{17}H_{21}ClN_2S$	N, 8.73	8.44
7-Chloro-4-(4-diethylaminobutylmercapto)-quinoline	146	0.02	$C_{17}H_{23}ClN_2S$	N, 8.68	8.66
7-Chloro-4-(5-isopropylaminopentylmercapto)-quinoline[m]	...	..	$C_{17}H_{23}ClN_2S$	N, 8.68	8.64
7-Chloro-4-(4-diethylamino-1-methylbutylmercapto)-quinoline	182	0.45	$C_{18}H_{25}ClN_2S$	C, 64.16	64.45
7-Chloro-4-(3-diethylaminopropylmercapto)-3-methylquinoline	176	0.47	$C_{17}H_{23}ClN_2S$	N, 8.68	8.64
7-Chloro-4-(2-diethylaminoethoxy)-quinoline[n]	...	..	$C_{15}H_{19}ClN_2O$	N, 10.05	9.96
7-Chloro-4-(4-diethylamino-1-methylbutyloxy)-quinoline	160[i]	0.25	....	......	...
7-Chloro-4-(2-(2-diethylaminoethylmercapto)-ethoxy)-quinoline[r]	186–188[i]	0.08	....	......	...

a number of which were originally prepared in the present work. A few acridyl sulfides, analogous to those presently described, have been prepared by Das-Gupta.[4]

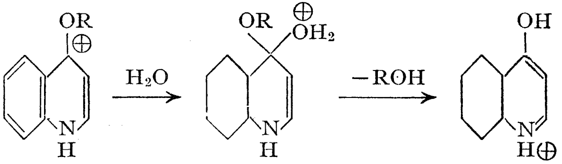
In the present work a series of quinolines and acridines substituted by ω-dialkylaminoalkylmercapto side chains has been prepared by reaction between a sodio-ω-dialkylaminoalkanethiol and a suitable nitrogen heterocyclic chloro compound. These syntheses offered little difficulty, and the desired products were usually isolated readily in high yields by distillation or crystallization.[5]

The synthesis of the oxygen-linked side chains from a sodio-ω-tertiary-aminoalcoholate and a nitrogen heterocyclic chloro compound[6] (*e. g.*, 4-chloroquinoline) gave excellent yields of crude products; purification proved difficult, however, since distillation even in high vacuum at comparatively low temperatures brought about partial thermal cleavage of the oxygen linkage. The oxygen linkage was also readily cleaved by acids, the ease of cleavage being related to the type of nitrogen heterocyclic nucleus and the type of basic side chain. It is apparent that these compounds can exist as resonance hybrids (I–III) and that the hybrid forms II and III are vinylogs of an imino ether rather than the normal phenolic ether type.



I II III

Hydrolytic cleavage in acid solution probably involves the attack of a water molecule on IV, the proton-coupled form of II, to give V, with subsequent release of an alcohol molecule to yield the hydroxyquinoline, VI.



IV V VI

The hybrid form III will not undergo cleavage, since it merely forms an oxonium salt in acid solution. For the 9-dialkylaminoalkoxyacridines the nuclear increase in resonance energy involving the third ring, and consequent stabilization of the forms analogous to II and III, decreases the stability of the oxygen-linked side chain compounds to the point at which they will undergo hydrolytic cleavage even with weak acids at room temperature within a few hours. A similar situation prevails with the corresponding sulfur-linked side chain compounds, although to a lesser degree because of the increased resonating property of the sulfur atom as compared with the oxygen atom, and consequent greater stabilization of the form corresponding to III.

It is interesting to note that in the corresponding imino-linked series the quinoline compounds are stable in acid solution for an indefinite period, whereas an acridine such as quinacrine does hydrolyze slowly under these conditions. This increased resistance of the imino-linked series toward hydrolytic cleavage is readily related to the greater stabilization of the resonance forms analogous to III, this stability being greater in the quinolines than in the acridines. Reaction rate

---

(4) Das-Gupta, *J. Indian Chem. Soc.*, **20**, 137 (1943); *C. A.*, **37**, 6665 (1943).

(5) Gilman and co-workers (THIS JOURNAL, **67**, 1845 (1945)) have reported that the treatment of 2-chloroquinoline with 2-diethylaminoethanethiol or the corresponding 3-propane analog, in an ethanolic solution of sodium ethoxide, results in the formation of the corresponding bis-(diethylaminoalkyl)-disulfides and not the expected quinolyl sulfides. This discrepancy with the present work cannot by explained.

(6) The converse reaction between the nitrogen heterocyclic hydroxy compound and an ω-dialkylaminoalkyl halide leads exclusively to N-substitution in most cases. *cf.* U. S. Patent 1,941,312

TABLE II (*Continued*)

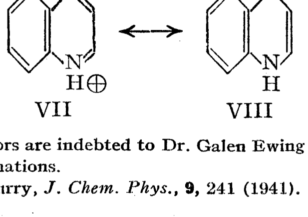
Base Analyses, % Calcd.	Base Analyses, % Found	Dipicrate M. p., °C.	Dipicrate Analyses, % Calcd.	Dipicrate Analyses, % Found	Salt M. p., °C.	Salt Analyses, % Calcd.	Salt Analyses, % Found	Salt Analyses, % Calcd.	Salt Analyses, % Found
S, 12.31	11.72	148–150^{a}	S, 6.55	6.75	106.5–107.5^{b}	N, 6.13	5.92	S, 7.02	7.21
......	...	130–131	S, 4.20	3.99	198–201^{c,d}	N, 7.76	7.67	Cl, 19.63	19.67
S, 11.12	11.00	164–165	S, 4.20	4.05	210–212.5^{c}	N, 7.76	7.80	Cl, 19.63	19.70
C, 61.10	61.31	213–214^{d}	N, 3.72^{g}	3.68	153.5–157.5^{b}	^{h}			
H, 6.50	6.73								
......	...	177–179	S, 4.20	4.31	188–190^{c}	N, 7.76	7.56	S, 8.87	8.86
S, 10.38	10.50	215–216	S, 4.18	4.33	175–178^{c}	S, 8.40	8.60	Cl, 18.57^{k}	18.53
S, 9.99	10.31	238–240^{d}	S, 4.11	4.40	227–228^{b,d}	S, 6.20	6.43	....	...
S, 9.93	9.96	195–196^{d}	S, 4.10	4.40	....	.....	..	....	...
S, 9.93	9.92	185–186	S, 4.10	4.13	224.8–225.4^{c}	N, 7.08	6.90	Cl, 17.91^{k}	17.63
H, 7.48	7.51	175–176	Cl, 4.46	4.44	....	.....	..	....	...
S, 9.93	9.95	196–197^{d}	S, 4.10	4.11	193–196^{c,d}	N, 7.08	7.10	Cl, 17.91^{k}	17.78
Cl, 12.72	12.44	211–212^{d}	N, 11.40^{p}	11.46	172–174^{c}	N, 7.97	7.76	Cl, 20.16^{k}	19.81
......	...	188–189	Cl, 4.55	4.55	112–114^{d,q}	Cl, 6.91	6.94	....	...
......	...	178–179	S, 4.02	4.04	103–105^{s}	N, 4.71	4.47	Cl, 5.96	5.98

[a] This compound was exceptional in that it formed only a monopicrate. [b] Diphosphate. [c] Dihydrochloride. [d] With decomposition. [e] Chloroquinoline: ref. 13. [f] M. p. 15–16° (from Skellysolve A). [g] Basic nitrogen by titration with perchloric acid in glacial acetic acid. [h] Calcd.: H_3PO_4, 39.9. Found: H_3PO_4, 40.5. [i] With extensive decomposition, see text. [j] M. p. 20–21° (from Skellysolve A). [k] Ionic halogen only. [l] M. p. 46–48° (from Skellysolve A). [m] M. p. 39° (from Skellysolve A–Skellysolve B, 10:1). [n] M. p. 34.5–35.0° (from Skellysolve B). The compound crystallized from dilute alcohol as a hydrate, m. p. 62–63°, which effloresced slowly at 25° and under conditions of low humidity to give the anhydrous form. [p] Nitro nitrogen by titanous chloride titration. [q] Citrate. [r] Side chain: Clinton, *et al.*, THIS JOURNAL, 67, 594 (1945). [s] Dihydriodide.

measurements on these three types of compounds would undoubtedly furnish interesting results.

A representative number of the compounds prepared in the present work were also investigated spectrophotometrically. These data and data on certain analogous imino-linked compounds are given in Table I.[7]

From these data it is readily apparent that the substitution of oxygen for the imino-linkage causes a pronounced hypsochromic and hypochromic effect coupled with diminution in the number of principal maxima. These effects are the result of the decreased number of resonance forms involved in the proton-coupled form of the molecule, as compared with a compound such as no. 7 (Table I). As would be expected,[8] the higher inherent resonance energy of the sulfur atom as compared to the oxygen atom produces a large bathochromic and hyperchromic effect (compare nos. 2 and 5), and indeed the principal maxima are further into the visible than those observed with the corresponding imino-linked compounds if weighting effects are taken into account. This indicates that the resonance hybrids, VII–VIII, possess a higher potential energy than the corresponding imino-linked compounds. This effect, however, is not nearly so apparent in the acridine series, in which the resonance of the acridine nucleus contributes a much larger part of the total resonance energy. Diminution in number of principal maxima in the sulfur-linked series is here again evident, however.



VII VIII

As would be expected, the use of aqueous base as solvent produces the normal hypsochromic shift (compare nos. 5, 6 and 7, 8), although the data available are insufficient to indicate possible isosbestric points. Certain anomalies are also apparent, *e. g.*, the disappearance of the twinned principal maxima in nos. 2 and 3, although this effect may be only apparent, due to lack of sufficient resolution.

A number of the compounds prepared in the present work were screened against Avian malaria with negative results. However, in screening tests against certain other organisms, including in particular *Brucella abortus*, some of the compounds proved highly active *in vitro*.[9]

Experimental[10]

Sulfur-linked Side Chains.—These compounds were prepared by the reaction between a sodio-dialkylaminoalkanethiol and a nitrogen heterocyclic chloro compound in absolute alcohol solution. Examples of this method follow; most of the compounds prepared are described and characterized in Table II. The yields in all cases were nearly quantitative. All but one of the thiols used in the present work have been previously described.[11]

---

(7) The authors are indebted to Dr. Galen Ewing and staff for the spectra determinations.

(8) *Cf.* McMurry, *J. Chem. Phys.*, **9**, 241 (1941).

(9) Private communication from Drs. C. A. Lawrence and E. W. Dennis.

(10) All melting points and boiling points are corrected. The authors are indebted to Mr. Morris E. Auerbach and staff for the analyses.

(11) Albertson and Clinton, THIS JOURNAL, **67**, 1222 (1945); Clinton and Salvador, *ibid.*, **68**, 2076 (1946); Laskowski and Clinton, *ibid.*, **69**, 519 (1947).

5-Isopropylaminopentanethiol.—This compound was prepared from 5-isopropylaminopentyl chloride hydrochloride by methods previously described.[11] **5-Isopropylaminopentylisothiouronium chloride hydrochloride** (94% yield) formed rosets of white needles from absolute alcohol–acetone, m. p. 149–151°.

Anal. Calcd. for $C_9H_{23}Cl_2N_3S$: N, 15.21; Cl, 25.66. Found: N, 15.48; Cl, 25.40.

The isothiouronium salt was converted in 73% yield to the thiol: colorless oil, b. p. 94.0° at 8 mm., $n^{25}{}_D$ 1.4682.

Anal. Calcd. for $C_8H_{19}NS$: N, 8.68. Found: N, 8.52.

The **picrolonate** formed large, blunt yellow needles from alcohol, m. p. 175–177°.

Anal. Calcd. for $C_{18}H_{27}N_5O_5S$: basic nitrogen, 3.29. Found: basic nitrogen, 3.27.

7-Chloro-4-(2-diethylaminoethylmercapto)-quinoline.—Ten and one-tenth grams of 2-diethylaminoethanethiol was added in one portion to a warm solution of 1.75 g. of sodium in 50 ml. of absolute alcohol, contained in a 250-ml., three-necked flask equipped with a reflux condenser, mechanical stirrer and dropping funnel. The solution was heated under reflux with stirring and there was added dropwise during twenty minutes a solution of 15.0 g. of 4,7-dichloroquinoline[12] in 100 ml. of absolute alcohol. There was an almost immediate precipitation of sodium chloride. The mixture was refluxed and stirred for an additional four hours, cooled, and then filtered. After removal of the alcohol *in vacuo* the residual orange oil was distilled *in vacuo.*

4-(2-Diethylaminoethylmercapto)-3,8-dimethylquinoline.—The reaction between sodio-2-diethylaminoethanethiol and 4-chloro-3,8-dimethylquinoline[13] was carried out as described above. The crude product, after removal of the alcohol *in vacuo,* was dissolved in 5% hydrochloric acid and the solution was made neutral to congo red by the addition of solid sodium acetate. The mixture was extracted thoroughly with ether to remove any unreacted chloroquinoline, the aqueous layer made strongly basic with 35% sodium hydroxide solution, and the precipitated oil extracted with ether. After drying and removal of the ether *in vacuo* the residual oil[14] was dissolved in alcohol and treated with somewhat more than two equivalents of picric acid in alcoholic solution. The resulting dipicrate crystallized from glacial acetic acid–alcohol solution in long, feathery, canary-yellow needles.

The dipicrate was reconverted to the base with 10% hydrochloric acid–ethyl acetate, etc., in the usual manner, and the recovered base was treated in acetone solution with an excess of ethereal anhydrous hydrogen chloride (15% by weight). Crystallization from absolute alcohol–ethyl acetate–ether gave short, pale yellow needles of the dihydrochloride.

The dihydrochloride loses one hydrogen chloride molecule on prolonged heating at 100° *in vacuo.*

6-Chloro-9-(2-diethylaminoethylmercapto)-2-methoxyacridine.—Fifty-three and two-tenths grams of 2-diethylaminoethanethiol was added to a solution of 9.2 g. of sodium in 1000 ml. of absolute alcohol. One hundred eleven and two-tenths grams of 6,9-dichloro-2-methoxyacridine was added to the resulting warm solution in one portion, and the heterogeneous mixture was refluxed and stirred for seven hours. Solution of the dichloroacridine was complete after about two hours; sodium chloride precipitation was rapid. After filtration the filtrate was concentrated *in vacuo* to a volume of 500–600 ml., made turbid by the addition of water, and cooled in ice. The mixture readily crystallized on scratching, and further dilution with water precipitated the base completely. After thorough drying the base was crystallized twice from Skellysolve B at −50°, to give a nearly quantitative yield of product as small yellow needles, m. p. 57–58°.

Anal. Calcd. for $C_{20}H_{23}ClN_2OS$: N, 7.47; Cl, 9.46. Found: N, 7.44; Cl, 9.40.

The monohydrochloride was precipitated from an acetone solution of the base by the addition of exactly a one mole proportion of concentrated hydrochloric acid; yellow needles, m. p. 200.5° (dec.).

Anal. Calcd. for $C_{20}H_{23}ClN_2OS \cdot HCl$: N, 6.81; Cl, 17.24. Found: N, 6.71; Cl, 17.02.

Attempts to prepare the dihydrochloride gave an orange-red crystalline product of m. p. 218–200° (dec.), containing varying amounts of water and more than two moles of hydrogen chloride (compare ref. 4).

6-Chloro-9-(4-diethylamino-1-methylbutylmercapto)-2-methoxyacridine.—This compound was prepared by a method analogous to the above procedure. The free base could not be obtained crystalline. The **monohydrochloride** formed orange-yellow needles, m. p. 167–168°.

Anal. Calcd. for $C_{23}H_{29}ClN_2OS \cdot HCl$: N, 6.18; S, 7.07. Found: N, 5.81; S, 6.93.

Oxygen-Linked Side Chains.—These compounds were prepared by the reaction between a sodium alcoholate and a nitrogen heterocyclic chloro compound in toluene solution. An example is given in detail below; most of the compounds prepared appear in Table II.

7-Chloro-4-(4-diethylamino-1-methylbutyoxy)-quinoline.—Sixty-three and six-tenths grams of redistilled 4-diethylamino-2-pentanol was added in one portion to a refluxing, stirred suspension of 6.9 g. of sodium in 100 ml. of dry toluene. After three hours the sodium had completely reacted. There was then added, in one portion, 59.4 g. of dry 4,7-dichloroquinoline, and the resulting clear solution was refluxed and stirred for twenty-four hours. The cooled mixture was filtered, and after removal of toluene *in vacuo* the residual oil was dissolved in 400 ml. of cold 4 *N* hydrochloric acid. The clear solution was neutralized to congo red by the addition of solid sodium acetate and extracted twice with ether. The aqueous layer was made strongly basic with 35% sodium hydroxide solution and the precipitated oil taken up in ether. After drying, the ether was removed *in vacuo* and the residual oil distilled up to a bath temperature of 150° at 0.20 mm. to remove the excess of 4-diethylamino-2-pentanol. The residual crude base was converted to the dipicrate by treatment with excess picric acid in alcohol solution.

The dipicrate was reconverted to the base by means of cold 10% hydrochloric acid–ethyl acetate, and after recovery from the hydrochloric acid solution the base was treated in absolute alcohol solution with a slight excess of citric acid monohydrate. The citrate formed rosets of white needles from absolute alcohol–ethyl acetate.

6-Chloro-9-(2-diethylaminoethoxy)-2-methoxyacridine was obtained in good yield in the above manner. A small amount of acridone (insoluble in toluene) also was formed in the reaction. The dried crude product was crystallized twice from Skellysolve B at −20°, forming bright yellow needles, m. p. 60.5–61.5°.

Anal. Calcd. for $C_{20}H_{23}ClN_2O_2$: N, 7.81; Cl, 9.88. Found: N, 7.81; Cl, 9.67.

Summary

There have been described a number of quinolines and acridines substituted by basic side chains linked to the nucleus by oxygen or sulfur. The spectroscopic relation of these compounds to the analogous imino-linked series, and their hydrolytic cleavage has been investigated.

RENSSELAER, NEW YORK RECEIVED JULY 25, 1947

---

[12] Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

[13] Steck, Hallock and Holland, *ibid.*, **68**, 129, 132 (1946). The authors are indebted to Dr. Edgar Steck for a supply of this material.

[14] When an attempt was made to distill this oil at 175° (bath) and 0.06 mm., extensive decomposition ensued, with distillation of a mixture of solid and a mobile, low boiling compound.

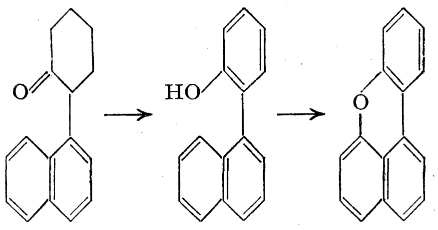
[CONTRIBUTION FROM THE CENTRAL EXPERIMENT STATION, U. S. BUREAU OF MINES]

Aromatic Cyclodehydrogenation. VI. Synthesis of Ring Oxygen Compounds[1]

BY MILTON ORCHIN[2]

In an effort to confirm the structure of 2-(1-naphthyl)-cyclohexanone, I, required in another investigation, this compound was dehydrogenated with palladium-on-charcoal in the liquid phase in an attempt to obtain the known 1-phenylnaphthalene. The benzene solution of the product from the reaction fluoresced in ordinary light and showed a brilliant blue fluorescence in ultraviolet light. The strongly fluorescent material was separated by chromatographic adsorption and it was possible to isolate from this fraction a colorless crystalline compound, $C_{16}H_{10}O$, melting point 108°; picrate, deep red needles, melting point 123°. The intense fluorescence of the compound, its melting point and composition, and the color and melting point of its picrate all correspond exactly to the properties of 1,9-benzoxanthene, III, isolated from coal tar by Kruber.[3] Kruber's proof of structure consisted of hydrogenation of the benzo ring followed by oxidative degradation of it to the known xanthone.

The formation of III from I can be explained by presuming the intermediate formation of 2′-hydroxy-1-phenylnaphthalene, II, followed by the unusual loss of hydrogen between the hydroxyl group and position 8 of the naphthalene nucleus

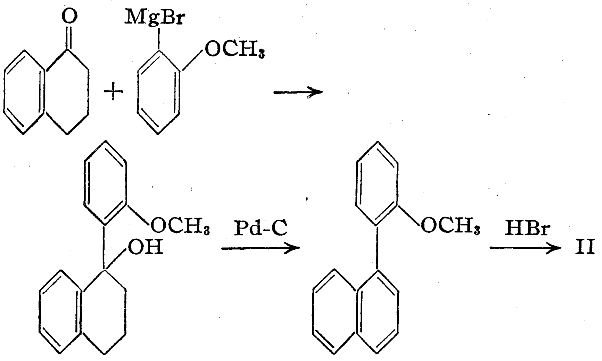


I II III

In order to substantiate this mechanism, 2′-hydroxy-1-phenylnaphthalene, II, was synthesized and treated with palladium-on-charcoal under the same conditions as prevailed in the similar treatment of I. The compound presumed to be 1,9-benzoxanthene, identical with that obtained from I, was isolated from the reaction mixture.

The intramolecular loss of hydrogen between a suitably situated hydroxyl group and an aromatic nucleus presents interesting synthetic possibilities. In an extension of the reaction, *o*-phenylphenol was treated with palladium-on-charcoal and diphenylene oxide was isolated in 8% yield from the products of the reaction. Diphenyl was also present in the products, indicating that the hydrogen liberated in the ring closure was utilized in a hydrogenolysis reaction. When the reaction was carried out in a sealed tube a 14% yield of diphenylene oxide and an 8% yield of diphenyl were obtained.

The synthesis of 2′-hydroxy-1-phenylnaphthalene was achieved by a three-step process, starting with the reaction between *o*-anisylmagnesium bromide and 1-tetralone



IV V

The carbinol, IV, was obtained in 74% yield. One-step dehydration–dehydrogenation with palladium-on-charcoal gave V directly in excellent yield. The over-all yield was not improved by the isolation of the intermediate 1-*o*-anisyl-3,4-dihydronaphthalene. Both the methyl ether, V, and the hydroxy compound, II, formed two different crystalline modifications. II was not extracted from its benzene solution by aqueous alkali.

Experimental[4]

2-(1-Naphthyl)-cyclohexanone, I.—1-Naphthylmagnesium bromide was prepared from 105 g. 1-bromonaphthalene (purified by fractionation), 13 g. magnesium, 200 cc. of dry ether and 350 cc. dry benzene. To this Grignard reagent there was added, with stirring, 66.0 g. of *o*-chlorocyclohexanone.[5] The dropwise addition of the ketone caused a vigorous reaction. After all the ketone was in, the mixture was refluxed for sixteen hours, then poured onto ice and steam distilled. Twenty-nine grams of naphthalene was collected in the distillate. The residue was a tacky red solid. It was taken up in ether, the ether solution washed with hydrochloric acid and water, dried, and the ether evaporated. The residue was distilled and 50 g. of a very viscous oil was collected between 170–240° (1 mm.). Since attempts to obtain crystalline material from this residue were unsuccessful, the mixture was dissolved in alcohol and treated with 25 g. of semicarbazide hydrochloride and 18.3 g. of sodium acetate. From the more soluble fractions of the semicarbazone mixture, 4.86 g. of semicarbazone, m. p. 213–215°, was obtained. To 4.5 g. of this semicarbazone there was added 25 cc. of water and 50 cc. of concentrated hydrochloric acid, and the mixture was refluxed for one hour. The aqueous solu-

---

(1) Published by permission of the director, U.S. Bureau of Mines, Department of the Interior. Not copyrighted.

(2) Organic chemist, Synthetic Liquid Fuels, Research and Development Division, U. S. Bureau of Mines.

(3) Kruber, *Ber.*, **70**, 1556 (1937).

(4) All melting points corrected. Analyses marked (a) by Arlington Laboratories, (p) by Mr. G. L. Stragand of the University of Pittsburgh.

(5) Secured from the Farchan Research Laboratories, 609 E. 127th Street, Cleveland 8, Ohio.

tion was decanted from the oil on the sides of the flask, the oil washed with water, and the water decanted completely. The oil was refluxed with benzene, the benzene solution concentrated, and petroleum ether added. On cooling, 3.25 g. of crystalline material, m. p. 81–84°, was obtained. The sample for analysis was crystallized twice from petroleum ether and had melting point 83.5–85.0°. *Anal.*[4a] Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.2. Found: C, 85.9; H, 7.2. The semicarbazone of the pure 2-(1-naphthyl)-cyclohexanone was obtained from dioxane-ethanol as a white powder, m. p. 213–215° (put in the bath at 204°). *Anal.*[4a] Calcd. for $C_{17}H_{19}N_3O$: N, 15.8. Found: N, 15.3.

1,9-Benzoxanthene from 2-(1-naphthyl)-cyclohexanone.—A mixture of 1.0 g. of the ketone, I, and 0.1 g. of 30% palladium-on-charcoal[6] was heated at 310–320° for forty minutes and at 325–340° for about twenty minutes. During this time about 133 cc. (N. T. P.) of hydrogen was evolved (1.4 moles of hydrogen per mole compound). The mixture was dissolved in benzene, filtered, and the filtrate extracted with aqueous potassium hydroxide. Acidification of the alkaline extract gave a trace of material which was discarded. The neutral fraction was chromatographed. Two brands were observed in the column. The less strongly adsorbed band fluoresced brilliantly in ultraviolet light; it was separated and eluted with benzene. The benzene was replaced with methanol and on cooling the solution about 60 mg. of colorless needles, m. p. 107–108°, was obtained. Recrystallization from methanol gave fine needles, m. p. 107.4–108.0°. The picrate was crystallized from ethanol and had the melting point 123.0–123.8°. The complex with *s*-trinitrobenzene was obtained as beautiful, brilliant red crystals (from methanol), melting point 147.8–148.4°. *Anal.*[4a] Calcd. for $C_{16}H_{13}N_3O_7$: N, 9.7. Found: N, 10.4. The ultraviolet absorption spectrum[7] of III (Fig. 1), its melting point, the melting points of the picrate and *s*-trinitrobenzene complex, were identical with those of III obtained from II as described below.

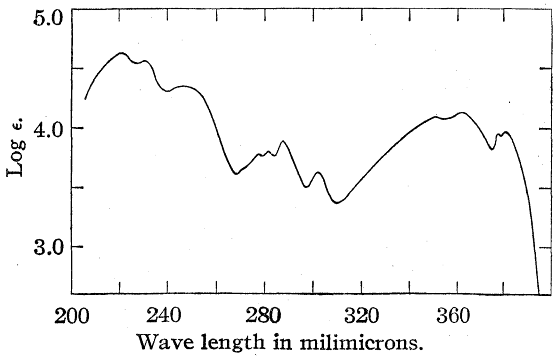


Fig. 1.—Ultraviolet absorption spectrum of 1,9-benzoxanthene.

1-*o*-Anisyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene, IV.—*o*-Anisylmagnesium bromide was prepared in quantitative yield (titration) from 82.2 g. of freshly distilled *o*-anisyl bromide, 12.0 g. of magnesium and 325 cc. of dry ether. To the clear brown-black solution there was added dropwise, with stirring, a solution of 64.0 g. of pure vacuum fractionated 1-tetralone in 150 cc. of dry ether.[8] After all of the tetralone was added the mixture was refluxed for seventeen hours; during this time about 200 cc. of ether was replaced with an equivalent volume of benzene. The mixture was poured onto ice and ammonium chloride. The organic layer was separated, washed well with water and saturated sodium chloride solution, and filtered through sodium sulfate. After removal of most of the solvent *in vacuo*, beautiful colorless crystals separated; these weighed 30.58 g. and melted at 96.0–100.2°. Concentration of the mother liquor gave 47.04 g. of additional carbinol of the same melting point. The mother liquor was evaporated and the residue distilled. The fraction of distillate boiling at 145–160° (2 mm.) was dehydrogenated with sulfur and 4.61 g. of 1-*o*-anisylnaphthalene, V, identical with that prepared below, was obtained. The total yield of carbinol, IV, was thus 74%. The sample of IV taken for analysis was crystallized from petroleum ether and had melting point 98.5–100.0°. *Anal.*[4a] Calcd. for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1; methoxyl, 12.2. Found: C, 80.5; H, 6.9; methoxyl,[9] 12.2.

1-*o*-Anisyl-3,4-dihydronaphthalene.—A mixture of 10 g. of IV and 50 cc. of 90% formic acid was refluxed for one hour. Separation and distillation of the dihydro compound gave 7 g. of a colorless glass, boiling point 160–162° (2–3 mm.), $n^{20}\text{D}$ 1.6265. Scratching caused crystallization and after recrystallization from petroleum ether the compound was obtained as thick, colorless crystals, m. p. 66.6–67.6°. *Anal.*[4a] Calcd. for $C_{17}H_{16}O$: C, 86.4; H, 6.8; methoxyl, 13.4. Found: C, 85.9; H, 6.9; methoxyl,[9] 13.2.

1-*o*-Anisylnaphthalene.—(a) A mixture of 30.0 g. of the carbinol, IV, and 1.0 g. of 30% palladium-on-charcoal[6] was heated with stirring at 240–250° for two hours, and for forty-five minutes at 250–300°. About 2 g. of water distilled from the mixture. The mixture was dissolved in benzene and filtered, and the benzene replaced with alcohol. Concentration of the alcohol solution gave 25.5 g. of colorless crystalline material, m. p. 87–90°. The mother liquor gave 0.3 g. additional material, thus making the total yield of crude material 93.5%. Recrystallization from alcohol gave crystals, m. p. 91.2–92.6°. *Anal.*[4a] Calcd. for $C_{17}H_{14}O$: C, 87.2; H, 6.0; methoxyl, 13.2. Found: C, 86.5; H, 5.9; methoxyl,[9] 13.2. During a recrystallization of this material from petroleum ether it was noted that the crystals appeared different from those previously obtained. These crystals had melting point 98.6–99.8°. When some of the low-melting form was dissolved in ethanol and the solution seeded with the high-melting form, material of melting point 98.6–99.8° was obtained. When the high-melting form was dissolved in ethanol and the solution seeded with the low-melting form, material of melting point 91.2–92.6° was obtained. When the low-melting form was melted and allowed to cool, the melting point of the solidified material was 91.0–98.5°.

(b) A mixture of 2.0 g. of 1-*o*-anisyl-3,4-dihydronaphthalene and 0.2 g. of palladium-on-charcoal[6] was heated at 280–320° for ninety minutes. During this time the theoretical quantity of hydrogen was evolved. Distillation of the mixture gave 1.77 g. of oil which crystallized on standing. Crystallization from benzene–ethanol gave material, m. p. 90.8–92.4°, identical with that obtained from the one step dehydration–dehydrogenation of IV.

2′-Hydroxy-1-phenylnapthalene, II.—A solution of 8.84 g. of V in 250 cc. of acetic acid and 90 cc. of 48% hydrobromic acid was refluxed for five hours. The solution was poured onto ice and the mixture extracted with ether–benzene. The organic layer was washed successively with water, sodium bicarbonate, water, and saturated sodium chloride solution. After drying the solvent was evaporated and the residue distilled to give 7.85 g. (94.5%) of colorless oil, boiling point 163–170° (3 mm.). The oil was crystallized with difficulty by cooling and scratching. On attempted recrystallization the compound separated in beautiful needles from alcohol or petroleum ether, but as soon as the solvent was removed the crystals lost their shape and became semi-fluid. If the resulting sticky material was scratched and allowed to stand, firm crystalline material was again obtained which had melting point 55–60°. A small sample was purified by chromatography on alumina–celite and the pure sample

---

(6) Linstead and Thomas, *J. Chem. Soc.*, 1127 (1940).

(7) We wish to thank Dr. R. A. Friedel for the spectrum data.

(8) We wish to thank Dr. Gilbert Thiessen and The Koppers Company for a generous gift of 1-tetralone.

(9) We wish to thank Mr. E. O. Woolfolk for this analysis and for valuable assistance with a portion of the experimental work.

recrystallized twice from petroleum ether by seeding with previously crystallized material. The final sample had melting point 60–61.5°. *Anal.*[4p] Calcd. for $C_{16}H_{12}O$: C, 87.2; H, 5.5. Found: C, 86.7; H, 5.8.

In one demethylation experiment the benzene solution of the products was extracted with alkali. Acidification of the alkaline extract gave only a small quantity of II; the bulk of II was found in the neutral fraction.

An infrared absorption spectrum showed a strong band in the 2.8 micron region, thus establishing the presence of a hydroxyl group.[7]

1,9-Benzoxanthene from 2′-Hydroxy-1-phenylnaphthalene.—A mixture of 3.0 g. of II and 0.3 g. of palladium-on-charcoal[6] was heated in a nitrogen atmosphere for two hours at 320–350°. The mixture was treated with benzene and filtered. To the concentrated benzene solution there was added 0.7 g. of 2,4,7-trinitrofluorene.[10] On cooling there separated 1.3 g. of dark brown crystals, m. p. 178–190°. Recrystallization from acetic acid gave 1.0 g. of the crystalline complex of 1,9-benzoxanthene and 2,4,7-trinitrofluorenone, m. p. 214.0–214.6°. The complex was dissolved in benzene and the solution poured onto a column of activated alumina. The benzoxanthene was eluted with benzene and the benzene solution evaporated to dryness, leaving 0.41 g. (13.5%) of III. Two crystallizations from ethanol gave the compound in long needles, m. p. 107.5–108.0°. *Anal.*[4p] Calcd. for $C_{16}H_{10}O$: C, 88.1; H, 4.6. Found: C, 87.8; H, 4.6.

Diphenylene Oxide from *o*-Phenylphenol.—A mixture of 5.00 g. of *o*-phenylphenol[11] was heated with 0.5 g. of 30% palladium-on-charcoal catalyst at 285–290° for three hours. The mixture was treated with petroleum ether and filtered. The filtrate was washed with aqueous alkali; acidification of the alkaline extract gave 4.25 g. of recovered phenylphenol. The petroleum ether solution containing the neutral material was dried and chromatographed on a mixture of activated alumina and celite. The components of the mixture were selectively eluted from the column by using mixtures of petroleum ether–benzene containing increasing quantities of benzene; percolate receivers were changed at 100-cc. intervals. The solutions in all receivers were separately evaporated to dryness and the residue, if any, weighed and its melting point determined. The first fractions gave a total of 140 mg. of material, m. p. 66–69°; mixed melting point with diphenyl gave no depression. The later fractions gave a total of 400 mg. (8%) of diphenylene oxide, m. p. 81.5–83.0°; mixed melting point with authentic diphenylene oxide gave no depression. When 5.0 g. of phenylphenol was heated in a sealed tube at 315° for fourteen hours with 0.5 g. of palladium charcoal, a yield of 14% pure diphenylene oxide and 8% diphenyl was obtained. The balance of the material was unconverted phenylphenol.

Summary

Liquid phase treatment of 2-(1-naphthyl)-cyclohexanone with palladium-on-charcoal gave a small yield of a compound whose properties were identical with those reported for 1,9-benzoxanthene. 2′-Hydroxy-1-phenylnaphthalene was probably the intermediate in this conversion since on similar treatment it also gave the compound presumed to be 1,9-benzoxanthene.

o-Phenylphenol when treated with palladium-on-charcoal gave diphenylene oxide. The intramolecular loss of hydrogen between an aromatic hydroxyl group and a suitably situated aromatic nucleus appears to be a general reaction.

1-*o*-Anisylnaphthalene was synthesized in 69% yield in two steps by condensing 1-tetralone with *o*-anisylmagnesium bromide and treating the resulting carbinol with palladium-on-charcoal.

PITTSBURGH, PENNSYLVANIA RECEIVED MAY 2, 1947

---

[10] Orchin and Woolfolk, THIS JOURNAL, **68**, 1727 (1946).

[11] Gift from the Dow Chemical Company.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of Some 6-Substituted-2-thiouracils[1]

BY MARY JACKMAN, A. J. BERGMAN AND S. ARCHER

Recently Astwood[1a] has shown that certain 6-alkyl- and 6-aralkyl-2-thiouracils, prepared by Anderson and co-workers[2] were powerful goitrogens. In the 6-alkyl-2-thiouracil series maximum activity was reached when the substituents ranged from ethyl through butyl and then dropped off rapidly. The most potent compounds, 6-*n*-propyl-2-thiouracil and 6-benzyl-2-thiouracil (an aralkyl derivative) appeared to be about ten times as active as thiouracil, heretofore considered to be the best antithyroid drug. Astwood screened only one 6-cycloalkyl derivative, namely, 6-cyclohexyl-2-thiouracil, and found that it was equal to thiouracil in effectiveness.

In the course of our work in this field we had occasion to prepare and test some thiouracils joined at the six position, either directly or through an aliphatic chain to alicyclic, heterocyclic and aromatic rings. In addition, 6-methylthiomethyl-2-thiouracil was prepared. The β-keto esters required for condensation with thiourea were prepared by one of the methods given below, depending upon the availability of the starting materials.

$$\mathrm{RCOOC_2H_5 + CH_3COOC_2H_5 \xrightarrow{NaOC_2H_5} RCOCH_2COOC_2H_5} \quad \text{(A)}$$

$$\mathrm{RCOCl + CH_3COCHNaCOOC_2H_5 \longrightarrow RCOCH(COCH_3)\,COOC_2H_5 \xrightarrow{NH_3} RCOCH_2COOC_2H_5} \quad \text{(B)}$$

$$\mathrm{RCOCH_3 + (C_2H_5)_2CO_3 \xrightarrow{NaNH_2} RCOCH_2COOC_2H_5} \quad \text{(C)}$$

Ethyl furoylacetate[3] and ethyl nicotinoylacetate[4] were prepared according to method A and then condensed with thiourea to form the corresponding

---

[1] Presented at the Atlantic City meeting of the American Chemical Society, April, 1947.

[1a] Astwood, Bissell and Hughes, *Endocrinology*, **37**, 460 (1945).

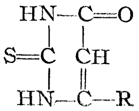
[2] Anderson, Halverstadt, Miller and Roblin, THIS JOURNAL, **67**, 2197 (1945).

[3] Wahl and Dahl, *Bull. soc. chim.*, [4] **13**, 279 (1913).

[4] Strong and McElvain, THIS JOURNAL, **55**, 818 (1933).

TABLE I

THIOURACILS



R =	Yield, %	M. p., °C. (cor.)	Solvent	Analyses, % Calcd. N	S	Found N	S	Activity
Cyclopropyl	60	236–239	Water	16.60	19.07	16.76	19.17	10
Cyclobutyl	77	211–212	Water	15.38	17.59	15.27	17.63	3
Cyclopentyl	69	220–222	Acetic acid-water	14.28	16.34	14.34	16.19	1–2
Cyclohexylmethyl	38	238–239.5	Acetic acid-water	12.49	14.29	12.50	14.37	5
Cyclohexylethyl	63	194–195.4	Alcohol	11.76	13.45	11.72	13.41	<1
Cyclohexylpropyl	72	181.5–182.8	Alcohol	11.10	12.70	10.84	12.64	1
Cyclopentylmethyl	68	197–200	Acetic acid-water	13.23	15.25	13.36	15.00	1
α-Phenylethyl	59	204.5–206	Acetic acid-water	12.06	13.80	12.12	14.00	2
α-Phenylpropyl	80	241.5–242.5	Acetic acid-water	11.38	13.02	11.44	12.78	1
Methylthiomethyl	60	231–233	Acetic acid-water	14.88	34.06	14.60	32.91[a]	<1
Furyl	23	284–286	Alcohol	14.43	16.51	14.56	16.38	1
β-Pyridyl·HCl	27	*ca.* 291	Hydrochloric acid	14.67	13.26	14.52	13.32[b]	<0.1

[a] When crystallized from dilute dioxane a strong mercaptan odor was noticed indicating that some decomposition was occurring. [b] The free base was obtained in the usual manner and crystallized from dilute acetic acid; m. p. >230°. *Anal.* Calcd.: N, 20.47; S, 15.62. Found: N, 20.30; S, 15.98. The base was suspended in water and hydrochloric acid added until it had all dissolved, the solution was filtered to remove traces of suspended matter and the hydrochloride was then thrown down by the addition of more acid.

TABLE II

β-KETO ESTERS, $RCOCH_2COOC_2H_5$

R =	Method	Yield, %	B. p. °C.	Mm.	Analyses, % Calcd. C	H	Found C	H
Cyclopropyl	C[a]	57	99–101	11	61.52	7.75	61.71	7.68
Cyclobutyl	B	19	112–115	19	63.51	8.29	63.90	8.02
Cyclopentyl	B	36	91–94	1.8	65.19	8.76	65.03	8.54
Cyclohexylmethyl	B	41	143–145	12	67.89	9.49	67.80	9.42
Cyclohexylethyl	B	27	115–118	0.8	68.99	9.80	69.30	9.64
Cyclohexylpropyl	B	17	139–142	2	69.96	10.07	70.06	10.07
Cyclopentylmethyl	B	28	105–106	2	66.64	9.15	66.20	8.89
α-Phenylethyl	B[b]	35	148–154	1.2	70.89	7.32	70.48	7.33
α-Phenylpropyl	B[b]	41	124–133	1.5	71.77	7.74	71.82	7.71
Methylthiomethyl	B[c]	12	142–150	29	47.70	6.87	48.05	7.06

[a] The yield of keto ester when prepared by method B was 24%. Both esters yielded identical thiouracils. [b] The required acids were prepared from ethyl phenylmalonate using the appropriate iodide as the alkylating agent, thus

$$C_6H_5CH(COOC_2H_5)_2 + RI \longrightarrow C_6H_5CR(COOC_2H_5)_2 \longrightarrow C_6H_5CR(COOH)_2 \longrightarrow C_6H_5C(R)COOH$$

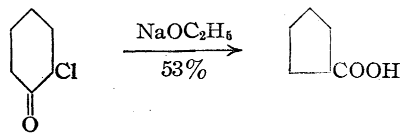
[c] The acid chloride was prepared according to the equations

$$HSCH_3COOH \longrightarrow CH_3SCH_2COOH \longrightarrow CH_3SCH_2COCl$$

thiouracils. It was hoped that a water-soluble thiouracil would prove to be active. Accordingly, 6-(3-pyridyl)-2-thiouracil was converted to the hydrochloride and tested as such. However, it was found that this substance was devoid of any antithyroid action.

With one exception, all of the other β-keto esters were prepared according to equation B. The method used was a slight modification of previously described procedures.[2,5] Whenever a water-insoluble amide was expected as a by-product in the ammonolysis step, the reaction mixtures were concentrated and the residues taken up in petroleum ether to effect a separation of the keto esters from solid material.

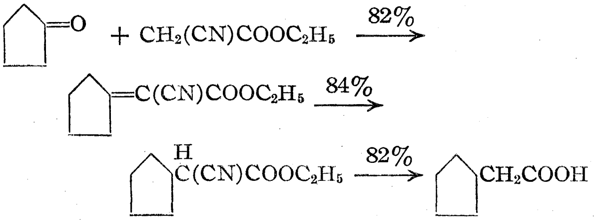
Cyclopentanecarboxylic acid was prepared conveniently from chlorocyclohexanone and sodium ethoxide, a reaction first described by Favorski.[6] The acid fraction obtained from the action of two moles of the base on one of the chloro-ketone was practically pure cyclopentanecarboxylic acid. The neutral fraction appeared to be a complex mixture and was not examined further. The next higher homolog was prepared by a three-stage synthesis from cyclopentanone in over-all yields of 57%.



---

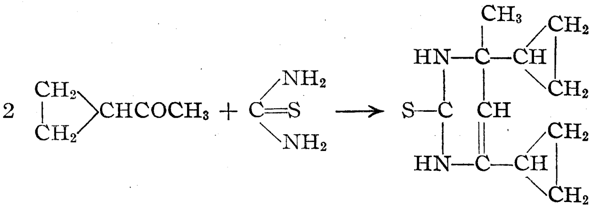
(5) Archer and Pratt, THIS JOURNAL, **66**, 1656 (1944).

(6) Favorski, *Chem. Zentr.*, **86**, I, 984 (1915).



Ethyl β-cyclopropyl-β-ketopropionate was prepared according to method B in 24% over-all yield based on the acid chloride. The carbethoxylation of cyclopropyl methyl ketone in the presence of sodium amide proved to be a more convenient synthesis since the yield in this one step method was 57%. Cyclopropyl methyl ketone condensed readily with ethyl oxalate to form the corresponding glyoxalate which, however, proved to be resistant to decarbonylation in the presence of iron and powdered soft glass.

In one experiment in which an impure sample of ethyl β-cyclopropyl-β-ketopropionate was used in the preparation of the thiouracil, an alkali-insoluble by-product separated when the reaction mixture was poured into water. This substance, m.p. 204–206°, was recovered unchanged after refluxing in either acid or basic media. We suggest that the compound is the thiotetrahydropyrimidine (I) since it could be prepared from cyclopropyl methyl ketone and thiourea in sodium ethylate solution.



I

This is in accord with the observations of Folkers and Johnson[7] who found that the major product arising from the interaction of acetophenone and urea was 4,6-diphenyl-4-methyl-2-oxotetrahydropyrimidine. This compound was also quite stable to the usual hydrolytic agents. Thiourea and acetophenone behaved similarly.[8] We are inclined to believe that (I) was formed from the ketone present as an impurity present in the keto-ester, since it was not encountered when pure ester was used in the preparation of 6-cyclopropyl-2-thiouracil.

Experimental[9]

Ethyl β-Cyclopropyl-β-ketopropionate.—To a stirred suspension of finely divided sodium amide (23.4 g.) in 150 ml. of dry ether cooled in an ice-bath there was added 25.2 g. of cyclopropyl methyl ketone. The mixture was then gently refluxed for one-half hour, cooled, and 70.8 g. of ethyl carbonate was added dropwise. The mixture was then refluxed for two hours, cooled and alcohol added to destroy excess sodium amide. The solution was added to 500 g. of ice and acidified to congo red. The organic layer was separated and the aqueous part extracted three times with ether. The combined ethereal extracts were washed with water, dilute sodium carbonate solution, again with water and then dried. After removal of the ether and a forerun consisting largely of ethyl carbonate the keto-ester was collected at 97.5–101° (11 mm.), 27 g. (57%). On redistillation almost all was collected at 99–101° (11 mm.).

Ethyl γ-Cyclopropyl-α,γ-diketobutyrate.—A mixture of 73 g. of ethyl oxalate and 42 g. of cyclopropyl methyl ketone was added dropwise to a solution of 11.5 g. of sodium in 150 ml. of absolute alcohol while the temperature was maintained below 40°. A yellow solid separated during the course of the reaction and after stirring for three hours the mixture was allowed to stand overnight. The pasty mass was added to 1.5 liters of water and the suspension was acidified with dilute sulfuric acid. When all the solid had disappeared the oil was drawn off and the aqueous layer then extracted with benzene. The combined organic layers were concentrated and the residue distilled at reduced pressure. Fifty grams of glyoxalate was collected at 149–154° (23 mm.) (55%). A fraction of b. p. 149° (23 mm.) was analyzed.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.59; H, 6.42.

6-Cyclopropyl-2-thiouracil.—After 131 g. of thiourea had dissolved in a stirred, boiling solution of 56.7 g. of sodium in 1225 ml. of absolute ethanol, 192 g. of *crude* ethyl β-cyclopropyl-β-ketopropionate was added dropwise in the course of one hour. Heating and stirring were continued overnight. Most of the alcohol was then removed and the residue added to 3 liters of water. The insoluble fraction was removed by filtration and the clear filtrate acidified to *p*H 3. The solid that separated was collected and crystallized from boiling water, wt. 97 g. (42%), m. p. 234–235° (cor.).

The alkali-insoluble fraction which weighed 14 g. was crystallized from alcohol twice; m. p. 204–206°. The melting point was not depressed when mixed with the compound described below.

Anal. Calcd. for $C_{11}H_{16}N_2S$: C, 63.43; H, 7.74; N, 13.45. Found: C, 63.51, 63.33; H, 7.97, 7.86; N, 13.26.

4,6-Dicyclopropyl-4-methyl-2-thiotetrahydropyrimidine.—A solution of 9.2 g. of sodium, 15.2 g. of thiourea and 32.8 g. of cyclopropyl methyl ketone in 200 ml. of ethanol was refluxed for three and one-half hours before being poured into 2 liters of water. The solid was filtered and recrystallized several times from ethanol, m. p. 207–208.2° (cor.).

Anal. Calcd. for $C_{11}H_{16}N_2S$: N, 13.45; S, 15.39. Found: N, 13.20; S, 15.38.

Cyclopentanecarboxylic Acid.—To a stirred solution of 83 g. of sodium in 2 liters of absolute alcohol there was added dropwise 240.5 g. of chlorocyclohexanone[10] over a period of several hours. The mixture was left overnight before the alcohol was removed on the steam-bath and replaced by an equal volume of water. The aqueous solution was extracted with ether and then acidified to *p*H 3. The oily acid that separated was gathered in ether, washed with water, dried over sodium sulfate and distilled. The acid boiled at 120–123° (27 mm.), wt. 110 g. (53%).

Ethyl Cyclopentylidenecyanoacetate.—A solution of 56.5 g. of ethyl cyanoacetate, 50.5 g. of cyclopentanone, 3.85 g. of ammonium acetate and 6 g. of acetic acid in 50 ml. of dry benzene was refluxed in an apparatus described by Cope[11] until the formation of water was complete. The mixture was cooled, extracted thoroughly with water and distilled to yield 72.3 g. (82%) of the unsaturated ester, b. p. 152–156° (18 mm.). The compound which

---

[7] Folkers and Johnson, THIS JOURNAL, **55**, 3367 (1933).

[8] Dziewonski, *et al.*, *C. A.*, **30**, 5227 (1936).

[9] All melting and boiling points are uncorrected unless otherwise specified. Analyses carried out under the supervision of M. E. Auerbach of this laboratory.

[10] Newman, Farbman and Hipsher, "Organic Syntheses," **25**, 22 (1945).

[11] Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, **63**, 3452 (1943).

solidified on cooling was recrystallized from petroleum ether, m. p. 55–57°.

Anal. Calcd. for $C_{10}H_{13}NO_2$: N, 7.82. Found: N, 7.54.

Cyclopentylacetic Acid.—When 17.9 g. of the above ester was reduced with the aid of Adams catalyst, there was obtained 15 g. of the saturated cyanoacetate. The ester (81 g.) was added dropwise with stirring to a boiling solution of 110 g. of potassium hydroxide in 130 ml. of water. The mixture was heated for six hours, cooled and acidified. The resulting di-acid was taken up in ether, washed with water and dried over sodium sulfate. The ether was removed and the residue heated to effect decarboxylation. The cyclopentylacetic acid was collected at 135–137° (27 mm.), yield, 47 g. (82%).

Summary

1. Twelve new 6-substituted thiouracils and their antithyroid activities are presented. Of the group 6-cyclopropyl-2-thiouracil and 6-cyclohexylmethyl-2-thiouracil appear to be the most interesting pharmacologically.

2. Ten new β-keto esters are described.

3. Convenient syntheses of cyclopentylacetic acid, cyclopentanecarboxylic acid and ethyl β-cyclopropyl-β-ketopropionate are reported.

4. A by-product formed in the reaction between crude ethyl β-cyclopropyl-β-ketopropionate and thiourea is shown to be 4,6-dicyclopropyl-2-thioketohydropyrimidine by an independent synthesis.

RENSSELAER, N. Y. RECEIVED MAY 9, 1947

[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

The Synthesis of Some 6-Substituted-2-thiouracils[1]

BY WILBUR H. MILLER, ALICE M. DESSERT AND GEORGE W. ANDERSON

The synthesis of 5- and 6-substituted-2-thiouracils from β-oxoesters and thiourea has been reported recently by Anderson, *et al.*[2] These compounds were evaluated in rats as antithyroid drugs[3] and several were found to be more active than the parent compound, 2-thiouracil, which has been used extensively for the treatment of hyperthyroidism in man.[4] In this paper several new 6-substituted-2-thiouracils are described. Some are closely related to the more active compounds previously reported.[2] Others are of new types in which various heterocycles are used as substituents.

These thiouracils have been prepared by condensing thiourea with the appropriate β-oxoester. For the preparation of most of these esters the *t*-butyl malonate method was used.[5] In several cases the acyl derivative of diethyl malonate was isolated along with the β-oxoester and these compounds are described in Table I. The acid chlorides were prepared in good yield using the appropriate acid and benzoyl chloride[6] or thionyl chloride.

Ethyl β-oxo-γ-(*p*-nitrophenyl)-butyrate was readily prepared by the acetoacetic ester method (ref. 2, Method A), but only a 28% yield in one of three attempts was obtained by the *t*-butyl malonate method. In the two unsuccessful experiments after adding *p*-toluenesulfonic acid large amounts of *p*-nitrophenylacetic acid were formed, apparently by decomposition of its *t*-butyl ester. Subsequent experiments showed that this ester was readily decomposed to the acid by *p*-toluenesulfonic acid in benzene, whereas the ethyl ester was stable. The β-oxoester on reaction with thiourea gave a product which could not be purified.

When ethyl β-oxo-β-(3-pyridyl)-propionate was prepared by the *t*-butyl malonate method the yield was low (14%) and appreciable quantities of an unidentified by-product (m. p. 161.5–162.5°) were obtained. This β-oxoester was obtained much more easily by the reaction between ethyl nicotinate and ethyl acetate[7] (25%).

When ethyl β-oxo-β-mesitylpropionate reacted with thiourea the thiouracil was not obtained and 75% of β-oxoester was recovered unchanged. The condensation for thiouracil formation perhaps occurs stepwise as in pyrazolone formation,[8] first by elimination of water from the β-oxoester and thiourea followed by a splitting out of alcohol from the intermediate compound. The two methyl groups *ortho* to the carbonyl in the mesityl portion of the ester may interfere at the first stage of the condensation either sterically or by reducing the activity of the ester through inductive effects.

The unsaturated β-oxoesters, ethyl 3-oxo-4-hexenoate, ethyl cinnamoylacetate and ethyl 3-oxo-5-hexenoate, yielded no definite product on the attempted reaction with thiourea. The last, prepared from allylmagnesium bromide and ethyl cyanoacetate, was not a pure product although it boiled over a very narrow range (Table I). When this product reacted with thiourea a 46% crude yield of 6-amino-2-thiouracil was obtained indicating the presence of ethyl cyanoacetate. No other thiouracil was found. The unsaturated esters were considered to be unstable under the usual

---

[1] Presented before the Division of Medicinal Chemistry of the American Chemical Society at the Atlantic City Meeting, April 17, 1947.

[2] Anderson, Halverstadt, Miller and Roblin, THIS JOURNAL, **67**, 2197 (1945).

[3] Astwood, Bissell and Hughes, *Endocrinology*, **37**, 456 (1945).

[4] Van Winkle, Hardy, Hazel, Hines, Newcomer, Sharp and Sisk, *J. Am. Med. Assoc.*, **130**, 343 (1946).

[5] Breslow, Baumgarten and Hauser, THIS JOURNAL, **66**, 1286 (1944).

[6] Brown, *ibid.*, **60**, 1325 (1938).

[7] Clemo and Holmes, *J. Chem. Soc.*, 1739 (1934).

[8] Torrey and Zanetti, *Am. Chem. J.*, **44**, 397 (1910).

TABLE I

PROPERTIES OF ETHYL β-OXOESTERS AND SUBSTITUTED MALONATES

Ethyl β-oxo	B. p., °C.	Mm.	Method	Yield, %	Formula	Analyses, %[f] Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
-γ-Methoxybutyrate	68–71	5	*t*-Butyl	40	$C_7H_{12}O_4$	52.5	51.8[g] 51.8	7.8	7.4 7.6
-γ-Ethylcaproate	95–96.5	9.3	*t*-Butyl	37	$C_{10}H_{18}O_3$	64.5	64.0	9.7	9.6
-γ-Phenylcaproate	126–128	1.5	*t*-Butyl	47	$C_{14}H_{18}O_3$	71.8	71.7	7.7	7.7
-γ-(*p*-Isopropylphenyl)-butyrate	135–140	0.5	*t*-Butyl	38	$C_{15}H_{20}O_3$	72.6	71.5[g] 71.5	8.1	8.3 8.1
-γ-(*p*-Chlorophenyl)-butyrate	139–140	1	*t*-Butyl	41	$C_{12}H_{13}O_3Cl$	59.9	59.2[g] 59.3	5.4	5.4
-β-(*m*-Chlorophenyl)-propionate	118–121	0.2	*t*-Butyl	43	$C_{11}H_{11}O_3Cl$	58.3	58.3	4.9	4.9
-γ-(2-Thienyl)-butyrate	143–145	5.5	[a]	22	$C_{10}H_{12}O_3S$	56.6	56.9	5.7	6.1
-γ-(*p*-Nitrophenyl)-butyrate	M. p. 78.5–		*t*-Butyl	28					
	79.5 (cor.)		[b]	22	$C_{12}H_{13}O_5N$	57.4	57.5	5.2	5.4
-β-Mesitylpropionate	125–125.5	1.5	[c]	41	$C_{14}H_{18}O_3$	71.8	71.9	7.7	7.7
-4-Hexenoate	105–108	15	*t*-Butyl[d]	46	$C_8H_{12}O_3$	61.5	61.5	7.8	7.5
-5-Hexenoate	89–90	10	Cyanacetic ester[e]		$C_8H_{12}O_3$	61.5	57.3	7.8	7.3
Diethyl malonates									
-α-Ethylbutyryl	134–135.5	8.8	*t*-Butyl	17	$C_{13}H_{22}O_5$	60.4	60.9	8.6	8.6
-α-Phenylbutyryl	148–152	1.2	*t*-Butyl	14	$C_{17}H_{23}O_5$	66.4	66.6	7.5	7.2
-2-Thienylacetyl	150–152	1.5	*t*-Butyl		$C_{13}H_{16}O_5S$	54.9	54.8	5.7	5.7

[a] Combined procedure of Breslow, *et al.* (ref. 5) and Riegel and Lilienfeld (THIS JOURNAL, **67**, 1273 (1945)); see experimental. [b] Acetoacetic ethyl ester and acid chloride (Anderson, *et al.* (ref. 2, method A)). [c] Prepared originally from ω-cyano-2,4,6-trimethylacetophenone supplied through the courtesy of Dr. A. Weissberger of Eastman Kodak Co. Method of Allen, Van Allan and Wilson, THIS JOURNAL, **66**, 1808 (1944). Analysis is of compound recovered from attempted reaction with thiourea. [d] Compound prepared by Breslow, *et al.* (ref. 5). [e] Anderson, *et al.* (ref. 2, method F). Calcd. analysis for 50–50 mixture of ethyl cyanoacetate and ethyl-3-oxo-5-hexenoate, C, 57.3; H, 7.0. [f] Microanalyses were carried out under the direction of Dr. J. A. Kuck to whom we are indebted for these data. [g] All analyses reported in this paper are the average of two or more determinations. The two analyses are indicated in this case because of the variance from theory.

conditions for the condensation reaction. Even at room temperature for twenty-four hours using ethyl 3-oxo-4-hexenoate no definite compound could be isolated although satisfactory yields of 6-*n*-butyl-2-thiouracil were obtained with ethyl β-oxoenanthate.

Of the twelve new 6-substituted-2-thiouracils shown in Table II three show greater antithyroid activity than 2-thiouracil in rats, but only 6-α-ethylpropyl-2-thiouracil shows sufficient activity to be considered promising for the treatment of hyperthyroidism. While its activity is less than those reported for the 6-*n*-propyl- and 6-benzyl-2-thiouracils,[3] it is over five times as active as the isomeric *n*-amyl compound. The specificity of the benzyl compound is great since it is about ten

TABLE II

PROPERTIES OF 6-R-2-THIOURACILS

Substituted thiouracil R (= 6)	Anti-thyroid activity[a]	M. p., °C. (cor.)	Yield, %, from β-oxoester	Formula	Analyses, %[b] Calcd. C	H	N	S	Found C	H	N	S
Trifluoromethyl[c]	<0.01	247–249	40	$C_5H_3N_2OSF_3$	30.6	1.5	14.3	16.4	30.9	1.8	13.9	16.4
Methoxymethyl	1.0–1.5	221–222	6	$C_6H_8N_2O_2S$	41.8	4.7	16.3	18.6	41.9	4.8	16.3	18.3
α-Ethylpropyl	7	223–224	24	$C_9H_{14}N_2OS$	54.5	7.1	14.1	16.7	54.9	7.3	13.8	16.1
α-Phenylpropyl[d]	0.5–1.0	244–244.5	53	$C_{13}H_{14}N_2OS$	63.4	5.7	11.4	13.0	63.6	5.9	11.5	13.1
p-Isopropylbenzyl	*ca.* 0.5	229–229.5	63	$C_{14}H_{16}N_2OS$	64.6	6.2	10.8	12.3	64.9	6.5	10.6	12.4
p-Chlorobenzyl	0.2	242–243	64	$C_{11}H_9N_2OSCl$	52.3	3.6	11.1	12.7	52.7	3.9	10.9	12.7
m-Chlorophenyl	<0.1	266–266.5	21	$C_{10}H_7N_2OSCl$	50.3	3.0	11.7	13.4	50.7	3.2	11.7	13.0
m-Methoxyphenyl[e]	<0.03	292–293	22	$C_{11}H_{10}N_2O_2S$	56.4	4.3	12.0	13.7	56.8	4.7	11.7	13.4
p-Methoxyphenyl[e]	<0.03	226–227	32	$C_{11}H_{10}N_2O_2S$	56.4	4.3	12.0	13.7	56.6	4.7	12.1	13.4
2-Furyl[d,f]	0.5	298–300 dec	7	$C_8H_6N_2O_2S$	49.5	3.1	14.4	16.5	50.1	3.7	14.4	16.7
3-Pyridyl[d]	<0.1	296–298 dec.	16[g]	$C_9H_7N_3OS$	52.7	3.4	20.5	15.6	52.8	4.6	19.9	15.3
2-Thenyl	3	248–250	37	$C_9H_8N_2OS_2$	48.2	3.6	12.5	28.6	48.5	4.0	12.3	27.4

[a] Thiouracil = 1.00 (weight basis): Method of Astwood, *et al.*,[3] and data supplied by Dr. Astwood. [b] Microanalyses were carried out under the direction of Dr. J. A. Kuck, to whom we are indebted for these data. [c] Prepared from ethyl-β-oxo-β-trifluoromethylpropionate, b. p. 47–49° at 25 mm., obtained in 83% yield by method of Swarts, *Bull. Acad. Belgique*, **5**, 12 (1926). [d] Reported also in THIS JOURNAL, **70**, 497 (1948), by Jackman, Bergman and Archer of the Sterling-Winthrop Research Institute. [e] From β-oxoesters supplied through the courtesy of Dr. A. Weissberger of Eastman Kodak Company. [f] Prepared from ethyl β-oxo-β-(2-furyl)-propionate, b. p. 139–140° at 12 mm., obtained in 48% yield by method of Barger, Robinson and Smith, *J. Chem. Soc.*, 721 (1937). [g] 20% based on ester used since 22% of β-oxoester recovered unchanged.

times as active as the 6-phenyl- and the 6-phenethyl-2-thiouracils[2,3] and since substituents in the benzyl reduce the activity markedly (Table II). The discrepancy between the activities of the 6-(2-thenyl)- and the 6-benzyl compounds also is greater than expected from a similar comparison of compounds with other physiological activity.[9] Theories about these variations could be put forth on a much more valid basis if more were known about the blood concentrations of the various compounds.

Experimental

Acid chlorides were prepared in most cases using 1.5 moles of thionyl chloride for each mole of acid. The mixture was refluxed for four and one-half hours on a steam-bath in a flask with a condenser protected by a Drierite tube. Excess thionyl chloride was distilled *in vacuo* and then the product was fractionated: α-ethylbutyryl chloride,[10] b. p. 138–142° (80%); α-phenylbutyryl chloride,[11] b. p. 111–114° (15 mm.) (88%); *p*-isopropylphenylacetyl chloride,[12] b. p. 107–110° (5 mm.) (86%); *p*-chlorophenylacetyl chloride,[13] b. p. 127–129° (15 mm.) (91%); *m*-chlorobenzoyl chloride,[14] b. p. 104–106° (14 mm.) (91%); 2-thienylacetyl chloride,[12,15] b. p., 62–65° (3 mm.) (70%); *p*-nitrophenylacetyl chloride,[16] m. p. 47–48° cor. (54%); nicotinyl chloride,[17] b. p. 89–91° (15 mm.) (84%). Prepared using the benzoyl chloride method[6] without modification were: methoxyacetyl chloride,[18] b. p. 112–113° (57%); crotonyl chloride,[6] b. p. 120–122.5° (51%); and acrylyl chloride,[19] b. p. 73–74° (72%).

β-Oxoesters for the most part were prepared by Method B, Ref. 5. The difficulties encountered for two of the esters have been described above. A combination procedure was necessary in a third preparation, that of **ethyl β-oxo-γ-(2-thienyl)-butyrate** as indicated in Table I. In this case after adding *p*-toluenesulfonic acid only a little gas was evolved. The product was worked up and vacuum distilled. At this point it was shown that the batch of *t*-butylmalonate which had been used contained much diethyl malonate. Consequently our distillate was treated according to the Riegel–Lilienfeld method (Table I, *a*) for the decomposition of acylated malonic esters by heating with β-naphthalenesulfonic acid. Based on 2-thienylacetyl chloride an over-all yield of 22% of β-oxoester was obtained. The 2-thienylacetyl derivative of diethylmalonate was also isolated.

***t*-Butyl *p*-Nitrophenylacetate.**—In order to test the reactivity of this compound toward *p*-toluene sulfonic acid, it was prepared according to the general method for the preparation of *t*-butyl esters.[20] The product was a olid, and after two recrystallizations from alcohol, 7.1 g. or 30% yield, m. p. 37–38° cor., was obtained.

Anal. Calcd. C, 60.8; H, 6.4; N, 5.9. Found: C, 59.0; H, 6.4; N, 5.8.

One gram of *t*-butyl *p*-nitrophenylacetate, 1.4 cc. of benzene and 0.02 g. of *p*-toluenesulfonic acid monohydrate (Eastman Kodak Co.) were heated together under reflux and the gas evolved collected over water. After making correction for the blank 108 cc. of gas was obtained. Theory for isobutylene was 95 cc. The gas decolorized bromine water. *p*-Nitrophenylacetic acid, m. p. 150–154°, was recovered in 88% of the theoretical amount. When ethyl *p*-nitrophenylacetate, m. p. 64°,[21] was treated similarly it was recovered unchanged.

Thiouracils were prepared as described previously.[2] Those 6-substituted-2-thiouracils purified by recrystallization from water and the parts of boiling water required to dissolve them (crude) were: 6-trifluoromethyl, 50; 6-α-ethylpropyl, 200; and 6-methoxymethyl (after hot extraction with alcohol), 50. Those recrystallized from glacial acetic acid and the cc. per g. (crude product) were: 6-α-phenyl, 20; 6-*p*-chlorobenzyl, 100; 6-*m*-chlorophenyl, 20. Those purified by hot extraction with alcohol and then recrystallized from glacial acetic acid (cc. per g. of product) were: 6-(*p*-methoxyphenyl), 14; 6-(*m*-methoxyphenyl), 75; 6-(2-furyl), 50; 6-(2-thenyl), tarry product removed by alcohol extraction and discarded, residue recrystallized from 20 cc. acid per g. of resulting product. By carefully acidifying to *p*H 4 a solution of the sodium salt and extracting this residue with acetone 6-(3-pyridyl) was obtained and the resulting product was recrystallized from cellosolve, 75 cc. per g. The 6-(*p*-isopropylbenzyl) was purified by several hot extractions[2] with alcohol in which it is moderately soluble.

Acknowledgment.—We are indebted to Dr. R. O. Roblin, Jr., of these Laboratories for advice and suggestions and to Dr. E. B. Astwood, Joseph H. Pratt Diagnostic Hospital, Boston, Massachusetts, for suggestions and for the data on antithyroid activity.

Summary

1. The syntheses of several new 6-substituted-2-thiouracils and of several new β-oxoesters have been carried out. Certain of the β-oxoesters prepared could not be converted to thiouracils and the implications are considered.

2. The antithyroid activities of the new compounds varied widely. While several of the compounds were more active in rats than 2-thiouracil, only 6-α-ethylpropyl-2-thiouracil approaches the activity of the best compounds reported previously.

STAMFORD, CONNECTICUT RECEIVED JULY 31, 1947

---

(9) Steinkoph and Ohse, *Ann.*, **437**, 14 (1924); **448**, 205 (1926); Barger and Easson, *J. Chem. Soc.*, 2100 (1938); Blicke and Burckhalter, THIS JOURNAL, **64**, 477 (1942); Lands, Nash and Hooper, *J. Pharmacol.*, **86**, 129 (1946).

(10) Whitmore, *et al.*, THIS JOURNAL, **63**, 643 (1941).

(11) Rising and Schwartz, *ibid.*, **54**, 2021 (1932).

(12) A new compound; identification only by conversion to β-oxoester (Table I).

(13) Friedmann and Masse, *Biochem. Z.*, **27**, 108.

(14) Limpricht and Uslor, *Ann.*, **102**, 263; Hope and Riley, *J. Chem. Soc.*, **121**, 2513.

(15) From 2-thienylacetic acid, m. p. 60–61.5° cor. Calcd. for $C_6H_6O_2S$: C, 50.7; H, 4.3; S, 22.6. Found: C, 51.0; H, 4.4; S, 22.9. Blicke and Zienty [THIS JOURNAL, **63**, 2945 (1941)] give m. p. 75–76°.

(16) Wedekind, *Ann.*, **378**, 289.

(17) Hukusima, *J. Chem. Soc. Japan*, **61**, 121 (1940); total time of heating reaction mixture in our experiment 65 hours.

(18) Leiner, *Ber.*, **70B**, 1040 (1937).

(19) Rehberg, Dixon and Fisher, THIS JOURNAL, **67**, 208 (1945).

(20) Abramovitch, Shivers, Hudson and Hauser, *ibid.*, **65**, 986 (1943).

(21) Radziszewski, *Ber.*, **2**, 209 (1869).

The Reaction of Pyrrolealdehyde with Rhodanine and Hydantoin[1]

BY WERNER HERZ[2] AND KARL DITTMER

In attempts to prepare β-2-pyrrolealanine, 2-pyrrolealdehyde was condensed with compounds containing active methylene groups. Unexpected products were obtained from the reaction of 2-pyrrolealdehyde with diketopiperazine and 2-acetyl-3-thiohydantoin. To elucidate the structures of these products will require further investigation. Likewise, the reaction of the aldehyde with hippuric acid appears to be more complex than reported.[3] Rhodanine and hydantoin, however, condensed with pyrrolealdehyde to give the expected compounds.

We wish to report at this time the reaction of 2-pyrrolealdehyde with rhodanine and hydantoin, and the hydrolysis of pyrrolalrhodanine to 2-pyrrolethiopyruvic acid. The reaction of 2-pyrrolealdehyde with hydantoin in acetic anhydride in the presence of sodium acetate gave a very small yield of what is believed to be pyrrolalacetylhydantoin. An analogous product was obtained by Barger and Easson[4] in the synthesis of β-2-thienylalanine.

Experimental

2-Pyrrolalrhodanine.—A finely ground mixture of 7 g. of pyrrolealdehyde,[5] 10 g. of rhodanine and 7 g. of anhydrous sodium acetate was refluxed with 40 ml. of glacial acetic acid for twenty minutes. It was cooled and filtered; the reddish-brown product was thoroughly washed with water to remove acetic acid. Dilution of the filtrate with water produced more pyrrolalrhodanine. The combined material was recrystallized from alcohol; by working up the mother liquors, a total of 6.5 g. (42%) was obtained, m. p. 286° on a Dennis melting point bar. The ochre plates were soluble in ethanol, acetone, ethyl acetate, partially soluble in ether, benzene and carbon tetrachloride and insoluble in water.

Anal. Calcd. for $C_8H_8N_2OS_2$: N, 13.32. Found: N, 13.11.

2-Pyrrolethiopyruvic acid.—Six grams of the preceding compound was powdered and suspended in 120 ml. of water containing 30 g. of barium hydroxide. The mixture was heated on the steam-bath until solution of the red material was complete. The solution was filtered and the filtrate cooled in an ice-bath. It was then carefully neutralized with dilute hydrochloric acid until precipitation was complete. The yellow product was filtered, washed with water and dried in a vacuum desiccator. The yield was 3.5 g., m. p. 130° (dec.). When exposed to air it decomposed rapidly. Attempts to recrystallize or reprecipitate it were unsuccessful, so that the crude material was used for the analysis.

Anal. Calcd. for $C_7H_7NO_2S$: N, 8.28; neut. equiv., 169. Found: N, 9.05; neut. equiv., 175–180.

The neutral equivalent could not be determined with accuracy because of the color of the solution.

Reaction of 2-Pyrrolealdehyde with Hydantoin.—A finely ground mixture of 1.7 g. of pyrrolealdehyde, 1.7 g. of hydantoin, and 1.7 g. of anhydrous sodium acetate was refluxed with 10 ml. of acetic anhydride for two and one-half hours. After cooling and extracting with water, a blackish-green residue remained. It was extracted with 50 ml. and again with 25 ml. of hot ethanol. The combined ethanol extracts, which showed a violet fluorescence, were treated with charcoal, evaporated to 25 ml., again treated with charcoal and evaporated to a volume of 15 ml. On chilling, 0.13 g. of light-green needles, m. p. 184–185°, separated. The compound was partially soluble in ether and cold ethanol and soluble in hot ethanol, water and acetic acid. The product imparted a violet fluorescence to its solutions.

Anal. Calcd. for $C_{10}H_9N_3O_3$: N, 19.17. Found: N, 19.18.

Fusion of the aldehyde, hydantoin and sodium acetate by the method of du Vigneaud and co-workers[6] at various temperatures resulted in tars only. Pyrrolealdehyde heated with hydantoin in absolute ethanol in the presence of catalytic amounts of methylamine hydrochloride and sodium carbonate led to tarry materials and recovery of unreacted hydantoin. When equivalent amounts of aldehyde and hydantoin in piperidine were heated at reflux for two minutes only unidentified compounds were isolated.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF COLORADO
BOULDER, COLORADO

RECEIVED AUGUST 25, 1947

---

[1] This work was in part supported by a research contract with the Office of Naval Research.

[2] Present address: Department of Chemistry, University of Illinois, Urbana, Illinois.

[3] Asahina and Mitsunaga, *J. Pharm. Soc. Japan*, 986 (1917).

[4] Barger and Easson, *J. Chem. Soc.*, 2100 (1938).

[5] Fischer and Orth, "Die Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1934, p. 152.

[6] du Vigneaud, McKennis, Simmonds, Dittmer and Brown, *J. Biol. Chem.*, **159**, 385 (1945).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

Alkylation of Substituted Malonic and Cyanoacetic Esters with 2-Diamethylaminomethylpyrrole. A Proposed Synthesis of β-2-Pyrrolealanine[1]

BY WERNER HERZ,[2] KARL DITTMER AND STANLEY J. CRISTOL

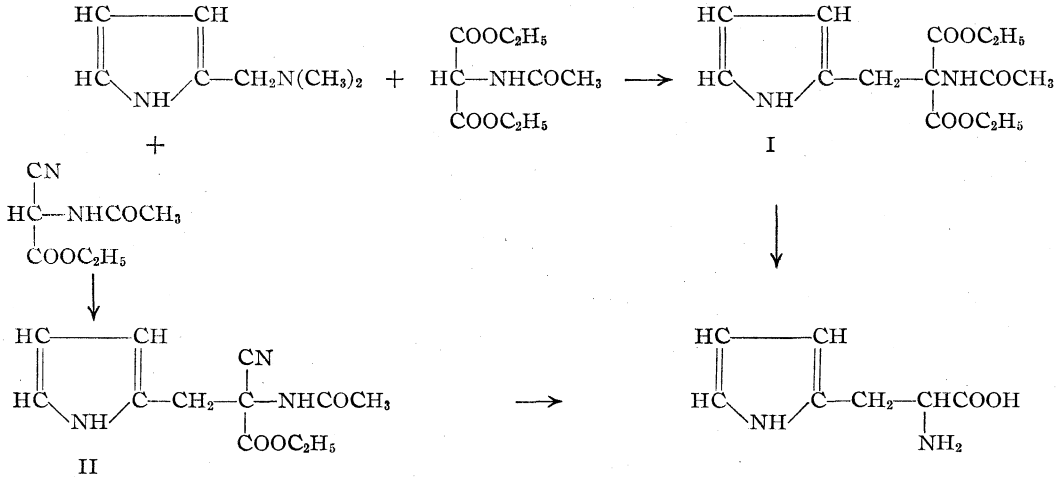
β-2-Thienylalanine[3,4,5] and β-2-furylalanine[6] have been shown to inhibit microbial growth, presumably due to their structural similarity to phenylalanine. The corresponding nitrogen analog, β-2-pyrrolealanine, is not described in the literature. As part of a program to correlate the structure of amino acids with their biological activity, it seemed desirable to prepare this substance so that it might be available for microbiological study.

Attempts to synthesize β-2-pyrrolealanine by condensation of 2-pyrrolealdehyde with compounds containing active methylene groups[7] were abandoned when adaptation of recently-developed methods for the synthesis of tryptophan[8,9,10] appeared more promising.

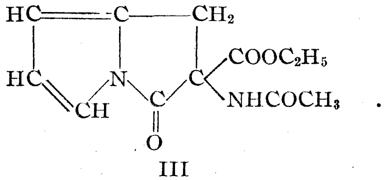
The present paper describes the use of 2-dimethylaminomethylpyrrole[11] in alkylation reactions with ethyl malonate, ethyl cyanoacetate, ethyl acetamidomalonate, ethyl acetamidocyanoacetate, and ethyl phthalimidomalonate and hydrolysis experiments of such of these products as were intermediates for the projected synthesis.

Pure β-2-pyrrolealanine could not be isolated, but fractions containing it were obtained. The amino acid was characterized by its phenylurea derivative. These fractions showed strong inhibition of growth of certain microörganisms, and this inhibition was found to be reversed by phenylalanine.

Alkylation with Dimethylaminomethylpyrrole.—The scheme outlined for the preparation of β-2-pyrrolealanine was



Howe and co-workers[10] alkylated ethyl acetamidomalonate with gramine (dimethylaminomethylindole) by heating these reagents in refluxing toluene or xylene in the presence of catalytic amounts of solid sodium hydroxide. Substitution of dimethylaminomethylpyrrole for gramine, however, did not lead to the expected product (I). On cooling the reaction mixture, there was obtained a substance in 70–80% yield, which has the correct molecular weight and analysis for structure (III).



III

Lactams of this type from substituted pyrroleacrylic and pyrrolepropionic acids have been reported.[12,13]

Under the same conditions, attempted alkylation of ethyl cyanoacetate and ethyl cyanoacetamidoacetate produced much decomposition and yielded dark oils and tars on evaporation of the

---

(1) This work was supported in part under a contract from the Office of Naval Research.

(2) Present address: Department of Chemistry, University of Illinois, Urbana, Illinois.

(3) du Vigneaud, McKennis, Simmonds, Dittmer and Brown, *J. Biol. Chem.*, **159**, 385 (1945).

(4) Dittmer, Ellis, McKennis and du Vigneaud, *J. Biol. Chem.*, **164**, 761 (1946).

(5) Beerstecher and Shive, *ibid.*, **164**, 53 (1946).

(6) Clark and Dittmer, unpublished work.

(7) Herz and Dittmer, THIS JOURNAL, **69**, 503 (1947).

(8) Snyder and Smith, *ibid.*, **66**, 350 (1944).

(9) Albertson, Archer and Suter, *ibid.*, **66**, 500 (1944); **67**, 36 (1945).

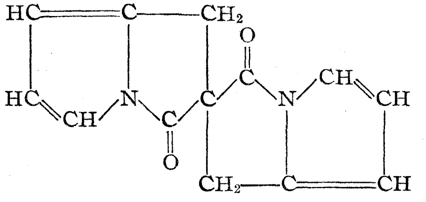
(10) Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945).

(11) Herz, Dittmer and Cristol, *ibid.*, **69**, 1698 (1947).

(12) Fischer and Neber, *Ann.*, **496**, 1 (1932).

(13) Küster, Brudi and Koppenhöfer, *Ber.*, **58**, 1014 (1925).

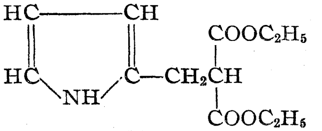
solvents which probably contained some of the condensation products but were not investigated due to the difficulties of purification. The alkylation of malonic ester produced, in addition to some oil, a small amount of white solid for which structure IV is suggested, such a compound arising by di-alkylation of malonic ester and lactam formation.



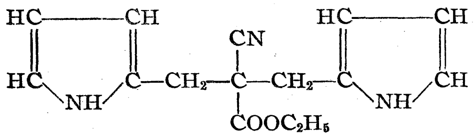
IV

In an effort to avoid lactam formation with ethyl acetamidomalonate and to obtain purer products with the other esters, use was made of an earlier procedure[8,14] which employed a quaternary salt of the tertiary amine, usually the methiodide, as alkylating agent and an inert solvent such as dioxane or dibutyl ether. Under these conditions, dimethylaminomethylpyrrole methiodide and ethyl acetamidomalonate also gave the lactam (III), though in lower yield, while malonic ester and ethyl cyanoacetamidoacetate gave dark uncharacterized oils.

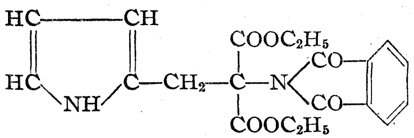
Albertson and co-workers[9] obtained the expected intermediate in the synthesis of tryptophan by the use of cold absolute ethanol as solvent for gramine and the malonate through the slow addition of dimethyl sulfate which served to quaternize the amine. Under similar conditions (I) was obtained from dimethylaminomethylpyrrole and ethyl acetamidomalonate in 85–95% yield. In the same fashion, using ethyl cyanoacetamidoacetate, (II) was formed in 90% yield. Alkylation of malonic ester produced an oil which was identified as (V) by conversion to the diamide. Ethyl cyanoacetate and ethyl phthalimidomalonate also could be alkylated; from the former the product (VI) in which both active hydrogen atoms were replaced by 2-pyrrole-methyl radicals was isolated and identified as the amide, while the yield of pure crystalline material (VII) from the phthalimidomalonic ester condensation was very low. An attempt to alkylate hydantoin by this method failed.



V



VI



VII

Hydrolysis to β-2-Pyrrolealanine.—Early attempts to prepare β-2-pyrrolealanine by the basic hydrolysis of some of the compounds described in the preceding paragraphs made use of the lactam (III) before its structure had been recognized. These efforts were not successful. On the other hand, sodium hydroxide hydrolysis of (I), followed by hydrolysis in neutral and again in basic solution, produced a mixture which on neutralization gave a strong ninhydrin test, although neither of the two possible intermediates, 2-pyrrolemethylacetoamidomalonic acid and the acetyl derivative of pyrrolealanine, separated in the course of the hydrolysis. Evaporation *in vacuo*, extraction with absolute ethanol and dilution with acetone or anhydrous ether gave fractions which were identical with the material obtained by the hydrolysis of (II).

The latter compound, because of greater convenience, was employed in preference to the acetamidomalonate. Hydrolysis with sodium hydroxide ranging in concentration from 10–25%, neutralization and evaporation *in vacuo* produced partially organic material which gave a positive Ehrlich and ninhydrin test. It inhibited the growth of *S. cerevisiae* and *E. coli* and was reversed by phenylalanine.

By the action of phenyl isocyanate on this material there was obtained a well-defined crystalline compound whose neutral equivalent, analysis and chemical properties agreed with those expected of the phenylurea derivative of β-2-pyrrolealanine. This derivative showed little inhibitory activity, but hydrolysis with barium hydroxide in an autoclave at 120° regenerated the activity. Attempts to obtain pure pyrrolealanine by evaporation of the phenylurea hydrolysate *in vacuo* yielded colored material which quickly decomposed but still produced some inhibition.

These results left little doubt that the original crude material contained some pyrrolealanine contaminated primarily with inorganic salts. So far, however, we have failed in all our attempts to isolate pure pyrrolealanine by precipitation from water with organic solvents and salts, or by the formation of derivatives such as the benzoyl, naphthylurea, naphthalenesulfonamide and the carbobenzoxy derivatives.

Experimental

Dimethylaminomethylpyrrole Methiodide.—Eleven and one-half grams of dimethylaminomethylpyrrole[11] was dissolved in 75 ml. of absolute ethanol and treated with 15 g. of methyl iodide in the course of fifteen minutes. Heat was developed and a precipitate appeared. Since discoloration occurred when the flask was allowed to remain in the light, it was kept in the dark at room tem-

---

[14] Snyder, Smith and Stewart, This Journal, **66**, 200 (1944).

perature for two hours and then placed in the refrigerator. The yield of pink dimethylaminomethylpyrrole methiodide, which decomposed in air and became black above 160°, averaged 17–18 g. (63–68%).

Reaction of Dimethylaminomethylpyrrole with Ethyl Acetamidomalonate. (A) In Toluene.—Sixty ml. of toluene or xylene containing 1 g. of powdered sodium hydroxide was heated to boiling in a flask fitted with nitrogen inlet, stirrer and condenser. Then 9.3 g. of dimethylaminomethylpyrrole and 16.2 g. of ethyl acetamidomalonate were added and the mixture was refluxed in an atmosphere of nitrogen with stirring for two hours. During this time the color of the solution became dark red. The mixture was filtered by means of a preheated funnel and cooled. The yield of beige-colored material was 13–15 g. (70–80%). Recrystallization from hot water gave compound (III) as white needles, m. p. 151°, which gave a positive Ehrlich test and was soluble in ethanol, hot water, methanol and chloroform, partially soluble in ether, and insoluble in cold water.

Anal.[15] Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19; mol. wt., 250. Found: C, 57.59; H, 5.57; N, 11.05; mol. wt. (Rast), 259.

(B) **In Dioxane, Using the Methiodide.**—By following the procedure of Snyder and Smith,[8] 6.6 g. of dark-colored product was obtained from 11.3 g. of ethyl acetamidomalonate and 13.2 g. of dimethylaminomethylpyrrole methiodide after partial removal of the solvent and dilution with water. It was purified by recrystallizing from an ethanol–water mixture and again from 15% ethanol. M. p. of the white crystals was 147°, mixed m. p. with the material from (A), 151°.

(C) **In Absolute Ethanol with Methyl Sulfate.**—In a flask fitted with a stirrer, condenser and a dropping funnel were placed 100 ml. of absolute ethanol and 1.72 g. of clean sodium. After all the sodium had dissolved, 16.2 g. of ethyl acetamidomalonate and then 9.3 g. of dimethylaminomethylpyrrole were added. While the flask was cooled in an ice-bath and the mixture was stirred, 15.8 g. of methyl sulfate was added dropwise at such a rate that the temperature did not exceed 35°. After completion of the addition, the mixture was stirred for one hour and allowed to stand at room temperature overnight. The alcohol was evaporated *in vacuo;* the residue was diluted with 200 ml. of water and chilled. 21 g. (94%) of slightly-colored product separated. It was purified by dissolving in a little acetone, treating with charcoal, filtering, chilling, diluting with ice water and keeping in the refrigerator overnight. The shiny white platelets of compound (I) melted at 91° and were soluble in ethanol, acetone and hot water.

Anal. Calcd. for $C_{14}H_{20}N_2O_5$: N, 9.46. Found: N, 9.45.

Reaction of Dimethylaminomethylpyrrole with Ethyl Malonate.—Following procedure (A), 8.2 g. of malonic ester was allowed to react with 6.2 g. of dimethylaminomethylpyrrole in boiling toluene. No crystals separated from the cooled reaction mixture. Removal of the solvent gave a red oil which did not crystallize. Trituration with 50 ml. of ethanol caused most of the oil to dissolve; 0.5 g. of white solid remained undissolved. It gave a positive Ehrlich test and was recrystallized from a very small amount of benzene. The white crystals of (IV), m. p. 157°, were soluble in chloroform, methanol, hot benzene and hot alkali, and sparingly soluble in water and cold benzene.

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.43; N, 12.38; mol. wt., 226. Found: C, 68.85; H, 4.74; N, 12.08; mol. wt. (Rast), 228.

Hydrolysis of the alcohol solution of the oil with ethanolic potassium hydroxide gave a very impure organic acid which decomposed rapidly.

Following procedure (C), 12 g. of ethyl malonate was alkylated with 9.3 g. of dimethylaminomethylpyrrole. The oil obtained on dilution of the alcohol residue with water was extracted with two 25-ml. portions of ether. The dried ether extracts were distilled in a vacuum. After some unreacted malonic ester and dimethylaminomethylpyrrole had been collected, the temperature rapidly rose to 180°; 6 g. (33%) of (V), boiling at 184–187° (17 mm.) and somewhat colored, was obtained as a viscous oil.

The product was treated with ten times its volume of concentrated ammonium hydroxide, shaken and allowed to stand for a few days. The diamide derivative of (V) separated in 60% yield in long needles and was recrystallized from a little ethanol. It melted at 202° with previous darkening above 195°, gave a positive Ehrlich test and was soluble in water, less soluble in alcohol and acetone. On boiling with sodium hydroxide, the odor of ammonia was noted.

Anal. Calcd. for $C_8H_{11}N_3O_2$: N, 23.19. Found: N, 23.05.

Ethyl α-Acetamido-α-cyano-β-(2-pyrrole)-propionate (II).—Following procedure (C), 9.3 g. of dimethylaminomethylpyrrole was used to alkylate 12.7 g. of ethyl cyanoacetamidoacetate. On evaporation of the alcohol *in vacuo*, dilution with water and cooling, 17 g. (90%) of nearly white crystals separated. They were purified by dissolving in acetone, treating with charcoal, filtering, diluting with water and chilling for several hours. The white plates of (II) melted at 122° and were soluble in ethanol, acetone, benzene and hot water, insoluble in petroleum ether.

Anal. Calcd. for $C_{12}H_{15}N_3O_3$: N, 16.86. Found: N, 16.92.

Ethyl bis-(2-Pyrrolemethyl)-cyanoacetate (VI).—The alkylation of 11.3 g. of ethyl cyanoacetate with 9.3 g. of dimethylaminomethylpyrrole by procedure (C) produced a colored oil which could not be crystallized. It was taken up in ether, dried, and distilled *in vacuo.* After some unreacted ester had come over, 3 g. (30%) of a heavy yellow oil, boiling at 169–170° (6 mm.), was collected. It gave a positive Ehrlich test and became glassy on chilling.

The amide of (VI) was prepared by shaking the oil with ten times its volume of concentrated ammonium hydroxide, allowing the mixture to stand at room temperature for several days and finally chilling it for two days. The needles obtained in 45% yield were recrystallized from hot water and gave a positive Ehrlich test. They were melted at 153° and were soluble in ethanol, acetone and methanol, insoluble in hydrocarbon solvents.

Anal. Calcd. for $C_{13}H_{14}N_4O$: N, 23.13; mol. wt., 242. Found: N, 23.20; mol. wt. (Rast), 242.

Diethyl 2-Pyrrolemethylphthalimidomalonate (VII).—Only a viscous yellow oil was obtained by the alkylation of 23.5 g. of diethyl phthalimidomalonate with 9.3 g. of dimethylaminomethylpyrrole in the usual manner. Extraction with ether and removal of the ether *in vacuo*, and similar treatment with ethanol, produced a dark semisolid mass which had not crystallized after two months. Part of this material was dissolved in much acetone and passed through an activated alumina column. The acetone was evaporated to small volume, cooled and diluted with water. On chilling, slightly colored crystals separated in very poor yield. An acetone solution of this product was treated with charcoal, filtered, diluted with water and chilled. The white plates melted at 133.5° and gave a positive Ehrlich test.

Anal. Calcd. for $C_{20}H_{20}N_2O_6$: N, 7.29. Found: N, 7.15.

Hydrolysis of Ethyl α-Acetamido-α-cyano-β-(2-pyrrole)-propionate (II).—Twenty grams of (II) was refluxed with a solution of 25 g. of sodium hydroxide in 200 ml. of water for twenty-one hours. The red solution was neutralized carefully (vigorous evolution of carbon dioxide was noted, filtered from silica, decolorized with charcoal) and cooled. It was then acidified to *p*H 3 with

---

[15] This carbon-hydrogen analysis was determined by E. W. D. Huffman, Denver, Colorado.

concentrated hydrochloric acid, quickly extracted with four 200-ml. portions of ether to remove acetic acid, neutralized to *p*H 6–7, and evaporated to dryness *in vacuo*. After addition of absolute ethanol, the residue was again evaporated to dryness to remove the last traces of water. The residue (10 g.) gave a positive ninhydrin test.

Extraction with 100 ml. of hot absolute ethanol, treatment with norite, filtration, evaporation to small volume, dilution with anhydrous ether and chilling gave a small amount of brown solid. Further dilutions with ether, followed each time by cooling for a day, produced a total of 1.75 g. of impure amino acid-salt mixture.

Pure pyrrolealanine has so far not been obtained from these fractions by various techniques including selective extraction, fractional precipitation, insoluble salt formation, crystallization, electrophoresis and ion exchange. Analyses for carbon, hydrogen and nitrogen were consistently about two-thirds of the required amounts.

However, when treated with phenyl isocyanate, the crude salt-amino acid mixture gave a 22% yield of a phenylurea derivative analyzing for that of pyrrolealanine. Likewise, all of the crude fractions obtained from the basic hydrolysis of (II) inhibited the growth of *S. cerevisiae* (Fleischmann strain 139) and *E. coli* (ATCC 9723) when tested by the techniques previously described.[4] For half-normal inhibition a concentration of 28–32 γ per tube of crude material was required (each tube contained 6.5 ml. of medium and 1 ml. of addenda). The toxicity of the crude pyrrolealanine was counteracted by phenylalanine. The phenylurea derivative showed only slight inhibition at levels of 200 γ per tube, but hydrolysis with barium hydroxide restored the original high degree of activity. Further attempts are underway to obtain the pyrrolealanine in pure form.

Hydrolysis of Ethyl 2-Pyrrolemethylacetamidomalonate (I).—Ten grams of the ester was refluxed with 80 ml. of 15% sodium hydroxide for seven hours, treated with charcoal, filtered, neutralized to *p*H 5–6 and cooled. The ninhydrin test was negative. Concentration to small volume at this stage yielded no organic precipitate. The slightly acid solution was refluxed for two hours, treated with 12 g. of solid sodium hydroxide and boiled for an additional eleven hours. It was neutralized carefully, filtered, acidified to *p*H 3 and quickly extracted with ether, neutralized again, treated with charcoal, filtered and evaporated to dryness *in vacuo*. The residue gave a strong ninhydrin test and was extracted as described in the preceding paragraph. The yield of crude product, representing the sum of the various fractions, averaged 3–5 g. This crude material was identical in behavior with the material obtained from the hydrolysis of II.

Phenylurea Derivative of β-2-Pyrrolealanine.—Two grams of crude salt-amino acid product was dissolved in 10 ml. of water. To the well-cooled solution there were added 6 ml. of 2 *N* sodium hydroxide in 1-ml. portions and 1.2 ml. of phenyl isocyanate in 0.2-ml. portions with vigorous shaking. When the odor of phenyl isocyanate could no longer be noticed, the mixture was filtered from the slight precipitate of diphenylurea, decolorized with charcoal, made barely acid with dilute hydrochloric acid and cooled overnight. The yield of pink solid was 0.8 g. An additional 0.22 g. was obtained by further acidification of the filtrate. Recrystallization from aqueous ethanol gave 0.78 g. (22%) of white crystals. After drying *in vacuo*, the product melted at 182–183° (capillary) and at 206° on a Dennis melting point bar within three seconds. It decomposed in air and was stored in a vacuum desiccator.

Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.51; H, 5.53; N, 15.38; neut. equiv., 273. Found: C, 61.6; H, 6.04; N, 15.19; neut. equiv., 275.

Hydrolysis of the Phenylurea.—Preliminary studies indicated that the phenylurea of phenylalanine could be hydrolyzed by 5% barium hydroxide. Fifty milligrams of the phenylurea of pyrrolealanine was placed in a test-tube together with 0.5 g. of barium hydroxide monohydrate and 9.5 ml. of water and heated at 120° in a pressure autoclave for six hours. The mixture was neutralized to *p*H 7 with 1 *N* sulfuric acid, filtered, and the volume adjusted to 20 ml. Of this neutralized filtrate 0.32 ml. of a 1 to 10 dilution inhibited the growth of *E. coli* to 50% of normal. Evaporation *in vacuo* gave 18 mg. of a brown residue, which decomposed very quickly, left a black residue on burning, and inhibited the growth of *E. coli*, but not as strongly as the solution.

Acknowledgments.—The authors wish to express their appreciation to Mrs. Charmion McMillan for the microbiological tests, and to Mr. Frank Rainwater for some of the carbon and hydrogen analyses; also to Professor Irving Goodman for the many hours spent in consultation during this work.

Summary

Dimethylaminomethylpyrrole was used to alkylate ethyl malonate, ethyl cyanoacetate, ethyl acetamidomalonate, ethyl cyanoacetamidoacetate, and ethyl phthalimidomalonate. The structures of the products have been given.

The product of the reaction between dimethylaminomethylpyrrole and ethyl cyanoacetamidoacetate on hydrolysis gave impure fractions of β-2-pyrrolealanine which was characterized as the phenylurea derivative.

These fractions inhibited the growth of *S. cerevisiae* and *E. coli*. The inhibition was reversed by phenylalanine.

BOULDER, COLORADO RECEIVED AUGUST 25, 1947

[Contribution from the Division of Chemistry and Pharmacy of the Reed and Carnrick Institute for Medical Research]

Synthetic Estrogens. I. 3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene, 3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-hexane and Some of their Organic Esters

By V. Niederl, C. A. Siconolfi, A. Bloom and C. T. Van Meter[1]

It is generally agreed that 3,4-bis-(*p*-hydroxyphenyl)-3-hexene (diethylstilbestrol) has been a valuable medicinal agent. Equally apparent for some time now, however, has been the fact that the administration of diethylstilbestrol is not infrequently accompanied by certain physiological disturbances commonly regarded as manifestations of toxicity. As in other similar instances, this situation has encouraged considerable research designed to produce related compounds which retain sufficient estrogenic activity to have practical value, and which at the same time are sufficiently non-toxic as to have favorable therapeutic indexes.

The structure of diethylstilbestrol suggests at once certain simple chemical alterations worthy of investigation. Thus various esters and ethers have been prepared and tested, as have also many other compounds differing from diethylstilbestrol primarily in degree of saturation, presence of alkyl and other substitutents in the hexane residue, and points of attachment of the benzene nuclei to the aliphatic chain. Various closely related intermediates and by-products formed during the synthesis of such compounds have also been tested for estrogenic activity.[2]

To date, however, little attention has been given to the possibility of producing derivatives with improved properties through the introduction of alkyl groups on the benzene nuclei while at the same time retaining the six carbon aliphatic chain.

Kaiser and Svarz[3] have prepared the 3,3′-diallyl, and dipropenyl diethylstilbestrols and the 3,3′-diallyl, dipropenyl, and di-*n*-propyl hexestrols, but found them to be weakly estrogenic. Other somewhat similar compounds have been prepared and tested, but they differ from the compounds pertinent to this study either in length of the main aliphatic chain or in points of attachment of the benzene nuclei thereto.[4–12]

It is the primary aim of this research to prepare and investigate for estrogenic activity and toxicity derivatives containing one methyl group in each benzene ring, with and without simultaneous changes in the degree of saturation in the hexane residue. In this report *m*-methyl derivatives of 3,4-bis-(*p*-hydroxyphenyl)-2,4-hexadiene and 3,4-bis-(*p*-hydroxyphenyl)-hexane, along with some of their esters, are described.

Pharmacology

In common with other groups of related estrogens the potency of individual members in the series herein reported varies considerably. Tested on ovariectomized rats by the vaginal smear method, the two dihydroxy compounds are more active on injection than when given orally, but this order of relative activity is reversed in at least some of the esters. As in the diethylstilbestrol and hexestrol series, esters of monobasic aliphatic acids higher than propionic show decreased activities, and certain special esters such as the alkylcarbonates, acid succinates, and *m*-sulfobenzoates show their usual relatively high activities. Hydrogenation of a potent hexadiene compound to the corresponding hexane compound increases the activity.

The estrogenic activities (rats, vaginal smear) of the more potent compounds are shown in Table I. These activities were determined according to the method of the League of Nations Health Organization.[13] Vaginal smears are regarded as positive (a) if cornified cells only are present, or (b) if a smear of many nucleated and some cornified cells and no leucocytes is followed by a smear showing many cornified and nucleated cells with few leucocytes. Control rats received U.S.P. Reference Estrone as the standard estrogenic substance.

The estrogenic activities in Table I assume added importance when considered in conjunction with the following typical toxicity data. Compounds (2) and (7) have been administered orally to mice, daily over a three week period, in doses up to five times the toxic dose for diethylstilbestrol with no abnormal findings on autopsy.

Injected intraperitoneally as suspensions in acacia, the M.L.D.$_{50}$'s (mice) are: diethylstilbestrol 18 mg., compound no. (2) 36 mg., and compound no. (7) 36 mg.

Favorable therapeutic indexes for these compounds are thus to be expected and early clinical work verifies this expectation.[14]

---

[1] Presented by C. T. Van Meter before the Division of Medicinal Chemistry of the American Chemical Society, Chicago, Illinois, Sept. 12, 1946.

[2] Solmssen, *Chem. Rev.*, **37**, 481 (1945).

[3] Kaiser and Svarz, This Journal, **68**, 636 (1946).

[4] Bretschneider, Bretschneider and Ajtai, *Ber.*, **74**, 571 (1941).

[5] Baker, This Journal, **65**, 1572 (1943).

[6] Campbell, *Proc. Roy. Soc.* (*London*), **B129**, 528 (1940).

[7] Dodds and Lawson, *ibid.*, **B125**, 222 (1938).

[8] Easson, Harrison, McSwiney and Pyman, *Quart. J. Pharm. Pharmacol.*, **7**, 509 (1934).

[9] Harden and Reid, This Journal, **54**, 4325 (1932).

[10] Linnell and Shaikahamud, *Quart. J. Pharm. Pharmacol.*, **15**, 384 (1942).

[11] J. B. Niederl, and co-workers, This Journal, **61**, 345 (1939); **64**, 885, 2486 (1942).

[12] Hudson and Walton, *J. Chem. Soc.*, 85 (1946).

[13] League of Nations *Bull. Health Organization*, **4**, 622 (1935).

[14] S. H. Sturgis, *Am. J. Obstet. Gynecol.*, **53**, 678 (1947).

TABLE I

	Compound	Dose, mcg.	Method of[a] administration	Response[b]
(1)	3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene	5	Inj.	100
		2.5	Inj.	30
		15	Oral	10
		5	Oral	0
(2)	Diacetate of (1)	15	Inj.	80
		15	Oral	65
(3)	Dipropionate of (1)	15	Inj.	0
		15	Oral	85
		10	Oral	30
		5	Oral	0
(4)	Dibutyrate of (1)	15	Oral	15
(5)	3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-hexane	1.5	Inj.	90
		1.0	Inj.	70
		0.6	Inj.	30
		15	Oral	65
(6)	Diacetate of (5)	15	Inj.	95
		5	Inj.	75
		2.5	Inj.	10
		10	Oral	70
		5	Oral	30
		2.5	Oral	0
(7)	Dipropionate of (5)	15	Inj.	60
		10	Oral	90
		5	Oral	50
		2.5	Oral	0
(8)	Dibutyrate of (5)	15	Oral	60
(9)	Dibenzoate of (5)	5	Oral	85
(10)	Di-*m*′-sodiumsulfobenzoate of (5)	10	Oral	50
		6	Inj.	100
(11)	Diacid succinate of (5)	15	Oral	100
		5	Oral	30
(12)	Diethocarbonate of (5)	50	Oral	100
		15	Oral	70

[a] Solutions in oil except (10) which was given in aqueous solution. [b] Per cent. of rats showing smears consisting predominantly of cornified cells.

The general plan of synthesis involves a Fries isomerization of *o*-cresyl propionate, esterification of the resulting *p*-hydroxyphenone, reduction of this phenone ester to the corresponding pinacol, dehydration of the pinacol to a 2,4-hexadiene derivative and finally hydrogenation to a hexane type of compound.

Experimental

_o_-Cresyl Propionate.[15]—One mole of *o*-cresol was esterified with 1.1 moles of propionyl chloride. That fraction distilling at 104–106° (14 mm.) was collected as the ester; b. p. 218° (1 atm.); yield, quantitative.

3-Methyl-4-hydroxypropiophenone.[15]—One mole of *o*-cresyl propionate dissolved in 500 cc. of nitrobenzene was subjected to a typical Fries rearrangement at room temperature using 1.1 moles of anhydrous aluminum chloride. After hydrolysis of the aluminum complex the nitrobenzene solution was extracted with 10% sodium hydroxide. Acidification of this extract precipitated a mixture of the *o*- and *p*-hydroxypropiophenones which was collected, dried and distilled under vacuum. The fraction boiling at 150–155° (1 mm.) was collected as 3-methyl-4-hydroxypropiophenone; m. p. 86°; yield, 75%.

The 2,4-dinitrophenylhydrazone was prepared; m. p. 238°.

Anal. Calcd. for $C_{16}H_{16}N_4O_5$: N, 16.28. Found: N, 16.13.

3-Methyl-4-propionoxypropiophenone.—One-half mole of 3-methyl-4-hydroxypropiophenone was placed in a 500-cc. round-bottom flask fitted with a reflux condenser and a dropping funnel through which 0.55 mole of propionic anhydride was slowly added. The mixture was heated gently with a small flame during this addition and strongly enough thereafter to maintain gentle ebullition for one hour. Propionic acid and excess propionic anhydride were then distilled from the reaction mixture. The residual oil on cooling yielded 109 g. (99%) of solid material, m. p. 48–50°. Recrystallization from petroleum ether gave small white crystals, m. p. 52–53°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.69; H, 7.43.

The 2,4-dinitrophenylhydrazone was prepared; m. p. 179–180°.

Anal. Calcd. for $C_{19}H_{20}N_4O_6$: N, 14.00. Found: N, 14.05.

Instead of separating the isomeric hydroxyphenones obtained in the Fries rearrangement and then propionylating the desired isomer as described above, the mixture of hydroxyphenones may be subjected to the propionylation reaction and the mixture then fractionally distilled. The 4-propionoxy isomer distils at 141–143° (2 mm.). Less thermal decomposition occurs in this alternative procedure.

3,4-bis-(_m_-Methyl-_p_-propionoxyphenyl)-3,4-hexanediol.—This pinacol was first prepared by the reduction of 3-methyl-4-propionoxypropiophenone according to the method of Dodds, *et al.*,[16] for *p*-methoxypropiophenone, using aluminum amalgam and moist ether. The following method, however, was much more convenient and gave much higher yields.

One hundred grams of 3-methyl-4-propionoxypropiophenone was dissolved in 750 cc. of ethyl acetate which previously had been saturated with water. Forty grams of aluminum foil (strips, 2″ × 1/2″) was etched with 10% sodium hydroxide solution, thoroughly amalgamated with 0.5% mercuric chloride solution, and washed successively with water, ethanol and ethyl acetate. The amalgam was then added quickly to the reaction flask and the mixture stirred for thirty minutes. During this time the temperature of the mixture had risen to a maximum of about 70° and had started to fall. After cooling aluminum hydroxide and unreacted aluminum were filtered off and washed several times with fresh portions of ethyl acetate. Removal of the ethyl acetate by distillation yielded a very sticky viscous oil which solidified slowly on long standing. Trituration of this solidified mass with a small quantity of cold isopropyl ether facilitated the separation of a white solid. After washing with isopropyl ether and recrystallizing from 70% ethanol, small white crystals of the pinacol were obtained; m. p. 152–153°.

Anal. Calcd. for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.73; H, 7.91.

In the over-all synthesis it is unnecessary to separate the pure pinacol as described above. Instead, the viscous oil remaining after removal of ethyl acetate may be subjected directly to the dehydration reaction to form the hexadiene compound. In this manner over-all yields of 50% (phenone ester to diene) were obtained.

3,4-bis-(_m_-Methyl-_p_-hydroxyphenyl)-3,4-hexanediol.—This compound was prepared by reducing 75 g. of 3-methyl-4-hydroxypropiophenone with 40 g. of aluminum foil as described above; yield, 26 g. (35%) of crystalline pinacol; m. p. 180–183°. Recrystallization from dilute acetic acid gave small white crystals of the pinacol, m. p. 182–183°.

---

(15) Hartung, Munch, Miller and Crossley, THIS JOURNAL, **53**, 4149 (1931).

(16) Dodds, Goldberg, Lawson and Robinson, *Proc. Roy. Soc.* (*London*), **B127**, 140 (1939).

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.57; H, 7.69.

The *p,p'*-dibenzoate of this pinacol, prepared by the Schotten–Baumann reaction, was obtained as small white needles, m. p. 252°.

Anal. Calcd. for $C_{34}H_{34}O_6$: C, 75.81; H, 6.36. Found: C, 75.59; H, 6.53.

3,4-bis-(*m*-Methyl-*p*-acetoxyphenyl)-2,4-hexadiene.—Five grams of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-3,4-hexanediol was suspended in a mixture of 15 cc. of acetic anhydride and 10 cc. of acetyl chloride, and the mixture refluxed gently for thirty minutes. After cooling the reaction mixture was poured into ice-water and allowed to stand with occasional stirring for two hours. The solid which separated was filtered, washed with water and then triturated with about 10 cc. of cold methanol. After filtering and drying 4.4 g. (80%) of solid material remained, m. p. 160–163°. Recrystallization from ethanol gave white crystals, m. p. 166–168°.

The tetrabromo derivative, prepared by bromination in carbon tetrachloride and purified by recrystallization from ethanol, formed white crystals, m. p. 148° dec.

Anal. Calcd. for $C_{24}H_{26}Br_4O_4$: Br, 45.79. Found: Br, 45.60.

3,4-bis-(*m*-Methyl-*p*-propionoxyphenyl)-2,4-hexadiene.—This compound was prepared as described above for the acetoxy analog using 5 g. of 3,4-bis-(*m*-methyl-*p*-propionoxyphenyl)-3,4-hexanediol, 15 cc. of acetic anhydride and 10 cc. of acetyl chloride; 4.1 g. (90%) of solid material was collected, m. p. 132–135°; recrystallization from ethanol gave white crystals; m. p. 139–140°.

3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene.—Two grams of 3,4-bis-(*m*-methyl-*p*-propionoxyphenyl)-2,4-hexadiene was suspended in 20 cc. of Claisen solution (100 g. of potassium hydroxide dissolved in 100 cc. of water and diluted, after cooling, with an equal volume of methanol). The mixture was warmed on a steam-bath until the solid was completely dissolved and then allowed to stand at room temperature overnight. After diluting to 150 cc. with water, the mixture was filtered and then acidified with 10% hydrochloric acid to a *p*H of about 3. The white flocculent precipitate which separated was filtered, washed with water and dried; yield, 1.4 g. (95%), m. p. 180–185°. Recrystallization from 50% ethanol gave white needles, m. p. 187–189°.

3,4-bis(*m*-Methyl-*p*-butyroxyphenyl)-2,4-hexadiene.—One gram of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene was dissolved in 10 cc. of anhydrous pyridine, 1.1 g. of butyric anhydride added and the mixture refluxed gently for ninety minutes. After cooling the reaction mixture was poured into 150 cc. of water and stirred for thirty minutes. The solid which separated was collected, washed with water and recrystallized from methanol, yielding one gram of small white crystals, m. p. 123–124°.

3,4-bis-(*m*-Methyl-*p*-palmitoxyphenyl)-2,4-hexadiene.—One and one-half grams of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene was dissolved in 10 cc. of anhydrous pyridine, 3 g. of palmityl chloride added and the mixture refluxed gently for thirty minutes. After cooling, the reaction product was poured into 100 cc. of water and allowed to stand for fifteen minutes. The mixture was then extracted with 150 cc. of ether and the ether solution then washed successively with 40 cc. of 10% hydrochloric acid, 40 cc. of 5% sodium hydroxide and then with water until the washings were neutral to litmus. After drying over anhydrous calcium chloride the ethereal solution was filtered, evaporated to dryness and the residue then recrystallized from ethanol, giving a white amorphous powder, m. p. 69–70°.

3,4-bis-(*m*-Methyl-*p*-benzoxyphenyl)-2,4-hexadiene.—This compound was prepared by the Schotten–Baumann method using 1 g. of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene. Recrystallization from ethanol gave white needles, m. p. 207–208°.

Disodium Salt of 3,4-bis-(*m*-Methyl-*p*-(*m'*-sulfobenzoxy)-phenyl)-2,4-hexadiene.—Three grams of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene was added slowly to a solution of 5 g. of benzoic acid-*m*-sulfochloride in 15 cc. of pyridine maintained at 80°. After all the hydroxy compound had been added, the mixture was heated for two hours at 80° and then poured into 150 cc. of water. The solution was then filtered, treated with saturated aqueous sodium chloride and centrifuged. The solid thus obtained was then dissolved in a minimum of water and the resulting solution was again treated with sodium chloride and centrifuged. This process was repeated once more and this time the resulting precipitate was pressed between filter papers and dried over sulfuric acid. The dried material was dissolved in a minimum of hot ethanol and the solution treated with benzene, whereupon the compound was obtained as a white, flocculent precipitate which was collected and dried. The compound decomposed at high temperatures.

bis-Acid Succinate of 3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene.—One gram of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene was dissolved in 10 cc. of pyridine, 1 g. of succinic anhydride added, and the mixture gently refluxed for two hours. After cooling the reaction mixture was diluted with 40 cc. of acetone and an excess of concentrated hydrochloric acid added. A viscous oil separated which was washed with water and recrystallized from dilute acetic acid to give small white crystals, m. p. 193°.

bis-Methylcarbonate of 3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene.—One gram of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene was dissolved in 15 cc. of pyridine and cooled to 0° in an ice-bath. Four cc. of methyl chlorocarbonate was added dropwise with shaking and cooling. The mixture was then allowed to come to room temperature and was poured into 100 cc. of water. The solid which separated was collected, washed first with water, and then with several small portions of ethanol and dried. Recrystallization from ethanol gave small white crystals, m. p. 171–172°.

bis-Ethylcarbonate of 3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene.—This compound was prepared as described immediately above by using ethyl chlorocarbonate. Recrystallization from ethanol yielded white crystals, m. p. 150–151°.

3,4-bis-(*m*-Methyl-*p*-propionoxyphenyl)-hexane.—Two grams of 3,4-bis-(*m*-methyl-*p*-propionoxyphenyl)-2,4-hexadiene was dissolved in 200 cc. of hot absolute ethanol and hydrogenated at 70° and about 70 atm. in the presence of Raney nickel. The mixture was then cooled, filtered and evaporated to dryness, whereupon 2 g. of solid material remained. Recrystallization from ethanol gave 1.6 g. (80%) of white crystals, m. p. 114–115°.

This compound was also prepared by hydrogenating the same quantity of the diene compound dissolved in 20 cc. of acetone, using 20 mg. of palladium black and an initial gage pressure of 48 lb. per sq. in. The theoretical pressure drop was attained in ten minutes; yield, 80% of pure product.

A study of the stereochemical aspects is in progress and will be reported later.

3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-hexane.—Two grams of 3,4-bis-(*m*-methyl-*p*-propionoxyphenyl)-hexane was saponified by treatment with 20 cc. of Claisen solution as described under 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene. Recrystallization from dilute acetic acid gave white crystals, m. p. 145°.

Esters of 3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-hexane.—Using identical methods, the same esters described in the hexadiene series were prepared.

Analytical data for all new compounds are summarized in Table II.

Acknowledgment.—Grateful acknowledgment is hereby expressed to Miss E. F. Deckert, Director of the Division of Pharmacology of the Reed and Carnrick Institute for Medical Re-

TABLE II

Compound	Molecular formula	M. p.,[a] °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene	$C_{20}H_{22}O_2$	187–189	81.60	81.73	7.53	7.41
Diacetate	$C_{24}H_{26}O_4$	166–168	76.16	76.30	6.93	6.96
Dipropionate	$C_{26}H_{30}O_4$	138–139	76.82	76.78	7.44	7.56
Dibutyrate	$C_{28}H_{34}O_4$	123–124	77.39	77.40	7.89	8.05
Dipalmitate	$C_{52}H_{82}O_4$	69–70	80.98	80.70	10.72	10.66
Dibenzoate	$C_{34}H_{30}O_4$	207–208	81.25	81.26	6.02	6.06
Dimethocarbonate	$C_{24}H_{26}O_6$	171–172	70.22	70.20	6.38	6.61
Diethocarbonate	$C_{26}H_{30}O_6$	150–151	71.21	71.19	6.90	7.17
Diacid succinate	$C_{28}H_{30}O_8$	193	68.00	68.03	6.11	6.35
Di-*m′*-sulfobenzoate (disodium salt)	$C_{34}H_{28}O_{10}Na_2S_2$	[b]	S, 9.07	8.79	Na, 6.51	6.41
3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-hexane	$C_{20}H_{26}O_2$	145	80.50	80.89	8.78	8.44
Diacetate	$C_{24}H_{30}O_4$	132	75.36	75.21	7.91	7.82
Dipropionate	$C_{26}H_{34}O_4$	115	76.06	76.09	8.35	8.28
Dibutyrate	$C_{28}H_{38}O_4$	100–101	76.67	77.32	8.73	8.76
Dipalmitate	$C_{52}H_{86}O_4$	68–69	80.56	80.67	11.18	10.77
Dibenzoate	$C_{34}H_{34}O_4$	199–200	80.60	80.54	6.61	6.56
Dimethocarbonate	$C_{24}H_{30}O_6$	148–149	69.54	69.34	7.30	7.24
Diethocarbonate	$C_{26}H_{34}O_6$	138	70.56	70.69	7.74	7.28
Diacid succinate	$C_{28}H_{34}O_8$	198–200	67.45	67.60	6.87	6.91
Di-*m′*-sulfobenzoate (disodium salt)	$C_{34}H_{32}O_{10}Na_2S_2$	[b]	S, 9.02	8.98	Na, 6.47	6.62

[a] All melting points are uncorrected. [b] Melts with decomposition at about 300°.

search, under whose guidance all determinations of estrogenic potency and toxicity on experimental animals have been conducted.

Summary

3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene, 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-hexane and some of their organic esters have been prepared. Many of these compounds are active estrogens.

JERSEY CITY, N. J. RECEIVED AUGUST 11, 1947

[CONTRIBUTION FROM THE RESEARCH DIVISION, THE UPJOHN COMPANY]

Steroid Acids and their Transformation Products. I. Thiol Esters[1a]

BY ROBERT H. LEVIN, A. VERN MCINTOSH, JR., GEORGE B. SPERO, DOUGLAS E. RAYMAN AND ELIZABETH M. MEINZER

The use of Raney nickel catalyst for the desulfurization and reduction of sulfur compounds has recently been extended to the preparation of aldehydes[1] and alcohols[2] from carboxylic acids via the corresponding thiol compounds. Among the acids used by Jeger and co-workers[2a] were 3β-acetoxy-*etio-allo*-cholanic acid and 3β-acetoxy-Δ^5-*etio*-cholenic acid. For the broader use of the thiol esters as starting materials for the side chain degradation of steroids we have prepared a number of these previously unreported esters.

The steroid thiol esters were prepared by two methods:[3] (A) reaction of the acid chloride with an excess of mercaptan in pyridine; and (B) treatment of the acid chloride with a suspension of lead mercaptide[4] in ether. Generally speaking method A gave slightly better yields of crystalline thiol ester, but the products from B were easier to purify to constant m. p. Table I summarizes our data. Several of these compounds were chromatographed over alumina. It was found that the acetoxy thiol esters could be readily purified in this way. However, a number of the crystalline formoxy compounds became oily when put over the column, probably because of deformylation at the 3-position.

Ethyl 3α-hydroxy-12α-acetoxy-*nor*-thiolcholanate (III) was obtained from 3α-hydroxy-12α-acetoxy-*nor*-cholanic acid (II)[5] using method A. This involves the interesting preparation of a non-aromatic hydroxy acid chloride by the use of thi-

---

[1a] Presented before the Division of Medicinal Chemistry, 112th A. C. S. Meeting, New York, N. Y., September 17, 1947.

[1] M. L. Wolfrom and J. V. Karabinos, THIS JOURNAL, **68**, 1455 (1946).

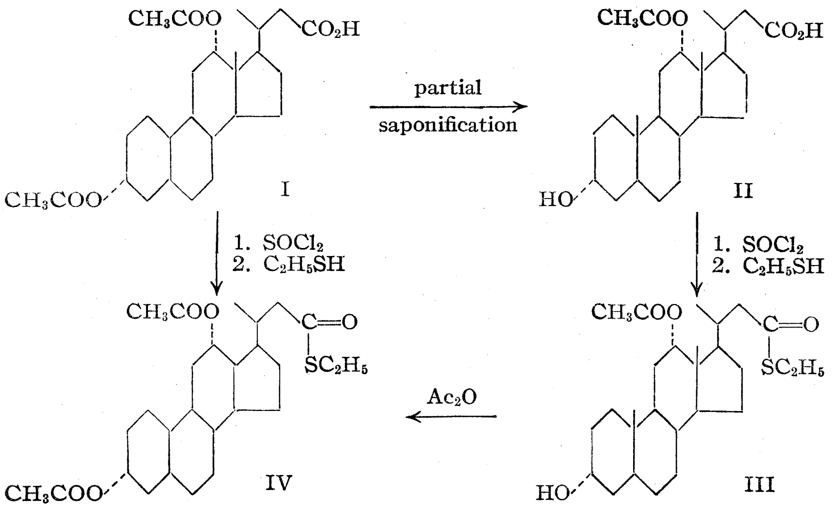
[2] (a) V. Prelog, J. Norymberski and O. Jeger, *Helv. Chim. Acta*, **29**, 360 (1946). (b) O. Jeger, J. Norymberski, S. Szpilfogel and V. Prelog, *ibid.*, **29**, 684 (1946). (c) L. Ruzicka, S. Szpilfogel and O. Jeger, *ibid.*, **29**, 1520 (1946).

[3] A. W. Ralston, E. W. Segebrecht and S. T. Bower, *J. Org. Chem.*, **4**, 502 (1939), have reviewed the literature.

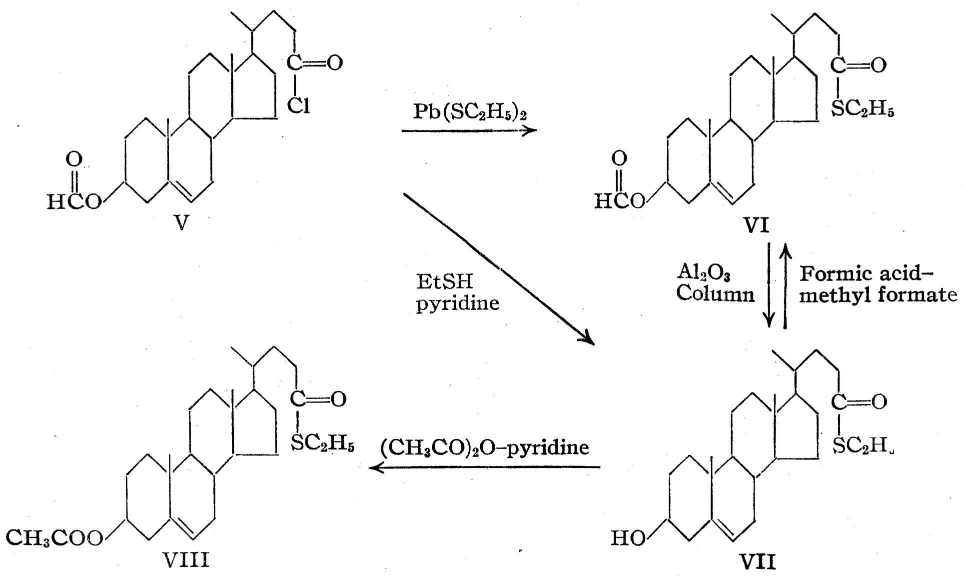
[4] P. Borgstrom, L. M. Ellis, Jr., and E. E. Reid, THIS JOURNAL **51**, 3649 (1929).

[5] Byron Riegel and A. Vern McIntosh, Jr., *ibid.*, **66**, 1102 (1944).

onyl chloride without protection of the hydroxyl group.[6] Compound III was isolated as an oil which did not crystallize after chromatography. However, on acetylation with acetic anhydride and pyridine, ethyl 3α,12α-diacetoxy-*nor*-thiol cholanate (IV) was formed and proved to be identical with the compound similarly prepared from 3α,12α-diacetoxy-*nor*-cholanic acid (I).



The lability of the 3-formoxy group is illustrated by reactions in the 3β-hydroxy-Δ^5-cholenic acid series. When 3β-formoxy-Δ^5-cholenyl chloride (V) was treated with lead ethyl mercaptide, ethyl 3β-formoxy-Δ^5-thiolcholenate (VI), m. p. 80–82°, was formed. Esterification of the acid chloride (V) with ethyl mercaptan and pyridine produced a compound, m. p. 108.5–109.5°, which was characterized as 3β-hydroxy-Δ^5-thiolcholenate (VII) by the reactions shown.



When 3β-formoxy-Δ^5-thiolcholenate (VI) was chromatographed over alumina, the hydroxy compound was obtained as the main fraction. Reformylation of VII with formic acid and methyl formate produced VI. Acetylation of the hydroxy compound (VII) gave 3β-acetoxy-Δ^5-thiolcholenate (VIII), identical with the compound produced by esterification of 3β-acetoxy-Δ^5-cholenic acid by methods A or B. The acetoxy thiol ester (VIII) was recovered unchanged after passage over the alumina column. When 3β-hydroxy-Δ^5-cholenic acid was treated with thionyl chloride and then ethyl mercaptan and pyridine, ethyl 3-chloro-Δ^5-thiolcholenate was formed in good yield and readily purified over an alumina column.

The treatment of these steroid thiol esters with Raney nickel will be discussed in a future paper.

We wish to acknowledge the technical assistance of Jeane F. DeWitt in part of this work.

Experimental

Preparation of Thiol Esters.—An example of each method will be given in detail.

Method A. Benzyl 3α,12α - diacetoxy - *nor* - thiolcholanate.—To 1.5 g. (0.0033 mole) of 3α,12α-diacetoxy-*nor*-cholanic acid was added 6 ml. (9.8 g., 0.082 mole) of purified thionyl chloride.[7] The acid dissolved within five minutes and the solution was allowed to stand, with occasional swirling, at room temperature for one hour. Twenty milliliters of a 1:1 mixture of anhydrous benzene and ether was then added and the whole was evaporated to dryness *in vacuo* at 40°. This process of treatment with benzene–ether was repeated twice in order to ensure the complete removal of excess thionyl chloride.

To the resulting acid chloride dissolved in 10 ml. of anhydrous benzene was added 0.4 ml. (0.005 mole) of dry pyridine and 2 ml. (1.12 g., 0.009 mole) of benzyl mercaptan. A precipitate formed. After standing for

---

[6] One of us (A. V. M.) while working in the laboratory of Professor Byron Riegel, had previously prepared this acid chloride and converted it quantitatively with concentrated aqueous ammonia into 3α-hydroxy-12-α-acetoxy-nor-cholanic acid amide, m. p. 198–199°, $[\alpha]_D$ +111.3° (in absolute ethanol). A Beilstein halogen test on the amide was negative. *Anal.* (By Dr. T. S. Ma) Calcd. for $C_{25}H_{41}O_4N$: N, 3.38. Found: N, 3.18.

[7] Fieser, "Experiments in Organic Chemistry," Part II, D. C. Heath and Co., New York, N. Y., 1941, p. 381.

TABLE I

THIOL ESTERS OF STEROID ACIDS

Compound	M. p., °C.[a]	Rotation[b] $[\alpha]_D$ deg.	Method of prepn.	Yield,[u] %	Molecular formula	Analyses,[p] %					
						Carbon		Hydrogen		Sulfur	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
Ethyl 3β-hydroxy-Δ⁵-thiolcholenate	108.5–109.5	−38.5[c]	A[q]	71	$C_{26}H_{42}O_2S$	74.59	74.64	10.11	10.07	7.66	7.79
Ethyl 3β-formoxy-Δ⁵-thiolcholenate	81–82	−47.5[d]	B	63	$C_{27}H_{42}O_3S$	72.60	72.07[s]	9.48	9.61	7.18	7.01[s]
Ethyl 3β-acetoxy-Δ⁵-thiolcholenate	101.5–103.5	−40.9[e]	A	73	$C_{28}H_{44}O_3S$	72.99	72.92[s]	9.63	9.69	6.98	7.36[s]
			B	71							
Isopropyl 3β-acetoxy-Δ⁵-thiolcholenate	131–133	−40.4[f]	A	74	$C_{29}H_{46}O_3S$	73.37	73.39	9.77	9.55	6.75	6.81
t-Butyl 3β-acetoxy-Δ⁵-thiolcholenate	169.5–171	−39.8[g]	A	75	$C_{30}H_{48}O_3S$	73.72	74.07	9.90	9.96	6.56	6.71
n-Hexyl 3β-acetoxy-Δ⁵-thiolcholenate	77.5–79.5	−35.4[h]	A	66	$C_{32}H_{52}O_3S$	74.37	74.70[s]	10.14	10.00	6.20	6.60
Ethyl 3-chloro-Δ⁵-thiolcholenate	103.5–105	−30.4[i]	A	51	$C_{26}H_{41}OSCl$	71.44	71.51[s]	9.46	9.58	8.11	8.75[t]
Ethyl 3β-acetoxy-5-chloro-*nor*-thiolcholanate	165–168	.....	B	18	$C_{28}H_{43}O_3SCl$	...	....	...	...	6.45	6.32
Ethyl 3β-acetoxy-Δ⁵-*bisnor*-thiolcholenate	132–133	−38.0[j]	B	81	$C_{26}H_{40}O_3S$	72.18	72.50	9.32	9.13	7.41	7.44
Ethyl 3α,12α-diformoxy thiolcholanate[r]	111–112	+92.1[k]	A	62	$C_{28}H_{44}O_5S$	68.25	68.39	9.00	8.89	6.51	6.51
			B	53							
Ethyl 3α-formoxy thiolcholanate	81–82	+41.3[l]	A	82	$C_{27}H_{44}O_3S$	72.27	72.53	9.88	9.74	7.14	7.23
			B	73							
Ethyl 3α,12α-diacetoxy-*nor*-thiolcholanate	91–91.5	+96.0[m]	A	89	$C_{29}H_{46}O_5S$	68.76	69.07	9.15	9.47	6.33	6.37
			B	79							
Benzyl 3α,12α-diacetoxy-*nor*-thiolcholanate	154–156	+95.5[n]	A	73	$C_{34}H_{48}O_5S$	71.79	71.56	8.51	8.79	5.64	5.66
Phenyl 3α,12α-diacetoxy-*nor*-thiolcholanate	146–147	+99.7[o]	A	80	$C_{33}H_{46}O_5S$	71.44	71.30	8.36	8.04	5.78	5.64

[a] All m. p.'s corrected. [b] Rotations taken in chloroform with a 1 dm. tube. [c] 207.8 mg. in 20 ml., $\alpha^{24.5}_D$ −0.40°. [d] 139.0 mg. in 10 ml., α^{25}_D −0.66°. [e] 200.3 mg. in 10 ml., α^{25}_D −0.82°. [f] 198.0 mg. in 10 ml., $\alpha^{24.5}_D$ −0.80°. [g] 198.6 mg. in 10 ml., α^{25}_D −0.79°. [h] 201.2 mg. in 10 ml., α^{25}_D −0.71°. [i] 69.0 mg. in 10 ml., α^{25}_D −0.21°. [j] 100.0 mg. in 10 ml., α^{26}_D −0.38°. [k] 203.0 mg. in 10 ml., α^{26}_D +1.87°. [l] 186.1 mg. in 10 ml., α^{25}_D +0.77°. [m] 100 mg. in 10 ml., α^{26}_D +0.96°. [n] 200 mg. in 10 ml., α^{26}_D +1.91°. [o] 199.0 mg. in 10 m., α^{26}_D +1.98°. [p] Analyses and rotations by the Upjohn microanalytical group unless otherwise indicated. [q] Starting with the 3-formoxy compound. [r] Desoxycholic acid is formulated as 3α,12α- according to the latest evidence (*Ann. Rev. Biochem.*, **15**, 162 (1946)). [s] Analysis by Oakwold Laboratories, Alexandria, Virginia. [t] Chlorine analysis. [u] These over-all yields have been calculated from starting acid. Varying amounts of unreacted acid were recovered, which would raise actual yield.

twenty-four hours at room temperature the mixture was diluted with 15 ml. of water and 15 ml. of ether. The precipitate dissolved and the ether–benzene phase was separated. The aqueous portion was extracted with two 15-ml. portions of ether and the combined ether–benzene layer was washed with 30-ml. portions of water, 1% sodium hydroxide, 1% hydrochloric acid and finally with water again. The neutral fraction was dried over anhydrous sodium sulfate and the solvent evaporated to dryness *in vacuo*. The residual oil was crystallized from 50 ml. of 95% alcohol to give 1.38 g. (73%) of product, m. p. 147–152°. After three recrystallizations from alcohol 1.23 g. (65.5%) of benzyl thiol ester with a constant m. p. of 154–156° (cor.) was obtained.

Method B. **Ethyl 3α,12α-Diformoxythiolcholanate.**—The acid chloride (prepared from 4.5 g. (0.01 mole) of 3,12-diformoxydesoxycholic acid in the manner described under A) was dissolved in 30 ml. of anydrous ether and added to 1.8 g. (0.0055 mole) of lead ethyl mercaptide covered with 20 ml. of anhydrous ether. The mixture was allowed to stand at room temperature with occasional swirling. The yellow lead mercaptide was gradually replaced by white lead chloride. After twenty-four hours the solution was filtered and the precipitate washed with 50 ml. of ether. The combined ether filtrate was washed with 100 ml. of 1% sodium hydroxide and 300 ml. of water, then dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo* on the steam-bath. The residual oil was dissolved in 50 ml. of hot alcohol and 10 ml. of water was added. On cooling under the water tap an oil separated, taking with it all the color in the solution. Crystallization then took place in the clear colorless solution, giving 2.2 g. of material. An additional 0.32 g. of crystals was obtained by crystallizing the oil from alcohol. The total yield was 2.6 g. (53% of the theoretical), m. p. 105–110°. After three recrystallizations the m. p. was constant at 111–112° (cor.).

Ethyl 3α-Hydroxy-12α-acetoxy-*nor*-thiolcholanate, (III).—A solution of 2.1 g. of 3α-hydroxy-12α-acetoxy-*nor*-cholanic acid[5] in 8 ml. of thionyl chloride was allowed to stand an hour at room temperature. After removal of the thionyl chloride, the 3α-hydroxy-12α-acetoxy-*nor*-cholanyl chloride was dissolved in 10 ml. of benzene by warming. The solution was cooled and 0.6 ml. of pyridine, then 1.9 ml. of ethyl mercaptan added. The reaction mixture was allowed to stand a day at room temperature, then diluted with 100 ml. of ether and washed successively with water, 1% sodium hydroxide, dilute hydrochloric acid and water. After drying of the ether and evaporation, the residue weighed 2.3 g. (96% of theoretical). Attempts to crystallize the thiol ester from various solvents failed. On chromatography over alumina[8] 81% of the recovered material was eluted in the main fraction, but could not be crystallized.

Ethyl 3α,12α-Diacetoxy-*nor*-thiolcholanate (IV).—A solution of 501 mg. of ethyl 3α-hydroxy-12α-acetoxy-*nor*-thiolcholanate in 10 ml. of acetic anhydride and 10 ml. of pyridine was heated on the steam-bath for one and one-half hours and the solvent was then distilled *in vacuo*. The residue was partly crystalline. It was chromatographed and the fractions eluted with benzene were combined and crystallized from alcohol and water, giving a yield of 120

---

(8) The alumina used in our chromatographic work was "Fisher Adsorption Alumina" obtained from the Fisher Scientific Company and used without further treatment.

mg., m. p. 85–87°. Recrystallization gave a product, m. p. 90–91°, identical with that obtained by esterifying $3\alpha,12\alpha$-diacetoxy-*nor*-cholanic acid.

Ethyl 3β-Hydroxy-Δ^5-thiolcholenate (VII).—The acid chloride prepared from 30.0 g. (0.075 mole) of 3β-formoxy-Δ^5-cholenic acid was dissolved in 200 ml. of benzene and treated with 37 ml. (0.50 mole) of ethyl mercaptan and 10 ml. of pyridine. After standing overnight at room temperature the reaction mixture was diluted with 250 ml. of water and extracted with 250 ml. of ether in portions. The ether layer was washed with 1% sodium hydroxide, 1% hydrochloric acid and water. After drying the ether was distilled and the residue crystallized from 300 ml. of alcohol and 50 ml. of water, giving 23 g. (72%) of ethyl 3β-hydroxy-Δ^5-thiolcholenate, m. p. 98–100°. Several recrystallizations from hexane–benzene raised the m. p. to 108.5–109.5°.

Deformylation of Ethyl 3β-Formoxy-Δ^5-thiolcholenate (VI) over Alumina.—Two hundred mg. of ethyl 3β-formoxy-Δ^5-thiolcholenate, m. p. 78.5–81.5°, was dissolved in 8 ml. of benzene and passed through a 10-g. alumina[8] column. The column was eluted, using the free flow method, with 8-cc. portions of benzene, benzene + 0.4% methanol, benzene + 1% methanol, benzene + 2% methanol, benzene + 4% methanol, benzene + 8% methanol and methanol. The benzene eluate contained 35 mg.% of crystalline material of m. p. 78–82° (starting material). The methanol fraction contained 135 mg. of crystalline material of m. p. 95–100°. After several recrystallizations from 3A alcohol[9] and from hexane (Skellysolve "B") the m. p. became constant at 105–108°. An admixture with a sample of ethyl 3β-hydroxy-Δ^5-thiolcholenate, m. p. 108.5–110°, melted at 108–110°. An admixture with starting material melted at 63–100°.

Formylation of Ethyl 3β-Hydroxy-Δ^5-thiolcholenate (VII).—A mixture of 710 mg. of ethyl 3β-hydroxy-Δ^5-thiolcholenate, m. p. 108–109.5°, 25 ml. of formic acid (87%) and 12.5 ml. of methyl formate was heated under reflux on the steam-bath for two and one-half hours; then the reaction mixture was evaporated *in vacuo* and the residue dissolved in ether. The ether solution was washed with 0.5% sodium hydroxide, then with water, and was dried over sodium sulfate. Evaporation *in vacuo* gave 452 mg. of ethyl 3β-formoxy-Δ^5-thiolcholenate (VI), m. p. 78–79.5.° Several recrystallizations from methanol, water and from alcohol brought the m. p. up to 80–82°. A mixture m. p. with authentic formoxy ester was not depressed.

Acetylation of Ethyl 3β-Hydroxy-Δ^5-thiolcholenate.—Three hundred mg. of ethyl 3β-hydroxy-Δ^5-thiolcholenate, m. p. 108–109.5°, was mixed with 5 ml. of acetic anhydride and 5 ml. of pyridine. After refluxing for two and one-half hours the mixture was evaporated to dryness on the steam-bath *in vacuo*. The residue was taken up in alcohol. The alcohol solution was diluted with water and extracted with ether. After washing with 1% sodium hydroxide and water the ether solution was dried over sodium sulfate and evaporated to dryness. The residue was crystallized from 3A alcohol to yield 290 mg. of ethyl 3β-acetoxy-Δ^5-thiolcholenate (VIII), m. p. 101–104°. After several recrystallizations, the melting point became constant at 101–102.5°. An admixture with a sample of authentic ethyl 3β-acetoxy-Δ^5-thiolcholenate, m. p. 101–103°, showed no melting point depression. An admixture with starting material melted at 79–82°.

Hydrolysis of 300 mg. of the thiol ester (VIII) with 1 g. of sodium hydroxide in 2.5 ml. of water and 15 ml. of alcohol gave an almost quantitative yield of 3β-hydroxy-Δ^5-cholenic acid.

Summary

A number of thiol esters of steroid acids have been prepared and characterized using ethyl, isopropyl, *t*-butyl, *n*-hexyl, benzyl and phenyl mercaptans; and the following acids: 3β-hydroxy-Δ^5-cholenic, 3β-hydroxy-5-chloro-*nor*-cholenic, 3-β-hydroxy-Δ^5-*bisnor*-cholenic, desoxycholic, *nor*-desoxycholic and lithocholic.

KALAMAZOO, MICHIGAN RECEIVED SEPTEMBER 2, 1947

---

[9] 3A alcohol is commercial 95% alcohol denatured by the addition of 5% methanol.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Chemical Interactions of Amino Compounds and Sugars. III.[1] The Conversion of D-Glucose to 5-(Hydroxymethyl)-2-furaldehyde[2]

BY M. L. WOLFROM, R. D. SCHUETZ[3] AND LIEBE F. CAVALIERI[3]

It is well established that D-glucose and other hexoses are converted to 5-(hydroxymethyl)-2-furaldehyde on heating with acids.[4] Scallet and Gardner[5] have previously demonstrated that 5-(hydroxymethyl)-2-furaldehyde is formed from D-glucose on refluxing in water alone.

The purpose of the work herein reported was to determine whether ultraviolet spectroscopy would give any insight into the mechanism and intermediates in the conversion of D-glucose to 5-(hydroxymethyl)-2-furaldehyde. Hydrochloric acid was the catalyst chosen for these studies.

When an aqueous solution (initial *p*H 6.5) of D-glucose was prepared from triply distilled water and refluxed, a series of changes could be detected in the ultraviolet absorption spectrum; these are shown in Figs. 1 and 2. After three and one-half hours (curve 1, Fig. 1) a distinct band with a maximum at 228 mμ was evident. After eight hours of

---

[1] Previous communication in this series: M. L. Wolfrom, L. F. Cavalieri and Doris K. Cavalieri, THIS JOURNAL, **69**, 2411 (1947).

[2] The subject matter of this paper has been undertaken in coöperation with the Committee on Food Research of the Quartermaster Food and Container Institute for the Armed Forces under a contract (W11-009-Q-M-70183 and W44-109-QM-1027) with The Ohio State University Research Foundation. The opinions or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the views or indorsement of the War Department.

[3] Research Associate of The Ohio State University Research Foundation, Projects 278 and 238, respectively.

[4] G. Düll, *Chem. Ztg.*, **19**, 216 (1895); J. Kiermayer, *ibid.*, 1003; W. Alberda van Ekenstein and J. J. Blanksma, *Chem. Weekblad*, **6**, 217 (1909); *Ber.*, **43**, 2355 (1910); W. N. Haworth and W. G. N. Jones, *J. Chem. Soc.*, 667 (1944); B. Singh, G. R. Dean and S. M. Cantor, THIS JOURNAL, **70**, 517 (1948).

[5] B. L. Scallet with J. H. Gardner, THIS JOURNAL, **67**, 1934 (1945).

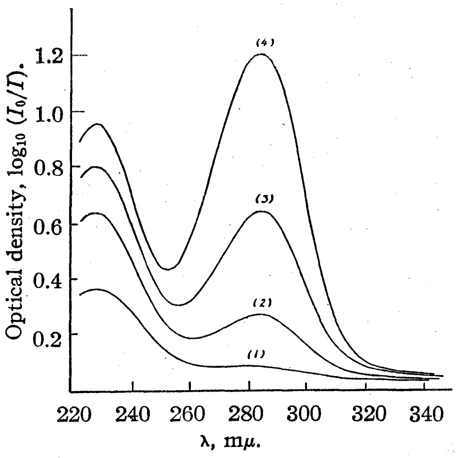


Fig. 1.—Absorption spectra of a 0.0500 molar aqueous D-glucose solution, initial *p*H 6.5, after refluxing for various time intervals: curve 1, after three and one-half hours; curve 2, after eight hours; curve 3, after twelve hours; curve 4, after seventeen hours. Beckman spectrophotometer (Model DU), 1-cm. cell, slit width 0.30–0.35 mm., optical densities 0.05–1.405.

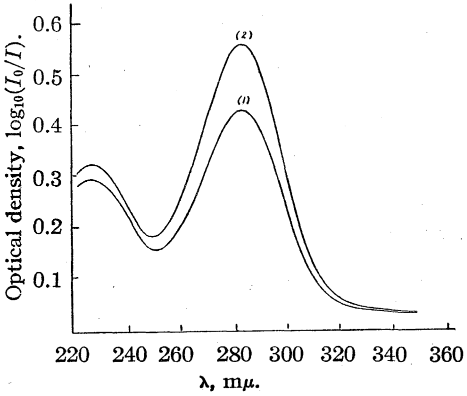


Fig. 2.—Absorption spectra of a 0.0500 molar aqueous D-glucose solution, initial *p*H 6.5, after refluxing for various time intervals. Samples were diluted four to one for absorption measurements: curve 1, after twenty hours; curve 2, after twenty-three hours; Beckman spectrophotometer (Model DU), 1-cm. cell, slit width 0.30–0.35 mm., optical densities 0.05–0.57.

heating (curve 2, Fig. 1), the maximum at 228 mμ was more pronounced and a second band was developing in the region of 285 mμ. At the end of twelve hours (curve 3, Fig. 1) the maximum at 228 mμ had increased and that at 285 mμ was increasing at an even greater rate. On continued heating for seventeen hours (curve 4, Fig. 1) the ratio of the substance producing the band at 285 mμ to the other (producing the band at 228 mμ) became very large. Finally, after a period of heating somewhat greater than twenty and twenty-three hours (curves 1 and 2, Fig. 2), respectively, the typical absorption spectrum of 5-(hydroxymethyl)-2-furaldehyde (Fig. 5) was developing.

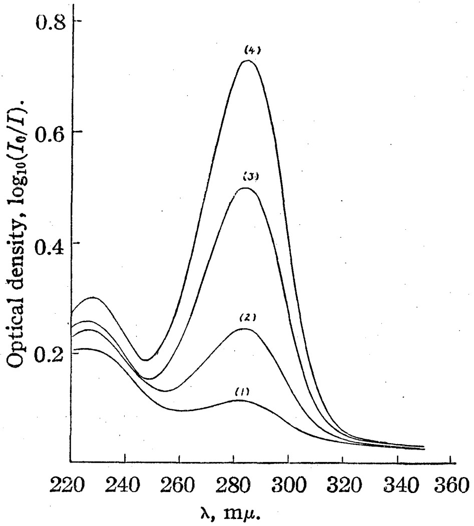


Fig. 3.—Absorption spectra of a 0.0500 molar aqueous D-glucose solution adjusted to an initial *p*H of 4.3 with hydrochloric acid, after refluxing for various time intervals: curve 1, after three and one-half hours; curve 2, after eight hours; curve 3, after twelve hours; curve 4, after fifteen hours. Beckman spectrophotometer (Model DU), 1-cm. cell, slit width 0.30–0.35 mm., optical densities 0.05–0.75.

When an aqueous solution of D-glucose was adjusted to an initial *p*H of 4.3 with hydrochloric acid and refluxed, a similar series of curves was obtained (Fig. 3). Here both bands are evident after three and one-half hours (curve 1) and again the band at 228 mμ was more pronounced. After eight hours (curve 2) both maxima, at 228 mμ and at 285 mμ, were of about equal intensity. At the end of twelve hours (curve 3) the ratio of

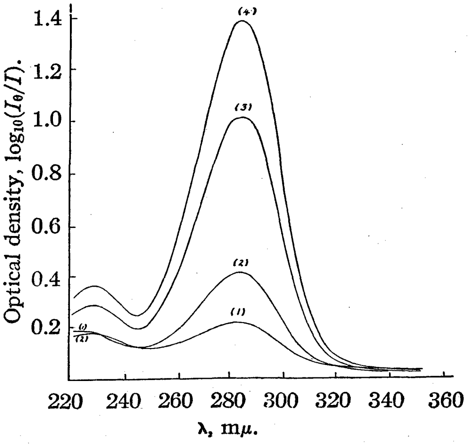


Fig. 4.—Absorption spectra of a 0.0500 molar aqueous D-glucose solution adjusted to an initial *p*H of 2.0 with hydrochloric acid, after refluxing for various time intervals: curve 1, after three and one-half hours; curve 2, after eight hours; curve 3, after twelve hours; curve 4, after fifteen hours. Beckman spectrophotometer (Model DU), 1-cm. cell, slit width 0.30–0.35 mm., optical densities 0.05–1.405.

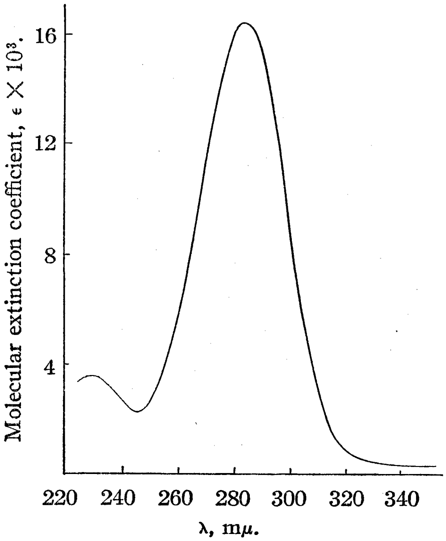
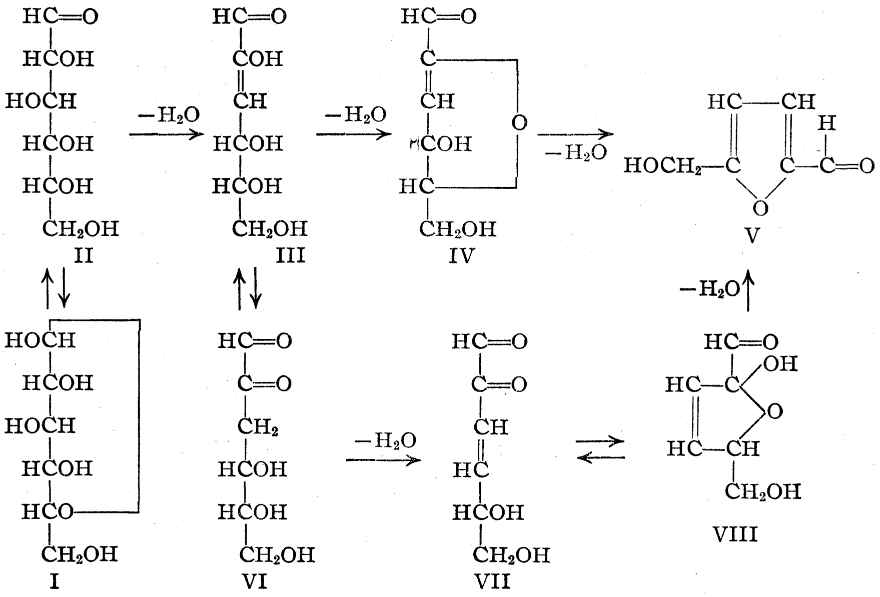


Fig. 5.—Absorption spectrum of pure 5-(hydroxymethyl)-2-furaldehyde[1] in water; concentration, 6.3627×10^{-5} mole per liter; $\epsilon = 1/c \ln (100/T)$ wherein c is the molar concentration and T is the percentage transmission; $\epsilon = 16{,}500$, max. 285 mμ (major peak), $\epsilon = 3{,}620$, max. 228 mμ (minor peak); slit width 0.32–0.35 mm., optical densities 0.016–1.048.

material producing the band at 285 mμ to that causing the band at 228 mμ had again become quite large. Finally, after heating for a period of fifteen hours (curve 4), the general absorption curve for 5-(hydroxymethyl)-2-furaldehyde (Fig. 5) was well developed.



The series of absorption curves (Fig. 4) resulted when an aqueous solution of D-glucose, adjusted with hydrochloric acid to an initial *p*H of 2.0, was refluxed. In curve 1, Fig. 4, after three and one-half hours, the maximum at 285 mμ was more pronounced than that at 228 mμ. After eight hours (curve 2, Fig. 4), the ratio of the compound responsible for absorption at 285 mμ to the one causing absorption at 228 mμ had again become large, and after twelve hours of continued refluxing, this ratio had further increased (curve 3, Fig. 4). Finally, after fifteen hours of heating, the typical absorption curve for 5-(hydroxymethyl)-2-furaldehyde resulted (curve 4, Fig. 4).

It is to be noted that the ultraviolet absorption spectra presented, at various time intervals, and at increasing initial *p*H values, during the conversion of D-glucose to 5-(hydroxymethyl)-2-furaldehyde are all very similar. Such differences as exist lie only in the rate at which the bands at 228 mμ and 285 mμ are developed. This indicates that the reaction mechanism involved in the formation of 5-(hydroxymethyl)-2-furaldehyde from D-glucose is independent of the initial *p*H value in the range studied (*p*H 6.5 to *p*H 2). These absorption curves, however, show that the reaction rate is dependent upon the acidity of the reaction medium, increasing with increasing acidity.

Further, it can be pointed out (curve 1, Fig. 1) that after three and one-half hours where the reaction is slowest (due to no added acid), there is absorption only at 228 mμ. That the substance producing this band is not 5-(hydroxymethyl)-2-furaldehyde is apparent from the fact that the major peak at 285 mμ is missing. In addition, the intensity of absorption at 228 mμ increased to a maximum after seventeen hours (curve 4, Fig. 1) where both peaks at 228 mμ and 285 mμ are present and then decreased to a corresponding value for 5-(hydroxymethyl)-2-furaldehyde as the reaction proceeded. It is probable that the intermediate producing the high absorption at 228 mμ is a conjugated acyclic diene as (or enal) since, Mulliken[6] and also Booker, Evans and Gillam[7] have shown, the cyclic dienes, which are necessarily oriented *cis*, would have shown a much weaker absorption in this region.

The absorption intensity at 228 mμ does not reach a very large value when aqueous solutions of D-glucose are refluxed at the lower initial *p*H.

---

(6) R. S. Mulliken, *J. Chem. Phys.*, **7**, 121 (1939).

(7) H. Booker, L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 1453 (1940).

This is due to the increased rate of conversion through the intermediates to 5-(hydroxymethyl)-2-furaldehyde. This is shown by curves 1 in Figs. 1, 3, 4, and curve 3 in Fig. 4.

To explain these absorption curves we can postulate that D-glucose, represented by I (other anomers and ring structures than I are possible), is transformed first into II or its aldehydrol. The intermediate III then results from II by loss of water, producing a conjugated enal. Evidence for III is found in both the region and the magnitude of absorption shown in curve 4, Fig. 1. Evans and Gillam[8] have demonstrated that α,β-unsaturated aldehydes (R—CH=CR'CHO) show high absorption in the general region of 230 mμ. In this intermediate (III), R is $(CHOH)_2CH_2OH$ and R' is the hydroxyl group. A similar type of intermediate was shown to be present in the conversion of 2,3,4,6-tetramethyl-D-1,2-glucoseen into 5-(methoxymethyl)-2-furaldehyde[9] in acid solution. There the 6-methyl ether of the conjugated enonal VII was established as an intermediate in this conversion by isolation as its crystalline phenylosazone.

The postulated intermediate III could produce IV by cyclic dehydration. The 5-(hydroxymethyl)-2-furaldehyde (V) could result from IV by a final dehydration producing a third double bond in conjugation with the two already present. The mechanism proposed here for the conversion of D-glucose to 5-(hydroxymethyl)-2-furaldehyde through the intermediates II, III and IV, is based upon that originally suggested by Hurd and Isenhour,[10] who, however, offered no experimental evidence to support it. The route through the intermediates VI, VII and VIII receives experimental support in the work of Wolfrom, Wallace and Metcalf.[9] The dehydrations postulated are the well-established ones of an hydroxyl group in the β position to a carbonyl. The resulting dehydrated products are α,β-unsaturated carbonyl compounds and we offer spectroscopic evidence for such intermediates.

Experimental

Materials.—The D-glucose used in this work was a very pure grade of the monohydrate.[11] It was crystallized from triply distilled water.

Absorption Measurements.—The D-glucose was weighed into a 500-ml. round-bottom Pyrex flask with a ground glass joint and connected to a reflux condenser. The solvent was added, and in the experiments where hydrochloric acid was used, the pH was adjusted at this point. The aqueous D-glucose solutions were refluxed by means of a Glas-col type electric heater. At definite time intervals aliquots were removed, cooled rapidly to room temperature, and immediately read in the spectrophotometer.

Acknowledgment.—The assistance of Clare B. Spitler and Doris K. Cavalieri is gratefully acknowledged.

Summary

The course of the formation of 5-(hydroxymethyl)-2-furaldehyde from D-glucose in the absence and presence of hydrochloric acid has been followed by ultraviolet absorption spectra measurements and on the basis of this, structures are proposed for several intermediates.

COLUMBUS, OHIO RECEIVED[12] OCTOBER 4, 1947

---

[8] L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 565 (1943).

[9] M. L. Wolfrom, E. G. Wallace and E. A. Metcalf, THIS JOURNAL, **64**, 265 (1942).

[10] C. D. Hurd and L. L. Isenhour, *ibid.*, **54**, 317 (1932).

[11] We are indebted for this material to Dr. S. M. Cantor of the Corn Products Refining Co., Argo, Illinois.

[12] The original manuscript with all essential data was received on September 23, 1946.

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

The Role of 5-(Hydroxymethyl)-furfural in the Discoloration of Sugar Solutions

BY BHAGAT SINGH,[1] G. R. DEAN AND SIDNEY M. CANTOR[2]

The acid catalyzed hydrolysis of starch at elevated temperature for the commercial production of D-glucose results in the formation of considerable coloring matter.[3] Under the same conditions of temperature and concentration the decomposition of pentoses to yield furfural and of hexoses to yield 5-(hydroxymethyl)-furfural (hereafter abbreviated in most cases to HMF) and levulinic and formic acids are well known phenomena. Various hypotheses have been advanced for the mechanism of color formation. Porst[4] believed that the color change might be due to furfural derived from the sugars and to traces of phenols and other derivatives which come from the decomposition of the small amount of protein contained in the starch. The possible participation of furfural and levulinic acid to form coumarone has been suggested as the cause of "humins" and color by Meunier.[5] The

---

[1] Corn Industries Research Foundation Fellow at Corn Products Refining Company 1943–1946.

[2] Present address: The American Sugar Refining Co., Philadelphia 48, Pa.

[3] During the course of this investigation this laboratory became associated with the coöperative project on non-enzymatic browning sponsored by the Committee on Food Research of the Quartermaster Corps of the U. S. Army. The relationship between this work and the general problem of color development in sugar containing systems was called to the attention of other laboratories in the project and a portion of the data was presented in the symposium on Non-Enzymatic Browning of the Division of Food and Agricultural Chemistry at the Chicago Meeting of the American Chemical Society in September, 1946, in an introductory paper entitled, "A Review of Some Sugar Reactions which Give Rise to Color," by Sidney M. Cantor and Charles D. Hurd.

[4] Porst, Orig. Com. 8th Intern. Congr. Appl. Chem., **13**, 205 (1912).

[5] Meunier, *Chemie et Industrie*, Special No. 583, February (1929).

literature on this subject has been reviewed recently.[6] Experience in this Laboratory had indicated that the major portion of the coloring matter arises from decomposition of the glucose molecule and that HMF is the precursor of coloring matter in starch hydrolyzates. It has been postulated that HMF polymerizes to give colored products of varying degrees of solubility.[7] The HMF molecule, arising from the dehydration of glucose, has a triene structure and shows absorption in the ultraviolet. It seems reasonable to suppose that polymerization (condensation) of this molecule might give rise to a molecule possessing the requisite number of conjugated double bonds for the selective absorption in the visible region. Modern concepts concerning the color of linear conjugated systems show that the presence of six to eight double bonds in a molecule gives rise to color.[8] This work was undertaken to make a quantitative spectrophotometric[9] study of (1) the destruction of glucose as a function of concentration, time and *p*H value of the system, (2) the role of HMF and levulinic acid in color formation, and (3) the possibility of condensation between glucose and amino acids under conditions employed for the commercial hydrolysis of starch, and its relation to the total color of the system.

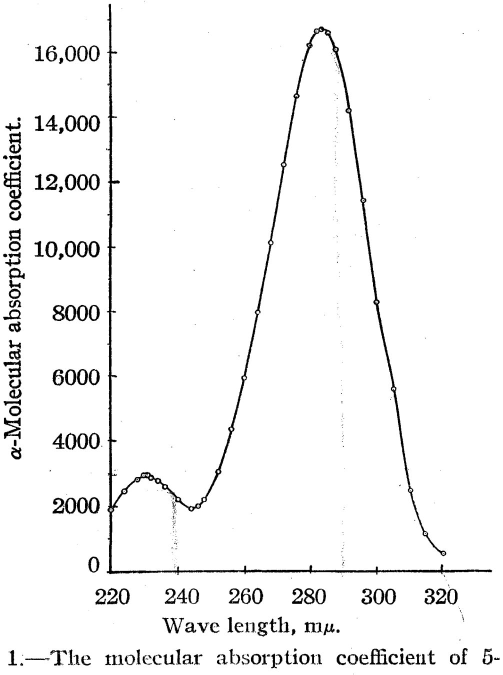


Fig. 1.—The molecular absorption coefficient of 5-(hydroxymethyl)-furfural.

Experimental

Dextrose.—Bureau of Standards D-**glucose** no. 41 or a sample of equivalent purity,[10] was used in all the experiments. Absence of absorption in the ultraviolet was used as a criterion of purity.

5-(Hydroxymethyl)-furfural.—HMF was prepared from sucrose by using the procedure of Middendorp.[11] The light yellow material was twice distilled under high vacuum (m.p. 31.5–32.0°, uncor.).

Levulinic Acid.—The white, crystalline solid (m.p. 32°, uncor.) was obtained after four recrystallizations of technical grade material.

Leucine (C. P. Pfanstiehl).—A Beckman Spectrophotometer (model DU) was used in this work for the examination of the ultraviolet and the visible spectra. The instrument was calibrated by using purified potassium chromate as an absorption standard and the performance compared with that recorded in the literature.[12] High temperature experiments were conducted in sealed tantalum bombs of approximately 20 ml. capacity. These bombs are test-tube shaped and are equipped with tantalum lined closures which are sealed by means of a screw and nut collar device. They were fabricated to specification by the Fansteel Metallurgical Corp.

All solutions were made up using doubly distilled water.

The results are given in optical density ($\log I_0/I$) *versus* wave length in millimicrons (mμ) except in cases where pure compounds, such as HMF and levulinic acid, were examined. For HMF and levulinic acid the molecular absorption coefficient, α, was calculated from Beer's law. Two centimeter fused silica cells were used for the ultraviolet region and one centimeter glass cells for the visible region.

All HMF values were determined in dilutions that gave an optical density between 0.5 and 1.0 at 284 mμ (slit width = 0.34 mm.). Color readings were obtained by integration of transmission curves throughout the visible spectrum range.

An arbitrary unit of color was used equal to 2.5 sq. in. of area under the curve.

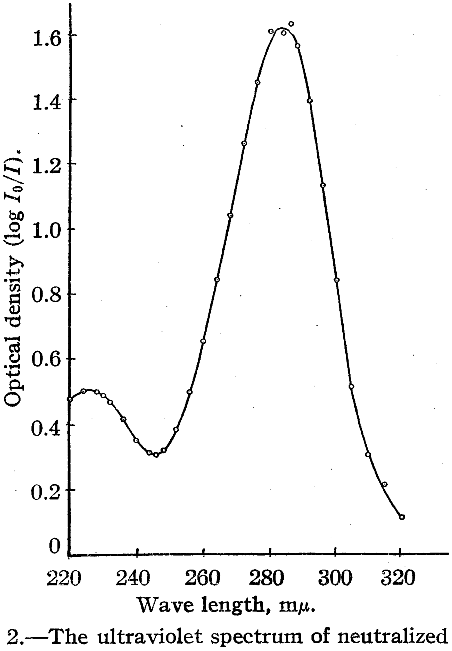


Fig. 2.—The ultraviolet spectrum of neutralized starch hydrolyzate: *p*H, 4.3; concn. 18%; diluted 1:100; 2-cm. cells.

---

(6) Hanahan, Thesis (M.S. in Chemistry), University of Illinois, 1942.

(7) Tanaka, "Sexagint Y. Osaka Chem. Inst. Dept. Science, Kyoto Imp. Univ.," 1927, 13–26; Blanksma and Egmond, *Rec. trav. chim.*, **65**, 309 (1946).

(8) Lewis and Calvin, *Chem. Rev.*, **25**, 273 (1939); Brooker, "Nuclear and Theoretical Organic Chemistry," Interscience Publishers, New York, N. Y., 1943, p. 89.

(9) The polarographic determination of 5-(hydroxymethyl)-furfural is the subject of a forthcoming paper.

(10) "Polarimetry, Saccharimetry and the Sugars," Circular C 440, National Bureau of Standards, p. 390.

(11) Middendorp, *Rec. trav. chim.*, **38**, 16 (1919).

(12) Hogness, Scheile and Sidwell, *J. Phys. Chem.*, **41**, 379 (1937).

Results

The absorption spectrum of pure HMF is shown in Fig. 1 and that of a dilute solution of a starch hydrolyzate in Fig. 2. The HMF spectrum shows two maxima, a major peak at 284 mμ and a minor one at 230 mμ.[13]

The molecular absorption coefficients compared with similar constants from other researches are shown in Table I.

TABLE I

MOLECULAR ABSORPTION COEFFICIENT OF 5-(HYDROXYMETHYL)-FURFURAL

Source	λ(max), mμ	(Liters mole^{-1} cm.$^{-1}$)	M. p., °C.
Scallet and Gardner[a]	283	14,330	
This paper	230, 284	3080, 16,700	31.5–32.0 (uncor.)
Schuetz and Wolfrom[b]	285	16,500	33.3–33.5 (cor.)

[a] Scallet and Gardner, THIS JOURNAL, **67**, 1934 (1945).
[b] Schuetz and Wolfrom, *ibid.*, **70**, 514 (1948).

The band around 280 mμ is usually taken as evidence for the carbonyl group; the intensity of this transition is determined partly by conjugation.

An estimate of the extent of destruction products in starch hydrolyzates was obtained by hydrolysis of a suspension of defatted corn starch. Conditions for hydrolysis were: starch concentration, 17.0% by weight; temperature, 145°; time, thirty minutes; acid concentration, 0.03 *N* HCl. After thirty minutes of reaction time 0.068% HMF (g./100 g. solution) was present and the color of the solution was 5.6 units. The final solution contained 18.5% of dry solids (approx. 16.7% D-glucose).

The ultraviolet spectra of heated 16% glucose solutions (0.03 *N* HCl, 145°) for the first ten minutes are shown in Figs. 3 and 4. There is evidence first of a band around 280 mμ and later a band around 230 mμ appears. The data are summarized in Table II.

TABLE II

DESTRUCTION OF D-GLUCOSE AS A FUNCTION OF TIME (16% GLUCOSE, 0.03 *N* HCl, 145°)

Time, minutes	Per cent. HMF (g./100 g. solution)	Color (arbitrary units)
2	Evidence for carbonyl groups[a]	No color
4	0.0005	No color
6	.0019	No color
8	.0044	0.3
10	.0075	0.6
12	.0122	1.0
14	.0187	1.5
20	.0332	3.2
30	.0635	5.6

[a] An absorption band around 280 mμ appears.

TABLE III

DESTRUCTION OF D-GLUCOSE AS A FUNCTION OF CONCENTRATION (0.03 *N* HCl, 145°, 30 MINUTES)

Per cent. glucose	Per cent. HMF (g./100 g. solution)	First order rate constant	Color
1	0.0039	1.3×10^{-4}	0.32
5	.0170	1.1×10^{-4}	2.17
10	.0360	1.2×10^{-4}	3.91
16	.0635	1.3×10^{-4}	5.59

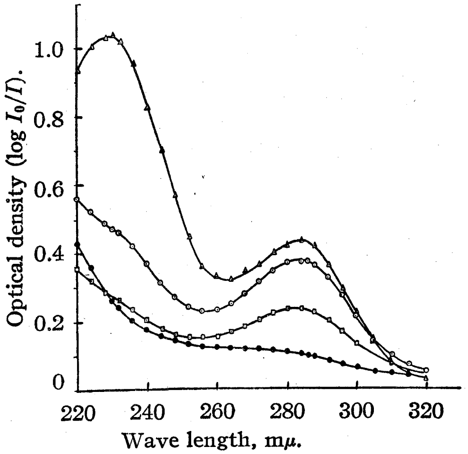


Fig. 3.—Effect of reaction time on the ultraviolet spectra of D-glucose destruction products; conditions: 16% D-glucose, 0.03 *N* HCl, 145.5°; 1% D-glucose, 0.03 *N* HCl, 145.5°; 2 cm. cells: ●, 1 minute, 16% glucose; ⊙, 2 minutes, 16% glucose; ⚠, 2.3 minutes, 16% glucose; ⊡, 2 minutes, 1% glucose.

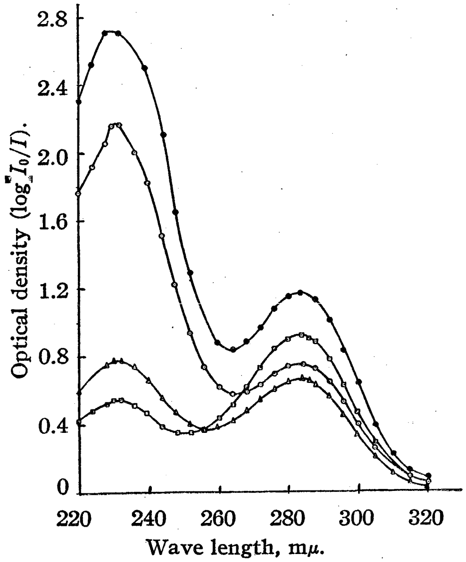


Fig. 4.—Effect of reaction time on the ultraviolet spectra of D-glucose destruction products; conditions: 16% D-glucose, 0.03 *N* HCl, 145.5°; 2 cm. cells: ⊙, 3 minutes; ●, 4 minutes; ⚠, 6 minutes, diluted 1:10; ⊡, 10 minutes, diluted 1:25.

The results of destruction of glucose as a function of concentration are summarized in Table III.

A study was made of the stability of the glucose molecule as a function of the *p*H value of the medium. Dilute hydrochloric acid was the only catalyst used for obtaining various *p*H levels. The results are summarized in Table IV and Fig. 5.

A comparative study of destruction as a function of *p*H using sucrose, D-fructose and L-ascorbic acid was also made. The results are given in Table V.

The destruction of pure HMF in water solution was studied at three different concentrations under conditions

---

[13] The authors are grateful to Prof. R. S. Mulliken of the University of Chicago for pointing out to them that a molecule containing a carbonyl group attached to a linear conjugated chain can have more than one electronic transition, one usually more intense than the other. See also McMurry, *J. Chem. Phys.*, **9**, 241 (1941).

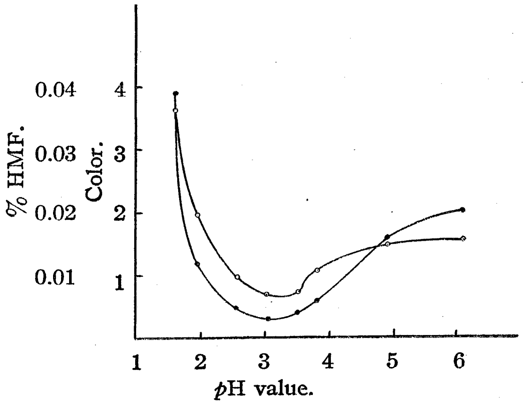


Fig. 5.—Effect of *p*H value on the formation of 5-(hydroxymethyl)-furfural and color in the D-glucose destruction reaction; conditions: 10% D-glucose; 145.5°; 30 minutes: ⊙, % 5-(hydroxymethyl)-furfural; ●, color in arbitrary units.

TABLE IV

DESTRUCTION OF D-GLUCOSE AS A FUNCTION OF *p*H VALUE (10% GLUCOSE, 145°, 30 MINUTES)

*p*H value Before heat	 After heat	Per cent. HMF (g./100 g. solution)	Color
1.60	1.60	0.0360	3.91
1.95	1.90	.0196	1.17
2.55	2.60	.0097	0.46
3.00	2.90	.0071	.30
3.53	3.58	.0072	.39
3.80	3.78	.0105	.61
4.92	4.30	.0148	1.56
6.10	4.30	.0156	2.02

TABLE V

DESTRUCTION OF SUCROSE, D-FRUCTOSE AND L-ASCORBIC ACID AS A FUNCTION OF *p*H VALUE (10% SOLUTIONS, 145° 30 MINUTES)

	Sucrose		D-Fructose		L-Ascorbic acid[a]	
*p*H value	Per cent.	HMF Color	Per Cent.	HMF Color	Per cent. furfural	Color
1.7	1.0	11.8	2.5	11.9	2.1	12.1
2.7	0.16	2.9	0.3	4.5		
3.9	.02	1.9	0.08	4.4	2.3[b]	11.4
6.0	.004	1.3	0.07	5.3		

[a] Furfural determined at 278 mμ (slit width 0.35 mμ). Purified furfural was supplied through the courtesy of the Quaker Oats Company. The furfural spectrum coincides with that of HMF except that maximum absorption occurs at 278 mμ (α = 14,600). [b] *p*H value 3.5.

prevalent in commercial starch hydrolysis (0.03*N* HCl, 145°, 30 minutes). The data are shown in Table VI.

TABLE VI

DESTRUCTION OF HMF UNDER HYDROLYSIS CONDITIONS (0.03 *N* HCl, 145°, 30 MINUTES)

Per cent. HMF in solution Before destruction	 After destruction	Per cent. HMF destroyed	Specific reaction rate *k*, minutes^{-1a}	Color (arbitrary units)
0.098	0.075	24.0	0.0089	2.75
.197	.150	24.8	.0091	3.93
.393	.305	22.4	.0085	6.34

[a] *k* = first order reaction rate constant.

The stability of HMF as a function of *p*H value is shown in Table VII.

TABLE VII

STABILITY OF HMF AS A FUNCTION OF *p*H VALUE (0.35% HMF SOLUTION, 145°, 30 MINUTES)

*p*H value Before heating	 After heating	% HMF decomposed	Color (arbitrary units)
1.75	1.77	24	6.0
2.28	2.28	12	3.8
2.88	2.90	12	2.6
3.95	4.13	0	1.5

A 0.27% water solution of pure levulinic acid (*p*H 3.14) was subjected to hydrolysis conditions (145° for thirty minutes). The ultraviolet spectra before and after heating are shown in Fig. 6.

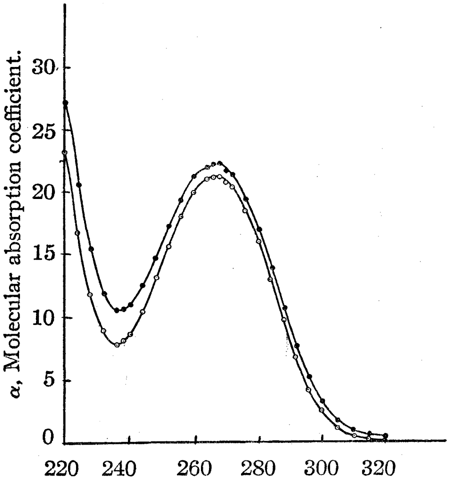


Fig. 6.—The ultraviolet spectrum of levulinic acid; effect of heating: concn., 0.27%; time, 30 minutes; temp., 145.5°; *p*H 3.14: ⊙, before heating; ●, after heating.

To determine the importance of the functional grouping attached to the number one carbon atom in glucose, 10% solutions of glucose and methyl α-D-glucoside were subjected to identical conditions (*p*H 6, 145°, thirty minutes). The results are given in Table VIII and Fig. 7.

TABLE VIII

DESTRUCTION OF GLUCOSE AND METHYL α-D-GLUCOSIDE UNDER HEAT (10% SOLUTIONS, 145°, 30 MINUTES)

	*p*H value Before heat	 After heat	% HMF (g./100 g. soln.)	Color
Glucose	6.10	4.30	0.0156	2.0
Methyl α-D-glucoside	6.0	5.95	No evidence	No color

Since starch hydrolyzates contain a small amount of nitrogenous substance (about 0.09% nitrogen on dry substance basis), the possibility of a glucose–(amino acid) condensation product was investigated. Of the two amino acids, glutamic acid and leucine, present in corn gluten in large amounts, leucine, the simpler of the two, was chosen for this study. The ultraviolet spectral data of 10% glucose (*p*H 5) and 10% glucose plus 0.4% leucine (*p*H 6), refluxed for three hours at 100°, are shown in Fig. 8.

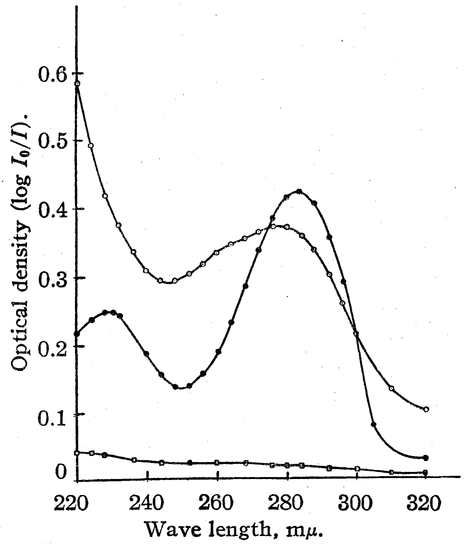


Fig. 7.—Ultraviolet spectra of destruction products of D-glucose and methyl α-D-glucoside; conditions: 145.5°, 30 minutes, *p*H 6 (2-cm. cells): ⊙, 10% methyl α-glucoside after heating; ●, 10% glucose (diluted 1:100) after heating; ⊡, 5% methyl α-glucoside before heating.

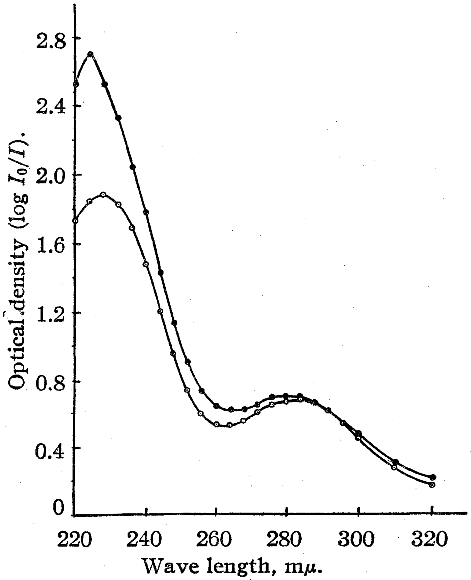


Fig. 8.—Ultraviolet spectra of heated D-glucose solution and D-glucose + leucine solution; conditions, refluxed 3 hours at 100°: ⊙, 10% D-glucose solution, *p*H 5; ●, 10% D-glucose + 0.4% leucine, *p*H 6.

Discussion

The results of hydrolysis of defatted corn starch indicate that a satisfactory definitive mechanism for the extent of the destruction reaction in starch hydrolyzates must be able to account for the presence of HMF (0.068%) and color (5.6 units). Solutions of 16% glucose heated under the same conditions contained 0.064% HMF and 5.6 units of color (Table II). Although the concentration of glucose during starch hydrolysis is variable (increases from zero to 16.7% in thirty minutes), nevertheless it is quite clear that the major portion of HMF and coloring matter in starch hydrolyzates can be accounted for by the destruction of the glucose molecule.

The destruction of glucose as a function of time (Fig. 3) shows first the appearance of a molecule containing the carbonyl group (absorption band around 280 mμ). That this substance is not HMF is apparent from the fact that the minor peak around 230 mμ is missing. The concentration of the substance, calculated as HMF, is 0.00145 g. per liter. HMF solutions of this order of concentration show two peaks. Shortly thereafter the spectrum of an HMF-like molecule appears in the sense that the absorption spectrum shows the two characteristic peaks at 285 mμ and 230 mμ. The changes in the relative heights of these peaks, however, suggest the presence of other substances besides HMF. Presumably, the first reaction is the opening of the pyranose ring and the development of the carbonyl group followed by dehydration. The ultraviolet spectral evidence for the first ten minutes (Fig. 4) shows the presence of HMF alone and then the rapid development of coloring matter. Such an induction period in the formation of coloring matter has been observed in other systems and has been attributed to some autocatalytic mechanism. However, the appearance of HMF during this induction period, together with the demonstration that coloring matter is formed from pure HMF as starting material, support the theory that HMF is the precursor of coloring matter during the acid decomposition of hexose-containing carbohydrates.

Table III shows that the rate of destruction of glucose with formation of HMF is independent of the glucose concentration, indicating a first order mechanism for the reaction. A slight rise in the first order rate constant might be anticipated in more concentrated glucose solutions because of the effect of glucose in increasing the hydrogen ion activity of the solution.[14] The destruction of glucose as a function of *p*H value[15] (Fig. 5) demonstrates the surprising stability of the glucose molecule in the neighborhood of a *p*H value of three where only one-fifth as much HMF and one-thirteenth as much coloring matter is produced as at *p*H 1.6. Ring stability appears to approach a maximum at this point.[16] The results seem to follow the concepts of prototropy developed by Lowry[17] and are reminiscent of the catalytic catenary of Dawson[18] connecting the velocity of a hydrolytic reaction in water with the corresponding *p*H value. Dawson studied the enolization of acetone (followed by rapid substitution of iodine) and the hydrolysis of ethyl acetate. The velocity

---

[14] Moelwyn-Hughes, *Trans. Faraday Soc.*, **24**, 321 (1928).

[15] Kroner and Kothe, *Ind. Eng. Chem.*, **31**, 248 (1939).

[16] Cantor and Peniston, THIS JOURNAL, **62**, 2113 (1940).

[17] Lowry, *J. Chem. Soc.*, **123**, 828 (1923).

[18] Dawson and Lawson, *ibid.*, 393 (1929).

of mutarotation of glucose[19] as a function of pH goes through a similar minimum. With sucrose and D-fructose there is no such minimum and the destruction is much greater than in glucose. As might be anticipated,[20] L-ascorbic acid undergoes extensive destruction under the conditions of the experiment (Table V).

The reaction in HMF solutions of different concentrations under starch hydrolysis conditions to produce coloring matter shows that about the same percentage of HMF is destroyed indicating a first order reaction (Table VI). Teunissen[21] has shown that the rate of decomposition of HMF at 100°, as followed by titration of organic acid decomposition products, follows a first order mechanism. No change occurred in levulinic acid solution on heating except a slight increase in ultraviolet absorption (Fig. 6). This is another demonstration of the fact that HMF is the sole precursor of coloring matter and that levulinic acid plays no part in this process.[22] The importance of the functional grouping on the aldehydic carbon atom of the glucose molecule to the destruction reaction is evident from the data on methyl α-glucoside under identical conditions (Table VIII and Fig. 7). Methyl α-glucoside shows a slight hydrolysis with subsequent destruction of the glucose formed (as evidenced by the development of the carbonyl group (Fig. 7)) while glucose gives rise to HMF and coloring matter.

The possibility of glucose–(amino acid) condensation is rather remote under the specified conditions (Fig. 8). Although the glucose solution containing leucine shows a slightly greater absorption in the far ultraviolet, the two spectra coincide around 280 mμ. Evidently about the same amount of HMF is produced in the two cases. Similarly, under these conditions no difference in HMF or color content could be noted between glucose solutions with or without leucine. Moreover, these experiments indicate no specific catalytic action of leucine in small concentration on formation of either HMF or coloring matter. Any such catalytic action at relatively high concentrations of amino acids is probably due to contribution either to the total ionic strength of the reacting system or to the hydrogen ion activity.

The results of this study suggest the importance of HMF, and consequently of hexoses, to the color problem. A recent report has indicated that furfural or HMF is partially responsible for color development in certain dried fruits.[23] Heretofore considerable attention has been devoted to the reaction between reducing sugars and amino acids or polypeptides (the Maillard[24] reaction) as the cause of browning in various foodstuffs, but this conclusion has been drawn only on the basis of model reactions between amino acids and aldoses and the presence of these substances in foodstuffs. It would now appear that the pH value of the food system in addition to the specific constituents of the system is an important factor in determining the course by which colored bodies are formed.

Summary

It is shown that a major portion of 5-(hydroxymethyl)-furfural and coloring matter in starch hydrolyzates comes from the destruction of the glucose molecule.

The absorption spectrum of 5-(hydroxymethyl)-furfural has been studied and it is found that there are two peaks, a major one around 284 mμ and a minor one around 230 mμ.

In the destruction of the glucose molecule on heating in an acid medium there is evidence first of an absorption band around 280 mμ and later a band around 230 mμ appears. It is postulated that the first reaction is the opening of the pyranose ring, development of the carbonyl group followed by dehydration. Later, color develops in the solution for which 5-(hydroxymethyl)-furfural is the precursor.

Solutions of different concentrations of 5-(hydroxymethyl)-furfural on heating in an acid medium show development of color and about the same percentage of destruction indicating a first order reaction. Levulinic acid in solution shows no apparent destruction on heating.

The glucose destruction reaction as a function of pH goes through a minimum around a pH value of 3. No such minima were found for D-fructose and sucrose. The extent of destruction for sucrose and D-fructose as compared with glucose is greater in acid media.

The importance of the functional grouping on the number one carbon atom in glucose is shown by the comparative destruction of glucose and methyl α-glucoside under comparable conditions. Glucose solutions produce 5-(hydroxymethyl)-furfural with consequent color while no destruction takes place in methyl α-glucoside solutions.

No evidence was found for condensation between glucose and leucine under the conditions of this study.

It is suggested as a result of the study that a similar mechanism may be partially responsible for the color which develops in certain natural products containing reducing sugars.

ARGO, ILLINOIS
RECEIVED JULY 25, 1947

---

[19] Hudson, THIS JOURNAL **29**, 1572 (1907); Lowry, *Chemistry and Industry*, **42**, 43 (1923).

[20] Seaver and Kertesz, THIS JOURNAL, **68**, 2178 (1946).

[21] Teunissen, *Rec. trav. chim.*, **49**, 784 (1930).

[22] Peniston (unpublished results) showed that even under conditions similar to those employed here (pH 1.6) the levulinic acid molecule does not break down.

[23] Stadtman, A. C. S. Meeting, Chicago, Illinois, September, 1946.

[24] Maillard, *Compt. rend.*, **154**, 66 (1912); *Ann. chim.*, **5**, 258 (1916).

[CONTRIBUTION FROM THE TEXTILE FOUNDATION AND THE FRICK CHEMICAL LABORATORY AT PRINCETON UNIVERSITY]

Open-Chain Sugars. I. Absorption in Ultraviolet of D-Glucose and L-Arabinose in Acid Solution

BY EUGENE PACSU AND LEJAREN ARTHUR HILLER, JR.

In 1913 Willstätter and Zechmeister[1] observed that the optical activity of D-glucose in hydrochloric acid increased to a great extent with the concentration of hydrogen chloride. Thus the specific rotations[2] of D-glucose in 41.4 and 44.5% hydrochloric acid were found to be, respectively, +106° and +165°, instead of the constant value of +52.6° in aqueous solution. In a later work Zechmeister[3] published the results of his systematic investigation of this interesting phenomenon. He found that the simple sugars in 42.0% hydrochloric acid at about 6 to 10° possessed the specific rotations: D-glucose, +113.3°; D-galactose, +160.4°; D-mannose, +54.6°; D-fructose, −180.0°; L-arabinose, +202.9°; D-xylose, +96.6°; L-rhamnose, −31.1°. Further increase in the hydrogen chloride content of the solvent resulted in the remarkably high specific rotation of +202° for D-glucose at −12° in 46.7% hydrochloric acid solution. The rates of these rotational changes were generally so rapid that they could not be determined at room temperature. However, they became measurable at 0°, giving, *e. g.*, for D-glucose in 40.6% hydrochloric acid ($[\alpha]^{0}\text{D} + 96.2°$; *c*, 0.990) $k = 1.6 \times 10^{-2}$ (decimal logarithms, minutes). For comparison, the rate of mutarotation of D-glucose in pure water at 0.7° is given as 7.4×10^{-4}. The reversibility of the process in 40.0% acid was proven when it was found that after neutralization of the various solutions with sodium bicarbonate the sugars were recovered unchanged or nearly so, quantitatively, each of them showing the respective normal value of constant rotation in the corresponding salt solution. Zechmeister also found that, *e. g.*, a 1.5% D-glucose solution in 40.0% hydrochloric acid at 10° remained practically colorless during a twenty-one hour period of time, thus indicating that very little, if any, decomposition had taken place.

For explanation of these experimental facts Zechmeister assumed that in concentrated hydrochloric acid two reactions were taking place with unequal rates: the instantaneous establishment of a new equilibrium between the α- and β-forms of the sugars, and, at sufficiently low temperature, the measurably slow, partial conversion of the latter into "a high-rotating modification." It had already been known for some time from the work of Armstrong and Hilditch[4] that, *e. g.*, D-glucose in 0.1 *N* hydrochloric acid rapidly acquires the ability to reduce potassium permanganate solution, a property which is completely lacking in the aqueous solution of either anomeric form of the sugar. They explained this curious behavior by assuming that a small amount of a new isomer, "γ-glucose," with ethylene oxide ring structure was being formed in acidic solution. This new modification was supposed to be responsible for the potassium permanganate reaction. Zechmeister pointed out that the formation in somewhat larger quantity of such a "γ-sugar" might account for the observed high optical activity and for the measurable rate and the reversible nature of the process. However, he also stated that it was difficult to see how a sugar molecule with ring structure could exist in fuming hydrochloric acid without suffering cleavage of its hemiacetal linkage. He suggested that combination between a hydrogen chloride molecule and the free aldehyde group of the sugar might give rise to a structure with very high optical rotational value.

In connection with our work on the acid-catalyzed degradation of cellulose it became necessary to know the specific rotations of D-glucose in strong mineral acids of various concentrations. We found[5] that solutions of D-glucose in 85% phosphoric acid and in 50.5% sulfuric acid ($d^{20}{}_4$ 1.40) gave the constant values $[\alpha]^{20}\text{D} + 68.0°$ and $[\alpha]^{20}\text{D} + 61.0°$, respectively, ten minutes after solution. We also found[6] that potassium permanganate in 0.25 *N* sulfuric acid solution selectively attacked cellulose by oxidizing its reducing group to carboxyl group. Since the potential reducing groups of the carbohydrates with ring structures are not oxidized by this reagent in neutral medium, we have concluded that in acidic environment a shift into the open-chain form of the sugars might occur with the formation of carbonyl groups which are then attacked by dilute potassium permanganate. Since it is known from Henri's work[7] that aldehydes possess a characteristic absorption band at the wave length of about 2800 Å., we undertook the measurements in ultraviolet of the acidic solutions of D-glucose to verify our deduction. First we measured at 25° the absorption of a 16% aqueous D-glucose solution ($[\alpha]^{20}\text{D} + 52.9°$) in the ultraviolet region 3100 to 2400 Å., by using a Beckmann photoelectric quartz spectrophotometer. Contrary to the finding of J. E. Purvis[8] and in agreement with statements in the general literature[9]

---

(1) R. Willstätter and L. Zechmeister, *Ber.*, **46**, 2401 (1913).

(2) All rotations in this paper refer to the sodium light.

(3) L. Zechmeister, *Z. physik. Chem.*, **103**, 316 (1923).

(4) E. F. Armstrong and T. P. Hilditch, *J. Chem. Soc.*, **115**, 1410 (1919); **117**, 1086 (1921).

(5) L. A. Hiller and E. Pacsu, *Textile Res. J.*, **16**, 568 (1946).

(6) L. A. Hiller and E. Pacsu, *ibid.*, **16**, 318 (1946).

(7) V. Henri, "Études de Photochimie," Gauthier-Villars et C^ie^, Paris, 1919, p. 64.

(8) J. E. Purvis, *J. Chem. Soc.*, **123**, 2519 (1923).

(9) F. Micheel, "Chemie der Zucker und Polysaccharide," Akad. Verlagsges., Leipzig, 1939, p. 218; B. Tollens–H. Elsner, "Kurzes Handbuch der Kohlenhydrate," J. A. Barth, Leipzig, 1935, p. 86.

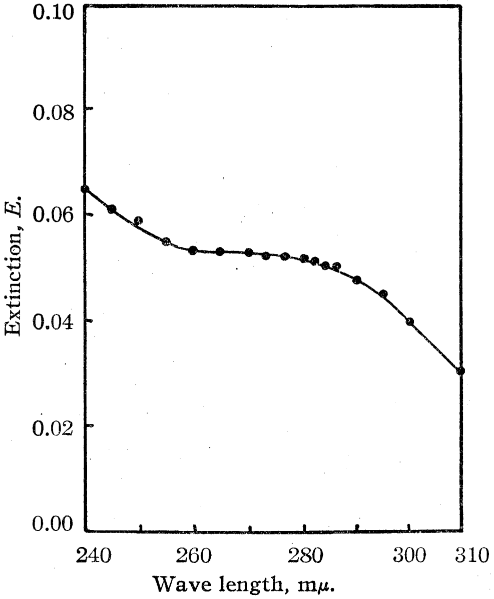


Fig. 1.—Absorption spectrum of a 16% D-glucose solution in water.

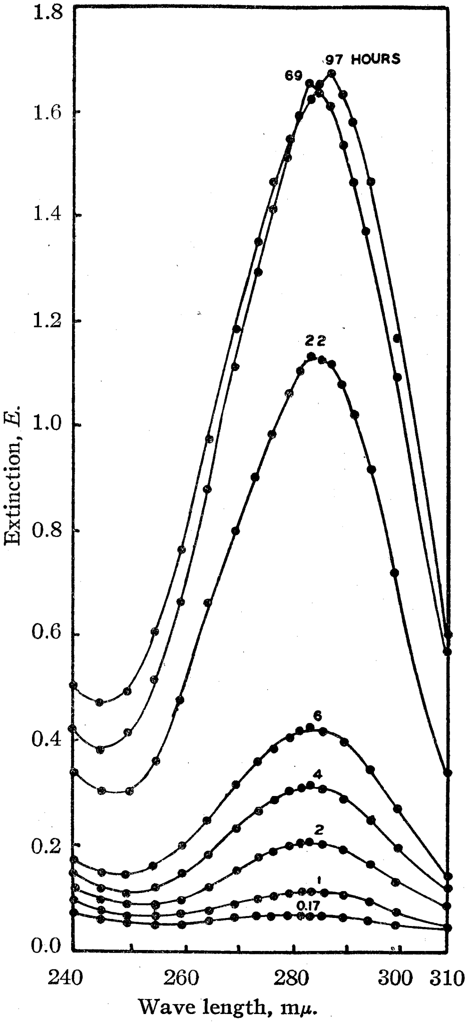


Fig. 2.—Change with time of the absorption spectrum of a 17.3% D-glucose solution in 50.5% sulfuric acid.

we found no selective absorption that would have indicated the presence of the oxo-form of glucose in the aqueous solution (Fig. 1). Then a 17.3% D-glucose solution in 50.5% sulfuric acid ($d^{20}{}_4$ 1.40) was employed with the result shown in Fig. 2. The absorption became evident ten minutes after dissolution of the sugar and showed a maximum at the wave length 2840 Å. The absorption steadily increased in intensity during the ensuing sixty-nine hours thus indicating that conversion of the non-absorbing cyclo-form of the sugar into the absorbing oxo-form took place gradually.[10] After the maximum intensity had been reached with the extinction value $E_\infty = 1.665$ the solution began to show a slight discoloration. Ninety-seven hours after the beginning of the experiment the absorption band had shifted slightly to 2880 Å., while only negligible increase (0.005) had occurred in the value of optical density. Since a plot of the difference between the logarithms of $E_\infty - E_0$ and $E_\infty - E_t$ against t time gave a straight line, it was concluded that the conversion of D-glucose with normal ring structure into the carbonyl-containing modification represented a first order reaction. From the slope of the line between the points for one hour and twenty-two hours the rate constant was calculated to be $k = 3.6 \times 10^{-4}$. In a similar experiment the absorption of L-arabinose was determined (Fig. 3). According to Zechmeister the rate of conversion in 40.6% hydrochloric acid of L-arabinose into a high-rotating form was so rapid as to make quantitative measurements even at 0° impossible. We used a 4.0% solution of L-arabinose in 50.5% sulfuric acid and recorded the change in the optical density of the solution with time at the peak of the absorption curve, namely, at the wave length 2840 Å. From a logarithmic plot of the observed data the rate constant was calculated to be $k = 4.5 \times 10^{-4}$.

It has been stated above that the rotational value of D-glucose in 50.5% sulfuric acid, $[\alpha]^{20}\text{D} + 61.0°$, was obtained about ten minutes after the sugar had first come into contact with the solvent. For an explanation of the fact that the optical rotation remains constant while the absorption develops, it may be assumed that two processes are taking place in the acid solution. The first reaction is probably the reversible formation of an

---

[10] The absence of hydroxymethylfurfural was demonstrated when 100 cc. of a twenty-two hours old 10% glucose solution in 50.0% sulfuric acid was, after dilution, extracted with ether and the concentrated ether layer was tested with resorcinol dissolved in concentrated hydrochloric acid with negative result. For comparison, 5 cc. of a 1% sucrose solution in 1 N sulfuric acid was boiled for three minutes and then extracted with ether; the ether extract gave a very strong positive test for hydroxymethylfurfural with the same reagent. Also, the absence of levulinic acid in the aged glucose solution was proved by the negative outcome of the iodoform test carried out on the aqueous residue of the moist ether extract.

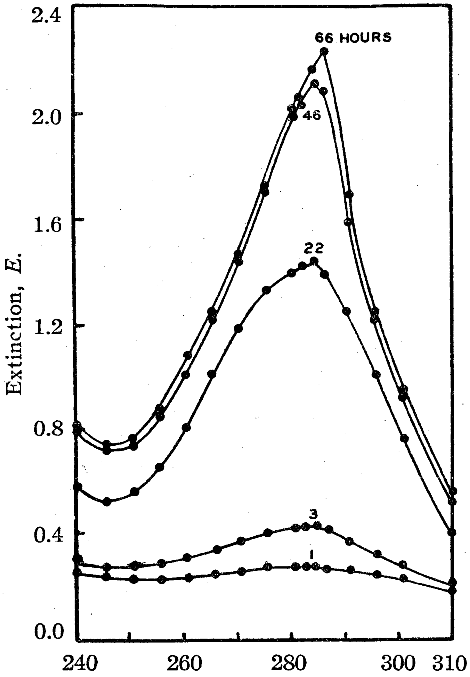
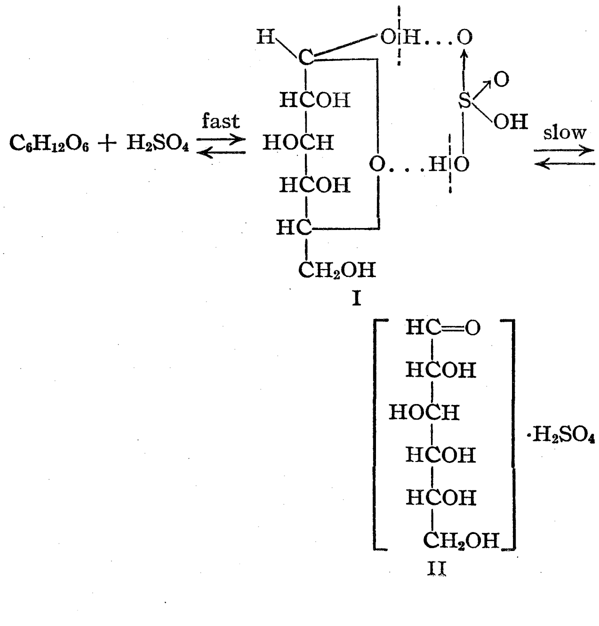


Fig. 3.—Change with time of the adsorption spectrum of a 4.0% L-arabinose solution in 50.5% sulfuric acid.

addition complex (I) between the anomeric forms of D-glucose and the acid molecule, which event proceeds with an unmeasurably high rate. The observed rotational value of $[\alpha]^{20}\text{D} + 61.0°$ would correspond to the optical activities of the components in the equilibrium mixture. This fast reaction would then be followed by a comparatively slow process which essentially consists of the opening of the ring structure in complex (I) to give rise to the carbonyl form of the sugar (II). Although this phase of the reaction becomes noticeable by the sensitive method of absorption measurement, yet the concentration of (II) is probably so small under our experimental conditions that the presence of this form remains undetected when the much less sensitive polarimetric method is employed.



Zechmeister postulated that the rotational value, $[\alpha]^{0}\text{D} + 62.0°$, obtainable by extrapolation to 0 time from the rate constant, $k = 1.6 \times 10^{-2}$, corresponded to a new equilibrium between the α- and β-form of D-glucose in the moment of dissolution of the sugar. In support of this argument he pointed out that this extrapolated value lies between the known specific rotations of the two anomeric forms. However, it seems to us more likely that the acid molecules play a decisive role in this reaction which, according to our assumption, should generally be initiated by the formation of molecular compounds like (I) between the sugar and acid molecules.

According to Zechmeister's experiments neutralization of the concentrated hydrochloric acid solutions of the sugars by sodium bicarbonate restored the constant specific rotations which were shown by the respective sugars in sodium chloride solutions of corresponding concentrations. We had, therefore, expected that after neutralization of our sulfuric acid solution with sodium bicarbonate the characteristic carbonyl band would

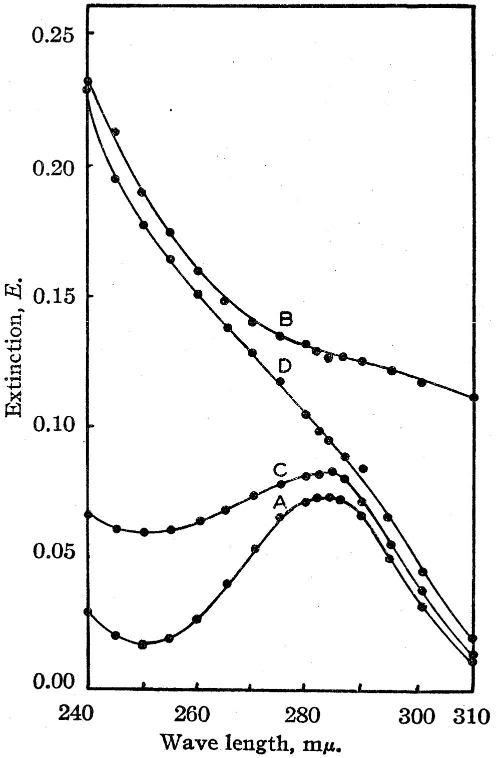


Fig. 4.—Disappearance of peak in neutralized D-glucose solution (2%): A, 1 day of standing; B, 1 day of standing + 2 drops alkali; C, 8 days of standing; D, 16 days of standing.

disappear and the solution would show the general absorption as has been found for D-glucose in neutral solution (Fig. 1). Pertinent experiments have revealed the remarkable fact that this is only true if the solution, after treatment with sodium bicarbonate, becomes slightly alkaline. In slightly acidic solution, however, the assumed open-chain form of the sugar persists for a comparatively long period of time. It is seen in Fig. 4 (C) that eight days after "neutralization" the slightly acidic solution still exhibited the characteristic absorption at 2840 Å., although the peak was not as sharp as that measured after the first day (A). It took altogether sixteen days until the absorption band completely disappeared in the slightly acidic solution (D). On the other hand, addition of two drops of dilute alkali to the one-day old solution resulted in the immediate disappearance (B) of the peak at 2840 Å.

In view of the present theory of mutarotation[11] these facts can not be interpreted readily. Further investigations are necessary before the significance of our observations to the true mechanism of mutarotation can be evaluated. We have already made initial attempts to isolate the postulated open-chain form of D-glucose by using superconcentrated hydrochloric acid solutions. So far we have not been able to isolate the free sugar in crystalline form, but we have succeeded in obtaining an amorphous acetate as the single product which, unlike the α- and β-pentaacetate, in chloroform solution shows strong selective absorption at the wave length of 2840 Å. The investigation is being continued.

Summary

It has been found that D-glucose and L-arabinose in 50.5% sulfuric acid solutions show strong absorption at wave length 2840 Å. which is characteristic for carbonyl-containing compounds. After neutralization with sodium bicarbonate the slightly acidic solution still exhibits this band which, however, instantaneously disappears on rendering the solution barely alkaline. A possible mechanism is suggested for explanation of the behavior in strong acids of sugars with ring structures by assuming the formation of molecular compounds between the acid molecules and the open-chain forms of the sugars.

From D-glucose in superconcentrated hydrochloric acid solution an amorphous acetate has been obtained which compound, unlike the α- and β-pentaacetate, in chloroform solution exhibits strong absorption at 2840 Å.

PRINCETON, NEW JERSEY RECEIVED AUGUST 14, 1947

---

[11] T. M. Lowry, "Rapports sur les Hydrates de Carbon," Xième Conférence de l'Union Internationale de Chimie, Liége, 1930.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Preparation of α-Carbalkoxyalkyl Methacrylates by Pyrolysis of the Corresponding α-Acetoxyisobutyrates

BY E. M. FILACHIONE, M. L. FEIN, J. H. LENGEL AND C. H. FISHER

In an earlier paper[2] it was demonstrated that α-carbalkoxyalkyl methacrylates[3] (II) can be made in satisfactory yields by pyrolyzing the corresponding α-acetoxyisobutyrates (I, R = Me or H; R′ = Me or Et).

$$\underset{\text{I}}{\mathrm{CH_3COOC(CH_3)_2COOCH(R)COOR'}} \xrightarrow[550^\circ]{450\text{ to}} \underset{\text{II}}{\mathrm{CH_2{=}C(CH_3)COOCH(R)COOR'}} + \mathrm{CH_3COOH}$$

The present paper records results obtained in a further study of the pyrolysis method of preparing methacrylates (II). The additional esters made pyrolytically are the methacrylates of allyl glycolate and of allyl, methallyl, tetrahydrofurfuryl, benzyl and β-chloroethoxyethyl lactates.

The α-acetoxyisobutyrates (I) used in the pyrolysis experiments were prepared in high yields by treating allyl glycolate and several lactic esters (allyl, methallyl, tetrahydrofurfuryl, benzyl and β-chloroethoxyethyl) with α-acetoxyisobutyryl chloride. The resulting acetoxyisobutyrates (Table I) were decomposed by passage through a Pyrex glass tube heated at about 450° (Table II).

Although the esters (I) pyrolyzed had three esterified carboxyl groups, decomposition occurred preferentially at the acetate group, the principal products being acetic acid and the corresponding methacrylates (II, yields, 65–85%). On the basis of these and earlier[2] findings, it is concluded that the pyrolysis method is generally useful for the preparation of methacrylates (II) of alkyl glycolates and lactates. Presumably the method is useful also for preparing esters (II) in which R is ethyl or higher, but less suitable for esters (II) in which R′ is a secondary or tertiary alkyl group. It is anticipated that only relatively low yields of carbalkoxyisopropyl methacrylates ($\mathrm{CH_2{=}C(CH_3)}$-$\mathrm{COOC(CH_3)_2COOR}$) would be obtained in the pyrolysis of $\mathrm{CH_3COOC(CH_3)_2COOC(CH_3)_2COOR}$,

---

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

[2] E. M. Filachione, J. H. Lengel and C. H. Fisher, THIS JOURNAL, **68**, 330 (1946).

[3] C. E. Rehberg, M. B. Dixon and C. H. Fisher, *ibid.*, **67**, 208 (1945); I. E. Muskat and F. Strain, U. S. Patent 2,384,119, Sept. 4, 1945.

TABLE I

PREPARATION AND PROPERTIES OF ACYLATED HYDROXY ESTERS

α-Acetoxyisobutyrate of	Yield, % of theoretical	B. p.				Mol. refraction		Sapon. equiv.		Carbon, %		Hydrogen, %	
		°C.	Mm.	d^{20}_4	$n^{20}D$	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Allyl lactate	89	82	0.2	1.0864	1.4357	62.11	62.11	86.1	86.8	55.80	55.41	7.02	7.04
Methallyl lactate	81	82–85	0.1	1.0713	1.4381	66.73	66.73	90.8	91.2	57.34	57.59[a]	..	..
Allyl glycolate	79	84–86	0.25	1.1224	1.4407	57.49	57.43	81.41	81.55	54.09	54.27[a]	..	..
Tetrahydrofurfuryl lactate	87	145	1.5	1.1347	1.4475	71.26	71.29	....	....	55.62	55.59	7.33	7.32
Benzyl lactate	86	136	0.6	1.1285	1.4812	77.45	77.77	102.8	102.7	62.32	62.05	6.54	6.53
β-Chloroethoxyethyl lactate	75	145	0.2	1.1798	1.4478	73.71	73.66	....	....	48.07	47.91	6.52	6.59

[a] By wet oxidation (D. D. Van Slyke and J. Folch, *J. Biol. Chem.*, **136**, 509 (1940)).

TABLE II

PYROLYSIS OF ACETYLATED HYDROXY ESTERS

Ester pyrolyzed, g. Acetoxyisobutyrate of	Temp., °C.	Feed rate, g./min.	Contact time, sec.	Ester decomposed, %	Methacrylate		Yields,[a] mole per mole of ester destroyed			
					Boiling range, °C.	Press., mm.	Methacrylate	Acetic acid		Acetone
								Titr.	Dist.	
Allyl lactate, 147	446	2.0	10.1	79	54–62	0.45	0.82	0.92	0.76	..
Methallyl lactate, 346	450	2.8	7.5	63	53–60	.2	.85	.97	.84	0.07
Allyl glycolate, 130	450	2.4	7.9	69	51–62	.35	.78	.96	.84	..
Tetrahydrofurfuryl lactate, 288	450	2.3	10.1	68	83–91[b]	.1	.65	.93	.80	.08
Benzyl lactate, 159	450	2.4	9.9	65	97–104[c]	.2	.71	.92	.72	.07
β-Chloroethoxyethyl lactate, 114	450	2.7	9.5	66	104–116[d]	.25	.79	.88	.66	.04

[a] Methacrylate yield based on that obtained in first distillation; acetic acid yield based on that obtained in redistillation. [b] Much polymerization occurred during distillation. [c] Hydroquinone distilled with the monomer. [d] Phenyl-β-naphthylamine used as inhibitor.

TABLE III

PROPERTIES OF MONOMERIC α-CARBALKOXYLALKYL METHACRYLATES

Methacrylate of	B. p.				Mol. refraction		Sapn. equiv.		C, %	
	°C.	Mm.	d^{20}_4	$n^{20}D$	Calcd.	Found	Calcd.	Found	Calcd.	Found[a]
Allyl lactate	52–53	0.15	1.0352	1.4452	50.75	50.98	99.10	99.15	60.59	60.63
Methallyl lactate	57–59	0.25–0.30	1.0160	1.4475	55.37	55.90	106.1	106.6	62.24	61.93
	66	0.55								
Allyl glycolate	73–74	1.0	1.0760	1.4513	46.14	46.12	92.09	92.66	58.69	58.39
	53–54	0.3								
Tetrahydrofurfuryl lactate	91–95	0.15–0.20	1.1015	1.4586	59.94	60.08	121.1	120.5	59.49	59.53
	109–110	0.7								
Benzyl lactate	92–95	0.1	1.0975	1.5002	66.09	66.53	124.1	118.8	67.72	67.68
	96–101	0.2								
β-Chloroethoxyethyl lactate[b]	97–99	0.15	1.1528	1.4579	62.35	62.64	....	....	...	...

[a] By wet oxidation (D. D. Van Slyke and J. Folch, *J. Biol. Chem.*, **136**, 509 (1940)). [b] Chlorine content, 13.36% (theoretical, 13.40%).

a more probable decomposition product[4] being $CH_2{=}C(CH_3)COOR$.

The methacrylates (Table III) were mass polymerized at 60 to 65° in the presence of a small quantity (0.1 to 0.15%) of benzoyl peroxide. With the exception of the β-chloroethoxyethyl ester (a soft, flexible, amber polymer that became brittle at approximately −5°), all the polymeric methacrylates were hard at room temperature and virtually colorless. The polymeric benzyl and tetrahydrofurfuryl esters became soft at approximately 45° and 35°, respectively. Presumably the polymeric allyl and methallyl esters, insoluble and infusible, were cross-linked.

The authors are indebted to Frances J. Cooper, Mary J. Welsh and C. L. Ogg for the saponification equivalents and ultimate analyses and to W. P. Ratchford and E. J. Schaeffer for pyrolyzing the acetoxyisobutyrates.

Experimental

Allyl Glycolate.—Water was distilled from a mixture of 210 g. of technical-grade glycolic acid (72.4% concentration) and 0.5 ml. of concentrated sulfuric acid for three hours at 100° and 20 to 30 mm. pressure. The resulting

---

[4] This assumption is based on the pyrolysis behavior[2] of $CH_3COOCH(CH_3)COOCH(CH_3)COOCH_3$, which yields methyl acrylate as the principal product.

residue (123 g. of polyglycolic acid having an equivalent weight on titration of 64.75; *i. e.*, 117.5% by weight as glycolic acid) was semi-solid.

A mixture of 32.4 g. of the polyglycolic acid (equivalent to 0.5 mole of glycolic acid and containing 0.13 ml. of sulfuric acid) and 2.5 moles of allyl alcohol was heated in a bomb (glass liner) for six hours at 120–139°. Anhydrous sodium acetate (0.6 g.) was added to the reaction mixture and the mixture was distilled to separate allyl glycolate (66% yield; b. p. 60–72° (8 mm.); d^{20}_{4} 1.0901; $n^{20}\mathrm{D}$ 1.4418; $M^{20}\mathrm{D}$ 28.09 (calculated, 28.00); saponification equiv., 122.5 (calculated, 116.1)). Muskat and Strain[5] prepared allyl glycolate but did not describe it.

Allyl Lactate.—This compound, previously described,[6,7,8] was prepared by the reaction of allyl alcohol with condensation products of glycerol and lactic acid. Water (116 g.) was distilled through a Vigreux column from a mixture of 81.7% edible-grade lactic acid (equivalent to 3 moles), 1 mole of glycerol and 0.75 ml. concentrated sulfuric acid for three hours. This was accomplished by heating the mixture on a water-bath while the system was at a pressure of 40–50 mm. The pale yellow, viscous residue (307 g.) had a saponification equivalent, including free acidity, of 101.4 (glyceryl trilactate, 102.7). A mixture of 50.5 g. of the glycerol–lactic acid product (equivalent to 0.5 mole of lactic acid) and 2.5 moles of allyl alcohol was heated in a bomb (glass liner) for two hours at 120–30°. The reaction mixture was treated with 0.5 g. of anhydrous sodium acetate and distilled in vacuum. Allyl lactate, b. p. 60–61° at 7 mm., $n^{20}\mathrm{D}$ 1.4363, was isolated in 73% yield.

Benzyl Lactate.—A mixture of 1 mole of methyl lactate, 4 moles of benzyl alcohol and 1 g. of aluminum isopropoxide was heated under a Vigreux column fitted with a variable take-off distilling head, methanol being distilled as formed (temperature of the reaction mixture increased gradually from 170 to 192°, and 36 ml. of distillate was collected during four to five hours). The reaction mixture was then distilled under reduced pressure. The yield of benzyl lactate, b. p. 103–104° at 1.3 mm., was 82%. The refractive indices, $n^{20}\mathrm{D}$, of two different preparations were 1.5143 and 1.5155. This compound has been made by the alcoholysis of ethyl lactate[9] and by the interaction of benzyl chloride and sodium lactate.[10]

Methallyl lactate was prepared by direct esterification of lactic acid with methallyl alcohol, some modifications of the previously reported method[6] being incorporated. A mixture of 110 g. of 81.7% of edible lactic acid, containing 1.0 mole of available lactic acid and 216 g. (3.0 moles) of methallyl alcohol, was refluxed and the vapors were led through a Vigreux column to a Barrett-type Dean-and-Stark moisture trap. The receiver of the moisture trap was jacketed and cooled by circulating cold water. After approximately seven hours removal of water virtually ceased, and 37 ml. of aqueous layer was collected. The reaction mixture was then distilled. There was obtained 86 g., or 60% of the theoretical amount of methallyl lactate, b. p. 85–90° at 15 mm., $n^{20}\mathrm{D}$ 1.4390.

Tetrahydrofurfuryl Lactate was prepared essentially as described previously[11,12] by alcoholysis of methyl lactate. The alcoholysis, however, was carried out in the absence of a catalyst. By refluxing a mixture of 10 moles of methyl lactate and 30 moles of tetrahydrofurfuryl alcohol with the continuous removal of methanol, an 85% yield of tetrahydrofurfuryl lactate was obtained; b. p. 84–86° at 0.1 mm., $n^{20}\mathrm{D}$ 1.4571, d^{20}_{4} 1.1360.

β-Chloroethoxyethyl Lactate.—Direct esterification of β-chloroethoxyethanol (diglycol chlorohydrin) with lactic acid, as previously described,[13] was used to obtain this ester, b. p. 91° at approximately 0.1 mm., $n^{20}\mathrm{D}$ 1.4567.

α-Carbalkoxyalkyl α-Acetoxyisobutyrates.—Acetoxyisobutyryl chloride was prepared and used to acylate the hydroxy esters as previously described.[2] Physical properties of the acyl derivatives (obtained in 80 to 90% yields) are recorded in Table I.

Pyrolysis.—In general the previous procedure was followed.[2] The acylated hydroxy esters were pumped[14] to the top of a vertical Pyrex glass tube (25 mm. diameter) heated electrically over a length of 33 cm. The thermocouple was located 10 cm. from the bottom of the heated zone. The pyrolysis tube was packed with short lengths of Pyrex glass tubing, and the free space of the heated zone was 78 ml.

The pyrolyzates, containing hydroquinone, were distilled in a 56-cm. Vigreux column in an atmosphere of carbon dioxide (Table II). The acetic acid fraction was collected at water pump pressure (in a solid carbon dioxide trap), whereas the methacrylates and undecomposed esters were isolated at pressures below 1 mm.

The constants of the methacrylates (Table III) were obtained on redistilled fractions. The methacrylates of tetrahydrofurfuryl lactate, benzyl lactate and chloroethoxyethyl lactate partly polymerized during distillation, resulting in losses.

Solubilities of the Polymeric Carbalkoxyethyl Methacrylates.—The polymeric methacrylates (0.1 g.) were allowed to stand at room temperature with approximately 1 ml. of solvent. The polymethacrylate of tetrahydrofurfuryl lactate swelled in toluene, benzene, ethylene dichloride, nitromethane, dioxane, acetone, methyl lactate and ethyl acetate. The polymethacrylate of benzyl lactate was soluble in nitromethane and partly soluble in toluene, benzene, ethylene dichloride, dioxane, acetone, methyl lactate and ethyl acetate. The polymethacrylate of β-chloroethoxyethyl lactate was soluble in toluene, benzene, ethylene chloride, nitromethane, dioxane, acetone, methyl lactate, and ethyl acetate. The polymers listed above were insoluble in heptane and ethanol, but dissolved slowly at room temperature in 10% sodium hydroxide. The polymers after swelling by acetone dissolved much more rapidly in the sodium hydroxide, presumably by saponification of the esterified lactic acid carboxyl group.

Summary

The method of producing α-carbalkoxyalkyl methacrylates ($CH_2{=}C(CH_3)COOCHRCOOR'$; R = H or Me) by pyrolysis of the corresponding α-acetoxyisobutyrates ($CH_3COOC(CH_3)_2COO$-$CHRCOOR'$) was used satisfactorily to prepare the methacrylates of allyl glycolate and of allyl, methallyl, benzyl, tetrahydrofurfuryl, and β-chloroethoxyethyl lactates. It is concluded that the pyrolytic method is generally useful for making α-carbalkoxyalkyl methacrylates.

The methacrylates polymerized readily when heated in the presence of benzoyl peroxide. The polymeric methacrylate of β-chloroethoxyethyl lactate was amber and flexible, the allyl and

---

(5) I. E. Muskat and F. Strain, U. S. Patent 2,370,574, Feb. 27, 1945.

(6) C. H. Fisher, C. E. Rehberg and Lee T. Smith, THIS JOURNAL, **65**, 763 (1943); C. E. Rehberg and C. H. Fisher, U. S. Patent 2,367,-798.

(7) C. E. Rehberg and C. H. Fisher, *J. Org. Chem.*, **12**, 226 (1947).

(8) I. E. Muskat and F. Strain, U. S. Patent 2,364,126, Sept. 4, 1945.

(9) R. Burns, D. T. Jones and P. D. Ritchie, *J. Chem. Soc.*, 400 (1935).

(10) M. Gomberg and C. C. Buehler, THIS JOURNAL, **42**, 2059 (1920).

(11) H. V. Claborn, U. S. Patent 2,222,363, Nov. 19, 1940; U. S. Patent 2,229,997, Jan. 28, 1941.

(12) M. L. Fein, W. P. Ratchford and C. H. Fisher, THIS JOURNAL, **66**, 1201 (1944).

(13) M. L. Fein and C. H. Fisher, *ibid.*, **68**, 2631 (1946).

(14) B. B. Corson and W. J. Cerveny, *Ind. Eng. Chem., Anal. Ed.*, **14**, 899 (1942).

methallyl polymers were hard, colorless, insoluble and infusible and the benzyl and tetrahydrofurfuryl polymers were hard and colorless.

PHILADELPHIA 18, PA. RECEIVED AUGUST 8, 1947

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE COLLEGE]

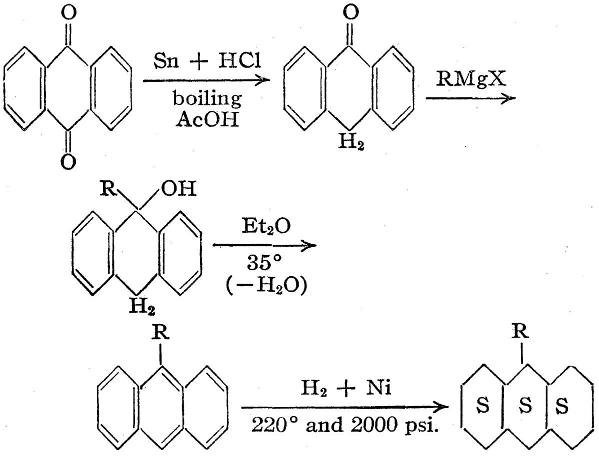
Higher Hydrocarbons.[1] V.[2] Alkyl Anthracenes and Alkyl Phenanthrenes

BY ROBERT W. SCHIESSLER, ANTON W. RYTINA AND FRANK C. WHITMORE[2a]

As part of our studies of the synthesis, purification and properties of high molecular weight hydrocarbons, the preparations of several alkyl-anthracenes and -phenanthrenes, together with the corresponding perhydro derivatives, have been completed. They are 9-*n*-butylanthracene, 9-*n*-butylperhydroanthracene, 9-*n*-dodecylanthracene, 9-*n*-dodecylperhydroanthracene, 9-*n*-dodecylphenanthrene and 9-*n*-dodecylperhydrophenanthrene.

The alkyl anthracenes were synthesized by a modification of the method of Sieglitz and Marx.[3] The method consists of the addition of anthrone to alkylmagnesium halides, followed by dehydration of the resultant tertiary alcohol to the desired alkyl anthracene:

Synthesis of 9-Alkylanthracenes.—



9-*n*-Dodecylphenanthrene was prepared by the addition of lauronitrile[2,4] to 9-phenanthrylmagnesium bromide[5] followed by reduction of the resulting 9-phenanthryl hendecyl ketone to the hydrocarbon by the modified Wolff–Kishner method.[6]

The perhydro derivatives of the hydrocarbons were prepared by complete hydrogenation over nickel catalyst[7] at 100–230° and 2300 p.s.i. hydrogen pressure.

It must be emphasized that the perhydro derivatives reported are mixtures of geometric isomers, and the properties given were determined on these mixtures of unknown composition. The difficulty of separating and identifying the various *cis-trans* structures precludes following any other course for our work.

Several of the important physical properties of the hydrocarbons are listed in Table I. The methods of determining the properties and their precision were discussed in the first paper of the series.[2] Numerous other properties have been determined and will be reported in the appropriate journals.

Experimental

Intermediates.—In order to simplify the purification of the final hydrocarbons, great care has been taken with the purification of intermediates. Where possible, distillation of intermediates through fractionating columns of 35–40 theoretical plates was carried out. The boiling points of the intermediates are uncorrected. The properties listed are for the constant boiling, constant refractive index fractions.

(a) ***n*-Butyl Bromide.**—Edwal Laboratories *n*-butyl bromide was carefully fractionated: b. p. 100° (733 mm.); n^{20}_{D} 1.4392.

(b) **Lauryl bromide**[8] was prepared by passing hydrogen bromide (from the direct combination of bromine and hydrogen) into Eastman Kodak Company technical lauryl alcohol at 120°. After washing twice with half its volume of cold (0–5°), concd. sulfuric acid and then with an equal volume of 95% methanol, the crude lauryl bromide was dried over anhydrous potassium carbonate and fractionally distilled through a 35–40 plate all glass column. The yield of pure bromide was 50% from this crude alcohol: b. p. 122° (4 mm.); n^{20}_{D} 1.4586.

(c) **Anthrone.**—Eastman Kodak Company anthraquinone (highest purity) was reduced to anthrone in 60% yield,[9] m. p. 156–157°.

(d) **9-Bromophenanthrene.**—Reilly Tar & Chemical Co. 90% phenanthrene was purified by the method of Cohen and Carmier[10]; m. p. 99.0–99.5°. A total of 508 g. of 9-bromophenanthrene was prepared in 55% yield following Austin[11]; m. p. 65–66°.

---

(1) American Petroleum Institute Research Project No. 42; Advisory Committee: L. C. Beard, Jr. (Chairman), J. R. Bates, L. M. Henderson, R. G. Larsen. R. F. Marchner, L. A. Mikeska, J. H. Ramser.

(2) Whitmore, Sutherland and Cosby, THIS JOURNAL, **64**, 1360 (1942); Whitmore, Cosby, Sloatman and Clarke, *ibid.*, **64**, 1810 (1942); Whitmore, Herr, Clarke, Rowland and Schiessler, *ibid.*, **67**, 2059 (1945); Whitmore, Schiessler, Rowland and Cosby, *ibid.*, **69**, 235 (1947).

(2a) Deceased, June 24, 1947.

(3) Sieglitz and Marx, *Ber.*, **56**, 1619 (1923).

(4) Ralston, Harwood and Pool, THIS JOURNAL, **59**, 986 (1937).

(5) Bachmann, *ibid.*, **56**, 1365 (1934).

(6) Whitmore, Herr, Clarke, Rowland and Schiessler, *ibid.*, **67**, 2059 (1945).

(7) A kieselguhr supported nickel supplied by the Universal Oil Products Co., Chicago, Ill.

(8) Further experience has shown that emulsion difficulty at the sulfuric acid wash step can be obviated by a preliminary simple distillation *in vacuo* of the Eastman Kodak Co. Technical Lauryl Alcohol. A considerable residue is eliminated.

(9) "Organic Syntheses," John Wiley and Sons, New York, N. Y., 1944, Coll. Vol. I, p. 60 (2nd edition).

(10) Cohen and Cormier, THIS JOURNAL, **52**, 4363 (1930).

(11) Austin, *J. Chem. Soc.*, **93**, 1762 (1908).

TABLE I

PROPERTIES OF THE HYDROCARBONS

Hydrocarbon	M. p., °C.	B. p., at 1.00 mm., °C.	$d^{98.9c}$	Viscosity at 98.9° (centi-poises)	n^{20}D	MR	
						Found	Calcd.
9-*n*-Butylanthracene	48.9	162.0	1.0007	4.630	Solid	Solid	75.5
9-*n*-Butylperhydroanthracene	Up to 38.3[a]	133.5	.8877	3.311	1.5049[b]	78.5	78.8
9-*n*-Dodecylanthracene	49.3	236.5	.9256	6.593	Solid	Solid	112.5
9-*n*-Dodecylperhydroanthracene	Up to 34.5[a]	214.5	.8522	5.147	1.4911[b]	115.9	115.7
9-*n*-Dodecylphenanthrene	75.8	237.0	.9292	5.979	Solid	Solid	112.5
9-*n*-Dodecylperhydrophenanthrene	Glass	213.0	.8571	5.134	1.4931	115.6	115.7

[a] Melting was complete at this temperature. [b] Supercooled sample. [c] Corrected for air buoyancy.

(e) **Lauronitrile**.—Prepared by the passage of ammonia through molten lauric acid (from the saponification of pure methyl laurate; m. p. of acid 44–44.5°) in 70% yield as described previously,[2,4] except that a few ml. of 85% phosphoric acid was added as a catalyst, substantially reducing the reaction time.[12]

9-*n*-Dodecylanthracene.—A Grignard solution was prepared in the usual manner from 1668 g. (6.7 moles) of lauryl bromide and 163 g. (6.7 moles) of magnesium in 92% yield, using 3.5 l. of diethyl ether as a solvent. An ether suspension of 368 g. (2.0 moles) of anthrone was added to this solution at 15°. After stirring for ten hours the reaction products were poured on a mixture of 1100 g. of ammonium sulfate and 1500 g. of ice with stirring. The ether layer was removed by distillation and the residue dissolved in 1200 ml. of toluene. The toluene solution was extracted exhaustively with 3% aqueous sodium hydroxide until the extracts were colorless. The toluene was distilled off and the residue dissolved in 1200 ml. of purified pentane, which was then passed successively through four 80 × 2 cm. columns of silica gel.[13] Upon evaporation of the pentane, 375 g. (49.5% yield) of crude hydrocarbon melting at 48–49° was obtained. The crude product was fractionally distilled through the high vacuum column[14] at 0.5 mm., yielding 371 g. of constant viscosity[15] constant melting 9-*n*-dodecylanthracene (see Table I).

9-*n*-Butylanthracene was prepared from *n*-butylmagnesium bromide and anthrone in the same manner as under 9-*n*-dodecylanthracene above. A total of 360 g. (43% yield) of constant melting, constant viscosity[15] hydrocarbon was obtained (refer Table I) after fractional distillation at high vacuum.[14]

9-*n*-Dodecylphenanthrene.—A Grignard reagent was prepared in 95% yield from 508 g. (1.98 moles) of 9-bromophenanthrene and 48.1 g. (1.98 moles) of magnesium turnings in a mixture consisting of 500 ml. of diethyl ether and 500 ml. of benzene. To this solution was added 293 g. (1.61 moles) of lauronitrile at reflux temperature. After stirring for sixteen hours the reaction product was decomposed with 110 ml. of concd. sulfuric acid, and 1500 g. of ice. The organic layer was dried by distillation of the solvents and yielded 465 g. of 9-phenanthryl hendecyl ketone: 80% yield; m. p. 72–73°; 2,4-dinitrophenylhydrazone m. p. 145.0–145.5°. The ketone was reduced in 0.5 mole portions by the modified Wolff–Kishner method,[6] yielding a total of 415 g. of 9-dodecylphenanthrene in 73% yield: m. p. 78–79° (mixed m. p. with 9-phenanthryl hendecyl ketone 65–71°). To ensure the complete removal of ketone, the hydrocarbon was treated with 0.5 mole of phenylmagnesium bromide. After decomposition with dilute sulfuric acid, drying over anhydrous potassium carbonate, and removal of the solvent, the hydrocarbon was treated with silica gel[13] in pentane solution and fractionated through the high vacuum column[14] to yield 408 g. of constant melting, constant viscosity[15] 9-*n*-dodecylphenanthrene (refer Table I).

9-*n*-Dodecylperhydroanthracene.—Prepared as a mixture of stereoisomers by the hydrogenation of 237 g. of pure 9-*n*-dodecylanthracene over 20 g. of nickel catalyst[7] at 100–230° and 2250–1000 p. s. i. of hydrogen pressure. In order to ensure complete hydrogenation, the crude material was passed through a train of silica gel[13] and fractionated through the high vacuum column.[14] The material boiling at 176–182° (0.3 mm.), 226 g., was rehydrogenated and treated as above to yield 218 g. of hydrocarbon boiling at 174° (0.1 mm.). The product was then passed through a column of activated silica gel[13] to remove traces of polar impurities.

9-*n*-Butylperhydroanthracene.—Hydrogenation of 155 g. of pure 9-*n*-butylanthracene employing the same method as listed above in three successive steps to ensure complete hydrogenation, yielded 141 g. of purified hydrocarbon after high vacuum fractionation,[14] boiling at 105° (0.3 mm.); n^{20}D 1.5048–50 (supercooled sample). The product is a mixture of stereoisomers, and was given a final treatment with silica gel[13] to remove traces of polar impurities.

9-*n*-Dodecylperhydrophenanthrene.—Prepared by the three-step hydrogenation of 218 g. of pure 9-dodecylphenanthrene over nickel catalyst[7] at 2600–1500 p. s. i. and 100–225°. The mixture of *cis–trans* isomers obtained from the third fractionation through the high vacuum column[14] boiled at 178° (0.2 mm.); n^{20}D 1.4926; 203 g. A final silica gel treatment was employed as described above.

Acknowledgment.—The authors express their appreciation to the American Petroleum Institute for the grant which made this research possible.

Summary

1. The methods of preparation, yields, and five important properties are given for two alkyl anthracenes, one alkyl phenanthrene, and the corresponding perhydro derivatives. The aromatic hydrocarbons are pure, but the perhydro derivatives are known to be mixtures of *cis–trans* isomers.

2. Data on the preparation, yields and properties of six intermediates are given.

STATE COLLEGE, PA. RECEIVED SEPTEMBER 6, 1947

---

[12] R. W. Schiessler and R. L. McLaughlin of these laboratories discovered the catalytic efficiency of phosphoric acid or silica gel for this reaction. Reaction time is reduced by approximately 50%, and ease of manipulation is increased.

[13] The activated silica gel (28–200 mesh) was supplied by the Davison Chemical Corp., Baltimore, Md.

[14] Nine to ten theoretical plates. To be described in a separate publication to be submitted to *Analytical Chemistry*.

[15] The viscosities of the fractions were determined and only those constant to within ±0.3% were accepted and combined as pure hydrocarbon. The importance and sensitivity of the viscosity method of determining uniformity of composition will be the subject of a separate publication.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS COMPANY]

Reaction of Methylcyclopentane with Propene in the Presence of Aluminum Bromide–Hydrogen Bromide

BY HERMAN PINES AND V. N. IPATIEFF

It has been reported previously[1] that methylcyclopentane reacts with olefinic hydrocarbons in the presence of either sulfuric acid or hydrogen fluoride to form alkylcyclohexanes and products resulting from a hydrogen transfer reaction. This study has now been extended in order to investigate the interaction of propene with methylcyclopentane in the presence of aluminum bromide–hydrogen bromide catalyst. The main purpose of this investigation was to determine whether the alkylation of methylcyclopentane can proceed without isomerization, which usually results in the expansion of the alkyl pentamethylene ring into an alkyl hexamethylene ring.

Since aluminum halide–hydrogen halide catalysts cause the isomerization of alkylcyclopentanes to alkylcyclohexanes[2] at room temperature, it was decided to carry out the alkylation reaction at −42°; at this low temperature the rate of isomerization of alkylcyclopentanes is relatively slow.

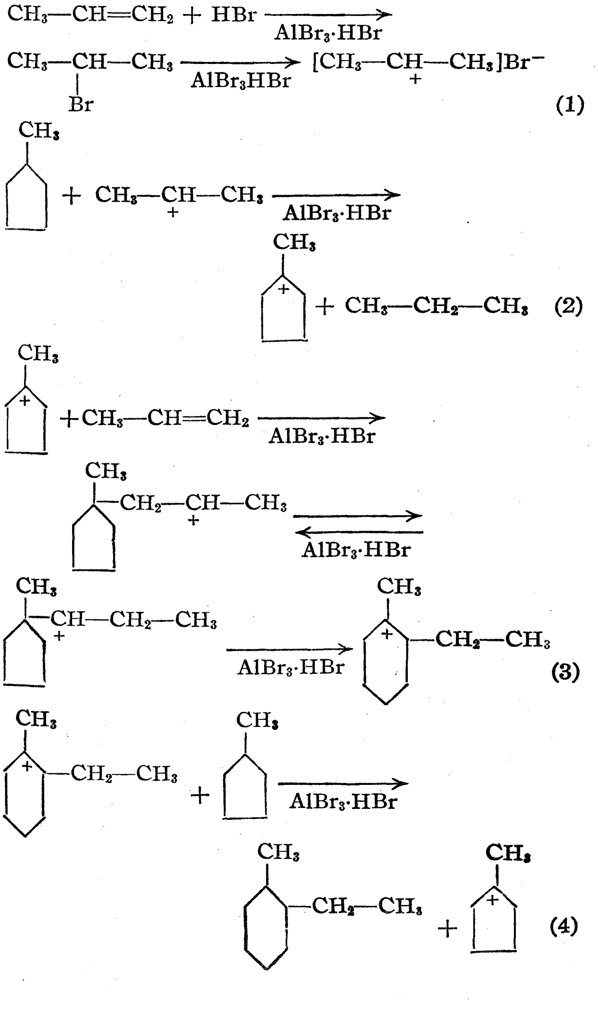
The alkylation of methylcyclopentane was carried out by passing propene and a small amount of hydrogen bromide into an agitated suspension of aluminum bromide in methylcyclopentane. The reaction product was then cooled to −76° and the liquid poured into water. The supercooling of the liquid before hydrolysis was necessary in order to avoid isomerization, which could occur if the decomposition were carried out at a higher temperature. The product obtained from this reaction, which consisted of saturated hydrocarbons, was distilled and analyzed. About 50% of the methylcyclopentane used for the reaction was recovered; the total hydrocarbons recovered from the reaction contained less than three per cent. of cyclohexane.

The higher boiling product consisted of a mixture of hydrocarbons, the major part of which distilled at 153–160°; and corresponded to a product of interaction of one mole of methylcyclopentane with propene. This hydrocarbon, which amounted to about 25 mole per cent. based on the propene used in the reaction, when passed over platinized alumina at 260°,[3] underwent almost quantitative dehydrogenation to aromatic hydrocarbons. The ease with which the dehydrogenation occurred indicates that the C_9H_{18} hydrocarbons consisted of alkylcyclohexanes. The gases obtained from the dehydrogenation reaction consisted of hydrogen only, which shows that geminal carbon atoms were not present in the cyclohexane ring.[4]

The aromatic hydrocarbons which were obtained from the dehydrogenation yielded, on oxidation with dilute nitric acid, about 70% of *o*-toluic acid. The presence of this acid indicates that the original product contained 1-methyl-2-ethylcyclohexane, which on dehydrogenation yielded *o*-ethyltoluene, and the latter oxidized to *o*-toluic acid.

The fractions boiling above 160° were also composed of alkylcyclohexanes since these compounds also underwent dehydrogenation to aromatic hydrocarbons: the structures of these compounds, however, were not identified because of their complexity.

The mechanism by which methylethylcyclohexane was formed from the interaction of methylcyclohexane and propene is the same as described previously.[1] The following are the probable steps that occur in this reaction



$$CH_3—CH=CH_2 + HBr \xrightarrow[AlBr_3·HBr]{} \quad CH_3—\underset{\underset{Br}{|}}{CH}—CH_3 \xrightarrow[AlBr_3HBr]{} [CH_3—\underset{+}{CH}—CH_3]Br^- \qquad (1)$$

---

(1) H. Pines and V. N. Ipatieff, THIS JOURNAL, **67**, 1631 (1945).

(2) H. Pines and V. N. Ipatieff, *ibid.*, **61**, 1076 (1939).

(3) V. N. Ipatieff and H. Pines, *ibid.*, **58**, 1056 (1936).

(4) V. N. Ipatieff, H. Pines and R. C. Olberg, *ibid.*, **68**, 1709 (1946).

The above indicated chain mechanism is similar to the one proposed by Schmerling[5] for the alkylation of isoparaffins. The exchange reaction indicated in equation II is similar to the one described by Bartlett, Condon and Schneider.[6]

Experimental

The apparatus consisted of a reaction flask provided with a Dry Ice cooled reflux condenser, mercury-sealed stirrer and inlet tubes for aluminum bromide and for the gaseous reagents. The outlet tube was connected in series to ice and Dry Ice traps and the latter was connected to a gas holder. The reaction flask was surrounded with boiling propane in order to maintain the temperature constant at −42°. Propene, which was stored in an aluminum bomb, was dried over anhydrone; hydrogen bromide was dried by passing it over aluminum bromide.

The flask and all tubings were thoroughly dried by passing dry nitrogen through them for several hours. Methylcyclopentane was introduced into the flask while dry nitrogen was passing through. An ampoule containing aluminum bromide was inserted in the apparatus and was broken therein while nitrogen was passing through. The flow of nitrogen was then discontinued and propene was passed into the flask over a period of two hours. Simultaneously with the propene, hydrogen bromide was passed into the reaction flask. The liquid reaction product, while still at −42°, was transferred into a trap maintained at −76°. The contents of the trap were then poured into 500 ml. of water contained in a three-neck flask and agitated by means of a mercury-sealed stirrer. The flask was connected to a series of traps in order to collect any escaping gases, if such were present. No evolution of heat was noticed when the product was added into water.

The hydrocarbon layer was separated, washed with alkali, water, dried over calcium chloride and distilled on a column of about fifteen-plate efficiency and at a reflux ratio of 20:1. The various narrow boiling fractions were redistilled and analyzed.

EXPERIMENTAL CONDITIONS AND RESULTS

Reagents employed, *M*:

Methylcyclopentane	63 g.	0.75
Propene	23 g.	.55
Aluminum bromide	20 g.	.075
Hydrogen bromide per min.	10–20 cc.	

Experimental conditions:

Temperature	−42°
Duration of reaction	2 hours

Product recovered, g.:

Gases	None
Hydrocarbon layer, g.	78.9
Organic material obtained from the hydrolysis of the catalyst layer, g.	1.1

Cut 1.—According to the index of refraction, Cut 1 is composed of 95% of methylcyclopentane and 5% of cyclohexane.

It underwent only slight dehydrogenation when passed over platinized alumina at 270°. The yield of methylcyclopentane–cyclohexane fraction based on total material recovered was 62%.

INVESTIGATION OF THE PRODUCT

Sixty-three grams of the hydrocarbon layer, after being washed and dried, was distilled. The following fractions were separated:

	B. p.	G.	$n^{20}D$
(1)	70–72°	31	1.4109
(2)	72–153	1.8	1.4273
(3)	153–157	15.0	1.4391
(4)	157–170	2.4	1.4405
(5)	170–180	1.5	1.4419
(6)	180–200	1.9	1.4453
(7)	200–210	6.7	1.4484
(8)	>210	6.2	1.4662

Cut 3.—According to physical constants, Cut 3 corresponds to C_9H_{18}. The yield of this fraction based on methylcyclopentane reacted was 53 mole per cent. or 27.4 mole per cent. based on propene reacted.

Thirteen grams of the hydrocarbon was passed, at a rate of 7 cc. per hour and a temperature of 265°, over 25 g. of 10–14 mesh size activated alumina containing 7% of platinum. Seven liters of gas was formed containing 89.6% of hydrogen. Ninety-one per cent. of liquid hydrocarbons was recovered with $n^{20}D$ 1.4946. Based on the hydrogen produced, virtually all of the material submitted to dehydrogenation was converted to aromatic hydrocarbons.

The dehydrogenated product distilled as follows: (1) b. p. 149–158°, 14%, $n^{20}D$ 1.4810; (2) 158–161°, 38%, 1.4922; (3) 161°, 37%, 1.5008; (4) 161°, 11%, 1.4998.

One half gram of Cut 3, obtained from the dehydrogenation, was refluxed for twelve hours with an acid consisting of 15 ml. of concentrated nitric acid and 25 ml. of water. About 0.35 g. of a crystalline product was obtained which was filtered and crystallized from hexane.

The crystalline material in the form of needles melted at 103°. It did not show depression in melting point when mixed with a known sample of *o*-toluic acid. Sharp depression in melting point, over 25°, was noticed when the sample was mixed with *m*-toluic acid, melting at 111°.

Anal. Calcd. for $C_8H_8O_2$: C, 70.59; H, 5.88. Found: C, 69.67; H, 5.90.

Cut 7.—According to physical constants, Cut 7 corresponds to $C_{12}H_{24}$.

Anal. Calcd. for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.59; H, 14.31.

Four grams of this product was dehydrogenated by passing it over platinized alumina at 200°. About 1.5 liters of gas was liberated, consisting of 98% hydrogen. The dehydrogenated product had an $n^{20}D$ 1.4921. The results obtained indicate that the product was composed of about 90% of aromatic hydrocarbons.

Summary

The reaction of methylcyclopentane with propene in the presence of aluminum bromide–hydrogen bromide catalyst has been investigated. The reaction was carried out at −42°.

The product obtained from the reaction consisted of alkylated cyclohexanes composed mainly of 1-methyl-2-ethylcyclohexane and of alkylcyclohexanes of the formula $C_{12}H_{24}$.

Under the condition of the reaction, methylcyclopentane underwent but slight isomerization. A mechanism of the alkylation is suggested.

RIVERSIDE, ILLINOIS RECEIVED MAY 28, 1947

---

(5) L. Schmerling, THIS JOURNAL, **66**, 1422 (1944).

(6) P. D. Bartlett, F. E. Condon and A. Schneider, *ibid.*, **66**, 1531 (1944).

[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

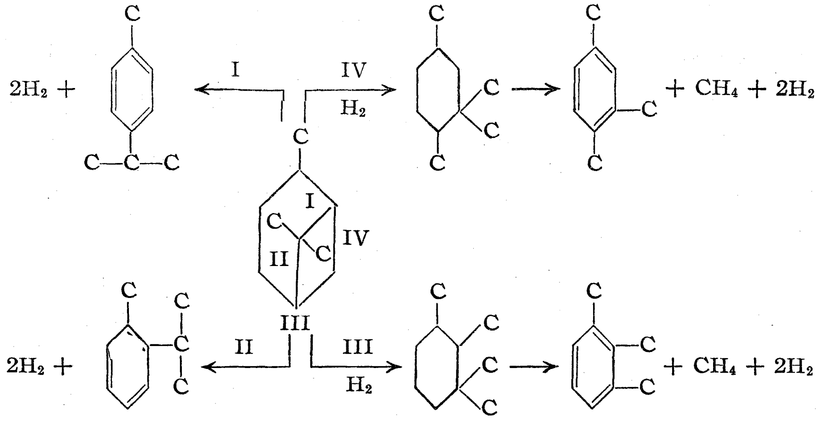
Studies in the Terpene Series. VIII.[1] Effect of Catalyst, Solvent and Temperature on the Dehydrogenation of Pinane and *p*-Menthane[2]

BY HERMAN PINES, R. C. OLBERG[3] AND V. N. IPATIEFF

Pinane has been reported to yield *p*-cymene and a small amount of *o*-cymene on dehydrogenation with such catalysts as platinized charcoal,[4] platinized asbestos[5] and nickel.[6]

In view of the fact that pinane on destructive hydrogenation[1] yielded a mixture of hydrocarbons consisting predominantly of 1,1,2,3-tetramethylcyclohexane and containing smaller amounts of 1,2-methylisopropylcyclohexane, 1,4-methylisopropylcyclohexane and 1,1,2,5-tetramethylcyclohexane, and in the light of the close similarity between hydrogenation and dehydrogenation, it was decided to reinvestigate the dehydrogenation of pinane and to determine whether or not polymethylated benzenes might be formed along with the previously reported *o*- and *p*-cymene.

In the present study it was found that when pinane was passed over platinized alumina, platinized pumice or platinized charcoal at 240–300° and at an hourly liquid space velocity of 0.2, dehydrogenation took place to yield a complex mixture of liquid products and gases consisting of hydrogen and methane. In addition to *o*- and *p*-cymene the liquid product contained 1,2,4- and 1,2,3-trimethylbenzene in considerable quantity. The relative amounts of the various hydrocarbons produced depended upon the conditions employed. Based upon previous hydrogenolysis studies with pinane and nickel–kieselguhr catalyst[1] in which 1,1,2,3-tetramethylcyclohexane was shown to be the principal hydrogenolysis product, the above results may be presumed to be obtained by the reactions.



It is believed that the hydrogen liberated in the formation of *o*- and *p*-cymene acts upon the unreacted portion of pinane to form 1,1,2,3- and 1,1,2,5-tetramethylcyclohexane which then, in part, may undergo dehydrogenation and demethanation to 1,2,3- and 1,2,4-trimethylbenzene, respectively. 1,2- and 1,4-methylisopropylcyclohexane may also be formed upon hydrogenolysis which upon subsequent dehydrogenation yield *o*- and *p*-cymene. However, at high temperatures or at conditions of low hydrogen concentration pinane gives increased yields of *p*-cymene suggesting that another reaction takes precedence. Therefore, the cleavage of the four-membered ring of pinane appears to take place by at least two different and concurrent reactions: (a) a hydrogenolysis to favor the formation of 1,1,2,5- and 1,1,2,3-tetramethylcyclohexane in approximately 2:1 molal ratio and 1,2-methylisopropylcyclohexane; the two tetramethylated cyclohexanes on subsequent dehydrogenation and demethanation yield 1,2,4- and 1,2,3-trimethylbenzene while 1,2-methylisopropylcyclohexane on dehydrogenation yields *o*-cymene; and (b) a straightforward rupture favoring the formation of *p*-cymene.

A study was made of the factors influencing the relative ease of cleavage of the four bonds constituting the four-membered ring of pinane. The role of temperature, nature of diluent, catalyst support and added hydrogen were investigated. The temperature was varied between 175 and 300°. Three types of diluents were employed: (1) hydrogen acceptors, such as pentenes and benzene, (2) hydrogen donors, such as methylcyclohexane and (3) "neutral acting" diluents such as *n*- and isopentane. In order to facilitate the cleavage of the four-membered ring, hydrogen gas was added to the reactions carried out at 175° with platinized alumina catalyst and at 300° with the less active platinized pumice catalyst.

The effect of temperature on the rupture of the

---

[1] For paper VII of this series, see V. N. Ipatieff, H. Pines and M. Savoy, THIS JOURNAL, **69**, 1948 (1947).

[2] This work was made possible through the financial assistance of the Universal Oil Products Company.

[3] Abstracted from the dissertation submitted to the Department of Chemistry, Northwestern University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy in June, 1947. It was presented before the Organic Division of the American Chemical Society at Atlantic City in April, 1947.

[4] R. P. Linstead, K. O. Michaelis and S. L. S. Thomas, *J. Chem. Soc.*, 1139 (1940).

[5] N. D. Zelinsky and R. J. Lewina, *Ann.*, **476**, 60 (1929).

[6] P. Sabatier and G. Gaudion, *Compt. rend.*, **168**, 670 (1919).

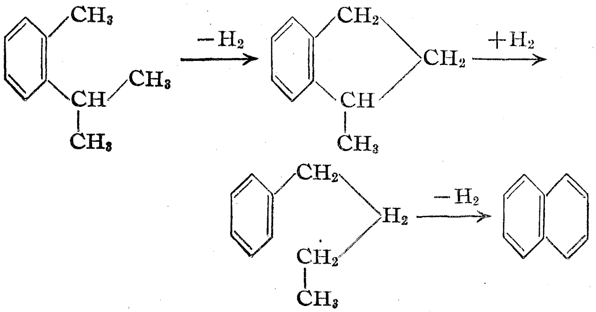
TABLE I

EFFECT OF TEMPERATURE

Experiment no.		1	2	3	4	5	6	7	8	9	10	11
Temperature, °C.		175	240	300	240	240	300	300	240	300	300	300
Diluent, kind		H_2	None		Isopentane	*n*-Pentane			Benzene		Pentene	
Diluent:Pinane, molal ratio		1.5:1			4:1	4:1	4:1	1:1	4:1	4:1	4:1	1:1
Number of passes over catalyst		3	3	3	1	1	1	1	1	1	1	3
Aromatic, vol. %		0	35	59	34	49	56	66	35	68	0	50
Bond cleavage, vol. %												
Bond I	*p*-Menthane	21	1	0	0	0	9	7	0	3	24	24
	p-Cymene	0	25	41	24	27	54	26	29	44		42
Bond II	*o*-Menthane	7	1	0	0	0	0	0	0	0		0
	o-Cymene	0	7	1	2	2	0	0	2	0		1
Bond III	1,1,2,3-Tetramethylcyclohexane	30	20	14	17	13	9	9	20	6		10
	1,2,3-Trimethylbenzene	0	0	5	0	0	0	13	0	0		0
Bond IV	1,1,2,5-Tetramethylcyclohexane	31	39	25	41	33	17	12	39	13		15
	1,2,4-Trimethylbenzene	0	0	9	3	9	2	23	1	12		1
Unidentified		11	7	5	14	17	9	10	9	21		8

bonds constituting the four-membered ring of pinane is shown in Table I; platinized alumina was used as a catalyst.

Higher temperatures favor the formation of larger amounts of *p*-cymene; this is especially evident when a "neutral" diluent such as *n*-pentane is used. *n*-Pentane in 4:1 molal ratio appears to enhance the Bond I cleavage to form *p*-cymene at 300° but has no effect at 240°. However, the extent of dehydrogenation appears to be increased at 240° when *n*-pentane is used as a diluent as evidenced by the fact that an equivalent or greater yield of aromatics is obtained in only one pass over the catalyst as compared to three passes when no diluent is used. Lower temperature and the absence of a diluent appears to favor the cleavage of Bond II to form 1,2-methylisopropylcyclohexane and *o*-cymene. At 300° small amounts of naphthalene were detected in the reaction product which may have been formed by the cyclodehydrogenation of *o*-cymene. When pure *o*-cymene was passed over platinum–alumina at 300° the reaction product contained 10–15% naphthalene, 50–60% unreacted *o*-cymene and 25–40% unidentified product, which may be 1-methylindane, but owing to the unavailability of pure 1-methylindane as a reference sample for infrared spectra analysis no proof of its presence could be obtained. Naphthalene was separated, recrystallized and identified by its melting point and mixed melting point with pure naphthalene. Its formation from *o*-cymene may be explained if one assumes the intermediate formation of 1-methylindane followed by ring fission and cyclic dehydrogenation to naphthalene.



The formation of new rings under conditions of catalytic dehydrogenation is not new.[7] Moreover, the formation of naphthalene from 1-methylindane by catalytic dehydrogenation over palladized charcoal at 450°[8] and from 1-methylindane and 1-methyloctahydroindene over platinized charcoal at 300° supports the above interpretation.

If, as postulated above, *p*-cymene formation is favored by the higher temperatures and conditions of low hydrogen concentration, it follows that the yield of *p*-cymene should be increased if the dehydrogenation is carried out in the presence of substances which would remove the hydrogen from the reaction zone as it is formed. Thus, the hydrogenolysis of the pinane should be minimized. The straight and branched chain pentenes and benzene were therefore used as hydrogen acceptors. It was thought that the pentenes should be particularly effective as hydrogen acceptors because of the ease with which they undergo hydrogenation of the pentanes.

The results obtained with both the branched and straight chain pentenes in the ratio of one mole of pentenes to one mole of pinane support the above advanced supposition. The pentenes act as true hydrogen acceptors and are completely converted to the pentanes. Bond I cleavage to form *p*-cymene is markedly facilitated since the hydrogen removed from the surface of the catalyst retards the hydrogenolysis of pinane. However, when the molal ratio of the pentenes to pinane

---

[7] (a) N. D. Zelinski, I. N. Titz and M. V. Gaverdowskaja, *Ber.*, **59**, 2590 (1926); (b) N. D. Zelinski and I. N. Titz, *ibid.*, **62**, 2869 (1929); **64**, 183 (1931); (c) S. R. Sergienko, *Doklady, U. S. S. R.*, **27**, 960 (1940); (d) H. Pines, A. Edeleanu and V. N. Ipatieff, THIS JOURNAL, **67**, 2193 (1945).

[8] L. Ruzicka and E. Peyer, *Helv. Chim. Acta*, **18**, 676 (1935).

is increased to 4:1, the dehydrogenation reaction is completely inhibited even at 300°. Presumably, the pentenes in this concentration so completely saturate the surface of the catalyst that the adsorption of pinane is prevented and pinane is recovered unchanged. Even *p*-menthane, which undergoes dehydrogenation almost quantitatively at 300° in the absence of a solvent, yields only 8% *p*-cymene under the above conditions; this amount of dehydrogenation occurred at the beginning of the run before the catalyst surface was completely saturated.

Although benzene may also act as a hydrogen acceptor, only about 3% of it was converted to cyclohexane at 300° when used in a ratio of 4 moles of benzene to 1 mole of pinane. Presumably, benzene is not as strongly adsorbed to the surface of the catalyst as the pentenes and therefore does not inhibit the dehydrogenation. The extent of dehydrogenation under the above conditions is somewhat increased and the Bond I cleavage to yield *p*-cymene is slightly enhanced. At 240° benzene, like *n*- and isopentane, has little effect upon the ratio of products obtained except that the *o*-menthane and *o*-cymene resulting from Bond II cleavage is diminished.

TABLE II

THE EFFECT OF HYDROGEN AND HYDROGEN-DONOR DILUENT

Experiment no.		1	12
Temperature, °C.		175	240
Diluent, kind		H_2	Methylcyclohexane
Diluent:Pinane, molal ratio		1.5:1	1:1
Number of passes over catalyst		3	1
Per cent. aromatic		0	25
Bond cleavage			
Bond I	*p*-Menthane	21	0
	p-Cymene	0	15
Bond II	*o*-Menthane	7	0
	o-Cymene	0	6
Bond III	1,1,2,3-Tetramethylcyclohexane	30	30
	1,2,3-Trimethylbenzene	0	0
Bond IV	1,1,2,5-Tetramethylcyclohexane	30	41
	1,2,4-Trimethylbenzene	0	0
Unidentified		11	8

Increasing the molal ratio of pentanes to pinane from 1:1 to 4:1 at 300° results in a greatly increased yield of *p*-cymene at the expense of 1,2,3- and 1,2,4-trimethylbenzene. There appears to be no difference in the action of *n*- and isopentane. These effects are shown in Table I.

In order to determine the effect of a hydrogen donor diluent, an equimolal mixture of methylcyclohexane and pinane was passed over platinized alumina at 240°. It was found that the methylcyclohexane underwent dehydrogenation and the hydrogen liberated facilitated the hydrogenolysis of Bonds II, III and IV. Only 15% of Bond I cleaved to form *p*-cymene. The same effect was experienced when hydrogen in 1.5:1 mole ratio was added to pinane at 175°, a temperature too low for dehydrogenation to occur. The hydrogenolysis of the four-membered ring of pinane was complete; bonds III and IV were predominantly cleaved. The effect of added hydrogen and hydrogen donor diluent is shown in Table II.

In order to determine whether the catalyst support influences the cleavage of the various bonds, platinized alumina, platinized charcoal and platinized pumice were used as catalysts. It was found that platinized alumina and platinized charcoal are of comparable high activity, but that platinized pumice has very low activity presumably because of its lower adsorptive capacity. The results obtained in the absence of a solvent at 300° are given in Table III.

The effect of hydrogen in causing the hydrogenolysis reaction to occur is clearly shown when platinum–pumice is used as the catalyst. In the absence of added hydrogen no noticeable reaction takes place, while in the presence of hydrogen

TABLE III

EFFECT OF CATALYST SUPPORT AT 300°

Experiment no.		3	13	14	15
Catalyst		Pt–Al_2O_3	Pt–C	Pt–Pumice	Pt–Pumice[a]
Number of passes over catalyst		3	1	1	2
% Aromatic		59	70	Trace	42
Bond cleavage on dehydrogenation, vol. %					
Bond I	*p*-Menthane	0	0	..	8
	p-Cymene	41	34		28
Bond II	*o*-Menthane	0	0	..	0
	o-Cymene	1	1		11
Bond III	1,1,2,3-Tetramethylcyclohexane	14	9	..	17
	1,2,3-Trimethylbenzene	5	4		0
Bond IV	1,1,2,5-Tetramethylcyclohexane	25	18	..	29
	1,2,4-Trimethylbenzene	9	18		2
Unidentified		5	16	..	6

[a] Small amount of hydrogen was passed over the catalyst.

42% of aromatic hydrocarbons are formed and the reaction product did not contain any unreacted pinane. Also, when platinized alumina is flushed with nitrogen before pinane is passed very little dehydrogenation occurs until the concentration of hydrogen has increased to the point where the hydrogenolysis reaction can readily take place. The above experiments indicate that the products of hydrogenolysis of pinane undergo dehydrogenation more readily than pinane itself.

In order to gain a better insight into the effect of temperature, solvents and catalyst support on the dehydrogenation activity of the catalyst toward pinane, a comparative study of the same variables on the dehydrogenation of *p*-menthane (1-methyl-4-isopropylcyclohexane) was made.

The dehydrogenation of *p*-menthane was carried out at 240° and 300° using platinized alumina catalyst. At 300° without solvent or in the presence of either pentane or benzene in 4:1 molal ratio dehydrogenation is virtually complete and *p*-cymene is obtained in 95–100% yield. The use of pentene as a solvent in 1:1 molal ratio likewise favors the complete conversion to *p*-cymene and pentane is obtained in the product. However, when the mole ratio of pentenes is increased to 4:1, *p*-cymene is obtained in only 8% yield at 240°, 270° or 300°. The dehydrogenation which does take place occurs at the beginning of the experiment before the catalyst surface has been completely covered with adsorbed pentenes.

The effect of various diluents upon the dehydrogenation of *p*-menthane in the presence of platinized alumina has been studied. The reaction has been carried out at 240° using a molal ratio of diluents to *p*-menthane of 4:1. The results are given in Table IV.

TABLE IV

EFFECT OF DILUENTS AT 240° ON DEHYDROGENATION OF *p*-MENTHANE

Solvent, molal ratio 4:1	*p*-Cymene, %
None	55
n-Pentane	78
Isopentane	80
Benzene	95
Pentenes	8

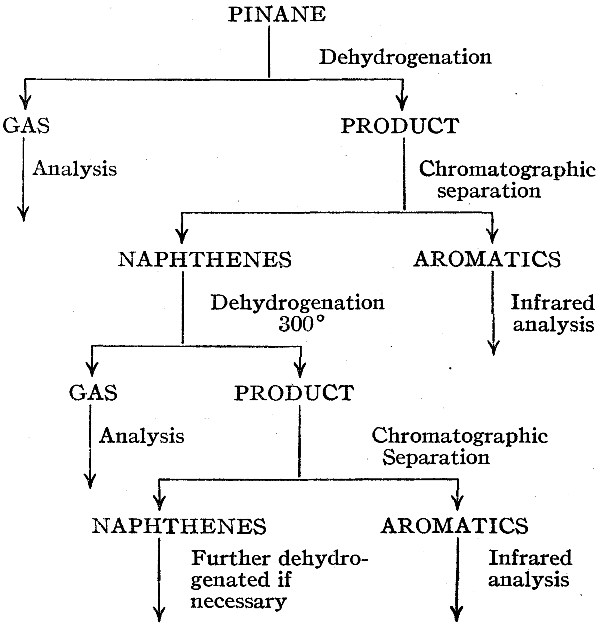
n-Pentane, isopentane and benzene used as diluents increase the extent of dehydrogenation; there is no difference in the effect of *n*- and isopentane. Benzene has the most beneficial effect, the dehydrogenation of *p*-menthane being virtually complete at 240°. Pentenes, however, in 4:1 molal ratio inhibit the dehydrogenation.

Experimental Part

Apparatus and Procedure.—The apparatus consisted of a graduated buret and a pump connected to a Pyrex glass reaction tube containing the catalyst bed, a water-cooled receiver–condenser, a Dry Ice–acetone cooled trap, and a calibrated gas-collecting bottle containing saturated salt solution. The reaction tube was heated in a thermostatically controlled vertical furnace, brought to the desired temperature, ranging from 175 to 300°, in a slow stream of hydrogen. The pinane of *p*-menthane, with or without diluent, was added at an hourly rate approximately equal to two-tenths the volume of the catalyst bed. The liquid product was collected in the water-cooled condenser–receiver and the dehydrogenation gas was freed of entrapped solvent by passing it through a Dry Ice–acetone cooled trap and collected in a gas bottle over saturated salt solution. The temperature and barometric pressure were recorded along with the volume of the gas obtained. In some instances the liquid product was repassed through the catalyst tube until no further reaction occurred. In the absence of solvents the extent of dehydrogenation could also be followed from the change in the refractive index with each successive pass. If a solvent was present it was removed by distillation through a distilling column of an efficiency of seven theoretical plates.

A diagrammatic sketch of the procedure for the determination of the composition of product obtained on the dehydrogenation of pinane is given below.

DIAGRAMMATIC SKETCH: DEHYDROGENATION OF PINANE



The aromatic hydrocarbons which were produced during the dehydrogenation were separated chromatographically according to the method of Mair and Forziati.[9] This was accomplished by diluting the solvent freed reaction product with four or five parts of pentane and by passing the mixture through a five-foot column containing 200–300 mesh silica gel. An almost quantitative separation of the aromatics and naphthenes was effected in this manner. The aromatic and naphthene portions were each distilled, and the aromatic portion was analyzed. The naphthene portion was again dehydrogenated and the aromatics formed were separated chromatographically and analyzed. This procedure was repeated until very little naphthene remained which was assumed to have the same composition as the naphthenes from which the last portion of aromatics was obtained.

Analytical Part

The naphthenic product obtained from the dehydrogenation of pinane, according to infrared spectral analysis, contained no pinane and corresponded to the monocyclic hydrocarbons $C_{10}H_{20}$.

Anal. Calcd. for $C_{10}H_{20}$: C, 85.63; H, 14.37. Found: C, 85.70; H, 14.27.

---

[9] B. J. Mair and A. F. Forziati, *J. Research Natl. Bureau Stand.*, **32**, 151, 165 (1944).

The mixture of *o*- and *p*-cymene were separated by fractional crystallization of their sulfonamide derivatives[10,11] from hot benzene. The less soluble *o*-cymene sulfonamide crystallized out in fine needle crystals, m.p. 152.5–153.5°, and gave no depression in melting point when mixed with a known sample of *o*-cymene sulfonamide.

Anal. Calcd. for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57. Found: C, 56.56; H, 6.77; N, 6.64.

***p*-Cymene sulfonamide** crystallized out from benzene in irregular plates, m.p. 115–116°.[10,11] *p*-Cymene was further characterized by chromic acid oxidation to terephthalic acid, the dimethyl ester of which melted at 141–141.5°.

1,2,4-Trimethylbenzene was characterized by conversion to the trinitro derivative,[12] m.p. 184–185°. It showed no depression in melting point when mixed with a trinitroderivative of a known sample of 1,2,4-trimethylbenzene.

1,2,3-Trimethylbenzene was identified by conversion to the tribromo derivative, m.p. 242–243°, which gave no depression in melting point when mixed with a synthetic sample of tribromo-1,2,3-trimethylbenzene.

Naphthalene was identified by its melting point 79.5–80°; it did not depress the melting point of a known sample of naphthalene.

Gaseous Product.—The gas was analyzed by absorption and combustion using a Goeckel type[13] gas analysis apparatus.

Infrared Spectral Analysis (by W. S. Gallaway).[14]—The analyses were made according to the procedure described previously.[1] The wave lengths used for calculating the composition of the various samples are given in Table V.

TABLE V

WAVE LENGTHS OF CHARACTERISTIC INFRARED ABSORPTIONS, μ

1,2,3-Trimethylbenzene	1,2,4-Trimethylbenzene	*p*-Cymene	*o*-Cymene
9.14	8.88	9.45	9.20
9.31	8.79	9.80	9.63
9.91	10.01	12.23	13.19
10.13	12.41		13.78
13.05			

Materials

Pinane was prepared by the hydrogenation of α-pinene which was obtained from the Hercules Company as Pinene 111 and is reported to contain less than 2% of camphene. The α-pinene was further purified by distillation through a column of twelve-plate efficiency using a reflux ratio of twelve to one. The middle portion boiling at 155–156°, n^{20}_{D} 1.4660, was dissolved in an equal volume of pentane and hydrogenated in a rotating autoclave at 50°, using nickel–kieselguhr catalyst[15] (10% by weight of α-pinene charged) and 100 atm. initial hydrogen pressure. The pinane distilled at 165–166°, n^{20}_{D} 1.4605, and did not contain any olefins.

***p*-Menthane** was prepared by the hydrogenation of *p*-cymene. The *p*-cymene was purified by washing repeatedly with sulfuric acid and distilling through a twelve-plate column. The portion boiling at 176.5°, n^{20}_{D} 1.4998, was hydrogenated in a rotating autoclave at 115° with nickel–kieselguhr catalyst and 100 atm. initial hydrogen pressure. The *p*-menthane produced contained no aromatics and distilled at 167°, n^{20}_{D} 1.4398.

***o*-Cymene** was prepared from *o*-bromotoluene and acetone via the Grignard reaction. The *o*-tolyldimethylcarbinol produced from this reaction was dehydrated by passing it over activated alumina at 320°. *o*-Isopropenyltoluene boiling at 171–173°, n^{20}_{D} 1.5253, was obtained in an over-all yield of 48% based upon the bromotoluene. *o*-Isopropenyltoluene was hydrogenated to *o*-cymene in a rotating autoclave at 40° with nickel–kieselguhr catalyst and an initial hydrogen pressure of 61 atm. The theoretical amount of hydrogen was absorbed. The *o*-cymene distilled at 174°, n^{20}_{D} 1.4994.

Platinum–Alumina Catalyst was prepared by heating platinum, 12.0 g., on a steam-bath with aqua regia, until solution was complete. The excess acid was removed by evaporating the solution almost to dryness and then adding a 100-cc. portion of water and again evaporating down; this procedure was repeated ten times. The chloroplatinic acid was dissolved in 200 cc. of distilled water and suction filtered to remove any contaminants. The clear filtrate was added to 150 cc., 120 g., of alumina (Alorco 10–12 mesh). The liquid completely covered the alumina. The solution was evaporated on a steam-bath with thorough stirring. When dry the catalyst has a uniform yellow-orange color. It was heated in a vertical furnace at 100° in an atmosphere of hydrogen for several hours. The temperature was then raised to 200° and the heating continued for several more hours. Finally, it was heated at 254° for two hours prior to use for dehydrogenation. The reduced catalyst has a uniform gray color.

Platinum–pumice catalyst was prepared according to the same method described for platinum–alumina catalyst, using 10.1 g. of platinum to 125 cc., 54.5 g. of pumice.

Platinum charcoal catalyst was prepared according to the method described by Linstead and co-workers[4] except that activated Burrell cocoanut charcoal (10–14 mesh) was used in place of norit charcoal in order to facilitate its use in a vertical catalyst tube.

Acknowledgments.—We are indebted to Dr. W. S. Gallaway of Universal Oil Products Company for the infrared spectral analyses, to Mr. M. Stross of Universal Oil Products Company for the gas analyses and to Mrs. Margaret L. Ladyard of Northwestern University for the microanalyses.

Summary

Pinane on dehydrogenation yields in addition to the previously reported *p*- and *o*-cymene also a large amount of 1,2,4- and 1,2,3-trimethylbenzene, the ratio of products obtained depending upon the temperature, solvent and catalyst support employed.

The cleavage of the four-membered ring of pinane appears to occur by two different reactions; a thermal cleavage to favor the formation of *p*-cymene and a hydrogenolysis which favors the formation of 1,1,2,3- and 1,1,2,5-tetramethylcyclohexane and *o*-menthane. The hydrogen liberated from the former reaction causes the latter reaction to occur. At high temperatures the tetramethylcyclohexanes undergo demethanation and dehydrogenation to the corresponding trimethylbenzenes.

The dehydrogenation of pinane is inhibited when it is diluted with four moles of pentenes. Pentane and benzene enhance the extent of dehydrogenation of pinane.

A comparative study of the dehydrogenation of *p*-menthane using the same variables was made.

EVANSTON, ILLINOIS RECEIVED AUGUST 2, 1947

---

[10] E. H. Huntress and F. H. Carten, THIS JOURNAL, **62**, 511 (1940).

[11] E. H. Huntress and J. S. Autenrieth, *ibid.*, **63**, 3446 (1941).

[12] Huntress and Mulliken, "Identification of Pure Organic Compounds," Order 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 530.

[13] "U. O. P. Laboratory Test Methods for Petroleum and Its Products"-g-84-40, Universal Oil Products Company, Chicago, Illinois (1940).

[14] Research Laboratories, Universal Oil Products Company.

[15] V. N. Ipatieff and B. B. Corson, *Ind. Eng. Chem.*, **30**, 1039 (1938).

[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, MONSANTO CHEMICAL COMPANY]

Copolymerization. IV. The Validity of the Tripolymer Equation for the Systems: Styrene–Vinyl Chloride–Methyl Acrylate and Styrene–Vinyl Chloride–Acrylonitrile

BY EARL C. CHAPIN, GEORGE E. HAM AND REID G. FORDYCE

The theory of the propagation step in copolymerizations developed by Alfrey and Goldfinger,[1] Mayo and Lewis[2] for two components was later extended to three component systems by Alfrey and Goldfinger[3] and finally to the more general case of n monomers by Walling and Briggs.[4] While a considerable amount of experimental data has been reported for two-component systems,[2,5–11] apart from the original experiments of Walling and Briggs[4] further experimental confirmation of the tripolymer equation has been lacking. It is the purpose of this paper to present additional copolymerization rate data in order to test the applicability of the tripolymer equation to systems other than those described by Walling and Briggs. It is also our purpose to present data based on tripolymer samples isolated at low conversions where the simple differential form of the tripolymer equation can be employed for direct comparison with experimental results.

The systems vinyl chloride–styrene–methyl acrylate and vinyl chloride–styrene–acrylonitrile were chosen since the tripolymer composition could be determined with accuracy by analysis. Thus chlorine, carbon and hydrogen analyses on products from the former system, and chlorine and nitrogen analyses on tripolymers from the latter system were sufficient to define the relative proportions of combined comonomers in each case.

The monomer reactivity ratios for the systems styrene–methyl acrylate[7] and styrene–acrylonitrile[5,10] have been reported. Since the tripolymer equation involves the monomer reactivity ratios of the three separate two component systems involved, it was necessary to determine first, monomer reactivity ratios for the systems, styrene–vinyl chloride, vinyl chloride–methyl acrylate and vinyl chloride–acrylonitrile. These data were then used to predict the compositions of tripolymers produced from different compositions of the three component systems cited above. Experimental data comparing the actual compositions with the calculated values were then obtained.

In determining the monomer–polymer composition curves for the three two-component systems, copolymerizations were allowed to proceed to low conversions (mainly <4%) and the initial product was isolated and purified. The amount of combined vinyl chloride was determined in all cases by chlorine analyses. Likewise for the tripolymer experiments, products at low conversions (mainly <4%) were isolated, purified and analyzed as indicated above.

Results and Discussion

The shapes of the monomer–polymer composition curves for the system vinyl chloride–styrene determined by solution and by emulsion polymerization are shown in Figs. 1 and 2, respectively. The experimental data are summarized in Table I. The following monomer reactivity ratios[12] gave the best curve fit to the data obtained:

	Solution polymerization	Emulsion polymerization
Styrene	35	35
Vinyl chloride	0.067	0.077

TABLE I

VINYL CHLORIDE–STYRENE COPOLYMERIZATIONS

Monomer mole % styrene	Time at polymerization temp., hours	Wt. % conversion	Chlorine Analyses I	Chlorine Analyses II	Copolymer mole % styrene
Solution polymerization, acetone, 48°, 0.5% Bz_2O_2					
83.6	18.2	3.0	0.31	0.32	99.0
71.6	24.0	2.6	.48	.52	98.5
60.6	24.0	4.4	1.00	1.00	97.2
49.6	24.0	4.0	1.12	1.16	96.7
38.8	24.0	2.0	1.35	1.79	95.5
13.1	67.0	4.0	6.87	7.27	80.9
9.9	166.0	1.2	9.06	9.14	76.0
7.6	239.5	4.6	14.79	15.17	62.8
3.2	339.5	3.6	35.27	35.33	26.8
Emulsion polymerization, 50°, 0.5% H_2O_2					
88.6	6.0	2.0	0.40	...	98.8
78.4	46.0	3.0	.63	0.99	98.6
58.9	46.0	1.0	1.62	...	95.3
39.7	70.0	1.9	3.17	...	91.0
9.7	70.5	0.6	16.18	16.55	59.8

In accordance wth arguments previously advanced,[10,11] the close proximity of the two curves shows that an oil-phase mechanism of emulsion polymerization is operative for this system. The data also show that styrene monomer has a much greater tendency than vinyl chloride to add either to a styrene free radical or to a vinyl chloride free

---

(1) Alfrey and Goldfinger, *J. Chem. Phys.*, **12**, 205 (1945).

(2) Mayo and Lewis, THIS JOURNAL, **66**, 1594 (1944).

(3) Alfrey and Goldfinger, *J. Chem. Phys.*, **12**, 322 (1945).

(4) Walling and Briggs, THIS JOURNAL, **67**, 1774 (1945).

(5) Lewis, Mayo and Hulse, *ibid.*, **67**, 1701 (1945).

(6) Alfrey and Lavin, *ibid.*, **67**, 2044 (1945).

(7) Alfrey, Merz and Mark, *J. Polymer Research*, **1**, 37 (1946).

(8) Alfrey and Goldfinger, *J. Chem. Phys.*, **14**, 115 (1946).

(9) Alfrey, Goldberg and Hohesnstein, THIS JOURNAL, **68**, 2464 (1946).

(10) Fordyce and Chapin, *ibid.*, **69**, 581 (1947).

(11) Fordyce and Ham, *ibid.*, **69**, 695 (1947).

(12) The constants reported in this paper represent the ratio of the rate constants for the reaction of the given radical with the corresponding monomer and with the other monomer, respectively. The values correspond to the r_1 and r_2 nomenclature of Alfrey, Mayo and Wall, *J. Polymer Science*, **1**, 581 (1946).

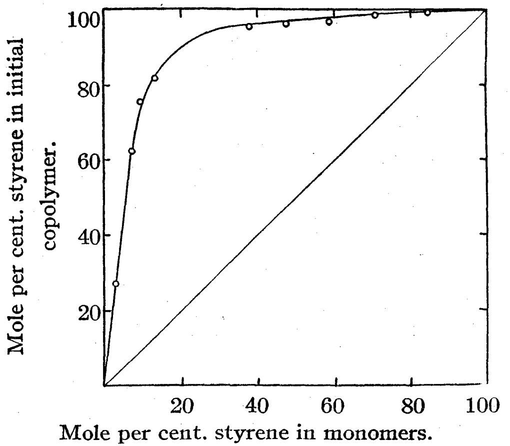


Fig. 1.—Monomer–polymer composition curve for the system vinyl chloride–styrene solution polymerization.

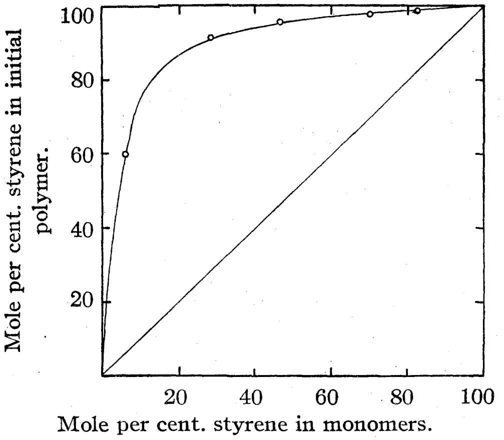


Fig. 2.—Monomer–polymer composition curve for the system vinyl chloride–styrene emulsion polymerization.

radical. Hence styrene–vinyl chloride batch copolymerizations carried to completion must necessarily produce samples highly heterogeneous with respect to composition. Inspection of the polymerization times required (Table I) shows that styrene–vinyl chloride copolymers do not form readily and copolymerize at a much slower rate than either constituent alone.

TABLE II

VINYL CHLORIDE–METHYL ACRYLATE COPOLYMERIZATIONS

Monomer mole % methyl acrylate	Time at polymerization temp., hours	Wt. % conversion	Chlorine analyses I	Chlorine analyses II	Copolymer mole % methyl acrylate
Mass polymerization, 50°, 0.05% Bz_2O_2					
7.5	7.0	1.7	27.12	27.32	44.1
15.4	6.0	3.0	13.30	13.75	69.9
23.7	4.0	5.9	10.84	10.94	75.3
32.6	7.0	2.2	7.24	7.61	82.8
42.1	7.5	4.0	5.69	5.98	86.4
52.1	7.5	4.1	4.00	4.45	90.0
74.4	12.0	4.5	1.18	1.50	96.8
86 7	16.0	4.6	0.68	0.76	98.3

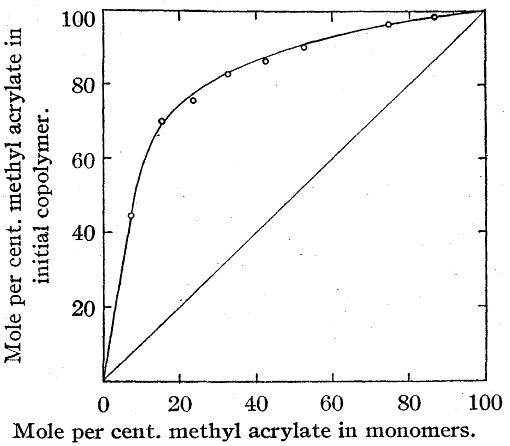


Fig. 3.—Monomer–polymer composition curve for the system vinyl chloride–methyl acrylate, mass polymerization.

The monomer–polymer composition curve for the system vinyl chloride–methyl acrylate copolymerized in mass is shown in Fig. 3, and the experimental data for this series of experiments are given in Table II. The monomer reactivity ratios for the two free radicals were found to be: vinyl chloride 0.083, methyl acrylate 9.0.

The relationship of monomer composition to copolymer composition for the system vinyl chloride–acrylonitrile determined in solution is represented in Fig. 4. The experimental data from which this curve[13] was drawn are given in Table III. The monomer reactivity ratios giving a good curve through the experimental points were found to be: vinyl chloride 0.074 and acrylonitrile 3.7.

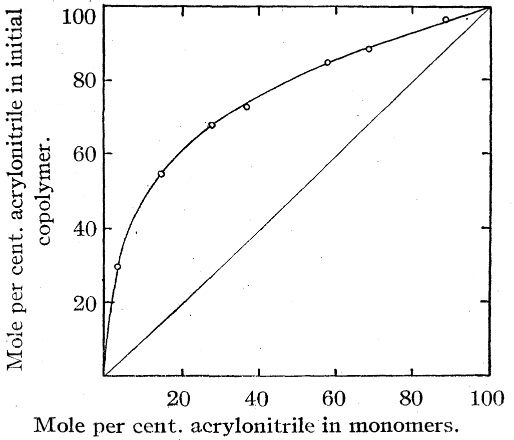


Fig. 4.—Monomer–polymer composition curve for the system vinyl chloride–acrylonitrile solution polymerization.

The monomer reactivity ratios reported above were determined by varying their values in the copolymer equation until a good curve through

---

[13] After completing this manuscript, U. S. Patent 2,420,330 by Shriver and Fremon was issued, showing a similar curve for this system.

TABLE III

VINYL CHLORIDE–ACRYLONITRILE COPOLYMERIZATIONS

Monomer mole % acrylonitrile	Time at polymerization temp., hours	Wt. % conversion	Chlorine analyses I	Chlorine analyses II	Copolymer mole % acrylonitrile
Solution polymerization, acetone, 50°					
4.0	20[a]	5.0	41.89	42.07	29.4
14.5	14[b]	<4.0	28.14	28.14	54.5
27.8	14[b]	<4.0	20.13	20.21	68.0
36.3	14[b]	<4.0	17.29	17.45	73.6
57.5	20[a]	6.0	9.86	9.87	85.0
68.5	14[a]	0.5	7.57	7.57	88.4
88.5	14[a]	4.0	2.16	2.47	96.5

[a] 0.5 wt. % Bz_2O_2. [b] 0.7 wt. % Bz_2O_2.

the experimental points was obtained. It is difficult, by this method, to define the limits of accuracy of the values since the curve fit is a matter of opinion. For example, relatively small changes in the r_1, r_2 values for the systems vinyl chloride–methyl acrylate and vinyl chloride–acrylonitrile result in curves which do not pass through the experimental points at all. The parameters reported for these systems, therefore, are probably accurate to within at least 10%. On the other hand, the monomer reactivity ratios for the system styrene–vinyl chloride must be considered to be less accurate. Relatively large changes in the r_1, r_2 values of this type of curve (large r_1—small r_2 values) do not result in a marked alteration of the curve shape. Moreover, the curve fit technique for a system of this type gives undue emphasis to certain experimental points, particularly in the region where the curve "breaks." Consequently, small analytical errors for such points produce considerable changes in the r_1 and r_2 values obtained by curve-fitting.

The Alfrey and Goldfinger equations[3] for predicting the initial polymer composition from a monomeric mixture of three components are of the form

$$\frac{d[M_1]}{d[M_2]} = \frac{\frac{[M_1][M_2]}{r_{21}r_{32}} + \frac{[M_1]}{r_{31}}\left(\frac{[M_1]}{r_{21}} + \frac{[M_3]}{r_{23}}\right)}{\frac{[M_1][M_2]}{r_{12}r_{31}} + \frac{[M_2]}{r_{32}}\left(\frac{[M_3]}{r_{12}} + \frac{[M_3]}{r_{13}}\right)} \cdot \frac{[M_1] + \frac{[M_2]}{r_{12}} + \frac{[M_3]}{r_{13}}}{[M_2] + \frac{[M_1]}{r_{21}} + \frac{[M_3]}{r_{23}}}$$

$$\frac{d[M_1]}{d[M_3]} = \frac{\frac{[M_1][M_2]}{r_{21}r_{32}} + \frac{[M_1]}{r_{31}}\left(\frac{[M_1]}{r_{21}} + \frac{[M_3]}{r_{23}}\right)}{\frac{[M_1][M_3]}{r_{13}r_{21}} + \frac{[M_3]}{r_{23}}\left(\frac{[M_2]}{r_{12}} + \frac{[M_3]}{r_{13}}\right)} \cdot \frac{[M_1] + \frac{[M_2]}{r_{12}} + \frac{[M_3]}{r_{13}}}{[M] + \frac{[M_1]}{r_{31}} + \frac{[M_2]}{r_{32}}}$$

where $[M_1]$, $[M_2]$ and $[M_3]$ represent monomer concentrations of the three components, $d[M_1]$, $d[M_2]$ and $d[M_3]$ represent the amounts of combined comonomers, respectively, in the polymer molecules first formed, and r_{12}, r_{21}, r_{13}, r_{31}, r_{23} and r_{32} are the monomer reactivity ratio parameters for the three two component systems involved, as defined recently by Alfrey, Mayo and Wall.[12]

Experimental data for the system styrene (M_1)–methyl acrylate (M_2)–vinyl chloride (M_3) are given in Table IV. Utilizing data previously published,[5,7,10] together with the monomer reactivity ratios reported above, the following values were used to predict polymer composition for this system: $r_{12} = 0.75$, $r_{13} = 35$, $r_{21} = 0.20$, $r_{23} = 9.0$, $r_{31} = 0.067$ and $r_{32} = 0.083$. A comparison of the predicted composition with the composition actually obtained is given

	Initial monomer composition	Weight per cent. Predicted polymer composition	Polymer composition by analysis
Styrene	20	45.2	47.6
Methyl acrylate	60	53.7	52.0
Vinyl chloride	20	1.1	1.3
Styrene	60	75.7	76.1
Methyl acrylate	20	23.6	22.8
Vinyl chloride	20	0.7	1.1

Similarly, the experimental data for the system styrene (M_1)–acrylonitrile (M_2)–vinyl chloride (M_3) are given in Table IV, and the following parameters were employed in calculating polymer composition: $r_{12} = 0.41$, $r_{13} = 35$, $r_{21} = 0.04$, $r_{23} = 3.7$, $r_{31} = 0.067$ and $r_{32} = 0.074$. The following results were obtained for this system

	Initial monomer composition	Weight per cent. Predicted polymer composition	Polymer composition by analysis
Styrene	32.0	66.1	67.1
Acrylonitrile	48.8	33.4	32.5
Vinyl chloride	19.2	0.5	0.4
Styrene	30.2	71.0	70.4
Acrylonitrile	15.4	26.8	26.2
Vinyl chloride	54.4	2.2	3.4

Agreement between the predicted and actual compositions shown above provides support for the monomer reactivity ratios reported and tends to confirm the validity of predictions based on the tripolymer equations.

Experimental

Vinyl Chloride Monomer.—Redistilled Dow Chemical Co. material was used for all experiments.

Styrene Monomer.—Redistilled Dow Chemical Co. N-100 material was used for all experiments.

Acrylonitrile.—Redistilled American Cyanamid Co. material was used.

Methyl Acrylate.—Redistilled Rohm & Haas material was used.

Benzoyl Peroxide.—The product of the Lucidol Corp. was used.

Acetone.—Redistilled material from the Commercial Solvents Corp. was employed.

Vinyl Chloride–Styrene Copolymerizations

Solution.—A solution comprising 50 g. of acetone and 50 g. of total monomer was taken for all experiments. Appropriate amounts (Table I) of styrene, acetone and benzoyl peroxide weighed into a 200-ml. pressure bottle were gradually cooled in a Dry Ice-bath to −50°. A suitable volume of liquid vinyl chloride also cooled to Dry Ice temperatures was added. A metal cap with tinfoil liner was tightly screwed on the bottle which was allowed to warm to room temperature and weighed.

TABLE IV

TRIPOLYMER MASS POLYMERIZATIONS

Monomer wt. %		Temp., °C.	Time, hours	Wt. % conversion	Analyses	Polymer wt. %
Vinyl chloride	20				C, 72.40, 72.79	1.5
Styrene	20	50	5.3[a]	3.0	H, 7.66, 7.84	46.5
Methyl acrylate	60				Cl, 0.74, 0.74	52.0
Vinyl chloride	20				C, 83.28, 83.41	1.2
Styrene	60	50	4[a]	2.3	H, 7.66, 7.72	76.0
Methyl acrylate	20				Cl, 0.55, 0.65	22.8
Vinyl chloride	19.2	50	5[b]	2.7	N, 8.57, 8.61	0.35
Styrene	32.0	25	48		Cl, 0.24, 0.25	67.1
Acrylonitrile	48.8					32.5
Vinyl chloride	54.4	50	11[b]	5.0	N, 6.93, 6.94	3.4
Styrene	30.2	25	48		Cl, 1.87, 1.97	70.4
Acrylonitrile	15.4					26.2

[a] 0.05 wt. per cent. Bz_2O_2. [b] 0.2 wt. per cent. Bz_2O_2.

Vinyl chloride added was determined by difference. The bottle was rotated end-over-end in a constant temperature water-bath regulated to 48 ± 0.05°. When a slight increase in viscosity was observed the bottle was removed, cooled to room temperature and weighed. Weight losses during the polymerization averaged 0.1–0.2 g. A mean value was taken for vinyl chloride concentrations during the polymerization, assuming total loss to be vinyl chloride monomer. The metal screw cap was punctured with an ice pick and utilizing the pick as a "needle valve," unpolymerized vinyl chloride was allowed to escape slowly without entrainment or frothing losses of the solution. The screw cap was then removed, the solution poured into 500 ml. of stirred 2B ethanol and the bottle and cap rinsed twice with 10-ml. portions of acetone. The polymer which precipitated as a fine powder was filtered on a Buchner funnel and washed with three fresh 500-ml. portions of denatured alcohol vigorously agitated in a Waring blender. The sample was finally filtered, dried in a circulating air oven at 50° for twenty-four hours and weighed. The product was analyzed in duplicate for chlorine by the Parr bomb method. Polymerization times, conversions and analytical data are summarized in Table I.

Emulsion.—A master emulsifier solution buffered to *p*H 8.0, comprising 500 g. of a 0.1 molar boric acid solution, 39.7 g. of 0.1 *N* sodium hydroxide, 10 g. of Santomerse D (the product of Monsanto Chemical Co.) and 8.3 g. of a 30% hydrogen peroxide solution was prepared. All emulsion polymerizations employed 100 ml. of this solution and 50 g. of total monomers. Appropriate amounts (Table I) of styrene and emulsifier solution weighed into 200-ml. pressure bottles were cooled in a Dry Ice-bath. A suitable volume of liquid vinyl chloride also cooled to Dry Ice temperatures was added. A metal cap with tin-foil liner was tightly screwed on the bottle which was allowed to warm to room temperature and weighed. Vinyl chloride added was determined by difference. The bottle was rotated end over end in a constant temperature water-bath regulated to 50 ± 0.05°. Polymerization times are shown in Table I. No convenient method was found for determining when low conversions had been attained, consequently many experiments were carried out to obtain the few results reported. On cooling to room temperature, the bottle was weighed. Weight losses during polymerization were 0–0.2 g. and, as explained above, a mean value was used for vinyl chloride monomer concentrations. The ice pick technique was used for venting vinyl chloride monomer, particular care being necessary in this case because of frothing. The screw cap was then removed and the emulsion poured into 500 ml. of 2B ethanol vigorously agitated in a Waring blender and the bottle and cap rinsed twice with 10-ml. portions of distilled water. The resulting suspension was heated to 60° and allowed to stand overnight to complete the coagulation. The product was filtered on a Buchner funnel, washed successively with three 1000-ml. portions of fresh alcohol, two 1000-ml. portions of distilled water, two 1000-ml. portions of alcohol, and then dried at 50° in a circulating air oven for twenty-four hours. Duplicate chlorine analyses by the Parr bomb method were obtained. Polymerization times, conversions and analytical data are summarized in Table I.

Vinyl Chloride–Methyl Acrylate Copolymerizations.—These copolymerizations were carried out in mass using 100-g. of total monomers. A polymerization technique identical with that described above for acetone solution polymerizations was employed. The water-bath temperature was regulated to 50 ± 0.05°. Vinyl chloride weight losses were 0–0.1 g. and a mean value was taken as before. After venting vinyl chloride monomer at room temperature, the products from the first four experiments (Table II) were precipitated by pouring the solution into 500 ml. of 2B ethanol vigorously agitated in a Waring blender. The resulting fine powder was filtered on a Buchner funnel, washed with three 1000-ml. portions of fresh alcohol and dried in a circulating air oven at 50° for forty-eight hours, then weighed. Products from the last four experiments were worked up in an identical way except that hexane was used instead of ethanol. In these cases a rubbery fibrous material was obtained instead of a fine powder. Since Parr bomb chlorine determinations gave erratic results for this copolymer series, chlorine analyses in duplicate were made by the Thompson–Oakdale method. Analytical data, conversions and polymerization times are summarized in Table II.

Vinyl Chloride–Acrylonitrile Copolymerizations.—This series was prepared in acetone solution using 50 g. of acetone and 50 g. of total monomers. The technique for charging the bottle and for polymerizing was identical to the method used for the vinyl chloride–styrene system in acetone solution. A water-bath temperature of 50 ± 0.05° was employed. Since the copolymers produced in this system were insoluble in the monomer–acetone solution, conversions were easily estimated from the amount of polymer formed. The bottles were cooled to room temperature, weighed and unpolymerized vinyl chloride released. Weight losses for this series were 0–0.4 g. and a mean value was taken as before. The fine suspension of copolymer was poured into 500 ml. of stirred 2B ethanol, filtered on a Buchner funnel and washed with three 1000-ml. portions of fresh alcohol. After drying at 60° for twenty-four hours in a circulating air oven, the product was weighed and analyzed in duplicate for chlorine by the Parr bomb method. Data for this copolymer series are summarized in Table III.

Tripolymer Experiments

Vinyl Chloride–Styrene–Methyl Acrylate.—These samples were prepared by mass polymerization in sealed

Pyrex tubes using 100 g. of total monomers. Appropriate amounts (Table IV) of styrene, methyl acrylate and benzoyl peroxide were weighed into a heavy-walled Pyrex tube 1″ in diameter, 2′ long and constricted 3″ below the open end. The solution was cooled in a Dry Ice-bath and a suitable volume of cooled vinyl chloride was added. The tube was sealed, allowed to warm to room temperature and the amount of vinyl chloride added determined by weight difference. The tube was immersed vertically in a water-bath regulated to 50 ± 0.05°. When a slight increase in viscosity was observed the tube was removed, cooled to room temperature and weighed. No vinyl chloride was lost in either experiment. The tube was cooled in a Dry Ice-bath, the constricted end opened and the whole allowed slowly to warm to room temperature. The solution was then poured into 500 ml. of 2B ethanol vigorously agitated in a Waring blender. The resulting fine powder was filtered on a Buchner, washed with three fresh 1000-ml. portions of alcohol. After drying the product for twenty-four hours at 50° in a circulating air oven, it was weighed, analyzed in duplicate for chlorine by the Thompson–Oakdale method and for carbon and hydrogen by the micro method. Polymerization times, conversions and analytical data are summarized in Table IV.

Vinyl Chloride–Styrene–Acrylonitrile.—These samples were prepared by mass polymerization in screw-cap 200-ml. pressure bottles using 60 g. of total monomers. The bottle was charged by adding appropriate weights (Table IV) of styrene, acrylonitrile and benzoyl peroxide to the bottle, cooling and adding vinyl chloride as before. The bottle was rotated end over end in a constant temperature water-bath first at 50°, then at 25° for the times shown in Table IV. Weight losses were 0–0.2 g. for the experiments. After venting vinyl chloride, the slightly viscous solution was poured into 500 ml. of stirred 2B ethanol and the bottle and cap rinsed with two 10-ml. portions of benzene. The resulting fine powder was filtered on a Buchner funnel, washed with three 1000-ml. portions of fresh ethanol and dried in a circulating air oven at 60° for forty-eight hours. The sample was weighed, analyzed in duplicate for chlorine by the Parr bomb method and for nitrogen by the Kjeldahl method. Data for these experiments are summarized in Table IV.

Summary

Monomer–polymer composition curves for the systems vinyl chloride–styrene, vinyl chloride–methyl acrylate and vinyl chloride–acrylonitrile have been determined. Coincidence of the solution and emulsion curves for the system styrene–vinyl chloride provides additional evidence for the oil phase mechanism of emulsion polymerization. Numerical values for monomer reactivity ratios for these systems are reported. Using these data an experimental investigation of the validity of the tripolymer equation was made. Good agreement was obtained between calculated compositions and compositions actually obtained.

DAYTON, OHIO RECEIVED JUNE 9, 1947

[CONTRIBUTION FROM SMITH, KLINE AND FRENCH LABORATORIES]

Analgesics. II. A New Synthesis of Aminophthalidylalkanes

BY GLENN E. ULLYOT, HERBERT W. TAYLOR, JR., AND NORMAN DAWSON

Recently we reported[1] the synthesis of a series of aminophthalidylalkanes, one of which, 1-amino-1-phthalidylpropane hydrochloride, showed considerable activity as an analgesic agent. The method of synthesis resulted chiefly in the lower melting racemic form, isomer B, but both racemic forms (isomers A and B) were isolated by careful fractional crystallization. Pharmacological tests indicated a difference in the toxicity and analgesic activity of these isomers, isomer A being more active and more toxic. For this reason, a need arose for a more convenient method of preparing sufficient amounts of isomer A for further pharmacological and clinical studies. This was accomplished according to Scheme I; only isomer A (VIII) was obtained.

In the synthesis previously reported, the asymmetry of the carbon atom next to the benzene ring was established first. The presence of this asymmetric center undoubtedly operated during the formation of the second asymmetric carbon center, so that there resulted unequal amounts of the two racemic forms of the nitro compound and, consequently, of the amine hydrochloride. In the synthesis reported here, our results may be accounted for by the reversal of the order of establishment of the asymmetric centers.

On attempting to proceed directly from *o*-carboxybutyrophenone without recourse to ester formation, it was found that ethyl nitrite failed to react with an ethereal solution of the ketone in the presence of anhydrous hydrogen chloride. This may have been because the keto acid existed chiefly as a lactol; in any event, the ester V was readily converted to VI.

Catalytic reduction of α-isonitrosoalkylphenyl ketones in the presence of three equivalents of anhydrous hydrogen chloride in absolute alcohol[2] has been shown to proceed first at the isonitroso group and then at the carbonyl group. Catalytic reduction of VI was readily effected; the course of the hydrogen uptake is shown in Fig. 1.

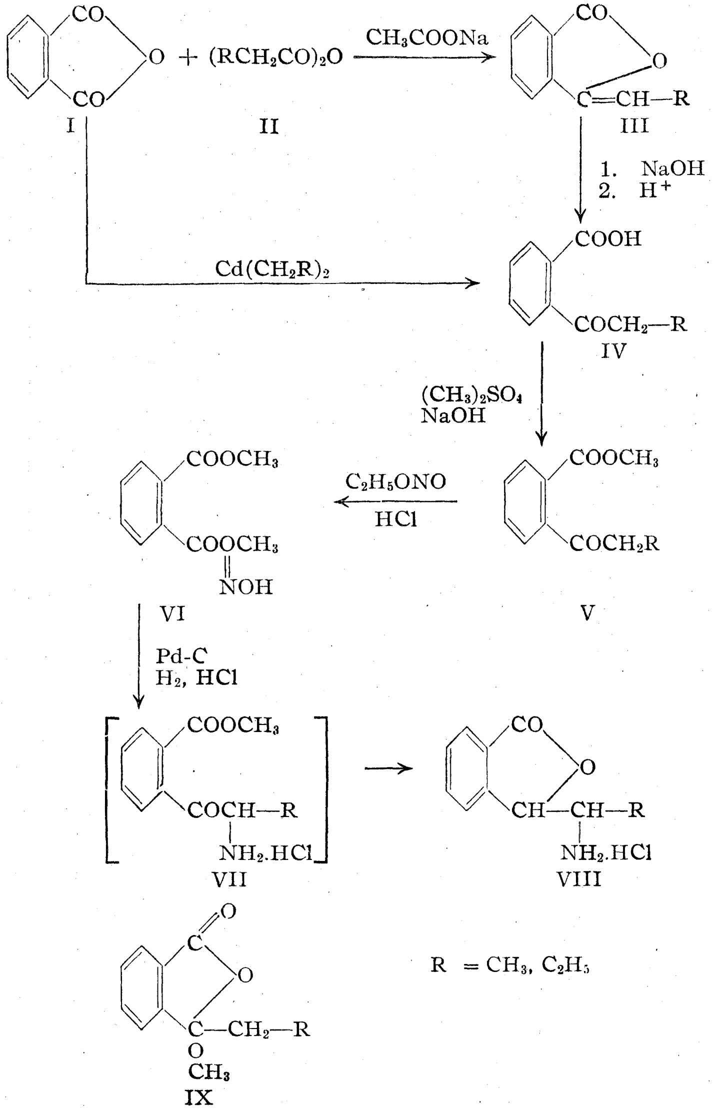
Unless the crude V was thoroughly washed with bicarbonate, considerable decomposition occurred during distillation and resulted in a material contaminated with propylidenephthalide (III). However, even after taking into consideration the amount of propylidenephthalide present in various batches of keto ester, treatment of this material with ethyl nitrite did not result in complete conversion into VI except in the case of ester no. 2

---

[1] Ullyot, Stehle, Zirkle, Shriner and Wolf, *J. Org. Chem.*, **10**, 429 (1945).

[2] Hartung, THIS JOURNAL, **53**, 2248 (1931).

SCHEME I



(see Table I). This may have been due to the presence of pseudo-ester (IX). Preparation of ester under conditions which might have been expected to lead to only IX[3] resulted in a product which gave a 55% yield of VI (Table I, no. 7). Absorption spectra data (Fig. 2) showed that the ester contained no propylidenephthalide and, therefore, it was at first thought to be a mixture of V and IX. However, the absorption curve of this ester (Fig. 2, curve f) was inappreciably different from that of "pure" V (Fig. 2, curve d), as was true of Compound V (Fig. 2, curve e) which was prepared from IV and diazomethane, a condition most likely to give only V. The significance of absorption spectra data and the isonitroso reaction with respect to normal and pseudo esters needs further clarification.

Our inference as to the presence of pseudo ester and its effect on the isonitroso reaction is based on the fact that when ester no. 2 was used in the isonitroso reaction, the reaction was complete and there were no mechanical losses, and on the fact that ester no. 7, which contained no propylidenephthalide, gave only a 55% yield of the isonitroso derivative.

The synthesis of 1-amino-1-phthalidylethane, isomer A (VIII, R = CH_3), also was accomplished according to Scheme I, thus indicating the general applicability of the procedure.

Experimental[4]

o-Carboxybutyrophenone (IV, R = $-C_2H_5$).—This compound was prepared in two ways. (A) The acid was prepared by the general procedure of De Benneville[5a] from dipropylcadmium and phthalic anhydride in a yield of 70%, m. p. 89° (lit.[1] 87–89°). (B) 3-Propylidenephthalide was prepared[5b,c] and hydrolyzed to the keto acid. Sodium acetate (164 g., 2.0 moles), *n*-butyric anhydride (632 g., 4.0 moles) and phthalic anhydride (296 g., 2.0 moles) were heated at 180–190° for seven hours, excess reagents were removed by distillation *in vacuo*, and the mixture was diluted with water and made alkaline with ammonium hydroxide. The propylidenephthalide, after extraction by chloroform and distillation, was obtained in a 70% yield, b. p. 143–145° (5 mm.) (lit.,[5c] b. p. 169–170° (12 mm.), n^{20}_{D} 1.586). The propylidenephthalide was hydrolyzed by warming it to 70° for thirty minutes in 50% isopropanol containing one equivalent of sodium hydroxide. Acidification of the deep red solution gave the product as an orange solid. This was obtained in pure condition in a 75% yield by dissolving it in sodium bicarbonate, adding sufficient acid to liberate 2% of the dissolved material, and extracting the mixture with chloroform. Acidification then precipitated a product which no longer gave a red color upon dissolving it in alkali; m. p. 86–89°. Evaporation of the chloroform extracts left an oil which distilled over the range 125–160° (3 mm.), but chiefly over the range of 125–140° (3 mm.). This gave a bright red solution when dissolved in 10% alkali and a violet-red color when dissolved in sulfuric acid. It may have been impure 2-ethyl-1,3-indanedione,[6] but it failed to give a 2,4-dinitrophenylhydrazone and did not crystallize. The indanedione is reported to boil at 135–140° (7 mm.) and to melt at 53–55°.[6]

Methyl Butyrophenone-o-carboxylate (V, R = —C_2H_5).—o-Carboxybutyrophenone (640 g., 3.33 moles) was esterified in a solution composed of methanol (1200 cc.) and sodium hydroxide (160.2 g., 3.99 moles) in water (240 cc.) by the slow addition with stirring of dimethyl sulfate (506 g., 3.99 moles). The product was extracted by ether, after removal of half the alcohol by distillation and dilution with water, washed thoroughly with one molar sodium bicarbonate solution and with a saturated sodium chloride solution, and dried over sodium sulfate.

---

(3) Newman and Lord, THIS JOURNAL, **66**, 731 (1944); Auwers and Heinze, *Ber.*, **52**, 584 (1919).

(4) The analyses were carried out by Miss Lillian Sillano and Mrs. Gertrude Carney.

(5) (a) De Benneville, *J. Org. Chem.*, **6**, 462 (1941); (b) "Beilstein," **10**, 712; Simonis and Arand, *Ber.*, **42**, 3726 (1909); (c) Bromberg, *Ber.*, **29**, 1437 (1896); "Beilstein," **17**, 342.

(6) (a) Wojack, *Ber.*, **71**, 1102 (1938); (b) Koelsch and Byers, THIS JOURNAL, **62**, 560 (1940).

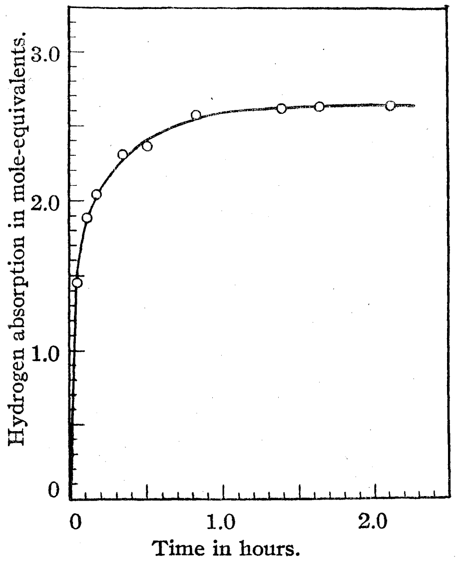


Fig. 1.—Catalytic hydrogenation of 0.158 mole of methyl α-isonitrosobutyrophenone-*o*-carboxylate.

After removal of the drying agent and the solvent, distillation of the residue gave a colorless product, b. p. 137–140° (4 mm.), n^{20}_{D} 1.5164–1.5190, in an 81–86% yield. The 2,4-dinitrophenylhydrazone prepared from this ester was obtained as orange crystals after recrystallization from alcohol, cap. m. p. 143–145°.

Anal. Calcd. for $C_{18}H_{18}O_6N_4$: C, 55.95; H, 4.70; N, 14.50. Found: C, 55.95, 55.97; H, 4.79, 4.80; N, 14.77, 14.59.

Certain preparations of this ester underwent decomposition during distillation. The variation in physical and chemical properties is shown by 1–5 in Table I. Analyses of these ester preparations for propylidenephthalide by absorption spectra data and by quantitative catalytic hydrogenation on a semi-micro scale gave the results shown in the last two columns.

TABLE I

Ester no.	n_D at	T, °C.	Maximum yield of VI in the isonitroso reaction in %	Propylidene phthalide content in mole % by Abspn. spectra[a]	Cat. hydg.
1	1.5233	20	81	..	...
2	1.5309	19.7	77	24	23
3	1.5490	20	42	..	48
4	1.5510	19.7	41	51	51
5	1.5190	20	84	3	2
Propylidene-phthalide	1.586	20	..	..	104
6	1.5161	20.5	87	3	nil
7[b]	1.5171	20.5	55	4	nil

[a] Based on percentage transmission at 310 millimicrons. We are indebted to Mr. Albert Sample and Mrs. Josephine Butler for the data. [b] The acid precursor was prepared by Method A.

Preparation no. 5 differed from no. 4 only in that it was washed before distillation until it was completely free of acid.

It thus appeared that these preparations were mixtures of V, IX and/or III. In an effort to prepare the ester V in a pure state, the acid IV was treated with diazomethane to give ester no. 6. An attempt to prepare pure pseudoester by the Fischer esterification method, using methyl alcohol and hydrogen chloride,[3] resulted in the product, no. 7, whose absorption spectra (Fig. 2, curve f) was unexpectedly found to be inappreciably different from that of ester no. 6 (Fig. 2, curve e).

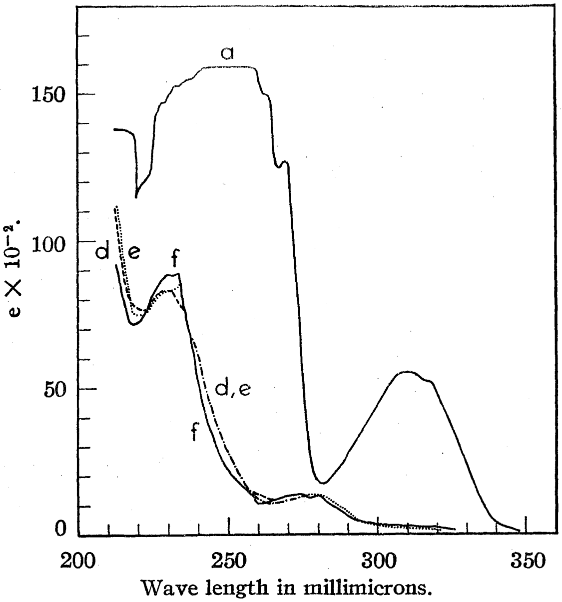


Fig. 2.—Absorption spectra: a, propylidenephthalide; d, ester no. 5, prepared from IV and methyl sulfate; e, ester No. 6 prepared from IV and diazomethane; f, ester No. 7, prepared from IV and methyl alcohol and hydrogen chloride.

Methyl α-Isonitrosobutyrophenone-*o*-carboxylate (VI, $R = -C_2H_5$).—The ester (V, $R = -C_2H_5$) (412 g., 2.0 moles) was dissolved in methylene chloride (1 liter) and treated at 5° successively with gaseous ethyl nitrite (3.0 moles in sixty minutes) and hydrogen chloride (3.0 moles in ninety minutes). One-half the solvent was removed by distillation, the residue was chilled, and the product was collected by filtration in 81–84% yield. Upon recrystallization from isopropanol (92% recovery), its corrected cap. m. p. was 150–151° with softening at 148°.

Anal. Calcd. for $C_{12}H_{13}O_4N$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.40, 61.75; H, 5.83, 5.62; N, 5.79, 5.98.

1-Amino-1-phthalidylpropane Hydrochloride, Isomer A (VIII, $R = -C_2H_5$).—The isonitroso compound (35 g., 0.158 m.) was dissolved in 95% alcohol (450 cc.). Twenty grams of previously used 10% palladinized charcoal catalyst and 42 cc. of concentrated hydrochloric acid were added. Hydrogenation was carried out in two hours at 30° at an initial hydrogen pressure of 500 lb./sq. in. The course of the hydrogen uptake was as shown in Fig. 1. The rapid absorption of two moles of hydrogen presumably indicates the formation of VII, half of which underwent slow reduction. After removal of the catalyst, the reaction mixture was taken to dryness *in vacuo*. The residue was collected and washed with acetone. The product, 1-amino-1-phthalidylpropane hydrochloride, isomer A, weighed 18.7 g., 55% yield, cap. m. p. 265–268° dec. (lit.[1] 268.5–270°). A sample was recrystallized from alcohol.

Anal. Calcd. for $C_{11}H_{14}O_2NCl$: Cl, 15.57. Found: Cl, 15.56, 15.56.

So far, the water-insoluble by-product of this reduction has not been identified.

Solvents other than 95% alcohol were tried, but all these—glacial acetic acid, or a mixture of dioxane and water to which three equivalents of concentrated hydrochloric acid per mole of compound reduced had been added, or absolute alcohol containing three equivalents of anhydrous hydrogen chloride as reduction media—gave considerably lower yields of amine salt. The yield was much lower when the amount of isonitroso compound reduced per given volume of solvent was greater than 35 g./450 cc., but a decrease in the amount reduced per given volume of solvent failed to increase the yield.

Methyl Propiophenone-*o*-carboxylate (V, R = CH_3).—*o*-Carboxypropiophenone, which was prepared by the methods used to prepare *o*-carboxybutyrophenone, was esterified in 87% yield; b. p. 137 (5 mm.) to 132° (4 mm.), $n^{20}\text{D}$ 1.5260–1.5290 (lit.,[7] b. p. 157–158° (19 mm.), $n^{16.4}\text{D}$ 1.5240).

Methyl α-Isonitrosopropiophenone-*o*-carboxylate (VI, R = CH_3).—This compound was recrystallized from methanol, m. p. 166–169° (Fisher block).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.84, 59.97; H, 4.93, 4.65; N, 6.33, 6.29.

1-Amino-1-phthalidylethane Hydrochloride, Isomer A (VIII, R = CH_3).—This compound was obtained in 64.9–74.5% yield and after recrystallization melted in the range 286–295° (lit.,[1] 292–296° dec.).

1-*p*-Nitrobenzoylamino-1-phthalidylethane (A) melted 188–189.5° after crystallization from alcohol (lit.[1] 188–189°).

Anal. Calcd. for $C_{17}H_{14}O_5N_2$: C, 62.57; H, 4.29; N, 8.58. Found: C, 62.47, 62.58; H, 4.29, 4.35; N, 8.54, 8.59.

Summary

1. A new synthesis of 1-amino-1-phthalidylalkanes has been reported.
2. This synthesis resulted in only one of the possible racemic forms of 1-amino-1-phthalidylethane and -propane.
3. In the preparation of the intermediate, methyl butyrophenone-*o*-carboxylate, the product underwent partial decomposition to propylidenephthalide unless carefully freed of acid before distillation.
4. Observations have been reported on the relationship between normal and pseudo-esters of butyrophenone-*o*-carboxylic acid in regard to their ultraviolet absorption spectra and their ability to undergo the isonitroso reaction.

---

[7] Beilstein X-S, p. 334.

RECEIVED MAY 16, 1947

[CONTRIBUTION NO. 109 FROM ENZYME RESEARCH LABORATORY, BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY, AGRICULTURAL RESEARCH ADMINISTRATION, USDA]

The Bitter Principles of Citrus Fruit. I. Isolation of Nomilin, a New Bitter Principle from the Seeds of Oranges and Lemons

BY OLIVER H. EMERSON

Limonin is a well recognized bitter principle in citrus plants that has been regarded as responsible for the bitter taste which sometimes appears in the juice of Navel oranges on standing or heating. Evidence which favors that view is presented here and points to a reaction whereby limonin may be formed from a precursor in orange juice. In addition a new bitter principle, "nomilin," has been isolated from the seeds of oranges and lemons. It appears closely related to limonin, and because of the similarity in properties it may also contribute to the bitter taste.

Limonin was first isolated by Bernay in 1841 and has since been obtained from a series of citrus and related *Rutaceae*,[1,2,3] having been found in the fleshy part of the fruit, the seeds, the bark and the roots. The chemical nature of the bitter principle has recently been discussed by Geissman and Tulagin.[4] It is well established that the substance is a dilactone of the formula $C_{26}H_{30}O_8$. It has no reactive hydroxyl groups, giving no methane with cold methylmagnesium iodide,[5] although Koller and Czerny reported it to give variable amounts when heated, which suggested to them the presence of a carbonyl group capable of enolization, although no carbonyl derivatives have been reported. No methoxyl or methylene dioxy groups have been detected, and the remaining three oxygen atoms are presumably present as cyclic ethers. Drastic treatment with potassium hydroxide yields 0.88 mole of acetone.[4]

The question of a carbonyl group, as postulated by Koller and Czerny, is obviously of importance to the problem of limonin. The absorption spectrum of limonin as measured by Geissman and Tulagin and in this Laboratory (Fig. 1) shows a weak band at about 290 mμ, log $E = 1.4$, which is suggestive of an isolated carbonyl group, though such a weak band could easily result from traces of an impurity. However, we have succeeded in preparing a beautifully crystalline oxime by treating limonin with hydroxylamine in the presence of pyridine, which will often permit the oximation of carbonyl groups that fail to react with hydroxylamine acetate.[6]

Isolimonin.—Besides limonin, Koller and Czerny[5] reported the isolation from orange seeds of an isomer of limonin melting at 258–259° which they called isolimonin. It crystallized from alcohol in thick "warty" crystals in contrast to the thin six-sided plates of limonin and differed from

---

[1] Schechter and Haller, THIS JOURNAL, **62**, 1307 (1940). This paper summarizes excellently the earlier literature.

[2] Mookerjee, *J. Indian Chem. Soc.*, **17**, 593 (1940).

[3] Seshadri and Veeraragavia, *Proc. Indian Acad. Sci.*, **11A**, 505 (1940).

[4] Geissman and Tulagin, *J. Org. Chem.*, **11**, 760 (1946).

[5] Koller and Czerny, *Monatsh.*, **67**, 248 (1936).

[6] Bachmann and Boatner, THIS JOURNAL, **58**, 2097 (1936).

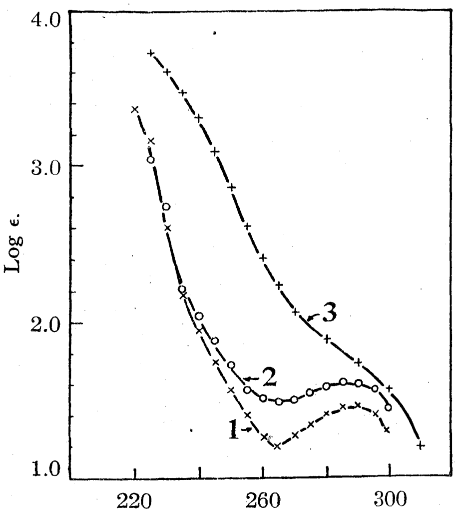


Fig. 1.—Absorption spectra in alcohol: (1) limonin; (2) nomilin; (3) nomilic acid.

that substance in being more soluble in alcohol, less soluble in benzene, in readily forming a diacetyl derivative and in giving two moles of methane with methylmagnesium iodide.

A bitter principle from very immature Navel oranges was investigated by Higby[7] who isolated it as shiny plates melting at 262–264°, $[\alpha]^{22}\text{D}$ $-111.5°$. He thought the substance to be isolimonin in view of the similarity in rotation and melting point. From the seeds of Valencia oranges he obtained limonin melting at 292°. Later he reported that the usual bitter constituent, at least in more mature fruit, is limonin,[8] a view in which Geissman and Tulagin concur. While other references to isolimonin occur in the literature,[2,3] it must be admitted that its characterization leaves much to be desired.

The isolation of the bitter principle from Navel orange juice as described by Higby[7] was repeated except that the final purification was done by solution in methylene chloride followed by the addition of alcohol, as described by Feist and Overberg.[9] Limonin was obtained agreeing in melting point[1,4,9] and optical properties[10] with the findings of other workers[1] and with preparations made in this Laboratory from the seeds of Valencia oranges and of lemons. From methylene choride–alcohol limonin separates in part as the characteristic unsolvated plates and in part as a loose solvate with methylene chloride crystallizing in needles, as described by Feist and Overberg for "citrolimonin" from lemon seeds.[11]

In an attempt to obtain isolimonin, ground and defatted Valencia orange seeds were extracted with acetone instead of the previously used alcohol[5] in the belief that the greater solubility of the bitter substances in the former solvent would make it more suitable. However, it was found after fairly exhaustive extraction that the seed meal was still intensely bitter. To water this extracted meal imparted a very bitter taste which disappeared on standing. The bitter substance was not extracted either by absolute or 95% ethanol but was extracted by 50% ethanol, or more conveniently by 1-butanol saturated with water. However, the chief bitter substance isolated was limonin. Thinking that this substance might be present as an unstable derivative soluble in water-containing organic solvents, we tried extraction under a variety of conditions in the hope of securing such a derivative but without success. It was noticed that the solvents which extracted limonin also removed considerable amounts of gummy material which may have interfered with the extraction of limonin by the dry solvents and permitted the formation of a transient, bitter colloidal solution in water. Only about one-third of the total limonin obtained was found in the acetone extract.

Nomilin.—From the mother liquors of limonin from both orange seeds and lemon seeds a second bitter principle was obtained. It was easily separated from limonin since it remained in solution in ethanol containing methylene chloride and also dissolved in hot 2-propanol, in which limonin is very sparingly soluble. It was further purified by recrystallization from methanol, from which it separated in beautiful needles melting at 279°, though unfortunately the melting point is somewhat dependent on the rate of heating.

The substance is notable for its tendency to form solvates with many solvents, which causes the appearance of crystals from different solvents to differ markedly. Several of the solvates required heating at 140° at 1 mm. for their decomposition.

In order to get reliable analytical data samples of the substance were recrystallized from 2-propanol, 1-butanol, ethyl acetate and methylene chloride–petroleum ether. Each sample was dried to constant weight at 140° at 1 mm. and analyzed. The agreement was satisfactory and in conjunction with the accurate Signer method[13,14] indicated the molecular formula to be $C_{28}H_{34}O_9$.

Since the substance is not an isomer of limonin though closely associated with it and presumably related to it chemically the name **nomilin** is proposed. Nomilin may be quite an important constituent of the total bitter material of orange seeds. Thus one batch of 17 kilos yielded 24 g. of limonin and 14 g. of nomilin.

It is conceivable that the isolimonin of Koller and Czerny was impure nomilin, but the Austrian workers reported their substance to give two moles

---

[7] Higby, This Journal, **60**, 3013 (1938).

[8] Higby, *California Citrograph*, **26**, 360 (1941).

[9] Feist and Overberg, *Ber.*, **69**, 1322 (1936).

[10] The optical properties of many of the crystalline preparations obtained were examined by Dr. Francis T. Jones, for whose kind cooperation I wish to express my sincerest thanks.

[11] The identity of "citrolimonin" with limonin, assumed by other workers,[1,7,12] is thus further substantiated.

[12] Koller and Czerny, *Monatsh.*, **70**, 26 (1937).

[13] Signer, *Ann.*, **478**, 246 (1930).

[14] Clark, *Ind. Eng. Chem., Anal. Ed.*, **13**, 820 (1941).

of methane with methylmagnesium iodide and to yield readily a diacetyl derivative, whereas nomilin has only one active hydrogen and is acetylated with difficulty if at all by refluxing for several hours with acetic anhydride and sodium acetate or with acetic anhydride and pyridine. In both cases the bulk of the nomilin was recovered unchanged, though some material was obtained whose high carbon content indicated the elimination of the hydroxyl rather than its acetylation.

The absorption spectrum of nomilin is shown in Fig. 1.[15] The similarity to that of limonin is striking. Like limonin, nomilin did not react with carbonyl reagents except under the powerful activating influence of pyridine. In contrast to the beautifully crystalline oxime of limonin, the oxime, semicarbazone and 4-phenylsemicarbazone of nomilin were amorphous products whose melting points, owing to decomposition, were indefinite.

Like limonin, nomilin is a dilactone and the lactone groups are readily opened by dilute alkali. In the case of nomilin the reaction was more complicated for acetic acid was split out, and on acidification there was obtained a lactone-acid for which the name *nomilic acid* is proposed. The analysis and titration of the free carboxyl group indicated the formula $C_{26}H_{32}O_8$. The spectrum is shown in Fig. 1. The intensification of the absorption and the shift toward the visible suggests a greater degree of conjugation in nomilic acid than exists in limonin or nomilin.

On fusion with potassium hydroxide at 300–340° nomilin, in contrast to limonin, did not give significant amounts of acetone.

Other Bitter Principles.—A third bitter substance (substance X) was obtained from the crude alcoholic mother liquors of orange seeds. It differed from limonin and nomilin by its very sparing solubility in methylene chloride and acetone. The solubility of the substance was greatest in ethyl and methyl alcohols among the common solvents tried, but even in these the product was only sparingly soluble and had a low temperature coefficient of solubility. The best preparation separated from methanol on concentration or on dilution with water in the form of delicate hair-like needles melting with profound decomposition at 315°. The Molisch test was negative. The analysis agreed with the formula $(C_9H_{12}O_4)_n$, but in view of the strong retention of methanol by nomilin encountered later this may be in error. The spectrum was similar to that of limonin but more generalized, with no suggestion of any definite bands. Purification was difficult because of the presence of amorphous material of similar solubility. Since it was a very minor constituent of orange seeds it was not further investigated. It was not observed in lemon seeds.

Development of the Bitter Substances in Navel Orange Juice.—Navel oranges are an important crop in California and the tendency of the juice to turn bitter is of serious concern. The problem was studied by Higby,[7] who concluded that in the intact orange limonin exists in the albedo and pulp in the form of a water-soluble, non-bitter precursor which might be the salt of the diacid derived by opening both lactone rings, or a glycosidic derivative of it.

The formation of the bitter substance was observed by extracting Navel juice with benzene as soon as possible after the juice was expressed, then again after four hours and again after standing overnight. The juice after the removal of benzene was not perceptibly bitter and the residues from the first and last extractions were only slightly bitter, the bulk of the bitter material being found in the second extract. Since limonin was the only bitter substance isolated from the benzene extracts it must be chiefly responsible for the bitter taste.[16] Also, whatever the precursor, the rate of conversion to limonin was such that in orange juice at *p*H 3.6 comparatively little was formed in the twenty minutes required for the first extraction, but the conversion was essentially complete in four hours. Potassium limonate equivalent to the amount isolated from bitter Navel juice was added to Valencia juice which does not normally turn bitter, also at *p*H 3.6, and the development of bitterness observed appeared to parallel that in Navel juice both in degree and rate.

Higby's[7] suggestion that the precursor of limonin in Navel orange juice is the diacid or a derivative of it such as the glucoside appears to be close to the truth, although conceivably the precursor might be one of the lactone acids since the related lactone acids, limonilic acid[4] and nomilic acid are not bitter. Accordingly, in view of the tendency of the lactone rings to reestablish themselves in acid solution, the precursor can be stable only in more nearly neutral tissues like the albedo, central bundle, and veins of the capillary membrane. The conversion of the precursor to limonin is a process catalyzed by hydrogen ion and by heat and is inhibited by neutralizing the juice which, however, makes it unpalatable. There is at present no evidence that enzymes are involved in the process.

Experimental

Limonin from Navel Oranges.—Immature Navel oranges (140 lb.) collected near Los Angeles about the middle of October, 1945, yielded five gallons of juice, which was strained through cheese cloth and thoroughly extracted with benzene. The pulp strained from the juice was extracted separately and the extract from it was united with that from the juice. The peel, consisting of flavedo with some albedo, was extracted with petroleum ether to remove the oil, pressed as dry as possible in a hydraulic press and then extracted with benzene. The benzene extracts were concentrated to 200 ml. and the limonin precipitated by the addition of three volumes of petroleum ether. Most of the product came from the juice and pulp, and the small amount from the peel may

---

(15) I wish to express my sincerest thanks to Mr. G. F. Bailey and to Mrs. Martha Adkins for measuring the absorption spectra reported in this paper.

(16) The isolation was done before the discovery of nomilin, which could easily have escaped detection.

well have come from albedo accompanying it. The crude limonin was purified by solution in a minimum amount of methylene chloride followed by the addition of three volumes of methanol or ethanol. A few recrystallizations brought the melting point up to 298–300°.[17] In an evacuated tube the substance melted at 301.5–302.5°. Previously reported melting points for limonin are: 299–300°,[1] 302–305,[4] 304.[9] The yield was 1.58 g.

A second lot of oranges (140 lb.) collected from the same area early in November, 1945, yielded 2.5 g. of limonin.

From methylene chloride, on dilution with ethanol or methanol, limonin separated as needles accompanied by the more characteristic plates. On heating *in vacuo* the needles readily lost methylene chloride which was trapped and identified. Needles (144 mg.) picked out with forceps and heated at 80° *in vacuo* lost 18.3 mg. or 12.7% of their weight. The complex $C_{26}H_{30}O_8 \cdot CH_2Cl_2$ contained 15.4% of methylene chloride by calculation. Even on standing in air the needles lost methylene chloride and became opaque.

Anal. Material dried at 80° at 1 mm. for 1 hour. Calcd. for $C_{26}H_{30}O_8$: C, 66.35; H, 6.42. Found: C, 66.45; H, 6.49.[18]

Rotation.—Material dried as above (227.9 mg.) made up to 25 ml. in acetone in a 2-dm. tube at 22° gave a rotation of −6.35 units in a saccharimeter; $[\alpha]^{22}_D$ −121°. Reported $[\alpha]^{20.5}_D$ −129°,[1] $[\alpha]^{25}_D$ −123°.[4]

Isolation of Limonin from Valencia Orange Seeds.—Orange seeds (22 lb.) were ground and defatted with petroleum ether and extracted with acetone. The acetone solution was concentrated to a thin sirup, diluted with ethanol and concentrated again, yielding most of the limonin. A little more was secured by the addition of water. Purification was done by crystallization from methylene chloride and alcohol as described above. The yield was 13 g.

The acetone-treated meal was then well extracted with 1-butanol saturated with water, and the extracts concentrated under reduced pressure. Some gummy water-soluble material separated first and was discarded. The bitter substances present separated in impure form on further concentration. These were filtered off. The butanol was finally concentrated to a sirup, diluted with ethanol and then with a little water, throwing out a last crop of bitter material.

The combined portions of crude bitter material were treated with acetone and a residue of some non-bitter material was removed. The acetone solution was concentrated to small volume and then diluted with ethanol. This precipitated the bitter substances still in an impure state. Purification was made by dissolving this material in methylene chloride and precipitating limonin by the addition of 3 volumes of ethanol.[19] This step was repeated until the limonin had a melting point of 298–300°. The total yield of pure liminon (after recrystallization) obtained from 22 lb. of orange seeds was 40 g., though a second batch of 37 lb., extracted directly with wet butanol, yielded only 24 g.

Isolation of Nomilin.—On concentrating the methylene chloride–alcohol mother liquors of limonin obtained on recrystallizing the bitter fractions described above there separated a mixture of a new substance and limonin. Nomilin was extracted from the mixture by boiling for a few minutes with a minimum amount of 2-propanol and filtering the hot solution. On cooling nomilin separated as stout crystals. Further purification was secured by recrystallization from methanol from which nomilin separated in slender needles. Nomilin is soluble to the extent of 1.5 to 2% in boiling methanol and in boiling 2-propanol, and somewhat more soluble in hot ethyl acetate. In other solvents its solubility is generally similar to that of limonin. The yield of nomilin from 37 lb. of orange seeds was 14 g.

On account of decomposition the melting point of nomilin is not very definite. With a block heated at the rate of 2° per minute it melted at 278–279° with evolution of gas when introduced at 273–275°. The use of a melting point tube sealed *in vacuo* did not sharpen the melting point as it did in the case of limonin.

For analysis samples were recrystallized from ethyl acetate, 2-propanol, 1-butanol and methylene chloride followed by the addition of petroleum ether. Each sample was dried to constant weight at 140° at 1 mm. The results are shown in Table I.

TABLE I

ANALYSES OF NOMILIN

Solvents used for crystallization	C	H	Molecular weight (Signer)
Butanol	65.45	6.90	
Butanol	65.46	6.75	
Isopropanol	65.57	6.81	
Isopropanol	65.26	6.77	
Methylene chloride	65.53	6.73	
Petroleum ether	65.35	6.63	
Ethyl acetate	65.30	6.74	511
Ethyl acetate			516
Average	65.42	6.67	513
Calculated for $C_{28}H_{34}O_9$	65.33	6.67	514.3

Molecular Weight.—This was done by the Signer method as described by Clark.[14] Owing to the difficulty of securing accurately calibrated Pyrex tubing for the volumetric part of the apparatus, ordinary 4.5–5.0 mm. tubing was used, and the lengths of the columns of solution were measured to an accuracy of about one-fourth mm. with a rule having a little foot to rest against the end of the tube. The corresponding volume was determined by means of mercury.

Nomilin (33.5 mg.) from ethyl acetate, dried as above in 1.075 ml. of acetone, was in equilibrium with 12.85 mg. of azobenzene in 1.158 ml., mol. wt., 511. Nomilin (33.2 mg.) in 0.855 ml. of acetone was in equilibrium with 13.81 mg. of azobenzene in 1.006 ml., mol. wt., 516.

Rotation.—Material recrystallized from 2-propanol and dried as above (298.9 mg.) made up to 25 ml. in acetone in a 2-dm. tube gave a rotation of −6.60 units in a saccharimeter at 23°

$$[\alpha]^{23}_D = -\frac{6.60 \times 0.346 \times 100}{2 \times 1.195} = -95.7°$$

Isolation of Limonin and Nomilin from Lemon Seeds.—Lemon seeds (15 lb.) were ground, defatted and extracted with 1-butanol as described for the orange seeds. Nomilin and limonin were separated and isolated as described above. The optical properties of the crystals and melting points coincided with the products from orange seeds.

Rotation of Nomilin from Lemon Seeds.—Material dried as described above, 273.8 mg., made up to 25 ml. in acetone in 2-dm. tube in a saccharimeter at 23°, rotation −6.05 units

$$[\alpha]^{23}_D = -\frac{6.05 \times 0.346 \times 100}{2 \times 1.095} = -95.7°$$

---

(17) All melting points were done in a copper block using short stemmed Anschütz thermometers and the substance was introduced a few degrees below the melting point.

(18) I wish to thank Dr. W. Gordon Rose for instruction and help in running microanalyses.

(19) The use of 2 volumes of 2-propanol instead of 3 volumes of ethanol was later found to be of advantage.

Reaction of Nomilin with Methylmagnesium Iodide.[20]—Nomilin (9.92 mg.) in pyridine gave 0.50 ml. of methane at 22°, 741 mm. Nomilin (11.59 mg.) in pyridine gave 0.57 ml. of methane at 22°, 741 mm. Calcd. for $C_{28}H_{34}O_9$: 1.05, 1.02 atoms of active H.

Action of Dilute Alkali on Nomilin.—Nomilin (237 mg.) was heated on the steam-bath with 40 ml. of 0.1 *N* NaOH with occasional swirling. After half an hour the solution was cooled, filtered from a small amount of undissolved material and acidified with 10 ml. of 0.5 *N* HCl. The crude nomilic acid which soon separated was purified by solution in a minimum amount of acetone followed by the addition of an equal volume of water, separating as beautiful needles, m. p. 205–206°; yield 190 mg. (88%). Further recrystallization brought the melting point up to 208–209° in an evacuated tube.

Anal.—Material dried to constant weight at 100°, 1 mm. Calcd. for $C_{26}H_{32}O_8$: C, 66.07; H, 6.82. Found: C, 66.00, 65.91; H, 6.95, 6.90.

For titration the substance was dissolved in 0.5 ml. of acetone followed by 0.1 ml. of 0.5 *N* sodium acetate and 5 ml. of water. Under these conditions the nomilic acid, displacing acetic acid, remained in solution during the titration. The final end-point was reasonably stable, the faint pink of phenolphthalein fading only after several minutes. A weight buret was used with solutions standardized to weight-normality.

Nomilic acid (10.30 mg.) neutralized 0.466 g. of 0.0485 *N* NaOH. Nomilic acid (10.05 mg.) neutralized 0.443 g. of 0.0485 *N* NaOH. Equivalent weight, 477, 468. Calcd. for $C_{26}H_{32}O_8$, 472.5.

Hydrolysis of Nomilic Acid.—Nomilic acid was warmed on the steam-bath with an excess of 0.0485 *N* NaOH and titrated back with 0.0497 *N* HCl using phenolphthalein.

Nomilic acid (6.03 mg.) was dissolved in 1.440 g. of NaOH solution and back-titrated with 0.0896 g. of HCl solution. Nomilic acid (5.48 mg.) was dissolved in 1.211 g. of NaOH solution, back-titrated with 0.691 g. of HCl solution. Equivalent weight calcd. for 1 COOH, 1 lactone, 236. Found: 238, 224.

Isolation of Acetic Acid.—The aqueous solution from which the nomilic acid had separated (50 ml.) was steam distilled, the volume being maintained approximately constant. The volatile acid neutralized 8.1 g. of 0.0485 *N* NaOH. The neutral solution was concentrated to 2 ml. and the salt converted to the *p*-phenylphenacyl ester. On recrystallization from dilute alcohol and then petroleum ether the ester melted at 110–111° and gave no depression with an authentic specimen of the *p*-phenylphenacyl ester of acetic acid of the same melting point. The optical properties of the crystals were examined by Dr. Francis T. Jones and found identical for the two preparations.

Potassium Hydroxide Fusion of Nomilin.—Nomilin (62 mg.) was dissolved in a solution of 1 g. of potassium hydroxide in 1 ml. of water and gradually heated to 340° in a bath of Wood's metal. The distillate was collected in a solution of 2,4-dinitrophenylhydrazine sulfate. Nothing resembling acetone dinitrophenylhydrazone was observed, which in blank test was isolated in good yields.

Limonin Oxime.—Limonin (100 mg.) and 100 mg. of hydroxylamine hydrochloride were dissolved in 2 ml. of pyridine and 2 ml. of absolute alcohol and refluxed for four hours. The solvent was removed under reduced pressure and the residue washed well with water and recrystallized from dilute alcohol. The product decomposed and melted in the neighborhood of 260–270°, depending on the rate of heating. The product recrystallized from dilute ethanol appeared to hold that solvent very retentively. For analysis it was recrystallized twice from methanol and once from butanol and dried at 100° at 1 mm.

Anal. Calcd. for $C_{26}H_{31}O_8N$: C, 64.30; H, 6.43; N, 2.89. Found: C, 64.22, 64.04; H, 6.41, 6.30; N, 3.06.

Reaction of Nomilin with Hydroxylamine.—This was conducted as in the preparation of limonin oxime. However, nomilin oxime would not crystallize from any solvent or solvent mixture tried. An attempt to chromatograph the substance in a column of calcium carbonate resulted in decomposition. A preparation precipitated from methanol by the addition of water and dried at 100° at 1 mm. gave low C values. Calcd. for $C_{28}H_{35}O_9N$: C, 63.48; H, 6.67; N, 2.65. Found: C, 63.12; H, 6.63; N, 3.00. A sample precipitated from benzene with petroleum ether gave high C values; found C, 64.10; H, 6.80.

The hydroxy-hydroxamic acid which might conceivably result from the reaction of hydroxylamine with a lactone ring should be $C_{28}H_{37}O_{10}N$, requiring C, 61.39; H, 6.82.

Isolation of Substance X.—This substance separated in little aggregates from the alcoholic mother liquors of limonin from orange seeds. The yield of crude material from 22 lb. of orange seeds amounted to about 500 mg., but purification was accompanied by much loss on account of the difficulty of separating it from amorphous material. Solution in methanol followed by concentration or by dilution with water appeared the most effective method tried. The best preparation consisted of hair-like needles melting with profound decomposition at 315°.

For analysis the substance was dried to constant weight at 56° at 1 mm. Calcd. for $(C_9H_{12}O_4)_n$: C, 58.66; H, 6.57. Found: C, 58.62, 58.71; H, 6.55, 6.49.

Acknowledgment.—I wish to express my sincere thanks to Dr. W. C. Platt for the gift of the orange seeds.

Summary

Limonin was the sole bitter principle isolated from pulp and juice of Navel oranges. This substance was also obtained from seeds of lemons and Valencia oranges.

A new bitter principle, $C_{28}H_{34}O_9$, for which the name "nomilin" is proposed, was isolated from orange seeds and lemon seeds. Nomilin has a hydroxyl group that reacts with methylmagnesium iodide, but not readily with acetic anhydride. Like limonin, nomilin is a dilactone, but on treatment with dilute alkali followed by acidification acetic acid is lost and lactone acid, nomilic acid, $C_{26}H_{32}O_8$, is obtained. In contrast to limonin, nomilin does not yield appreciable amounts of acetone on fusion with potassium hydroxide. Limonin and nomilin both react with hydroxylamine in the presence of pyridine, limonin oxime being a beautifully crystalline substance.

The non-bitter precursor of limonin in Navel orange juice behaves like the diacid obtained by opening both lactone rings, but it is possible that the precursor may be a lactone acid or a compound of the diacid or lactone acid such as a glycoside.

ALBANY, CALIFORNIA RECEIVED AUGUST 21, 1947

---

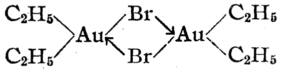
(20) I wish to express my sincerest thanks to Professor A. J. Haagen-Smit and Dr. G. Oppenheimer of California Institute of Technology for this determination.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Trimethylgold[1a]

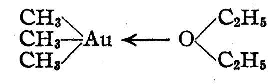
BY HENRY GILMAN AND LAUREN A. WOODS[1b]

The extensive and elegant studies by Gibson and co-workers[2] on organogold compounds have shown that all of the trivalent gold compounds which they investigated were four-covalent. For example, diethylgold bromide was assigned the following structure



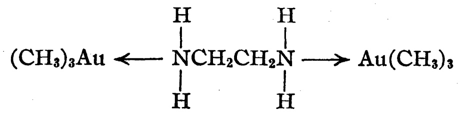
They expressed the view "of the impossibility of existence of compounds having the empirical R_3Au (R = alkyl)."[3] In support of this generalization were the numerous attempts[4] to prepare an R_3Au compound by the Grignard reagent, and by other indirect procedures, under various experimental conditions and with a series of radicals.

We have succeeded in preparing trimethylgold in ether solution by the reaction of methyllithium with gold tribromide or dimethylgold bromide at $-65°$. The free trimethylgold, however, was highly unstable and began to decompose at about -40 to $-35°$. The products of this thermal decomposition were gold, methane, and ethane. No molecular weight was determined for the trimethylgold, but it is possible that there is a co-



ordination in ether[5] and that Gibson's postulate of trivalent gold compounds being four-covalent is valid with our compound. Also it is understandable why the Grignard reagent did not give the R_3Au type, for the R_2AuX type was probably formed in the early stages and this would go more effectively to the R_3Au type with a more reactive organometallic compound like methyllithium and at low temperatures.

The trimethylgold can be stabilized by adding ethylenediamine, 2-aminopyridine, or benzylamine. The resulting coördination compounds may provisionally be represented by structures of which the following is typical



$$(CH_3)_3Au \longleftarrow \overset{\displaystyle H}{\underset{\displaystyle H}{N}}CH_2CH_2\overset{\displaystyle H}{\underset{\displaystyle H}{N}} \longrightarrow Au(CH_3)_3$$

By analogy with triethylgallium, it might be expected that the coördination compound of trimethylgold with amines would be more stable than the coördination compound with ether; for the simple triethylgallium reacts violently with water, the etherate $[(C_2H_5)_3Ga \cdot (C_2H_5)_2O]$ vigorously, and the ammine $[(C_2H_5)_3Ga \cdot NH_3]$ only very slowly.[6] Some other amines appeared not to form stable coördination compounds with trimethylgold. Also, an orienting experiment indicated that ethylenediamine did not stabilize the homologous triethylgold. This observation was not surprising, for other studies[7] have shown that the ethyl derivatives of copper, thallium and other metals appear to be significantly less stable than the corresponding methyl derivatives.

On the basis of some theoretical considerations it appeared that if the radical attached to gold were neopentyl instead of methyl the organogold compounds might be more stable. This found some qualitative support on the basis of the rates of deposition of gold from the organogold compounds; however, it is doubtful whether the stability could be increased sufficiently to make possible the isolation of the free trineopentylgold.

Cleavage Reactions.—Hydrogen chloride readily cleaved trimethylgold, and also its coordination compound with ethylenediamine, to form dimethylgold chloride and methane.

$$(CH_3)_3Au + HCl \longrightarrow (CH_3)_2AuCl + CH_4$$

In the presence of bromide ion, dimethylgold bromide was formed in preference to the chloride even though an excess of hydrochloric acid was present.

Inasmuch as trialkylgold compounds are readily prepared from alkyllithium compounds and gold tribromide, their cleavage by hydrogen chloride at $-65°$ offers a method of choice for the preparation of dialkylgold halides.

Although trimethylgold was not cleaved by phenol or trichloroacetic acid[8] at $-65°$, it was readily cleaved by thiophenol or thioglycolic acid to form dimethylgold thiophenate and dimethyl-

---

[1] (a) Paper LXIV in the series: "The Relative Reactivities of Organometallic Compounds." The preceding paper is with Tolman, THIS JOURNAL, **68**, 522 (1946). (b) Present address: Medical School, U. of Michigan, Ann Arbor, Michigan.

[2] Some recent references are Gibson and Weller, *J. Chem. Soc.*, 102 (1941), and Ewens and Gibson, *ibid.*, 109 (1941).

[3] Burawoy, Gibson and Holt, *ibid.*, 1024 (1935). See, also, Gibson, *Brit. Assoc. Advancement Sci. Rept.*, 35 (1938) [*C. A.*, **33**, 2838 (1939)]; Gibson and Colles, *J. Chem. Soc.*, 2409 (1931); and Gibson, "*Troisième Conseil de Chimie Solvay:* Rapports et Discussions," 422 (1928).

[4] Kharasch and Isbell, THIS JOURNAL, **53**, 2701 (1931).

[5] Gilman and Jones, *ibid.*, **62**, 1243 (1940). If the trimethylgold is associated there might be the possibility of structures formed as a consequence of an attachment of carbon atoms of another $(CH_3)_3$-Au group through and between the hydrogen atoms to an incompleted valence shell of gold. See, Pitzer and Gutowsky, *ibid.*, **68**, 2204 1946), on the structure of trimethylaluminum. Also, particularly, Rundle and Sturdivant, *ibid.*, **69**, 1561 (1947), for the possibilily of a structure related to tetramethylplatinum where a methyl group is bonded to more than one other atom.

[6] Dennis and Patnode, *ibid.*, **54**, 182 (1932). See, also, pp. 556–557 in Gilman, "Organic Chemistry," John Wiley and Sons, N. Y. (1943).

[7] By R. G. Jones and L. A. Woods.

[8] Trichloroacetic acid has been used by W. E. Catlin to measure the rates of cleavage of relatively unreactive organolead and organotin compounds.

gold carboxymethylmercaptide, respectively.

$$(CH_3)_3Au + HSR \longrightarrow (CH_3)_2AuSR + CH_4$$

The ability of RSH compounds to cleave triethylbismuth and tetraethyllead at a much more rapid rate than some phenols and carboxylic acids has been reported.[9]

Trimethylgold did not react with benzoyl chloride at temperatures up to −20°, whereas, under essentially the same conditions, methylcopper reacted with benzoyl chloride to form acetophenone.[10] This lower reactivity of trimethylgold toward some functional groups might have been predicted on the basis of the generalization that in any group or sub-group the higher the ionization potential of a metal the less reactive will be its organometallic compounds.[11a]

Disproportionation and Thermal Decomposition.—When an ether suspension of gold tribromide is added to an ether solution of trimethylgold at −75°, then stirred for two hours and allowed to come to room temperature, dimethylgold bromide is one of the products. This indicates that the following reaction occurred

$$2(CH_3)_3Au + AuBr_3 \rightleftarrows 3(CH_3)_2AuBr \qquad [I]$$

A reaction of this type is rather general with organometallic compounds and a related equilibrium has been reported with organoberyllium compounds[11b]

$$2RBeX \rightleftarrows R_2Be + BeX_2$$

In the disproportionation or redistribution reaction[11c] [I], one might expect to find some methylgold dibromide. This appears to be the case when dimethylgold bromide is refluxed in ether solution. Incidental to the thermal decomposition of methylgold compounds, it should be mentioned that the solid bis-(trimethylgold)-ethylenediamine explodes violently when heated in an open crucible.

Experimental

Trimethylgold.—A suspension of 8.74 g. (0.02 mole) of gold tribromide[12] in 60 cc. of ether was cooled to −65° and stirred while a solution of 0.06 mole of methyllithium in 50 cc. of ether was added over a period of three hours. The mixture gave a negative color test I.[13] The suspension was allowed to warm up slowly to room temperature. At about −40 to −35° a gold mirror began to form on the walls of the flask. The mixture was gently refluxed for two hours and the evolved gas was collected and analyzed. The gas consisted of 0.023 mole (76.8% yield) of ethane, and 0.011 mole (18.4% yield) of methane.

In all reactions involving organolithium compounds a nitrogen atmosphere and dry reagents were used.

bis-(Trimethylgold)-ethylenediamine.—A solution of 1.54 g. (0.005 mole) of dimethylgold bromide in 60 cc. of ether was cooled to −65°, and 0.0065 mole of methyllithium in 25 cc. of ether was added with stirring during fifteen minutes. The resulting clear solution was stirred for one-half hour, and then 1.5 cc. of 95% ethylenediamine was added. The milky solution was stirred for one hour at −65° before it was allowed to warm up to room temperature. No precipitate of metallic gold appeared. The ether solution was washed with 25-cc. portions of water and evaporated. The crystalline residue was dissolved in 10 cc. of ether, and then 15 cc. of petroleum ether (b. p. 28–38°) was added. On slow evaporation of the solution in a refrigerator, colorless crystals were formed and these were dried in a desiccator over phosphorus pentoxide in the dark. The yield was 1.2 g. (88%) of compound free of halogen, soluble in ether, insoluble in ethanol or petroleum ether (b. p., 28–38°), and very sensitive to light. The compound decomposed in a melting point capillary over the range 94–98°.

Anal. Calcd. for $C_4H_{13}NAu$: N, 5.14; Au, 72.40. Found: N, 5.21, 5.15 and 5.4; Au, 72.2 and 71.9.

When 0.2 g. of the complex was warmed in an open porcelain crucible preparatory to analysis, it exploded violently and pulverized the crucible. A drop of concentrated nitric acid added to the dry powder also detonates it. When moistened carefully and treated with dilute acids it precipitates gold. This indicates that the complex may be decomposed to trimethylgold and ethylenediamine and that the trimethylgold then breaks down promptly to gold and the hydrocarbons.

Trimethylgold α-Aminopyridine.—This compound was prepared from 0.005 mole of trimethylgold and 0.0075 mole of α-aminopyridine in ether at −65°. After washing the ether solution with water and then removing the ether by evaporation, the oil was dried over phosphorus pentoxide to give 1.1 g. (65.5%) of compound which gave a negative bromine test, and was partially soluble in petroleum ether (b. p. 60–68°) or benzene. From these solutions, metallic gold precipitated in a short time.

Anal. Calcd. for $C_8H_{15}N_2Au$: N, 8.32; Au, 58.62. Found: N, 8.24; Au, 58.46.

Trimethylgold Benzylamine.—This compound, prepared from 0.005 mole of trimethylgold and 0.0075 mole of benzylamine, was purified with some difficulty by crystallizing several times from petroleum ether (b. p. 28–38°) to give white needles melting at 51.5–53°. The yield was 1.0 g. (57.3%).

Anal. Calcd. for $C_{10}H_{18}NAu$: N, 4.01; Au, 56.40. Found: N, 4.30; Au, 56.75.

Attempts to stabilize trimethylgold with the following nitrogen compounds were unsuccessful: aniline, dimethylaniline, *p*-phenylenediamine, piperidine, ethylamine, dimethylamine and glyoxime.

Cleavage of bis-(Trimethylgold)-ethylenediamine with Hydrogen Chloride.—To a solution of 1.36 g. (0.005 mole) of bis-(trimethylgold)-ethylenediamine in 25 cc. of ether cooled to −65° was added, with stirring and over a twenty-minute period, 0.01 mole of hydrogen chloride in 85 cc. of ether. A white precipitate formed, and after the mixture had warmed up to room temperature it was stirred for one-half hour and then refluxed for five minutes. The evolved gas was collected and found to consist of 0.0049 mole (98% yield) of methane.

The ether solution was washed with 25 cc. of water, and the crude dimethylgold chloride remaining after evaporation of the solvent was purified by recrystallization from petroleum ether (b. p. 28–38°) to yield 1.2 g. (91.6%). The dimethylgold chloride, as well as a mixture with an authentic specimen, melted at 71–72°.

Cleavage of Trimethylgold and Triethylgold with Hydrogen Chloride.—A solution of 0.01 mole of trimethylgold, prepared from dimethylgold bromide and methyllithium in 80 cc. of ether at −65°, was treated with 0.01 mole of hydrogen chloride in 35 cc. of ether. The yield of methane was 0.0088 mole (88%); and the yield of dimethylgold bromide was 2.7 g. (88%) (melting point and also mixed m. p. with an authentic specimen was 67–68°).

A solution of trimethylgold, prepared from 8.74 g.

---

[9] Gilman and Nelson, THIS JOURNAL, **59**, 935 (1937).

[10] Gilman and Woods, *ibid.*, **65**, 435 (1943).

[11] (a) Gilman and Jones, *ibid.*, **62**, 2353 (1940); (b) Gilman and Schulze, *ibid.*, **49**, 2904 (1927); (c) Calingaert and Beatty in Chap. 24 of Gilman, "Organic Chemistry," John Wiley and Sons, New York, N. Y., 1943.

[12] Prepared in accordance with the directions of Gibson and Colles, *J. Chem. Soc.*, 2407 (1931).

[13] Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

(0.02 mole) of gold tribromide and 0.074 mole of methyllithium in ether at −65°, was cleaved with 0.04 mole of hydrogen chloride in 50 cc. of ether. The yields of dimethylgold bromide varied from 3.07 to 3.98 g. (50–65%).

By a similar procedure, diethylgold bromide (m. p. 56.5–58°) was prepared in a yield of 57.5%.

Dineopentylgold Bromide.—A suspension of 8.74 g. (0.02 mole) of gold tribromide in 60 cc. of ether was cooled to −65° and rapidly stirred while 0.06 mole of neopentylmagnesium chloride[14] in 125 cc. of ether was added over a period of seventy-five minutes. The mixture was stirred for an additional two hours after which it gave a negative color test I.[13] Then a solution of 0.023 mole of hydrogen chloride in 35 cc. of ether was added during twenty minutes, and after two hours the mixture was allowed to warm up to −15° and then treated with 15 cc. of water. The ether solution was separated and the solvent removed under reduced pressure to leave a crystalline residue. This was extracted with 100 cc. of petroleum ether (b. p. 28–38°), the solution was washed with a little water, dried over sodium sulfate, and allowed to evaporate spontaneously in a refrigerator. The yield of product melting at 121.5–123° was 1.0 g. (11.9%).

Anal. Calcd. for $C_{10}H_{22}BrAu$: Au, 47.02. Found: Au, 46.80.

Cleavage of Trimethylgold with Thioglycolic Acid and with Thiophenol.—A solution of 0.0093 mole of methyllithium in 25 cc. of ether was added to a stirred suspension of 1.54 g. (0.005 mole) of dimethylgold bromide in 60 cc. of ether at −65°. After one-half hour, 0.84 g. (0.0093 mole) of thioglycolic acid in 20 cc. of ether was added slowly. Then, after two hours, the mixture was allowed to warm up to room temperature, poured into 20 cc. of water, and the ether removed by evaporation. The aqueous suspension was treated with 10% hydrochloric acid until precipitation was complete. Crystallization from ethanol yielded 1.5 g. (94%) of crystalline dimethylgold carboxymethylmercaptide.

Anal. Calcd. for $C_4H_9O_2SAu$: Au, 61.94. Found: Au, 62.40.

The cleavage with thiophenol was carried out under the same conditions and concentrations as with thioglycolic acid. After extraction of the product with 2 cc. of 10% potassium hydroxide in 10.0 cc. of water, the residue was dissolved in 80 cc. of warm ether and then 15 cc. of methanol was added. From the resulting solution, by spontaneous evaporation, was obtained 1.49 g. (88.5%) of pale-yellow crystals of dimethylgold thiophenate melting at 132–133° and decomposing above 138°.

Anal. Calcd. for $C_8H_{11}SAu$: Au, 58.62. Found: Au, 58.52 and 58.62.

Phenol and trichloroacetic acid did not react with trimethylgold in ether at −65°.

Trimethylgold and Benzoyl Chloride.—A solution of 0.005 mole of trimethylgold in 75 cc. of ether at −65° was stirred while 0.7 g. (0.005 mole) of benzoyl chloride in 25 cc. of ether was added over a period of ten minutes. After two hours the solution was allowed to slowly warm up to room temperature. Gold was precipitated at about −30°, and gas was evolved. The mixture was refluxed briefly and all of the evolved gas was collected. The yield of ethane was 0.0039 mole (52%), and the yield of methane was 0.0011 mole (7.3%). The ether solution was treated with 40 cc. of 10% potassium hydroxide and 20 cc. of methanol, and the mixture was shaken until the odor of benzoyl chloride disappeared. The yield of benzoic acid was 98%, and there was no qualitative test for ketone. This experiment was repeated with the same results.

Reaction of Methyllithium with Methyl Iodide in Presence of a Small Amount of Gold Tribromide.—A solution of 7.1 g. (0.05 mole) of methyl iodide in 15 cc. of ether was added to a suspension of 1.09 g. (5 mole per cent.) of gold tribromide in 15 cc. of ether. To this mixture was added 0.05 mole of methyllithium in 40 cc. of ether over a period of twenty minutes. The suspension refluxed rapidly and gas was evolved. After standing for five hours, the apparatus was swept out with nitrogen. A bluish-purple suspension, probably colloidal gold, was visible throughout the reaction. The yield of ethane was 0.029 mole (58%), and the yield of methane was 0.013 mole (13%). In a duplicate experiment, the same observations were made, and the yield of ethane was 0.026 mole (52%), and the yield of methane was 0.021 mole (21%).

In a control experiment in which the methyl iodide was omitted, there was obtained 0.0025 mole of ethane and 0.0024 mole of methane.

Thermal Decomposition of Dimethylgold Bromide.—A solution of 1.54 g. (0.005 mole) of dimethylgold bromide in 25 cc. of ether was refluxed for forty-eight hours. The solution turned reddish brown after a short time, and metallic gold separated. The gas resulting from the decomposition amounted to 0.00308 mole of ethane (61.5% based on two methyl groups from dimethylgold bromide).

The red solution was filtered and the residue washed with ether until the washings were colorless, to give 0.612 g. (62%) of gold.

From the ether was recovered 0.144 g. (9.4%) of dimethylgold bromide, by extraction of the residue with petroleum ether (b. p., 28–38°); and by extraction of the residue with chloroform (in accordance with a procedure of Brain and Gibson)[15] there was obtained 0.21 g. (11.3%) of what appeared to be methylgold dibromide on the basis of solubilities.

The residue, remaining after the chloroform extraction, was apparently the water-soluble hydrated gold tribromide, as evidenced by physical properties.

Analytical Procedures.—Nitrogen analyses were carried out by a slow and careful combustion in a micro-Dumas apparatus. It was necessary to have the long burner as hot as practicable to ensure the complete combustion of the low molecular weight hydrocarbons resulting from the sudden decomposition of the gold compounds.

For gold analyses, the weighed sample was wrapped in ashless filter paper, placed in a weighed porcelain crucible and moistened with 10% hydrochloric acid. This crucible was placed in a Gooch crucible and slowly warmed on a hot-plate until the gold compound decomposed. The paper was carefully burned off, and the residue heated for one-half hour to one hour over a Meker burner.

The halogen analyses were carried out by decomposing the compound with warm alcoholic potassium hydroxide, filtering off the metallic gold, acidifying the filtrate with nitric acid, and titrating the halogen by the Volhard method.

Summary

Trimethylgold, the first R_3Au type prepared, has been synthesized by the reaction of methyllithium with gold tribromide or dimethylgold bromide at −65°. The compound is highly unstable, and begins to decompose at about −40 to −35° into gold, methane and ethane.

Coördination compounds with amines like ethylenediamine are more stable. These, like the trimethylgold, are cleaved smoothly by hydrogen chloride and RSH compounds to give dimethylgold salts.

As might have been predicted, trimethylgold is of a low order of chemical reactivity toward some functional groups. It does, however, react with gold tribromide to give dimethylgold bromide.

Triethylgold appears to be distinctly less stable than trimethylgold.

AMES, IOWA RECEIVED MARCH 21, 1947

---

[14] The authors are grateful to Dr. F. C. Whitmore for the neopentylmagnesium chloride.

[15] Brain and Gibson, *J. Chem. Soc.*, 762 (1939).

An Apparatus for Refined Thermal Analysis Exemplified by a Study of the System *p*-Dichlorobenzene–*p*-Dibromobenzene–*p*-Chlorobromobenzene

BY A. N. CAMPBELL AND L. A. PRODAN

Introduction

The relative merits of the various types of cooling curve have been discussed by Burgess[1] and by Rosenhain.[2] Although it is easy, in systems showing solid solution formation, to locate the freezing point, *i. e.*, the liquidus, it is not easy to determine the temperature of complete solidification, *i. e.*, the corresponding point on the solidus curve. Theoretically it should be possible to do this, but in practice the change of slope is too ill-defined to admit of certainty. The present paper describes a successful attempt to overcome this difficulty. Our method consists in the application of Plato's method,[3] whereby a straight-line cooling curve is obtained, and the use of an environment of rigidly controlled temperature, together with minor refinements.

During the liquid–solid transformation of a system which forms solid solutions, the temperature does not remain constant but decreases as the solid solution deposits. The gradient remains essentially constant from the freezing point to the melting point, where a break in the cooling curve marks the disappearance of the liquid phase. The solid solution then cools rapidly from this point until the cooling rate of the furnace is re-established.

As a test of the apparatus we chose the ternary system *p*-dichlorobenzene–*p*-chlorobromobenzene–*p*-dibromobenzene, which has been investigated for freezing points only by Bruni and Gorni.[4]

These authors find that all three binary systems form a continuous series of solid solutions, the two systems containing dichlorobenzene as one component each exhibiting a minimum freezing point. Adding chlorobromobenzene to dichlorobenzene produces a depression in the freezing point of the mixture up to a concentration of 3.5%, after which the freezing point of the mixture rises continuously to the freezing point of pure chlorobromobenzene. Similarly, the system dichlorobenzene–dibromobenzene exhibits a minimum freezing point at 2.5% dibromobenzene. In all three systems the freezing curves lie below the straight line joining the freezing points of the components, but the liquidus curve for the system chlorobromobenzene–dibromobenzene approaches very closely to a straight line. Küster[5] examined the freezing curve of the system dichlorobenzene–dibromobenzene but overlooked the minimum freezing point discovered by Bruni and Gorni, who also determined the freezing surface of the ternary system. The liquidus isotherms in triangular projection are all convex toward the lowest temperature (the freezing point of pure *p*-dichlorobenzene, 52.7°), indicating that the freezing surface of the isobaric model is concave downward. Moreover, the surface lies completely below the plane passin through the freezing points of the three pure components. The freezing surface assumes a more interesting form in the dichlorobenzene corner.

The shape of their isotherms clearly characterizes the system as an example of Schreinemakers' type 1.3.3. (c), that is, there should exist a ternary freezing point, at which the compositions of liquid and solid solutions are the same, but which is neither a maximum nor a minimum temperature. Nevertheless, Bruni in the first edition of his book, "Über die feste Lösungen,"[6] states that a minimum freezing temperature exists in the ternary system. This statement is absent from a later edition of the book. Our own results show that in the ternary system, there is neither a minimum freezing temperature nor a point of identity of composition of liquid and solid solutions.

Data for the solidus curves of the binary systems and the solidus surface of the ternary system appear to be almost completely lacking. Kruyt[7] has determined the approximate position of the melting curve for the system dichlorobenzene–dibromobenzene. His results indicate a maximum freezing interval of approximately 14°, but with this our results are in serious disagreement.

Experimental

Construction of the Apparatus

The Environment.—In order to obtain regulated cooling entirely independent of external conditions, an arrangement had to be constructed whereby the loss of heat by radiation from the furnace is constant. The apparatus designed for this purpose is shown in Fig. 1.

A circular tank, 45 cm. in diameter, was constructed from #24 gage copper sheet (1). In the center of this tank a cylinder 15 cm. in diameter was soldered. The central opening was lined with asbestos paper and the annular space was filled with water, the total capacity being about 20 liters. The tank was set on a 0.5 inch thick soft asbestos sheet (10), which served as insulation while the side surface was insulated with two layers of felt cloth (3). Inlet (4) and outlet (5) pipes for the water circulation system were placed at the top and bottom, respectively, the latter pipe being provided with a stopcock for controlling the rate of flow of the water. A circular top (2) for the tank was cut from $^5/_8$ inch Transite asbestos board. A hole 4 cm. in diameter cut in the center of the cover was the only means of access to the interior of the furnace (8), which was fastened to the cover by means of three Transite blocks bolted in place, as shown in the top view of the tank. The leads were brought out to terminals (9) (Fig. 1).

The desired working range of the apparatus was from 20 to 100°; to obtain linear cooling at a reasonably rapid

---

(1) G. K. Burgess, *Bull. Bur. Standards*, **5**, 199 (1908).

(2) W. Rosenhain, *Proc. Phys. Soc.*, **21**, 180 (1908).

(3) W. Plato, *Z. physik. Chem.*, **55**, 46 (1906); **58**, 350 (1907).

(4) G. Bruni and F. Gorni, *Atti R. Accad. Lincei*, **8**, 212 (1899).

(5) F. Küster, *Z. physik. Chem.*, **50**, 65 (1905).

(6) Bruni, 27 (1901 edit.).

(7) H. R. Kruyt, *Z. physik. Chem.*, **79**, 657 (1912).

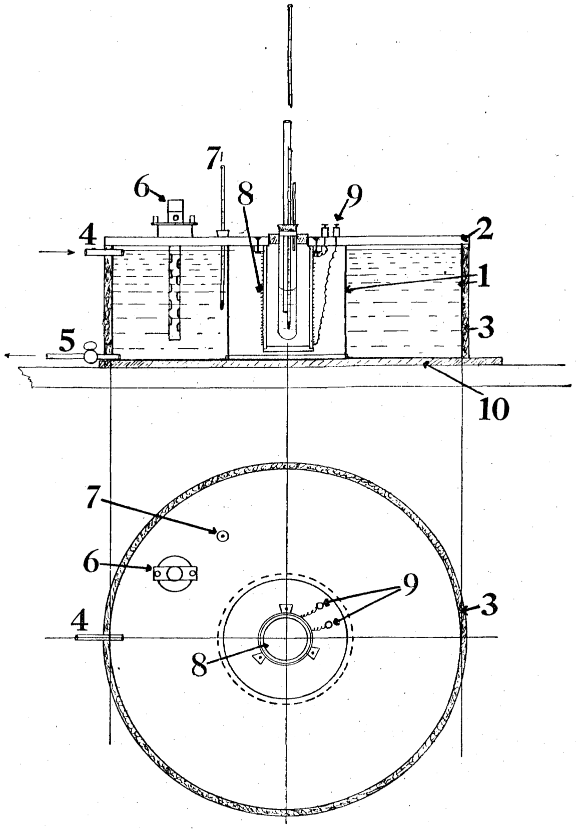


Fig. 1.—Apparatus: scale: $^1/_4''$ = 6 cm.

rate necessitated an environment temperature 10–20° below the lower working limit. An environment temperature of 10° was found by experiment to be adequate, though a lower temperature was preferable. To maintain the temperature of the environment constant a thermostated circulation system was introduced. The temperature of the environment was read on the thermometer (7). A mercury thermoregulator (6), sensitive to 0.02, mounted on the cover, served to control the temperature of the circulating system.

The Cooling Circuit.—The cooling system is shown diagrammatically in Fig. 2. Tank A represents the environment already described. Tank B, containing kerosene, was 30 inches in height and 10 inches in diameter. It was provided with a thick, tightly fitting wooden cover and was insulated with felt. The cooling coil (14) was made from $^3/_8$ inch copper tubing and was actually the freezing coil of a methyl chloride refrigerator unit. The outlet pipe (5) from the tank A directed the water through a copper coil (15), which was immersed in the kerosene, to water pump (12). The outlet pipe from the pump was connected to the inlet (4) of tank A. A rubber tube, not shown in the diagram, was connected to the inner end of the inlet pipe (4); its purpose was to conduct the violent incoming stream of water to the bottom of the tank, thereby producing a rotary circulation of the water in the annular space. This method of stirring proved to be so satisfactory that no mechanical stirrer was required in tank A.

Operation.—The temperature of the kerosene tank (B) was maintained constant at 1 ± 0.5° by means of a bimetallic thermoregulator (16) connected in series with the a. c. line and the refrigerator motor. The kerosene tank was stirred with a vigorous current of air.

The temperature of bath A was kept constant at 10 ± 0.02° by means of regulator (6). Closing of the relay circuit caused the circulating pump to operate. The temperature of bath B, which could not be lower than 0°, defined the lower operating temperature limit of bath A. Due to heat absorption in the connecting lines and pump, bath A could not be operated below 10° without placing undue strain on the pump and its motor. Insulating the connecting lines and pump with heavy felt minimized the heat absorption, but even so the pump operated almost continuously when the furnace was at 90°.

Furnace Construction.—A 14.5 cm. length of 5 cm. diameter hard glass tubing, wall thickness 2 mm., was wrapped with two thicknesses of asbestos paper soaked in sodium silicate solution. Fifty turns of #22 gage B and S nichrome wire were wound on this form. To obtain uniform heating of the melt a flat heating coil was provided

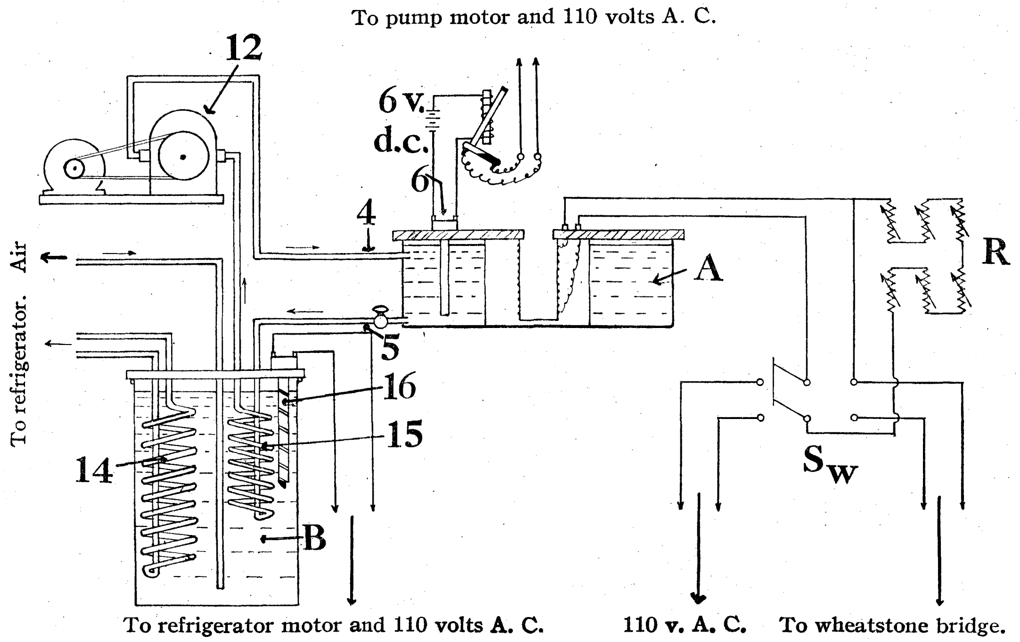


Fig. 2.—Wiring.

at the lower end of the furnace tube; it was wired in series with the main coil. The completed furnace was lined with two layers of asbestos paper and the whole fastened to the water-bath cover as shown in Fig. 1. The total resistance of the furnace was 49 ohms.

The Electrical Circuit.—The control circuit is shown in Fig. 2. Accurate temperature control was obtained by adjustment of an external resistance (R) in series with the furnace and source of current. The resistance consisted of six wire-wound rheostats in series, having a total resistance of 850 ohms and a maximum current capacity of 3 amperes. The source of current was the 110-volt a. c. line, but the fluctuations in line voltage made this a not entirely satisfactory source of power; a battery of storage cells, such as was used by Plato,[3] would have been better. A double-pole double-throw switch (Sw) was wired into the circuit in such a way that in one position the 110-volt line was connected to the furnace and resistance R in series, and in the other position the external resistance alone was connected to a Wheatstone bridge circuit.

Temperature Measurement.—All temperatures were measured on a mercury in glass thermometer, having a scale of 0–110° in 0.1°. The thermometer was calibrated against an identical type of thermometer certified by the National Bureau of Standards. By means of a reading lens temperatures were read to ±0.01°. The exposed stem correction was applied to all readings.

Calibration of the Apparatus.—A Pyrex test-tube, 2.5 cm. in diameter and 13 cm. long, formed the containing vessel for the melt. This tube was fixed in the furnace with a rubber stopper. It was fitted with a rubber stopper on which were mounted the stirrer and the thermometer.

From the results of a large number of trials using paraffin oil and the organic melts in the furnace, a cooling rate of 1.5° in five minutes was decided on. With paraffin oil as the calibrating fluid, the circuit resistance was adjusted so that the thermometer registered 95° with the stirrer running. Then, largely by trial and error, resistance was slowly inserted in the furnace circuit in steps; each increment of resistance was measured by throwing the d. p. d. t. switch to the Wheatstone bridge circuit. Readings were taken every minute to assure a constant cooling rate of 0.3° per minute. It was often necessary to remove resistance from the circuit in order to maintain the linear cooling rate, but all adjustments were recorded. When the temperature range of 95 to 20° had been covered in this manner, temperatures were plotted against resistances. The points so obtained were scattered but it was possible to draw a rough curve. A second calibration run was carried out in a similar manner using the rough calibration curve as a guide. The results of this run were plotted with the data from the first run on the same graph, the rough calibration curve being appropriately modified. A third calibration run based on the modified curve produced the final refined calibration curve. From this curve the exact resistance to be inserted in the circuit every 2.5 minutes to produce a linear cooling rate of 0.3° per minute could be read. Plotting temperature against time a straight line resulted deviating from perfect linearity by no more than 0.2°.

Stirring.—The greatest practical difficulty was encountered in the attempt to devise a flawless stirring mechanism. Mechanical stirrers are useless for this work.

Efficient stirring in a closed system was finally obtained by employing a fluctuating air pressure. The complete stirring assembly is shown diagrammatically in Fig. 3. The motor-driven reciprocating mechanism (1) was coupled to a piston (2) working in a $^{3}/_{8}$ inch bore glass cylinder (3). The piston consisted of a 0.25 inch glass rod 12 inches long, over one end of which a piece of soft rubber tubing was fastened. This piston was a very loose fit in the cylinder. A piece of rubber pressure tubing (4) connected the cylinder to a second piece of glass tubing (5) which, in turn, was joined to a long tube of smaller bore having an outlet closed by a clamp on an attached length of rubber tubing (7). When the U-tube, formed by the two parts of the apparatus, and the reciprocating mechanism were clamped to a suitable stand, the U was filled with mercury. The top end of tube (6) was connected by means of rubber tubing to the stirring tube (8), placed close to the thermometer (11) which was centered in the main container (9). The stirring tube was merely a piece of $^{3}/_{8}$ inch bore glass tubing, whose immersed orifice was slightly constricted. An outlet tube (10) consisting of a 6 inch length of $^{3}/_{16}$ inch bore glass tubing, was connected to the U-tube (12) by a short length of rubber tubing. This U-tube contained concentrated sulfuric acid, partly as a trap to keep moisture out of the apparatus, but chiefly because sulfuric acid offered less resistance than mercury to the oscillating air pressure within the closed system.

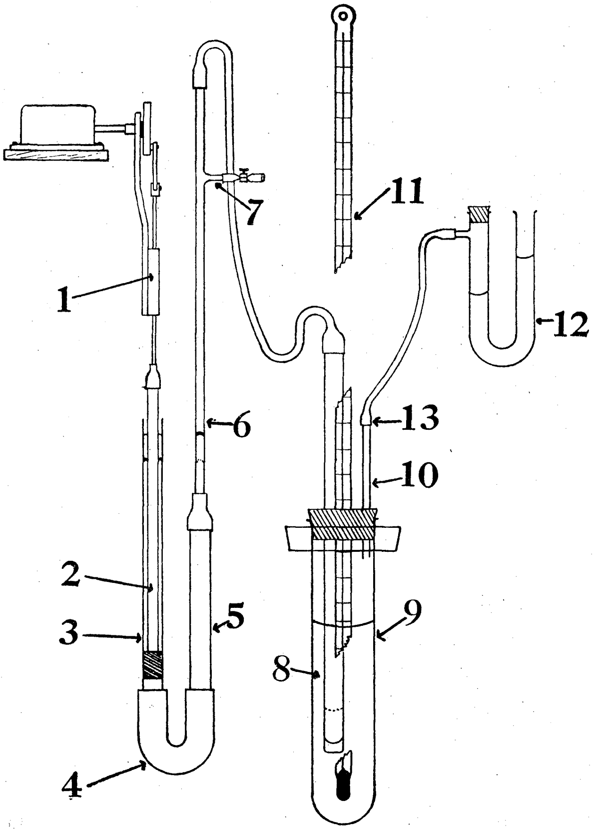


Fig. 3.

As the piston oscillated in the cylinder at a rate of approximately 4 strokes per second, the mercury in the U-tube was forced to oscillate in resonance with it. The oscillation of the mercury column in tube (6) produced a sympathetic oscillation of the air in the system which was transferred to the liquid in the stirring tube (8). The throw of the reciprocating mechanism was adjusted so that the fused melt oscillated a distance of 1.5 inches in the stirring tube. The position of the liquid level in tube (8) could be adjusted quickly by altering the air pressure within the system through tube (7). This apparatus, when properly adjusted, produced a vigorous and efficient agitation of the melt and depositing crystals. The position of the orifice of the stirring tube was critical. For best results it was immersed two-thirds of the total depth of the melt. In contrast with the abrupt cessation of the mechanical stirrers and the attendant break in the cooling curve, the stirring action stopped gradually; the cooling curves showed no evidence of a break when the stirring ceased completely. Employment of the closed system was also advantageous since losses by evaporation were minimized; loss through the stirring tube was very slight.

Performance of the Apparatus.—In order to show the accuracy with which the temperature of complete solidification (solidus line) can be obtained, Fig. 4 is a plot of the cooling data of a binary mixture containing 30.03 mole per cent. dibromobenzene and 69.97 mole per cent. dichlorobenzene. This mixture showed one of the largest cooling intervals. When the results are plotted, as was always done, on millimeter paper so that 1 mm. equals 0.04° of temperature or two minutes of time, the freezing and melting points are clearly defined as 59.49° and 55.20°, respectively. All curves were repeated on the same mixture, and mixtures of approximately the same composition were frequently made up for double checking.

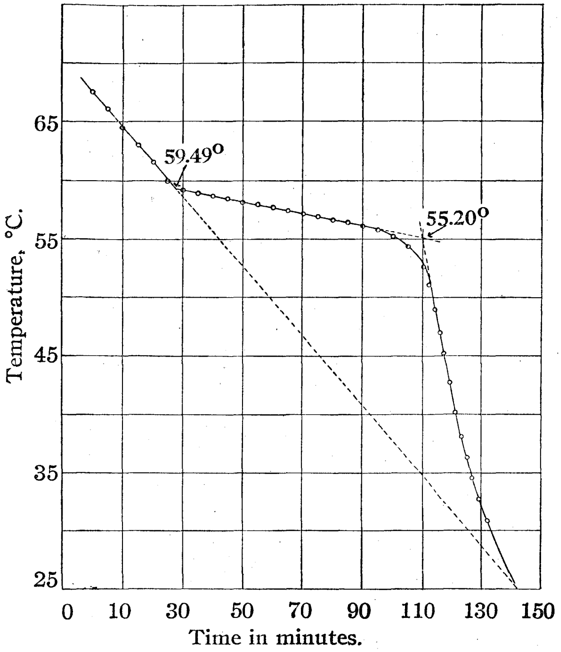


Fig. 4.—A typical cooling curve: freezing point, 59.49°; melting point, 55.20°; internal 4.29°.

Purification of Materials.—Each of the materials, *viz.*, *p*-dichlorobenzene, *p*-dibromobenzene, and *p*-chlorobromobenzene, was steam distilled once from dilute sulfuric acid, once from dilute sodium hydroxide and finally distilled using a short column. The dichlorobenzene thus obtained melted at 52.5°, but a cooling curve showed a freezing interval of 0.8°, indicating impurity. The ortho-isomer (b. p. 179°) was separated from the desired para-isomer (b. p. 173°) by crystallization from ethyl alcohol. After six crystallizations, the material froze at 53.08° with no detectable freezing interval.

The dibromobenzene was treated in a similar manner. Distillation as a means of purification was useless since the *meta*-isomer boils at exactly the same temperature as the *para*-isomer, *viz.*, 219°. Six crystallizations from ethyl alcohol yielded a product freezing at 87.30°.

Distillation is again useless as a method of separating *p*-chlorobromobenzene from its isomers, but purification by crystallization from ethyl alcohol was again effective. Eight crystallizations were necessary to obtain a product which froze at 64.58° with a freezing interval of 0.07°.

All these substances were stored over concentrated sulfuric acid for two months before use.

Results

Freezing Points of the Pure Components.—The freezing point of *p*-dichlorobenzene is variously reported as 52.7° (Bruni)[8]; 52.7° (Küster, *loc. cit.*); 52.8° (Nagornow[9]); 52.9° (Narbutt[10]); 53.1° (Speranski[11]); 53.0° (Kruyt, *loc. cit.*); 53.13° ± 0.02 (Cooper[12]). Our value is 53.08 ± 0.02°.

The freezing point of *p*-chlorobromobenzene is given as 67° by Auwers[13] and by Bruni,[8] as 64.7° by Speranski[11] and as 64.6° by Narbutt.[10] Our freezing point of 64.58° agrees with that of Narbutt.

The dibromobenzene used by Bruni[8] froze at 85.9°. Küster[5] and Narbutt[10] report 86.4° and 86.9°, respectively, while reports by Kruyt[7] and Narbutt[10] give 87.2° and 87.1°, respectively. The value obtained from our cooling curves is 87.30 ± 0.02°, a higher value than any previously reported. There was no crystallization interval, so our preparation was undoubtedly pure.

Transition Temperature of *p*-Dichlorobenzene.—When examining the cooling curves of *p*-dichlorobenzene closely, a break in the line of cooling was discovered. In four experiments, the break resulted at 39.8, 39.7, 39.6 and 39.4°, respectively. The change in slope at 39° was not abrupt and it was thought at first that the effect was due to an error in the calibration of the apparatus. A search of the literature revealed, however, that a transition point had been reported by Beck and Ebbinghaus[14] at 39.5°. Conflicting data have been reported by Wallerant,[15] who concluded from the results of microscopic studies that *p*-dichlorobenzene is trimorphic, the reversible transitions occurring at 29 and 25°. That *p*-dichlorobenzene does exist in at least two forms under atmospheric pressure appears to be an

TABLE I

THE SYSTEM: *p*-DIBROMOBENZENE–*p*-CHLOROBROMOBENZENE

Mole % dibromobenzene	F. p. in °C.	M. p. in °C.	Mole % dibromobenzene	F. p. in °C.	M. p. in °C.
2.85	65.10	64.60	54.70	77.06	74.32
2.89	65.01	64.46	62.00	78.67	77.14
2.92	65.11	64.89	65.08	79.55	77.00
7.09	65.97	65.34	69.25	80.70	77.96
8.84	66.32	65.60	69.25	80.68	77.91
16.06	67.90	66.61	75.00	81.75	80.54
16.21	67.88	66.98	80.01	83.16	80.85
24.89	70.00	68.40	83.21	84.07	81.59
25.01	69.89	68.43	88.00	84.76	83.96
26.21	70.11	68.55	89.76	85.24	83.60
34.89	72.42	70.80	94.08	86.26	84.95
38.00	72.97	71.37	95.11	86.33	85.37
39.18	73.44	71.08	95.98	86.50	86.14
47.83	75.39	72.42	97.59	86.95	86.40
51.92	76.25	74.53	98.30	87.12	86.55
52.52	76.47	73.52			

---

[8] G. Bruni, *Gazz. chim. ital.*, **30**, II, 127 (1900).

[9] Nagornow, *Z. physik. Chem.*, **75**, 578 (1911).

[10] J. Narbutt, *Ber.*, **52**, 1028 (1919).

[11] Speranski, *Z. physik. Chem.*, **51**, 45 (1905).

[12] N. C. Cooper, *Can. Chem. Met.*, **9**, 59 (1925).

[13] V. Auwers, *Z. physik. Chem.*, **30**, 312 (1899).

[14] Beck and Ebbinghaus, *Ber.*, **39**, 3870 (1906).

[15] F. Wallerant, *Compt. rend.*, **158**, 385 (1911).

undisputed fact. From the results of thermal analysis we conclude that a transformation in the solid state occurs at 39.6°.

The Binary System p-Dibromobenzene–p-Chlorobromobenzene.—The complete data for the system dibromobenzene–chlorobromobenzene are given in Table I.

The equilibrium diagram for this system is given in Fig. 5. The liquidus curve appears to be almost a straight line but it is actually S-shaped, the high temperature portion lying above and the low temperature portion below, the straight line joining the freezing points of the pure components. The system is an example of Roozeboom's Type I.

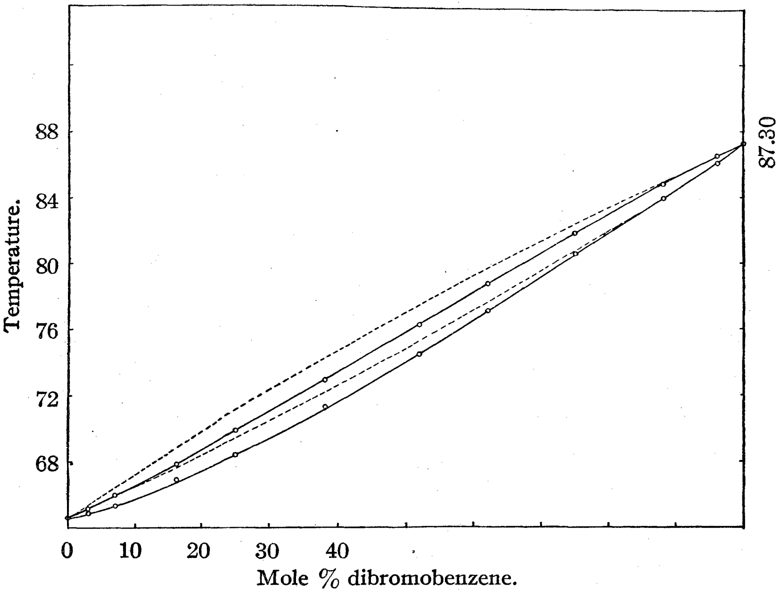


Fig. 5.—The binary system: p-dibromobenzene–p-chlorobromobenzene: —O—, exptl.; - - - - calculated.

Perhaps the most reliable equations for the calculation of solidus and liquidus curves are those of Seltz,[16] in the derivation of which he uses the concepts of activity and fugacity introduced by G. N. Lewis for ideal liquid solutions.

Using these equations and the following heats of fusion, the liquidus and solidus curves were calculated. Heats of fusion[17]: p-$C_6H_4Cl_2$ = 29.50 ± 0.11 cal. per gram = 4340 cal./mole; p-C_6H_4ClBr = 23.42 ± 0.09 cal./gram = 4484 cal./mole; p-$C_6H_4Br_2$ = 20.80 cal./gram = 4908 cal./mole. The solidus and liquidus curves thus calculated are expressed as dotted lines in Fig. 5.

The Binary System p-Dichlorobenzene–p-Dibromobenzene.—The system p-dichlorobenzene–p-dibromobenzene falls under Type III of Roozeboom. Data relevant to this system are given in Table II and the results are expressed graphically in Fig. 6. A distinct minimum freezing temperature of 52.90° was detected at a concentration of 1.22 mole per cent. dibromobenzene. As this minimum freezing mixture contained so little dibromobenzene particular care was exercised in establishing the positions of liquidus and solidus curves in this region. In Fig. 6 the region of the minimum is presented in a separate diagram, greatly enlarged.

TABLE II

THE SYSTEM p-DICHLOROBENZENE–p-DIBROMOBENZENE

Mole % dibromobenzene	F. p. in °C.	M. p. in °C.	Mole % dibromobenzene	F. p. in °C.	M. p. in °C.
0.30	53.06	53.01	20.13	55.95	54.37
0.62	53.02	52.95	30.03	59.49	55.20
1.01	52.93	52.91	40.08	63.81	59.14
1.20	52.90	52.90	47.96	67.05	62.93
1.60	52.94	52.90	57.06	71.13	67.09
1.98	52.96	52.91	64.89	74.18	70.66
2.56	53.00	52.94	74.93	78.26	75.62
3.03	53.03	52.95	85.01	82.11	80.09
4.91	53.15	53.01	95.03	85.70	84.59
9.90	53.68	53.37			

The experimentally determined liquidus and solidus curves are both straight lines over a restricted concentration range of approximately 40 to 80% dibromobenzene. As in the system chlorobromobenzene–dibromobenzene, the liquidus curve of this system is S-shaped. At no point does the liquidus curve lie above the straight line joining the freezing points of the pure components.

The Binary System p-Dichlorobenzene–p-Chlorobromobenzene.—Examination of the data in Table III and the plot of these data in Fig. 7 shows that the experimental curves for both liquidus and solids lie far below the straight line joining the freezing points of the pure com-

TABLE III

THE SYSTEM p-DICHLOROBENZENE–p-CHLOROBROMOBENZENE

Mole % chlorobromobenzene	F. p. in °C.	M. p. in °C.	Mole % chlorobromobenzene	F. p. in °C.	M. p. in °C.
0.41	53.08	53.03	5.04	53.11	53.03
0.98	53.05	53.01	5.96	53.16	53.10
1.54	53.03	52.99	10.00	53.48	53.26
2.16	52.99	52.96	25.04	54.55	54.26
2.57	52.96	52.96	38.00	55.83	55.37
2.96	53.00	52.97	50.03	57.36	56.61
2.97	53.00	52.96	60.03	58.50	57.78
3.91	53.05	53.00	74.99	60.67	60.15
4.03	53.05	52.99	90.73	62.91	62.61
4.53	53.09	53.00	97.00	64.06	63.85

---

[16] H. Seltz, THIS JOURNAL, **56**, 307 (1934); Marsh, "Principles of Phase Diagrams," McGraw-Hill, New York, 1935, p. 43.

[17] J. Narbutt, *Z. Elektrochem.*, **24**, 339 (1918).

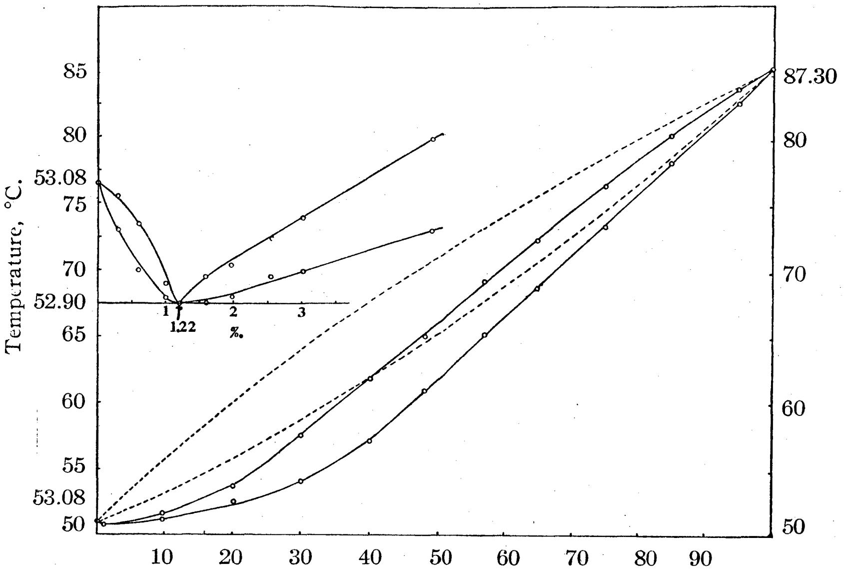


Fig. 6.—The binary system: *p*-dichlorobenzene–*p*-dibromobenzene: —O—, experimental; - - - - calculated.

ponents, and that the experimental curves lie considerably below the calculated curves which straddle the straight line. Calculated and experimental curves agree only in so far as the freezing intervals are approximately the same. As with the system dichlorobenzene–dibromobenzene this binary system possesses a minimum freezing point, lying at 52.96° and 2.57 mole per cent. chlorobromobenzene.

The Ternary System *p*-Dichlorobenzene–*p*-Chlorobromobenzene–*p*-Dibromobenzene.—Table IV contains all data relevant to the freezing and melting points of the ternary mixtures examined. The data have been classified into five sections, corresponding to five quasi-binary[18] systems investigated.

Construction of some of the isotherms of the ternary system by graphical interpolation from the quasi-binary sections gave the diagram of Fig. 8. The isotherms shown are those lying on the solidus surface at the temperatures indicated.

A very similar diagram for the liquidus isotherms was obtained. In the body of the diagram the isotherms were substantially straight lines. This can be seen from Fig. 9, which illustrates the relations between the solidus and liquidus isotherms. Each liquidus isotherm (full curve) with its corresponding solidus isotherm (broken line) constitutes the boundary of a heterogeneous liquid–solid region. Tie-lines have been inserted qualitatively to illustrate the direction of crystallization and composition changes in the ternary system. The exact directions of the tie-lines are not known. They could be determined only by analysis of the first portion of solid phase separating from a liquid solution of known composition.

The liquidus and solidus isotherms in the dichlorobenzene corner are represented on a larger scale in Figs. 10, 11 and 12. The position and the shape of the isotherms preclude any possibility of the existence of a ternary minimum freezing point as was suggested by Bruni.[19] Plotting selected liquidus and corresponding solidus isotherms, the unusual diagram of Fig. 12 was obtained. Tie-lines have been inserted in order that the heterogeneous bands may be easily distinguished. More bands than the three shown were not plotted because of the complexity introduced by overlapping of the very wide bands in this region.

It is apparent that at no point do solidus and liquidus curves coincide and this is convincing evidence that there is no minimum of temperature in the ternary system. Evidence resting purely on temperature measurement might be open to doubt since the extreme temperature range in this region is not more than 0.1°, although we believe that the sensitivity of our apparatus is such that a minimum of temperature would have been detected directly had it existed.

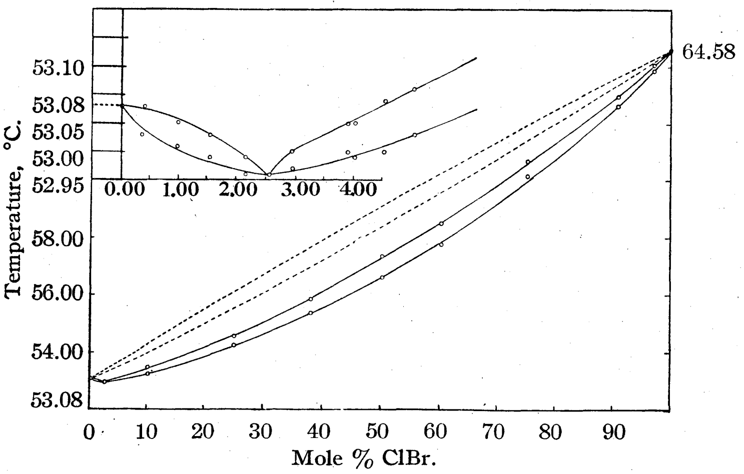


Fig. 7.—The binary system: *p*-dichlorobenzene–*p*-chlorobromobenzene; —O—, experimental; - - - - calculated.

Discussion

The great delicacy of the technique described

---

(18) *Cf.* Marsh, ref. 16, p. 151, for the use of this expression.

(19) G. Bruni, "Über die feste Lösungen," 1901, p. 27.

is proved by the fact that the temperatures of complete solidification and hence the form and direction of the solidus line are clearly discernible on the cooling curves.

The experimental results indicate a temperature of reversible transition for *p*-dichlorobenzene of 39.6°. Cooling curves of those binary mixtures which contained this substance as one of the components were examined for a break. In mixtures containing from 95 to 100% *p*-dichlorobenzene a change in slope of the cooling curve was detected. The effect of the addition of *p*-dibromobenzene or *p*-chlorobromobenzene to the pure *p*-dichlorobenzene was to depress the transition temperature of the latter. Beck and Ebbinghaus[14] have determined the transition curve for the system *p*-dichlorobenzene–*p*-dibromobenzene and find it to be a straight line running from 39.5°, the transition temperature of pure *p*-dichlorobenzene, to −8°, the transition temperature of pure *p*-dibromobenzene. Our apparatus was unable to detect the transformation of *p*-dibromobenzene and, since the break in the cooling curve of pure dichlorobenzene was barely detectable, it is not

TABLE IV

THE SYSTEM *p*-DICHLOROBENZENE–*p*-CHLOROBROMOBENZENE-*p*-DIBROMOBENZENE

Mole % dichlorobenzene	Mole % chlorobromobenzene	F. p. in °C.	M. p. in °C.
	Section 1		
0.00	48.08	76.25	74.53
7.87	44.31	74.22	72.15
10.65	42.84	73.54	70.86
21.59	37.72	70.35	67.14
25.10	35.90	69.33	66.47
37.33	30.13	65.67	62.73
38.47	29.50	65.32	62.42
47.61	25.11	62.57	59.69
62.74	17.92	58.72	56.38
72.41	13.27	56.42	55.20
81.35	8.96	54.67	54.19
92.38	3.65	53.34	53.22
96.39	1.74	53.05	52.98
97.18	1.35	53.01	52.95
98.24	0.85	52.97	52.94
98.80	0.63	52.95	52.92
99.32	0.33	53.02	52.98
	Section 2		
0.00	62.00	72.97	71.37
10.00	55.80	70.47	68.29
25.00	46.50	66.30	63.01
40.00	37.20	62.82	60.76
50.00	31.00	60.37	58.29
65.00	21.70	57.10	55.60
80.00	12.40	54.55	54.06
90.00	6.20	53.46	53.30
95.00	3.10	53.10	53.03
97.36	1.63	52.99	52.93
98.22	1.09	52.94	52.90
99.09	0.56	53.03	52.97
99.55	0.25	53.08	53.00
	Section 3		
0.00	74.99	69.89	68.43
10.24	67.34	67.58	66.24
25.28	56.05	64.39	63.09
39.99	45.02	61.12	59.42
41.00	44.24	60.99	59.32
50.22	37.34	59.10	57.72
65.74	25.44	56.44	55.46
71.77	21.15	55.49	54.92
81.64	13.77	54.20	53.89
91.28	6.54	53.35	53.27
94.94	3.80	53.11	53.03
96.51	2.63	52.99	52.94
97.44	1.94	52.97	52.93
98.37	1.22	53.00	52.95
99.19	0.61	53.06	53.01
	Section 4		
0.00	25.00	81.75	80.54
10.00	22.50	78.96	78.04
25.00	18.75	73.87	71.47
40.00	15.00	68.49	65.39
50.00	12.50	64.82	60.86
65.00	8.75	59.49	57.35
80.00	5.00	55.28	54.39
91.00	2.25	53.51	53.30
95.00	1.25	53.15	53.08
97.50	0.63	52.99	52.93
98.80	0.30	52.96	52.92
99.50	0.13	53.05	52.98
	Section 5		
90.93	7.97	53.35	53.21
95.15	3.99	53.11	52.99
97.82	2.00	52.95	52.92
98.18	0.63	52.94	52.91
98.40	0.41	52.93	52.91
98.80	0.00	52.90	52.90

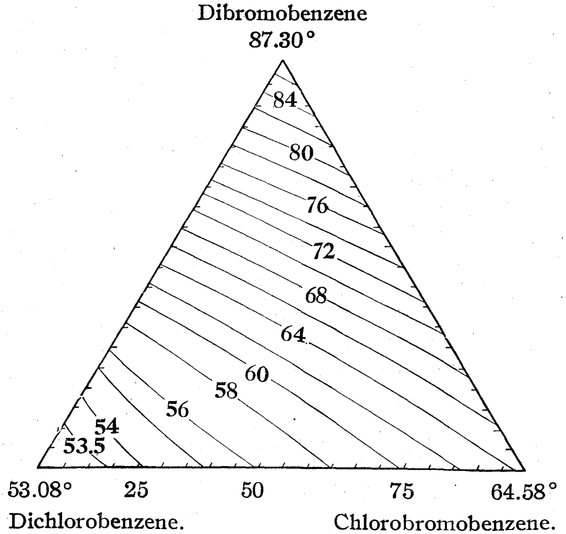


Fig. 8.—Solidus isotherms in the system: p-$C_6H_4Cl_2$:p-C_6H_4ClBr:p-$C_6H_4Br_2$.

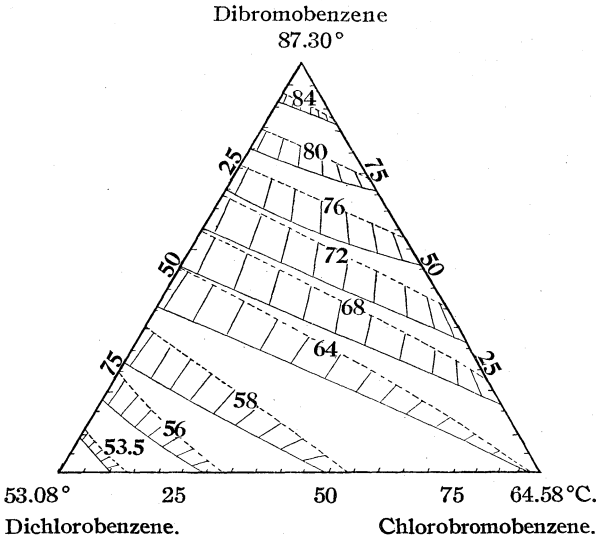


Fig. 9.—Selected heterogeneous bands in the system p-$C_6H_4Cl_2$:p-C_6H_4ClBr:p-$C_6H_4Br_2$: —, liquidus; - - - -, solidus.

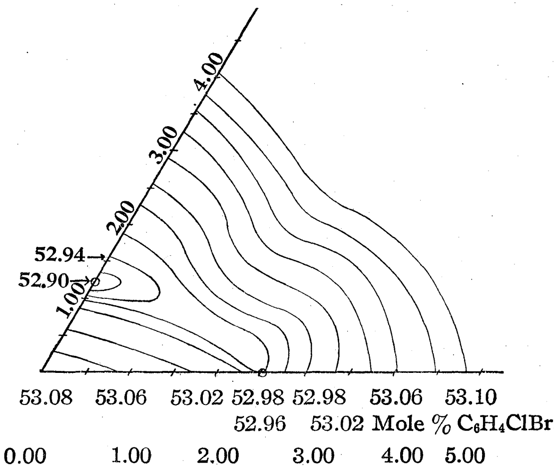


Fig. 10.—Liquidus isotherms in the p-$C_6H_4Cl_2$ corner.

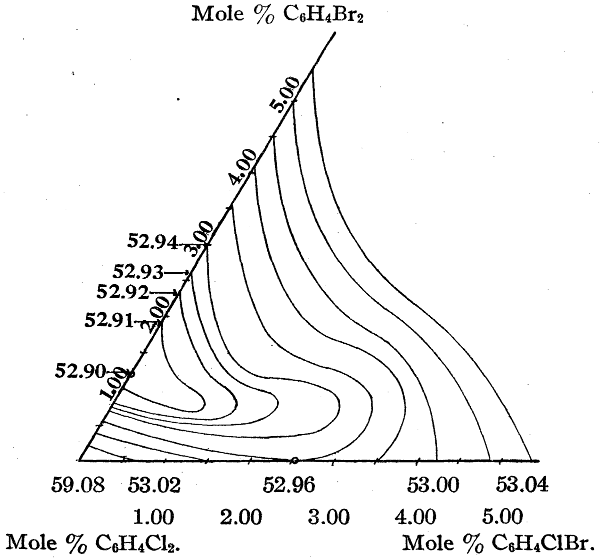


Fig. 11.—Solidus isotherms in the p-$C_6H_4Cl_3$ corner.

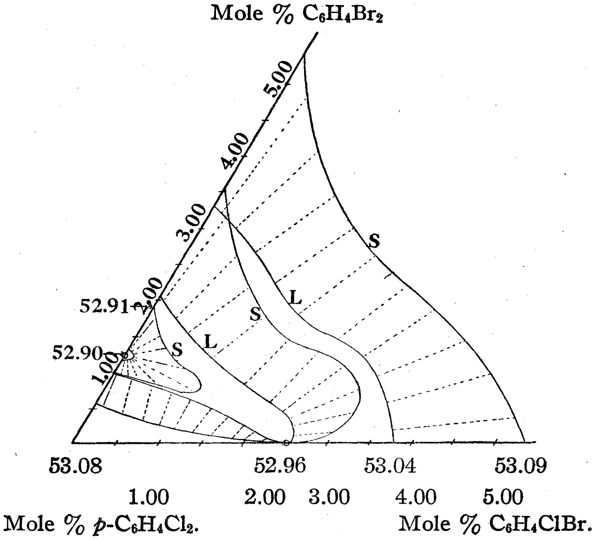


Fig. 12.—Selected isotherms in the p-$C_6H_4Cl_2$ corner: L, liquidus; S, solidus.

surprising that it disappeared completely in mixtures containing more than 5% of either of the other two components.

In view of the great similarity in molecular and crystallographic structure it is not surprising that these dihalogen benzenes should be miscible in all proportions in both liquid and solid states. All three binary systems, however, exhibit a decided tendency toward positive deviation from Raoult's law; at some lower temperature a miscibility gap may come into being.

The p-dichlorobenzene molecule, which is the lightest of the three, is perfectly symmetrical and has no dipole moment. Apparently this molecule possesses properties not associated with the asymmetrical chlorobromobenzene molecule or even with the symmetrical dibromobenzene molecule. Addition of a higher melting foreign material of similar structure such as p-chlorobromobenzene or p-dibromobenzene produces a depression in the freezing point of the pure dichlorobenzene. The heavier, higher melting dibromobenzene produces the greater and more rapid depression. More of the lighter chlorobromobenzene molecule, relative to the quantity of dibromobenzene, is required to produce a given freezing point depression.

Summary

An apparatus is described by means of which it is possible, by means of thermal analysis, to determine not merely the liquidus but also the solidus curve, and therefore the extent of solid solution.

As a test of technique, the system p-dichlorobenzene—p-dibromobenzene – p - chlorobromoben-

zene has been investigated. The results of this investigation are as follows:

The freezing points of pure *p*-dichlorobenzene, *p*-chlorobromobenzene and *p*-dibromobenzene were redetermined as 53.08, 64.58 and 87.30°, respectively. It was confirmed that pure *p*-dichlorobenzene exists in at least two forms under atmospheric pressure, the reversible transformation occurring at 39.6°.

p-Dibromobenzene and *p*-chlorobromobenzene are miscible in all proportions in both liquid and solid states; the freezing points of all solutions lie between the freezing points of the pure components. The binary system *p*-dichlorobenzene–*p*-dibromobenzene exhibits a minimum freezing temperature of 52.90° at a concentration of 1.22 mole per cent. dibromobenzene. The components are miscible in all proportions in both liquid and solid states. The binary system *p*-dichlorobenzene–*p*-chlorobromobenzene exhibits a minimum freezing temperature of 52.96° at a concentration of 2.57 mole per cent. chlorobromobenzene. The components are miscible in all proportions in both liquid and solid states.

The ternary system *p*-dichlorobenzene–*p*-chlorobromobenzene–*p*-dibromobenzene exhibits miscibility in all proportions in both liquid and solid states. No ternary solution of minimum freezing point exists; neither is there any temperature at which the compositions of liquid and solid solutions coincide.

WINNIPEG, CANADA RECEIVED MARCH 24, 1947

[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE UNIVERSITY OF AKRON, GOVERNMENT LABORATORIES]

Potentiometric Determination of Oxygen Using the Dropping Mercury Electrode[1]

BY H. A. LAITINEN,[1a] T. HIGUCHI[1b] AND MICHAEL CZUHA[1b]

A dropping mercury electrode in a solution free of capillary-active substances or electro-reducible or oxidizable substances assumes a potential corresponding to the electrocapillary zero potential of mercury. Under these conditions, the electrokinetic potential of mercury, with respect to the solution, is zero. To maintain the dropping electrode at any other potential, it is necessary to supply electrons or to remove electrons from the reservoir of mercury connected to the capillary from which the mercury is dropping. Thus, it is necessary to maintain a continuous flow of electrons to charge electrically the double layer existing between the mercury and the solution because the double layer is continually being formed. The polarographic charging or condenser current is a familiar manifestation of this phenomenon. The charging current as shown in Fig. 1 is negative in sign (corresponding to an anodic process at the dropping electrode) at potentials more positive than the electrocapillary maximum, at which point the charging current changes sign and increases in positive value as the potential is made more negative.

Any substance, such as oxygen, which is reducible on the positive side of the electrocapillary maximum, will yield a polarographic diffusion current which is positive in sign and hence opposed in direction to the charging current. For very small concentrations of oxygen, it is evident that at some value of the potential the diffusion and charging currents will be equal in magnitude but opposite in direction and hence will cancel. Since the instantaneous value of the diffusion current varies with the one-sixth power of the time and is independent of the potential while the charging current at a constant potential varies with the two-thirds power of the time,[2] it is evident that the null potential must vary with time in such a way that the instantaneous current will be zero at all times.

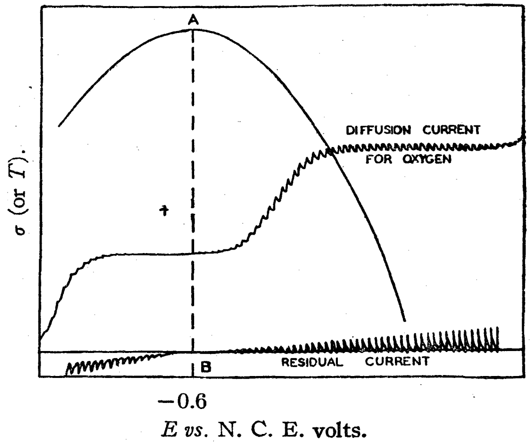


Fig. 1.—Electrocapillary curve.

To calculate the magnitude of the effect, it is convenient to equate the total charge, $(q_c)_t$, held by the drop at any time, t, with the number of coulombs, $(q_d)_t$, lost by the drop through the electro-reduction of oxygen molecules from the beginning of the drop formation to time, t, or

$$(q_c)_t = (q_d)_t \qquad (1)$$

---

[1] This investigation was sponsored by the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the government synthetic rubber program.

[1a] Noyes Chemical Laboratory, University of Illinois.

[1b] University of Akron, Government Laboratories.

[2] I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941.

The charge held by the drop at any time, t, is given by

$$(q_c)_t = A_t k(E - E_{\text{max.}})_t \qquad (2)$$

where A_t is the area of the drop at time, t, k is the capacity of the double layer per unit area (microfarads per square centimeter), $E_{\text{max.}}$ is the potential corresponding to the electrocapillary maximum and E is the potential of the dropping mercury electrode in volts. From geometric considerations

$$A_t = 4\pi^{1/3}(3/4d)^{2/3}m^{2/3}t^{2/3} \qquad (3)$$

if the spherical drops grow at a uniform rate of m/d cubic centimeter per second where m is the mass of mercury flowing per second and d is the density of mercury. Substituting (3) in (2)

$$(q_c)_t = 4\pi^{1/3}(3/4d)^{2/3}k(E - E_{\text{max.}})_t t^{2/3}m^{2/3} \qquad (4)$$

The charge lost because of reaction of oxygen at the drop surface can be obtained by integrating the Ilkovic equation[3] (where i_t is the diffusion current at time, t)

$$\begin{aligned}(q_d)_t &= {}^{t}i_t\mathrm{d}t = {}^{t}4(7/3)^{1/2}(3/4d)^{2/3}\pi^{-1/6}\, nFD^{1/2}Cm^{2/3}t^{1/6}dt \\ &= 6/7\ 4(7/3)^{1/2}(3/4d)^{2/3}\pi^{-1/6}nFD^{1/2}\, Cm^{2/3}t^{7/6} \qquad (5)\end{aligned}$$

Substituting (4) and (5) into (1) and solving for $(E - E_{\text{max.}})_t$

$$(E - E_{\text{max.}})_t = \frac{6}{\sqrt{21\pi}}\,\frac{nFCD^{1/2}t^{1/2}}{k} = 7.128 \times 10^4\,\frac{nCD^{1/2}t^{1/2}}{k} \qquad (6)$$

where nF is the number of coulombs of electricity involved per mole, D is the diffusion coefficient in square centimeters per second and C is the concentration of reducible substance in millimoles per liter.

To evaluate the final expression for the specific case of oxygen, $n = 2$, $D = 2.6 \times 10^{-5}$, from the polarographic measurements of Kolthoff and Miller[4] and $k = 42.2$ microfarads per square centimeter (0.1 N KCl), the value of Ilkovic.[5]

Since the latter value was determined by Ilkovic from the slope of the polarographic residual current curve, 42.2 was used rather than the value of 48.8 microfarads per square centimeter reported by Philpot.[6] The final expression (6) becomes

$$E - E_{\text{max.}} = 17.2Ct^{1/2} \qquad (7)$$

where the potential shift is measured in volts, the concentration in millimoles per liter and the drop time in seconds.

According to equation (7), the potential difference is zero at the beginning of the drop formation and increases as the square root of the time until the drop breaks. This variation is brought about by the fact that the instantaneous diffusion current is independent of the potential, while the charging current is proportional to the potential difference $(E - E_{\text{max.}})$. Thus, for the observed current to be zero at every instant, the potential difference must fluctuate with time. The voltage fluctuation should be directly proportional to the oxygen content of the electrolyte, but independent of the rate of flow of mercury (m).

If a high capacity condenser is inserted into the circuit to lower the voltage fluctuation to a negligible value, the observed potential will correspond to the maximum potential difference of the undamped system just before the drop breaks. This relationship can readily be derived by equating the total number of coulombs of electricity due to the diffusion current during the life-time of the drop with that due to the charging current at a constant potential. Since the charging current at any instant is determined by the diffusion current, the magnitude of the former is unaffected by the presence or absence of damping condensers. At the time of the drop break, the final charge (equation 2) and therefore the final potential difference is the same in the damped and undamped systems.

Equation (7) relates the potential of the system with the concentration of oxygen actually dissolved in the electrolyte. To determine the actual oxygen content of any non-reducible gas it is necessary only to bring the electrolyte into equilibrium with the gas before measuring the potential.

In such case, equation (7) would take the form

$$\text{Percentage oxygen in gas} = \frac{(E - E_{\text{max.}})}{\dfrac{10\alpha}{22.4}\,17.2t^{1/2}} \qquad (8)$$

where α is the absorption coefficient of oxygen in the electrolyte expressed in cubic centimeters per liter and the total gas pressure is one atmosphere.

At 25°, $\alpha = 28.3$[6a] and the equation reduces to

$$\text{Percentage oxygen} = \frac{(E - E_{\text{max.}})}{217t^{1/2}} \qquad (9)$$

where $(E - E_{\text{max.}})$ is expressed in millivolts.

The object of the present investigation was to determine the effects of the factors "C" and "t" in equation (6) and to determine whether the potential is independent of the rate of flow of mercury.

Apparatus

Design of Cell for Continuous Measurements.—A cell suitable for the present investigation had to fulfill the following requirements: (1) Arrangements had to be made to bring the electrolyte rapidly in equilibrium, with respect to its oxygen content, with the sample gas. (2) The dropping electrode had to be shielded from any turbulence caused by flow of gas through the solution. (3) The reference electrode had to have constant reversible potential and possess relatively low resistance. It had to be placed so that the re-

---

[3] D. Ilkovic, *Collection Czechoslovak Chem. Commun.*, **6**, 498 (1934); *J. chim. phys.*, **35**, 129 (1938).

[4] I. M. Kolthoff and C. S. Miller, THIS JOURNAL, **63**, 1013 (1941).

[5] D. Ilkovic, *Collection Czechoslovak Chem. Commun.*, **8**, 170 (1936).

[6] St. L. Philpot, *Phil. Mag.*, [7] **13**, 775 (1932).

[6a] The value of 28.3 holds only for pure water. When an appreciable amount of electrolyte is present the value is, of course, lower.

ducible products, if any, of the electrode could not affect the dropping electrode. (4) The mercury from the dropping electrode had to be removed in a manner to minimize contact with the electrolyte. Any mercurous chloride formed through interaction of the mercury with the electrolyte might affect the dropping electrode potential. (5) To permit continuous operation, it was advisable to construct the cell in such a manner as to permit cautious partial replacement of the electrolyte. This prevented accumulation of contaminants over a long period of time.

A schematic diagram of the apparatus which was employed in this study is shown in Fig. 2. The apparatus was designed to meet the conditions previously set forth.

Operation of the Unit.—The electrolyte in a 1-liter stoppered flask (Reservoir A) in Fig. 2 was maintained at constant head in the scrubbing vessel B. The solution was allowed to flow at a predetermined rate of 1.1 ml. per minute through capillary tube C into the dropping mercury electrode cell D, past the silver–silver chloride reference electrode E, to the outlet F.

The gas sample was first saturated with water vapor from the electrolyte solution in vessel G and then part of the gas stream was forced through the fritted glass disc H into the scrubbing vessel B where the electrolyte received a preliminary scrubbing with the gas sample. The final solubility equilibrium between the oxygen in the sample and the electrolyte solution was obtained by passing another portion of the gas stream through the fritted disc I into the dropping mercury electrode cell. The gas was allowed to escape through two spray trap bulbs, J and K, on either side of the cell.

Mercury from reservoir L was forced through the dropping mercury electrode capillary M. The funnel-shaped shield, surrounding the tip of the capillary, served to protect the slowly forming mercury drops from agitation of the rising gas bubbles, and also to direct the mercury drops into the siphon, thus removing them from the cell.

An important feature of the design of the equipment was the continuous removal of any reducible materials such as mercurous chloride and silver chloride which would form at the electrodes in small concentrations in a stationary system. The flow of electrolyte was in such a direction as to prevent the accumulation of calomel around the dropping electrode. For the same reason, the reference electrode was situated in the outflowing stream of electrolyte.

Operational Characteristics of Cell Assembly.—To determine the rate of approach to solubility equilibrium, the rate of change of the potential difference was determined using purified nitrogen as the gas sample. Starting with an air-saturated 0.1 *N* potassium chloride solution throughout the reservoirs and the cell, a thousand-fold decrease in oxygen concentration was observed in one minute.

To check the possible interference from back-diffusion of oxygen, the nitrogen stream was shut off after reaching a constant potential reading. No noticeable change in potential (less than 1 millivolt) was observed after 5 minutes of standing.

Potential Measurements.—A Beckman Research Model G *p*H meter, operated as a millivoltmeter, was used for the measurement of the cell e. m. f. This instrument was found to be particularly suitable because of its sensitivity and rapid response. In an undamped system, the meter was permitted to remain continuously in the circuit, and the maximum e. m. f. developed during the formation of each drop was determined by balancing the slide wire so that the galvanometer showed zero deflection at the end of the drop formation.

To determine whether the e. m. f. in a damped system corresponds to the maximum e. m. f., a condenser of 16 m. f. d. capacitance was connected across the dropping electrode system. The observed non-fluctuating e. m. f. was found to be identical (within 2 millivolts) with the maximum e. m. f. observed in the undamped system, as was expected from the theoretical considerations. Since it was found that a time lag of two to three minutes was introduced by the necessity of charging the condenser, it proved to be more convenient to measure the maximum e. m. f. in the undamped system. However, a damped system would probably be more practicable in a continuously recording apparatus.

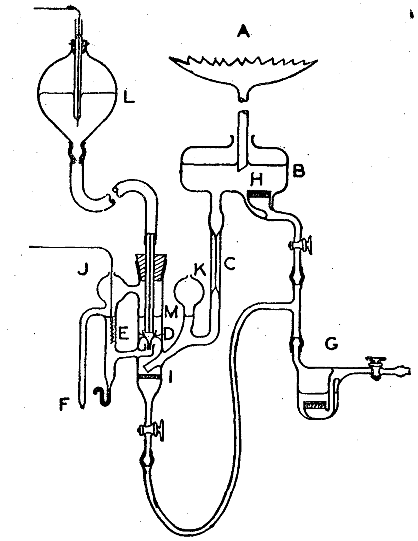


Fig. 2.

Results and Discussions

Variation of Potential with Concentration.—A series of oxygen–nitrogen mixtures of known composition was obtained from General Electric Wire Works, Cleveland, Ohio. The oxygen contents of the samples were 0.200, 0.554 and 1.028%. The mixture with lowest oxygen content was prepared by accurately mixing pure oxygen and nitrogen, while the other mixtures were prepared by mixing and analysis by a combustion method. The oxygen content for each mixture was guaranteed to be accurate to within 0.01 per cent. (absolute).

Air-free nitrogen was prepared by the conventional method of passage over copper turnings heated to 400°. The purity was indicated by the fact that the maximum potential difference developed during the formation of the mercury drops was less than 2 millivolts (corresponding to less than 0.005% of oxygen). The e. m. f. observed with the purified nitrogen against the particular silver–silver chloride electrode in 0.1 *N* KCl was 500 millivolts, as compared with the theoretical value of 558 millivolts calculated from the potential of the electrocapillary maximum (550 millivolts in 0.1 *N* KCl against normal calomel electrode). The disagreement would correspond to 0.1% of oxygen, and a fluctuation of 58 millivolts would then be expected during the drop formation. The discrepancy may be partly attributed to a lack of equilibrium at the silver–silver chloride electrode, but should be further investigated. For all practical purposes, the value of 500 millivolts can be used as the potential corresponding to the electrocapillary maximum because the error could not exceed 0.005% of oxygen.

The observed ΔE values, using 1 N potassium chloride as the electrolyte, are plotted against the oxygen concentration in Fig. 3 (A). The curve is linear for oxygen concentrations from 0 to 0.5% but shows a slight curvature at 1.0%.

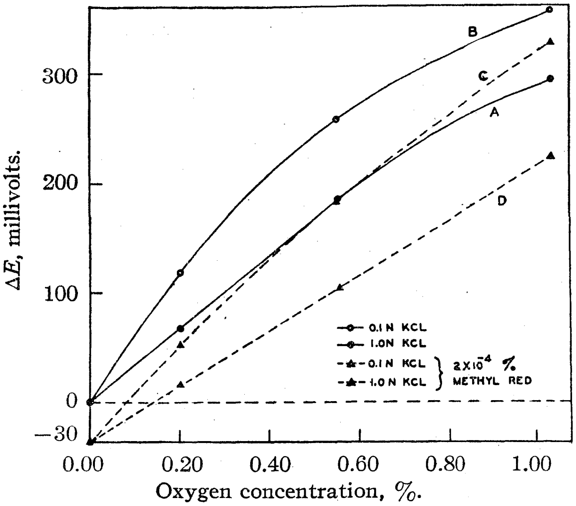


Fig. 3.—Potential shift *vs.* O_2 concentration.

A similar plot, Fig. 3 (B), with 0.1 N potassium chloride as the electrolyte, shows a more pronounced curvature and a greater sensitivity for a given percentage of oxygen. The change in sensitivity can be attributed to the increase in oxygen solubility and to the decrease in capacity of the double layer as the potassium chloride concentration is decreased.

A strict proportionality between ($E - E_{\text{max.}}$) and concentration could not be expected to hold for an ($E - E_{\text{max.}}$) value greater than about 300 millivolts since the diffusion current of oxygen is not reached until a potential of about minus 200 millivolts (with reference to silver–silver chloride). Other factors which could affect the linear relationship are a lack of constancy of the capacity of the double layer at varying potentials, especially in dilute salt solutions, and a maximum on the oxygen-reduction curve induced by effects of electrical stirring.[7] Such a maximum can be suppressed by the addition of capillary-active substances, which compress the electrical double layer at the mercury–solution interface, and therefore would also increase the capacity of the double layer. Thus, the sensitivity would be decreased by the addition of maximum suppressing agents.

These effects were studied by the addition of 2×10^{-4}% of methyl red as a maximum suppressor. The range of linearity was increased and the sensitivity was decreased both in 0.1 N and 1 N potassium chloride, as is shown in Fig. 3 (C and D, respectively). Methyl red undergoes reduction at the dropping mercury electrode at a potential slightly more positive than the electrocapillary maximum. Therefore, the curves can be extrapolated to a false oxygen content at zero potential, because methyl red behaves like oxygen in producing a cathodic current.

Further work is in progress to find a suitable non-reducible oxygen suppressor for practical analytical work.

The data represented in Fig. 3 were obtained at a drop time of approximately 3.7 seconds, except for curve C which was obtained at 2.8 seconds per drop.

Variations of Potential with Flow Rate of Mercury.—According to equation (7), the observed potential difference should be independent of the rate of flow of mercury through the capillary. This would indicate that the experimental readings would be independent of the capillary characteristics, and dependent only on the drop time. Experimental verification of this lack of dependency would be of considerable practical importance for routine analytical purposes.

In Fig. 4, the observed potential values at two known oxygen concentrations are plotted against the rate of flow of mercury for several capillaries chosen to cover a wide range of values of "m." The measurements were made at a constant drop rate to eliminate this variable. It is evident from the curve that the observed potential is for all practical purposes independent of "m" over a twofold change in the flow rate. The slight variation is probably due to a deviation from the Ilkovic equation because of the large drops associated with large "m" values.

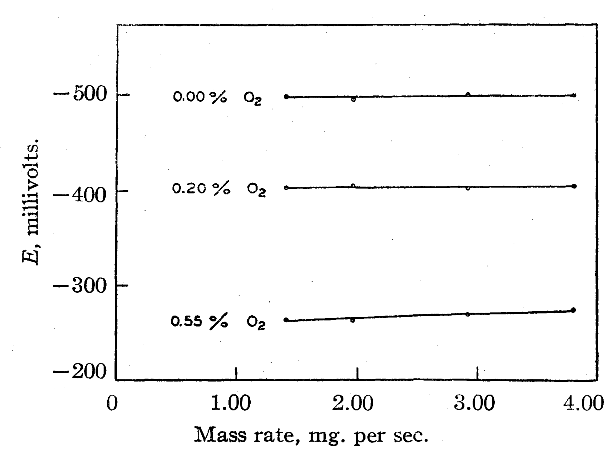


Fig. 4.—Effect of mass rate on observed potential: electrolyte, 0.1 N KCl; drop time, 4.0 sec.

Variation of Potential with Drop Time.—Since the instantaneous potential of the dropping

---

[7] J. Rasch, *Collection Czechoslovak Chem. Commun.*, **1**, 560 (1929); E. Varasove, *ibid.*, **2**, 8 (1930); B. Rayman, *ibid.*, **3**, 314 (1931); E. Hamamoto, *ibid.*, **5**, 427 (1933).

mercury electrode should vary linearly with the square root of time (equation 8) and is independent of "m," the maximum e. m. f. for a constant oxygen concentration should give a straight line when plotted against the square root of drop time, either for various capillaries or for a given capillary operated at various heights of a mercury column.

In Figure 5, ΔE is plotted as a function of $t^{1/2}$ for a single capillary (m = 2.27 milligrams per second; t = 3.52 seconds at 55 centimeters of mercury pressure) operated at various heights of a mercury column. The three standard oxygen mixtures were studied in 0.1 N potassium chloride in the presence and absence of methyl red. In the absence of methyl red, a distinct curvature was noted at short drop times, under which conditions the oxygen maximum is known to be most pronounced.[8] In the presence of methyl red, a linear relationship was observed over a range of drop time from 2 to 6 seconds, except in cases where the e. m. f. exceeded 300 millivolts, above which the true diffusion current of oxygen is not reached and linearity would no longer be expected.

In practice, it is recommended that a drop time of 3 to 5 seconds be used.

Application to Gases.—The new method should be applicable to a wide variety of gases, such as nitrogen, hydrogen or hydrocarbon gas mixtures, since such gases are in general inert at the dropping mercury electrode at the range of potentials involved. The only serious interferences which can be foreseen would be caused by strong oxidizing agents, such as halogen vapors which are readily reducible at the dropping electrode, and by materials which anodically depolarize the dropping electrode by the formation of insoluble mercury salts or stable mercury complexes. Examples of the latter class of interfering materials are hydrogen sulfide and hydrocyanic acid.

Substances that are readily adsorbed on the mercury surface would be expected to change the sensitivity of the method. For example, naphthalene and mercaptan vapors would be expected to show such adsorption effects. It would seem likely that the addition of maximum suppressing agents which themselves are strongly adsorbed would minimize the interference of adsorbable impurities in the sample. Capillary-active ions such as iodide would shift the electro-capillary maximum in addition to changing the capacity of the double layer.

Application to Water or Aqueous Solutions.—In principle, the method could be applied in the absence of oxygen to the determination of traces of strong oxidizing agents in aqueous solutions.

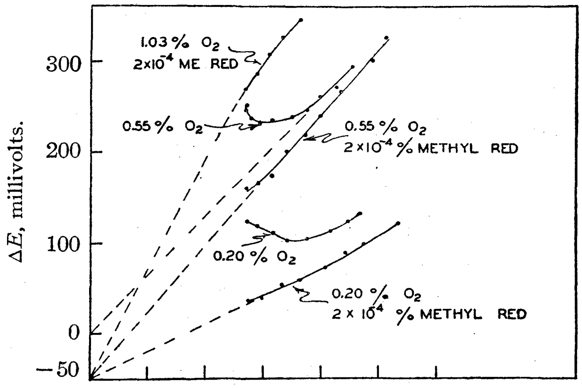


Fig. 5.

In addition to the interferences mentioned for gaseous substances, interference would be caused by many strong oxidizing agents in solution in water. Examples are ferric iron, permanganate and mercurous or mercuric salts, all of which are reducible at potentials more positive than the electrocapillary maximum and which would show the same effect as oxygen.

The change in the capacity of the double layer with changing electrolyte concentration and by adsorbable materials such as soaps or proteins would be a more serious problem in the analysis of solutions, especially in the case of essentially electrolyte-free water.

Conclusions

1. A simple, rapid and sensitive potentiometric method for the determination of traces of oxygen in gases or in solution, based upon measurement of the null potential of a dropping mercury electrode, has been developed.

2. The maximum potential difference developed during the growth of the mercury drops varied linearly with oxygen concentration over a potential range of zero to 300 millivolts, in the presence of maximum-suppressing agents. The potential varied as the square root of the drop time and was independent of the rate of flow of mercury through the capillary at a constant drop time.

3. Using 0.1 N potassium chloride, with a trace of methyl red as a maximum suppressor, the method was sensitive to 0.01 per cent. of oxygen in a gas; linear relationship was attained over the range of zero to 1 per cent. of oxygen.

4. The sensitivity of the method varied with changes in the capacity of the electrical double layer at the mercury solution interface caused by changes in electrolyte concentration or by traces of capillary-active materials.

RECEIVED JUNE 23, 1947

---

[8] J. Heyrovsky, "A Polarographic Study of the Electrokinetic Phenomena of Adsorption, Electroreduction and Overpotential displayed at the Dropping Mercury Cathode," Actualities Scientifiques et Industrielles, No. 90, Paris, 1934.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Thermodynamics of Hexafluoroethane from Calorimetric and Spectroscopic Data

BY E. L. PACE[1] AND J. G. ASTON

The existence of barriers hindering the mutual internal rotation of methyl groups in a wide variety of compounds has been demonstrated from thermal, spectroscopic and other sources. An empirical method of calculation has been proposed, based on the assumption that the value of the potential barrier hindering the rotation of the groups depends exclusively on repulsive forces between hydrogen atoms.[2] The discovery of barriers in 1,1,1-trifluoroethane[3] and 1,1,1-trichloroethane[4] of the order of 3000 calories per mole raises the question of whether the restricted rotation is uniquely a function of the repulsion of hydrogen atoms. It was the purpose of the present work with hexafluoroethane, the fluorine analog of ethane, to furnish more information to help answer this question.

The Calorimetric Sample.—The calorimetric sample was prepared and purified at the Fluorine Laboratory of The Pennsylvania State College under the direction of Dr. J. H. Simons.

The sample was freed of air and introduced into the calorimeter in the customary manner. The heat capacity, the heat of transition and the heat of fusion were determined with this sample. The remaining measurements were made with the portion of the original sample remaining after the first 1.5 cc. of product withdrawn from the low-temperature column had been discarded. This fractionation was found necessary when a preliminary set of vapor pressures indicated the presence of a small amount of highly volatile impurity. The operation removed about 75% of the volatile impurity and made it possible to obtain a satisfactory set of vapor pressures.

The Heat Capacity Measurements.—The apparatus and method used in the determination of the heat capacities has been previously described.[5a,b] The temperature indications of thermocouple S-7 were used as a standard with thermocouple S-4 as a check. Correction was made for the change in the calibration of these thermocouples based on a recent comparison with oxygen and normal hydrogen vapor pressures. At the oxygen boiling point the indication of thermocouple S-7 was 0.02° and thermocouple S-4 was 0.04° lower than the last comparison. At the hydrogen triple and boiling point S-7 was 0.08° and S-4 0.2° lower than the last comparison. One calorie is taken equal to 4.1833 international joules. The temperatures are reported on the basis of 273.16° K. as the ice-point temperature.

The heat capacities as measured are listed in Table I. The values at rounded temperatures are summarized in Table II. Because the slope of the heat capacity curve in the premelting region showed no abrupt change it was not possible to estimate the temperature at which premelting of the sample began or to extrapolate the curve of heat capacities with no premelting. Therefore no correction was made for premelting in the heat capacities below the melting point.

TABLE I

THE MOLAL HEAT CAPACITY OF HEXAFLUOROETHANE

Mol. wt. 138.02; 0.44183 mole, 99.84 mole per cent. pure; 0.0°C. = 273.16°K.; 1 cal. = 4.1833 int. joules.

Temp., °K.	C_p, cal./deg./mole
Crystal I	
Series III	
11.51	1.885
12.57	2.269
14.26	3.020
16.40	3.913
18.59	4.994
21.15	6.056
24.06	7.081
27.51	8.117
31.64	9.148
36.10	10.196
40.81	11.158
45.86	12.014
51.20	12.713
56.54	13.33
61.84	13.96
67.12	14.65
Series IV	
73.27	15.36
81.44	16.30
89.45	17.23
97.14	18.31
Series I	
59.11	13.64
66.24	14.52
72.85	15.31
77.78	15.89
Series II	
87.60	16.98
93.10	17.76
98.75	18.61
Crystal II	
Series V	
110.92	21.01
117.24	21.30
123.81	21.68
130.37	22.08
137.77	22.70
145.32	23.39
152.00	24.26
158.53	25.25
Series VI	
110.96	21.03
118.93	21.40
126.91	21.91
133.95	22.44
141.17	23.04
148.61	23.86
156.25	24.87
163.64	26.15
Liquid	
Series VII	
174.88	29.62
177.71	29.79
180.97	29.96
184.28	30.22
187.51	30.49
190.67	30.86
Series VIII	
176.77	29.67
180.94	29.89
185.26	30.26
190.40	30.84

---

[1] Phillips Petroleum Fellow, 1944–1946.

[2] Aston, Isserow, Szasz and Kennedy, *J. Chem. Phys.*, **12**, 336 (1944).

[3] Russell, Golding and Yost, THIS JOURNAL, **66**, 16 (1944).

[4] Rubin, Levedahl and Yost, *ibid.*, **66**, 279 (1944).

[5] (a) Aston and Messerly, *ibid.*, **58**, 2354 (1936); (b) Messerly and Aston, *ibid.*, **62**, 886 (1940).

TABLE II

THE MOLAL HEAT CAPACITY OF HEXAFLUOROETHANE AT ROUNDED TEMPERATURES

Mol. wt. 138.02, 0°C. = 273.16°K.; 1 cal. = 4.1833 int. joules.

Temp., °K.	C_p, cal./deg./mole	Temp., °K.	C_p, cal./deg./mole
Crystal I		Crystal II	
12	2.070	105	20.75
15	3.285	110	20.97
20	5.590	120	21.46
25	7.330	130	22.09
30	8.740	140	22.89
35	9.945	150	23.98
40	11.000	160	25.50
50	12.55	170	27.42
60	13.75	Liquid	
70	14.98	175	29.62
80	16.15	180	29.88
90	17.31	185	30.25
100	18.79	190	30.77
		195	31.38

Allowance was made for vaporization and sublimation of the sample into the filling by making use of the density of the liquid and solid[6] and the measured vapor pressures and heats of vaporization. In the worst case this correction amounted to 3% in the energy and 0.7% in the number of moles of sample.

The accuracy of the calorimeter is normally 0.3% in the temperature range between 30 and 200° K. However, at the higher temperatures because of the uncertainty introduced by the presence of appreciable amounts of the sample in the filling line the accuracy may fall to 0.5%. Below 30° K. the error may rise to 1% at 20° K. and 5% at 12° K. due to uncertainty in the derivative of the resistance thermometer and the insensitivity of the standard thermocouples. Actually, the heat capacities below 20° K. deviate from a smooth curve by less than 1%. Runs made in duplicate over the entire temperature range above 55° K. reproduced the heat capacity curve with a precision well within the value stated above.

The Solid–Liquid–Vapor Triple Point.—The triple point was determined by observing the equilibrium temperature of the solid, liquid and vapor as increasing fractions of the sample were melted by the addition of measured quantities of energy. From these data and the heat of fusion, the amount of liquid soluble, solid insoluble impurity was found to be 0.16 mole per cent. for the first sample introduced into the calorimeter. After removal of this sample from the calorimeter and fractionation through the laboratory low-temperature column, the amount of liquid soluble, solid insoluble impurity was reduced to 0.08 mole per cent.

The solid–liquid–vapor triple point calculated for the pure compound was 173.09 ± 0.05° K. for the first sample and 173.11 ± 0.05° K. for the second. The average value was 173.10 ± 0.05° K. Values reported in the literature are 172.7° K. (−100.5° C.)[6] and 176.9° K. (−106.3° C.)[7].

The Vapor Pressure.—The vapor pressure of the liquid and solid hexafluoroethane was measured in the usual manner.[5a,b] The values listed are for international millimeters of mercury.

The data were fitted by equations derived by the method of least squares. The equation for the liquid is

$$\log_{10}P_{\text{mm.}} = -\frac{1125.329}{T} - 2.33917\log_{10}T - 0.00109858T + 14.22568 \quad (1)$$

and for the solid

$$\log_{10}P_{\text{mm.}} = -\frac{2227.0}{T} - 0.0915\log_{10}T - 0.05161T + 24.307 \quad (2)$$

Vapor pressure determinations made after one third of the sample had been distilled from the calorimeter indicated the presence of a volatile impurity which affected the pressures by an amount corresponding to 0.05° near the normal boiling point.

The observed vapor pressures differed, on the average, from those calculated from the formulas by ±1.4 mm. for the solid and ±0.02 mm. for the liquid. The vapor pressures observed by Ruff and Bretschneider[6] were 6 to 10 mm. higher for the solid and 5 mm. higher to 10 mm. lower for the liquid.

Because of the presence of a small amount of volatile impurity in the sample satisfactory equilibrium was not obtained in the vapor pressure of the solid even though the sample was allowed to stand for several hours before each measurement was made. However, the impurity did not noticeably disturb the equilibrium in the case of the liquid vapor pressures.

The triple point pressure was determined from observation of the equilibrium pressure simultaneously with the equilibrium temperature during the determination of the triple point and purity of the sample.

The equilibrium triple point pressure was calculated by adding to the pressure (extrapolated) at the 100% melted point the pressure rise for the sample from the 50% melted to the 100% melted point. The equilibrium triple point temperature was determined in an analogous manner.

The normal boiling point of hexafluoroethane calculated from the vapor pressure equation (1) is 194.87° K. (−78.29° C.). Values previously reported in the literature are −78.1° C. (195.1° K.; 0.0° C. = 273.16° K.)[6] and −79° to −78.6° C. (194.2 to 194.6° K.)[7]

The Heat of Transition and Transition Temperature.—The method used in measuring these properties in a similar case has been previously described.[5a] The data are summarized in Tables III and IV.

---

[6] Ruff and Bretschneider, *Z. anorg. allgem. Chem.*, **210**, 173 (1933).

[7] Swarts, *Bull. soc. chim. Belg.*, **42**, 114 (1933).

TABLE III

THE HEAT OF TRANSITION OF HEXAFLUOROETHANE

Mol. wt. 138.02; 0.44183 mole; 0°C. = 273.16°K.; 1 cal. = 4.1833 int. joules.

Temp. interval, °K.	Total cor. heat input cal./mole	$\int C_p dT$ cal./mole	ΔH transition cal./mole
100.223–109.172	1179.9	−287.8	892.1
99.946–107.543	1134.6	−241.5	893.1
100.537–107.454	1114.6	−221.2	893.4
		Average	892.9 ± 1.7

TABLE IV

EQUILIBRIUM TEMPERATURES OF THE TRANSITION OF HEXAFLUOROETHANE

% Transformed	T, °K. S-7
14.8	103.86
46.3	104.00
78.0	104.05
(100.0) (extrapolated)	104.10
Average	103.98

The Heat of Fusion.—The data for the heat of fusion are summarized in Table V. Because the heat capacity curve below the triple point did not have the usual change in shape resulting from the effect of premelting the heat capacity values were used with no premelting correction in applying the $\int C_p dT$ correction. The weight of the sample was corrected for vaporization into the filling line of the calorimeter.

TABLE V

THE HEAT OF FUSION OF HEXAFLUOROETHANE

Mol. wt. 138.02; 0.44183 mole; triple point 173.10 ± 0.05°K.; 0°C. = 273.16°K.; 1 cal. = 4.1833 int. joules.

Temp. interval, °K.	Total cor. heat input, cal./mole	$\int C_p dT$ cal./mole	ΔH, cal./mole
168.471–174.406	894.0	−252.0	642.0
167.333–174.603	948.6	−307.4	641.2
168.543–173.806	863.6	−221.8	641.8
		Average	641.7 ± 1.5

The Heat of Vaporization.—The heat of vaporization was measured in the usual manner.[8] The results are listed in Table VI. The molal heat of vaporization at the normal boiling point calculated from the equation in the table is 3859.7 calories.

The Vapor Density.—The vapor density, determined in the usual manner,[8] is summarized in Table VII.

The molecular weight calculated by the method of limiting density is 138.26. The formula weight of the pure compound is 138.02.

The second virial coefficient at 298.16° K. in the last column of Table IX was calculated from the density data. The discrepancies noted in individual values indicate an uncertainty of about ±10%. The experimental coefficients are in good agreement with the value of −0.268 liter/mole calculated from the modified Berthelot equation of state with a value of 292.9° K. for T_c as given by Swarts[7] and 29.9 atm. for P_c as determined from T_c by the empirical method of Meissner and Redding.[9a] Using the three and five constant equations of state, respectively, derived by Gouq Su[9b] we obtain −0.244 and −0.262.

TABLE VI

THE HEAT OF VAPORIZATION OF HEXAFLUOROETHANE

Mol. wt. 138.02; 0°C. = 273.16°K.; 1 cal. = 4.1833 int. joules.

Moles vaporized	Mean temp. of vaporization, °K.	Total cor. heat input, cal./mole	$\int C_p dT$ cal./mole	ΔH at mean temp. of vaporization to real gas state cal./mole Obsd.	Calcd.[a]
0.09578	179.96	4062.9	−20.8	4042.1	4038.9
.09499	180.22	4101.9	−67.0	4034.9	4035.8
.09496	188.30	3923.0	+10.8	3933.8	3938.7
.09556	190.05	3878.4	+30.1	3908.5	3917.7
.11406	194.87	3880.0	−22.6	3857.4	3859.7
.11436	194.90	3896.9	−36.9	3860.0	3859.4
.11169	195.10	3871.8	−10.0	3861.8	3857.0
.12946	195.21	3874.9	−11.5	3863.4	3855.7

[a] Calculated from $\Delta H = 6201.1 - 12.015T$.

TABLE VII

THE VAPOR DENSITY OF HEXAFLUOROETHANE AT 298.16° K.

Pressure, atm.	Density, g./cc.	P/d, obs.	P/d, calcd.[a]	B,[c] liters/mole
0.99938	0.0056995	175.347	175.415	−0.224
.99066	.0056464	175.449	175.430	− .212
.78270	.0044522	175.801	175.758	− .208
.69896	.0039740	175.883	175.890	− .216
.68887	.0039144	175.984	175.905	− .199
.63925	.0036331	175.952	175.984	− .222
.47859	.0027161	176.205	176.236	− .223
.00000		176.983[b]		

[a] Calculated from $P/d = 176.983 - 275.07d$. [b] Extrapolated. [c] $B = -0.268$ from Berthelot equation, $B = \left(\frac{9PV_gT_c}{128P_cT}\right)\left(1 - 6\frac{T_c^2}{T^2}\right)$ $T_c = 292.9$°K, $P_c = 29.9$ atm.

The Second Virial Coefficients from Heats of Vaporization and Vapor Pressures.—The second virial coefficients can be determined as a function of temperature from the heat of vaporization and vapor pressure data. The method has been described previously.[10] The data are summarized in Table VIII. In view of the agreement of the value of B obtained above using the five constant equation of Gouq Su with that from the Berthelot equation, further tests of his equation were not made.

The Entropy from Calorimetric Data.—The calculations of the entropy for the liquid at the melting point, for the gas at a temperature of 176.61° K. at which its vapor pressure is $^1/_3$ atm., and for the gas at the normal boiling point are summarized in Tables IXa and IXb.

---

(8) Aston, Sagenkahn, Szasz, Moessen and Zuhr, THIS JOURNAL, **66**, 1171 (1944).

(9) (a) Meissner and Redding, *Ind. Eng. Chem.*, **34**, 521 (1942); (b) Gouq Su, *ibid.*, **38**, 803 (1946).

(10) Aston, Fink, Bestul, Pace and Szasz, THIS JOURNAL, **68**, 52 (1946).

TABLE VIII

VOLUMES OF SATURATED VAPOR OF HEXAFLUOROETHANE FROM HEATS OF VAPORIZATION AND VAPOR PRESSURES

T, °K.	P, atm.	dP/dT, mm./deg.	ΔH, cal./mole	V_l, liters/mole	V_g, liters/mole	B, liters/mole This research	B, liters/mole Berthelot[a]
179.96	0.41563	20.369	4042.1	0.083	34.694	−0.837	−0.822
180.22	.42265	20.644	4034.9	.083	34.132	− .815	− .819
188.30	.69261	30.597	3933.8	.084	21.515	− .758	− .738
190.05	.76593	33.123	3908.5	.085	19.572	− .766	− .721
194.87	.99979	40.804	3857.4	.086	15.312	− .641	− .678
194.90	1.00141	40.856	3860.0	.086	15.310	− .653	− .678
195.10	1.01220	41.198	3861.8	.086	15.166	− .611	− .676
195.21	1.01820	41.388	3863.4	.086	15.095	− .624	− .675

[a] Calculated from Berthelot equation.

TABLE IXa

THE MOLAL ENTROPY OF LIQUID HEXAFLUOROETHANE

Mol. wt. 138.02; 0°C. = 273.16°K.

	E. u.
0.0–11.35°K., Debye extrapolation (θ = 87.5, 6 degrees of freedom)	0.65
11.35–104.10°K., graphical	21.65
Transition, 892.9/103.98	8.59
104.10–173.10°K., graphical	11.70
Fusion, 641.7/173.10	3.70
Entropy of liquid at solid–liquid–vapor triple point	46.29 ± 0.14

TABLE IXb

THE MOLAL ENTROPY OF GASEOUS HEXAFLUOROETHANE AT CERTAIN TEMPERATURES

Mol. wt. 138.02; 0°C. = 273.16°K.

	E. u. 176.61° K.	E. u. 194.87° K.
Liquid at triple point	46.29	46.29
173.10-T°K., graphical	0.62	3.59
Vaporization at T°K.	23.10	19.81
Gas imperfection correction	0.09	0.19
Correction to 1 atm.	−2.18	0.00
Entropy, ideal gas at T°K., 1 atm.	67.92 ± 0.20	69.88 ± 0.20

The Entropy from Molecular and Spectroscopic Data.—The molecular data were taken from the available electron diffraction measurements for several fluorinated hydrocarbons including hexafluoroethane.[11] From these data, a C–F bond distance of 1.35 Å. and a C–C distance of 1.45 Å. were assumed. The CF_3 group was assumed to be tetrahedral.

The resulting moments were $I_x = 306.6 \times 10^{-40}$ g. cm.^{2}, $I_y = I_z = 435.6 \times 10^{-40}$ g. cm.^{2} and $I_{\text{red.}} = I_x/4 = 76.7 \times 10^{-40}$ g. cm.^{2} A symmetry number of six for the rigid molecule was used in the calculations.

The entropy due to translation and external rotation was calculated from

$$S_{t+r} = 4.575\ (3/2 \log M + 4 \log T + 1/2 \log I_xI_yI_z - \log 6) + 265.289 \quad (5)$$

where $I_xI_yI_z$ is the product of the principal moments of inertia.

The entropy contribution for the degree of freedom corresponding to the free rotation of the CF_3 group was obtained from

$$S_f = 4.575\ (1/2 \log T + 1/2 \log I_{\text{red.}}\ 10^{-40} - \log n) - 1.540 \quad (6)$$

in which $n = 3$ is used. Because of the presence of restricted rotation, the contribution S_f was reduced by an amount $(S_f - S)$ as given by Pitzer's tables.[12]

The frequency assignment in Table X[13] is based on the infrared spectrum[14] of the gas obtained by Dr. J. Rud Nielsen of the University of Oklahoma Research Institute along with a value of ν_8 obtained at the Naval Research Laboratory by Dr. Donald Smith, and a Raman spectrum[15] of the liquid obtained in the Spectroscopy Laboratory of The Pennsylvania State College under the direction of Dr. D. H. Rank.

TABLE X

THE FREQUENCY ASSIGNMENT FOR HEXAFLUOROETHANE, POINT GROUP D_{3d}

Designation	Description	Species	Activity	Frequency obsd., cm.$^{-1}$
ν_1	CF stretching	A_{1g}	R. pol.	1420
ν_2	CF_3 deformation	A_{1g}	R. pol.	809
ν_3	CC stretching	A_{1g}	R. pol.	349
ν_4	Torsion	A_{1u}	inactive	
ν_5	CF stretching	A_{2u}	I.	1116.9
ν_6	CF_3 deformation	A_{2u}	I.	714.0
ν_7	CF stretching	E_u	I.	1250.5
ν_8	CF_3 deformation	E_u	I.	522.5
ν_9	Bending	E_u	I.	216
ν_{10}	CF stretching	E_g	R. dep.	1237
ν_{11}	CF_3 deformation	E_g	R. dep.	620
ν_{12}	Bending	E_g	R. dep.	380

Calculations of the entropy have been made with the barrier hindering the internal rotation adjusted to obtain the best agreement with experiment. The results at 176.61° K. and 194.87° K. are given in Table XI.

---

[11] Brockway, Secrist and Lucht, Abstracts, Buffalo Meeting of American Chemical Society, September, 1942.

[12] Pitzer, *J. Chem. Phys.*, **5**, 469 (1937).

[13] Frequencies labeled according to Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., New York, N. Y., 1945, p. 343.

[14] From the paper by Nielsen, Richards and McMurry presented at the Symposium on Molecular Structure and Spectroscopy, Columbus, Ohio, June, 1947.

[15] Rank and Pace, *J. Chem. Phys.*, **15**, 39 (1947).

TABLE XI

THE ENTROPY OF HEXAFLUOROETHANE IN THE IDEAL GAS STATE AT CERTAIN TEMPERATURES FROM MOLECULAR AND SPECTROSCOPIC DATA

T, °K.	176.61	194.87
V, cal. per mole	4350	4350
$S_{t,r}$	60.79	61.58
S_f, one degree of freedom	5.73	5.83
S_v	3.97	4.82
$-(S_f - S)$	−2.52	−2.41
Total	67.97	69.82
Calorimetric	67.92	69.88

A potential barrier of 4350 calories per mole restricting the free rotation of the CF_3 group in hexafluoroethane gives the best fit between the theoretical and experimental entropy of the gas.

That a barrier exists is indicated by the appearance of only seven lines in the Raman spectrum. If rotation were free, the activity of the fundamental frequencies of species E_u, when added to that of A_{1g} and E_g which are already active in the Raman spectrum, should result in more lines in the Raman spectrum.

Heat capacity data on the gas would be helpful in confirming the value for the height of the barrier. Its present value indicates that potential barriers are not due to peculiar properties of hydrogen atoms.

Acknowledgments.—We wish to thank Dr. J. H. Simons of the Fluorine Laboratory for the calorimetric sample of high purity. We are indebted to Dr. D. H. Rank of the Spectroscopy Laboratory for the Raman Spectrum and to Dr. J. Rud Nielsen of the University of Oklahoma Research Institute for the infrared spectrum and the aid in its interpretation. The work was made possible by the financial aid provided by the Phillips Petroleum Fellowship.

Summary

1. The heat capacity of hexafluoroethane has been measured from 11.2 to 195.0° K. as well as the density of the gas at 298.16° K.
2. The molal heat of transition of hexafluoroethane has been measured and the average transition temperature determined.
3. The molal heat of fusion together with the solid–liquid–vapor equilibrium temperature of the pure compound has been determined.
4. The vapor pressures of the solid and the liquid to the normal boiling point have been measured.
5. The molal heat of vaporization of hexafluoroethane has been determined for the liquid as a function of the temperature as well as the volumes of the saturated vapor.
6. From the experimental data, the entropy of the gas has been computed at the normal boiling point and at a temperature at which the vapor pressure of the liquid is one-third of an atmosphere.
7. The entropy of the gas has been calculated from a frequency assignment based on the infrared spectrum of the gas and a Raman spectrum of the liquid. A potential barrier of 4350 calories per mole hindering the mutual rotation of the CF_3 groups gives the best agreement between the calculated and the calorimetric entropy.

STATE COLLEGE, PA. RECEIVED APRIL 9, 1947

[CONTRIBUTION FROM WESTERN REGIONAL RESEARCH LABORATORY[1]]

Equilibrium Moisture and X-Ray Diffraction Investigations of Pectinic and Pectic Acids

BY K. J. PALMER, R. C. MERRILL AND M. BALLANTYNE

In order to obtain some insight into the influence of polar groups on the sorption[2] of water by hydrophilic polymers, the equilibrium moisture contents have been determined for a series of pectinic and pectic acids[3] which have methyl ester contents between 0.2 and 10.9%. This range in methyl ester content corresponds to a variation in free carboxyl groups in the polygalacturonic acid part of the sample of about 23 to 99% when the nonuronide content is taken into account. This series of samples, therefore, offers the opportunity of determining the influence of free and esterified carboxyl groups on the equilibrium moisture content at various relative humidities. There was also the possibility that the data could be used to deduce the amount of water associated with the free and esterified carboxyl groups. Unfortunately, this latter possibility is not realized because, as it turned out, the equilibrium moisture content was essentially independent of the degree of esterification.

It is now quite evident that in addition to the polar groups, the packing of the chains in the crystalline regions plays an important role in determining the equilibrium moisture content of many hydrophilic polymers. For this reason, X-ray diffraction photographs of powders of each sample

---

[1] Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Not copyrighted.

[2] The term sorption is used in this paper to indicate the uptake of water; desorption the reverse of this process.

[3] The terms pectinic and pectic acid are used in this paper in accordance with the recommendation of the Committee for Revision of the Nomenclature of Pectic Substances, *Chem. Eng. News*, April 25, 609 (1944).

equilibrated at various relative humidities between zero and 95% were taken. The results of this investigation are reported in this paper.

Experimental

The pectinic and pectic acids were prepared and purified by previously published methods.[4a,b] Table I lists some of the significant analytical data for these compounds. Column one of Table I gives the number of the sample, while column two of Table I gives the methyl ester content as well as the method of de-esterification. The letters A, B and E used in column two of Table I refer to acid,[5] alkaline,[6] and enzymatic[7] de-esterification, respectively. The samples were de-ashed either with ion-exchange resins[4a] or by precipitation in acid alcohol. The ash content of each sample is shown in column three of Table I. The uronic acid content, expressed as uronic acid anhydride, is given in column four of Table I, while column five of this table gives the value of the intrinsic viscosity.

TABLE I

ANALYTICAL DATA FOR THE PECTINIC AND PECTIC ACID SAMPLES USED IN THIS INVESTIGATION

Sample	MeO,[a] %	Ash, %	Uronic acid anhydride, %	Intrinsic viscosity, (η)	De-esterification, %
L51	10.9	0.4	(80)	9.3	(23)
804	8.0 A	1.18	82	4.2	44
L64	7.4 E	0.4	79	5.5	47
L37P	5.8 E	0.4	82	4.8	59
L81	4.5 E	0.5	80	5.2	68
805	3.0 A	1.53	89	2.8	81
L67	2.7 E	0.29	81	3.5	81
619	0.4 B	0.6	86	2.7	97.4
L69	0.2 E	0.2	82	3.7	98.6

[a] The letters A, B and E signify acid, base and enzyme de-esterification, respectively.

Before samples were equilibrated at various relative humidities, they were humidified for forty-eight hours by placing them in a desiccator containing water. Alcohol sorbed as a result of the method of preparation is presumably removed by this procedure.[8] The desorption equilibrium moisture content was obtained in the following manner.[9] Two-hundred milligrams of each humidified sample were put in a small weighing bottle having a ground-glass top. Duplicate bottles of each sample, with tops on edge, were placed in a series of ten vacuum desiccators having relative humidities of 2, 6, 15, 24, 36, 49, 58, 84, 88, and 95%. The relative humidities in the desiccators were controlled by using sulfuric acid solutions of suitable concentrations. The desiccators were then evacuated and allowed to stand in a constant-temperature room held at 25 ± 1° for a period of two weeks. Thereafter the samples were weighed every week. In all cases at the end of five weeks the weights had not varied by more than 0.3 mg. from the weighings of the previous week, except for the samples at 95% relative humidity. In the latter case the weighings fluctuated in general by about 3 mg. This fluctuation was probably due to inadequate temperature control (±1°). At all relative humidities except 95%, equilibrium was assumed to have been reached when the samples maintained constant weight to within 0.3 mg. over a period of one week. At 95% relative humidity, the samples were assumed to be at equilibrium at the end of the five-week period.

The moisture content was determined by heating the samples in a vacuum oven at 70° for sixteen hours and noting the loss in weight. This leads to an essentially constant dry weight, although like the proteins,[10] further heating results in a measurable, though very slight, loss in weight.[11] The percentage loss in weight of the duplicate samples agreed in all cases (except at 95% relative humidity) to within 0.2%. The equilibrium sorption water contents were obtained by placing the vacuum oven-dried samples back into the various constant relative humidity desiccators and determining the gain in weight. The same weighing procedure was followed as described above for desorption.

X-Ray powder photographs were taken by placing some of the equilibrated material in thin-walled soft glass capillaries. The filled capillaries were allowed to stand with one end open in the appropriate sulfuric acid desiccator for an additional week. Upon removal from the desiccators the open end of each of the capillaries was quickly sealed by a small flame. Copper radiation filtered through a thin nickel foil was used.

Results

The equilibrium moisture contents of the various samples investigated, expressed in per cent. of dry weight, are given in Table II. The first column of Table II lists the number of the sample. In the next ten columns the equilibrium moisture contents at 25° are given for the relative humidities shown at the top of the columns. The last column indicates whether equilibrium was attained by desorption or sorption. At relative humidities of 84% and above, the sorption and desorption values were found to be the same within experimental error; therefore, only one value is listed. The moisture contents given for 95% relative humidity are not as accurate as those for the other relative humidities because of the difficulty experienced in reaching what could be reliably taken as a constant weight during equilibration.

Figure 1 shows a plot of the equilibrium moisture content *versus* relative humidity for both sorption and desorption for pectinic acid L81. The moisture isotherm curves are so similar for all the samples investigated that only those for L81 are shown.

The X-ray patterns of pectinic and pectic acids show in general three characteristic reflections,[12] although under certain conditions, such as high water content or heat degradation, several additional reflections appear. A typical X-ray diffraction photograph of a high-molecular weight pectinic acid is shown in Fig. 2. The inner rather diffuse ring is the only one which shows an appreciable variation with water content. Plots of this spacing against moisture content are shown in

---

(4) (a) H. S. Owens, H. Lotzkar, R. C. Merrill and M. Peterson, THIS JOURNAL, **66**, 1178 (1944); (b) T. H. Schultz, H. Lotzkar, H. S. Owens and W. D. Maclay, *J. Phys. Chem.*, **49**, 554 (1945).

(5) A. G. Olsen, R F. Stuewer, E. R. Fehlberg and U. M. Beach, *Ind. Eng. Chem.*, **31**, 1015 (1939).

(6) R. M. McCready, H. S. Owens and W. D. Maclay, *Food Ind.*, **16**, 794 (1944).

(7) H. S. Owens, R. M. McCready and W. D. Maclay, *Ind. Eng. Chem.*, **36**, 936 (1944).

(8) E. F. Jansen, S. W. Waisbrot and E. Rietz, *ibid.*, **16**, 523 (1944).

(9) B. Makower and D. L. Dehority, *ibid.*, **35**, 193 (1943).

(10) H. B. Bull, THIS JOURNAL, **66**, 1499 (1944).

(11) C. M. Johnson, *Ind. Eng. Chem., Anal. Ed.*, **17**, 312 (1945).

(12) K. Wuhrmann and W. Pilnik, *Experimentia*, **1**, 330 (1945). K. J. Palmer, R. C. Merrill, H. S. Owens and M. Ballantyne, *J. Phys. and Colloid Chem.*, **51**, 710 (1947).

Table II

Moisture Contents at 25° in Per Cent. of Dry Weight at the Relative Humidities Shown at the Top of the Column

Sample	2%	6%	15%	24%	36%	49%	58%	84%	88%	95%	Remark
L51	2.5	...	8.3	11.1	14.2	17.4	19.6	26.4	34.5	57	Desorption
	...	4.5	7.7	9.7	11.7	15.8	17.4				Sorption
804	2.6	5.4	...	11.5	..	18.3	20.6	28.7	36.3	44.7	Desorption
L64	2.8	...	9.4	11.8	15.1	18.6	20.3	28.0	36.8	53	Desorption
	...	4.2	7.0	9.1	12.4	16.6	18.6				Sorption
L37P	...	...	8.9	11.3	14.3	17.7	20.0	27.8	37.3	63	Desorption
	...	3.2	7.6	8.9	11.2	16.0	18.1				Sorption
L81	2.8	5.6	9.1	11.6	14.7	18.2	20.5	29	..	52.5	Desorption
	2.0	4.2	6.6	9.0	12.4	16.3	19.1				Sorption
805	2.9	6.0	...	11.8	..	18.1	20.1	29.3	36.6	46.2	Desorption
L67	3.2	5.2	9.4	12.0	15.1	18.4	21.0	30.1	38.7	56	Desorption
	...	...	8.7	10.7	13.1	15.8	19.1				Sorption
619	2.6	5.2	...	10.7	..	17.0	18.9	..	34.4	43.3	Desorption
L69	2.8	5.8	9.1	11.7	14.6	18.3	20.4	28.7	36.9	51	Desorption
	2.0	4.3	6.4	8.9	12.2	15.5	18.5				Sorption

Figs. 3, 4 and 5 for the various samples investigated.

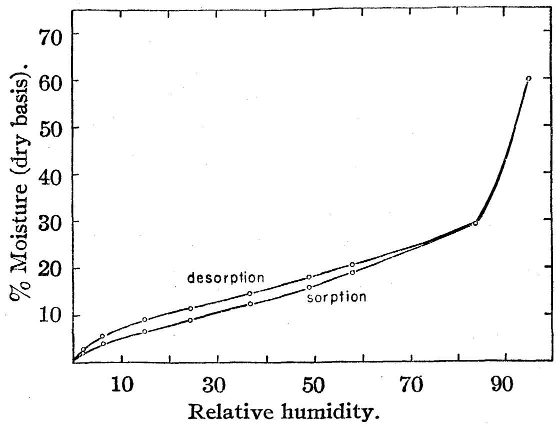


Fig. 1.—Sorption and desorption moisture isotherms for pectinic acid L81 at 25°.

Discussion

Equilibrium Moisture Content.—As shown in Table II, one of the results which is immediately evident from this investigation is that the equilibrium moisture content is essentially independent of methyl ester content over the whole relative humidity range with the possible exception of the results obtained at the highest relative humidities. This is rather surprising in view of the fact that the methyl ester content varies between 10.9 and 0.2%. This represents a change from about one free carboxyl per four galacturonide units to one free carboxyl for each galacturonide unit.

The constancy of the equilibrium water content with variation in free carboxyl groups is illustrated in Fig. 6. In this figure the water sorbed is plotted against the per cent. of free carboxyl groups. The latter value was determined from the uronic anhydride values listed in Table I. For example, sample L64 has a methyl ester content of 7.4% and a uronic anhydride value of 79%. This corresponds to 7.4(100/79) = 9.36% methyl ester on the basis of the galacturonide content. On the same basis completely esterified pure polygalacturonic acid would have a methyl ester content of 17.6%; therefore, 46.6% of the carboxyl groups in L64 are not esterified. The results of similar calculations on the other samples are shown in column six of Table I.

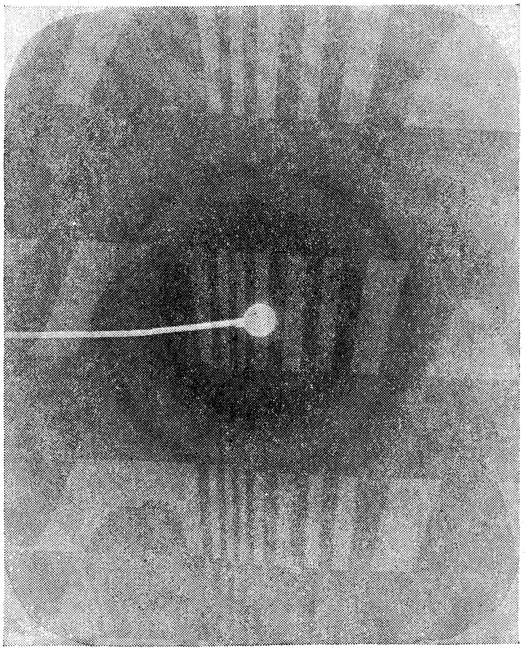


Fig. 2.—X-Ray diffraction photograph of pectinic acid L64, equilibrated at 36% relative humidity. CuKα, Ni filter, camera distance 5.0 cm.

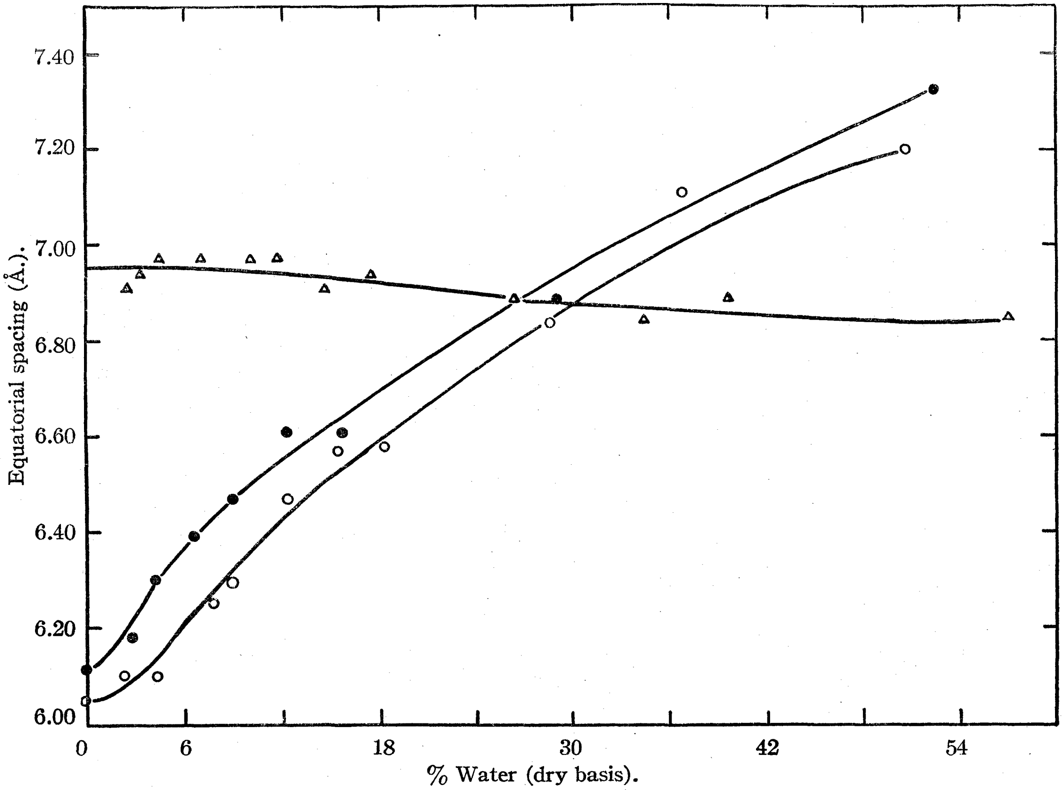


Fig. 3.—Variation of the interplanar spacing calculated from the equatorially accentuated X-ray reflection plotted against moisture content for pectinic acids L51, L81 and for pectic acid L69. Samples equilibrated by sorption: ○ L69, 0.2% MeO; ● L81, 4.5% MeO; △ L51, 10.9% MeO.

The fact that all of the curves in Fig. 6 are essentially horizontal indicates that the number of free carboxyl groups does not affect the equilibrium moisture content of the pectinic acids in the relative humidity range of 2 to 88% at 25°. Results of an equilibrium moisture content study on several proteins[13] indicate that the carboxyl groups in these materials also do not play a major role in determining the water sorption capacity of proteins. On the other hand, a recent study of the equilibrium moisture content of casein and several derivatives in which the amino groups have been benzoylated[14] show that the amino group markedly affects water sorption.

The results obtained in the case of the pectinic acids can be interpreted in several ways. The most obvious is to assume that the hydroxyl groups are primarily responsible for the high water sorption of the pectinic acids. This assumption receives some substantiation from the fact that the equilibrium water content is markedly reduced when the hydroxyl groups are esterified with proprionic acid[15] in contrast to the negligible effect observed when the carboxyl groups are esterified.

On the other hand, the comparatively low water sorption of cellulose and the fact that carboxyl groups usually show a greater affinity for water than hydroxyl groups[16] indicate that the mechanism of water sorption by long-chain polymers involves factors other than the hydration affinity of the polar groups.

One important factor is the availability of the polar groups in the crystalline regions. The fact that water does not penetrate the crystallites in native cellulose, for example, in spite of the numerous polar groups, is well established.[17] The ability of the crystallites in native cellulose, silk and presumably nylon[18] to resist penetration by water is probably due to the fact that the polymer chains can pack well together, because in these substances there are no bulky side chains. The close packing of the chains allows a large number of secondary interchain bonds to be established which, acting together, give rise to a comparatively stable structure.

A second, though closely related, way for a polar

---

(13) H. Fraenkel-Conrat and H. S. Olcott, *J. Biol. Chem.*, **161**, 259 (1945); H. S. Olcott and H. Fraenkel-Conrat, *Ind. Eng. Chem.*, **38**, 104 (1946).

(14) E. F. Mellon, A. H. Korn and S. R. Hoover, THIS JOURNAL, **69**, 827 (1947).

(15) The sorption equilibrium water content of pectin propionate when in equilibrium with an atmosphere having a relative humdity of 50% is only 2.1%.

(16) O. L. Sponsler, J. D. Bath and J. W. Ellis, *J. Phys. Chem.*, **44**, 996 (1940).

(17) P. H. Hermans and A. Weidinger, *J. Colloid Science*, **1**, 185 (1946). See also P. H. Hermans, "Contribution to the Physics of Cellulose," Elsevier Publishing Co., New York, N. Y., 1946, p. 50.

(18) M. Dole and A. D. McLaren, THIS JOURNAL, **69**, 651 (1947).

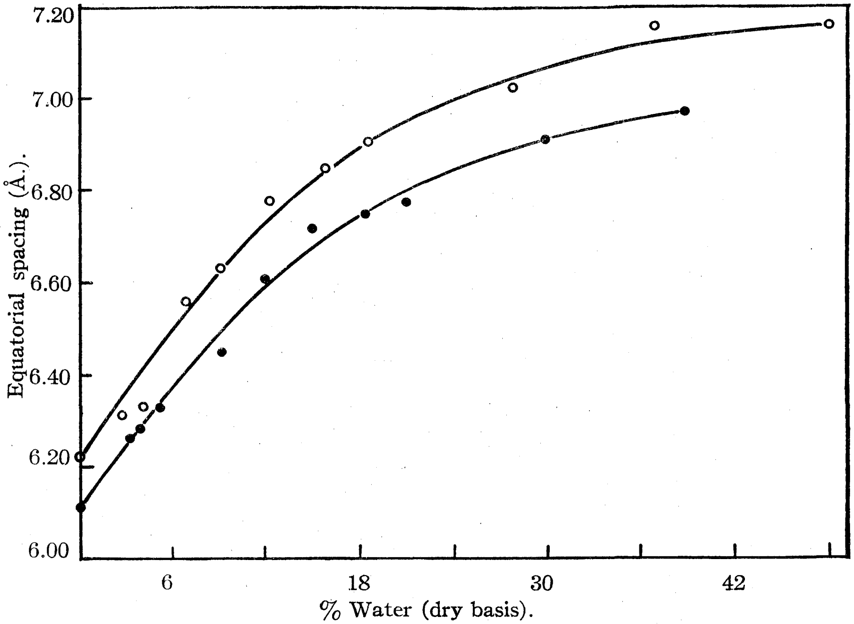


Fig. 4.—Variation of the interplanar spacing calculated from the equatorially accentuated X-ray reflection plotted against moisture content for pectinic acids L64 and L67. Samples equilibrated by sorption: ●, L67, 2.75% MeO; ○, L64, 7.4% MeO.

group to show an unexpectedly low affinity for water is by formation of an interchain bond with another polar group of sufficient strength to resist the dissociating effect of water even though water penetrates between the chains in the crystallites. The pectinic and pectic acids appear to behave in this way. The greater hygroscopicity of the free carboxyl group over the esterified one is probably compensated for in the pectinic acids by the relatively strong interchain hydrogen bonds formed between two adjacent carboxyl groups. The existence of stronger interchain bonds in pectic acid as compared to high methyl ester pectinic acids is substantiated by the fact that pectic acid is not soluble in water at its natural *p*H, whereas the high methyl ester pectinic acids readily go into solution.

Another example of the importance of the availability of the polar groups as sorbing sites in determining the equilibrium moisture content is illustrated by the results found for sodium pectate.[19] The crystallites in sodium pectate sorb a maximum of about 24% water at a relative humidity of 95% at 25°, although the water content of the sample is 64%. The probable reason for this discrepancy is evident from the X-ray photographs. At low moisture contents the X-ray photographs show poor crystallinity; consequently, water readily penetrates between the chains and hydrates the polar groups. When the water content in the crystallites approaches 20% the sodium pectate chains begin to assume a crystalline arrangement. The increase in crystallinity during sorption is apparent from the X-ray photographs.[19] After the hydrated sodium pectate chains have crystallized, the interchain forces (probably involving water bridges) are evidently sufficiently strong to resist further penetration by water molecules. As a consequence the polar groups in the crystallites of sodium pectate are not available for further sorption at relative humidities above about 40% at 25°.

Hysteresis.—In all cases where both desorption and sorption moisture data have been obtained on the pectinic and pectic acids it is evident that a definite hysteresis occurs. Whether the hysteresis is real or due to a very slow approach to equilibrium cannot be stated with certainty, since the definition of equilibrium has been arbitrarily taken as the attainment of a constant weight for one week. The observed hysteresis is reversible in the sense that a sample can be repeatedly taken around the hysteresis loop.

In the two samples L81 and L69 investigated at low relative humidities, the hysteresis appears to persist down to the lowest relative humidities investigated. This has also been observed in many other cases where water sorption is accompanied by swelling,[20] but is not observed, in general, in those cases where the sorbate does not cause swelling.[21] The extension of the hysteresis to essentially zero relative humidity is probably a manifestation of the fact that when swelling occurs the last traces of water to be removed are internally bound, *i.e.*, inside the crystallites, whereas the first water taken up is sorbed in the amorphous regions and on the surface of the crystallites.

This hypothesis is supported by the results obtained on sodium pectate.[19] In this case the X-ray spacings can be more reliably measured than in the case of the pectinic acids and the results show that the interchain separation in the crystallites continues to decrease down to zero moisture content, but on sorption there is a definite lag in the uptake of water by the crystallites. In other words, the crystallites also exhibit a hysteresis which appears to extend to zero moisture content. A similar effect probably occurs in the pectinic acids, although it may be less pronounced and in

---

(19) K. J. Palmer, T. M. Shaw and M. Ballantyne, *J. Polymer Science*, **2**, 318 (1947).

(20) J. B. Speakman, *J. Textile Inst.*, **27**, T185 (1936).

(21) L. F. Gleysteen and V. R. Dietz, *J. Research Nat. Bur. Stds.*, **35**, 285 (1945).

any case is more difficult to demonstrate because the X-ray reflection is too diffuse to measure accurately.

Free Energy and BET Constants.—The free energy of water sorption at saturation is given by the equation

$$\Delta F = \frac{-RT}{M}\int_0^1 \frac{a\mathrm{d}x}{x}$$

where a is the weight of water sorbed per 100 g. of dry sample, x is the relative aqueous vapor pressure, R the gas constant, T the absolute temperature, and M the molecular weight of water.[10,22] The values for ΔF_{25} in column three of Table III were obtained by multiplying the area under plots of a/x against x by RT/M. The values so found for the free energy are from 500 to 1000 cal./mole larger than for the proteins investigated by Bull.[10] Extrapolation of the a/x *versus* x curve to x equals one gives the amount of water, $(a_s)_{25}$, sorbed at saturation per 100 g. of sample. In column four of Table III, the values of $(a_s)_{25}$ are listed. These values are only approximate because of the difficulty of getting reliable moisture data at the relative humidity of 95% and the resulting uncertainty involved when the curve is extrapolated.

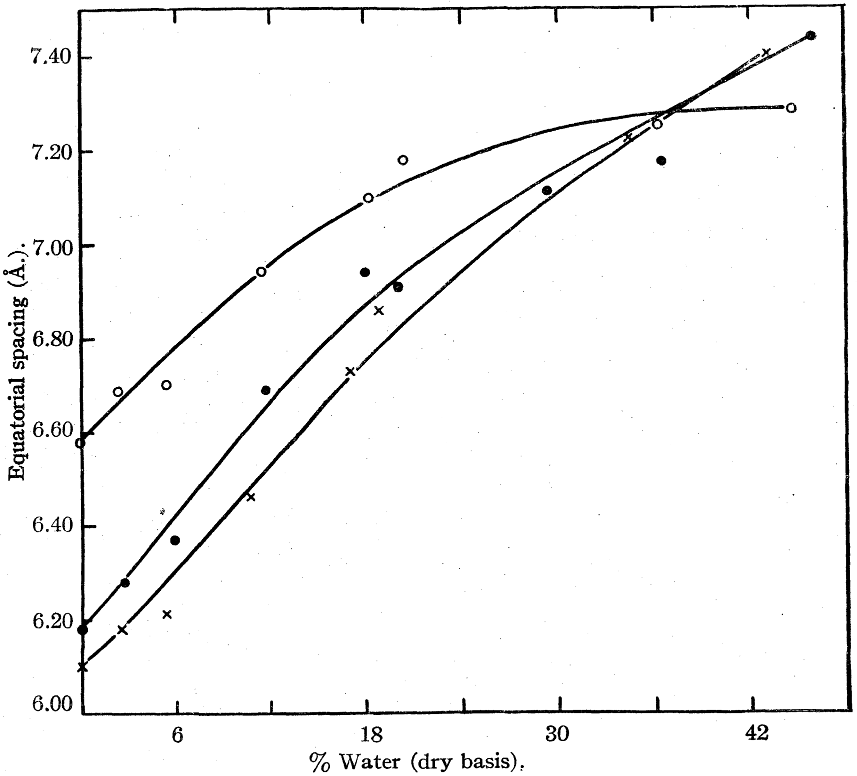


Fig. 5.—Variation of the interplanar spacing calculated from the equatorially accentuated X-ray reflection plotted against moisture content for pectinic acids 804 and 805 and pectic acid 619. Samples equilibrated by desorption: ×, 619, 0.4% MeO; ●, 805, 3.0% MeO; ○, 804, 8.0% MeO.

TABLE III

FREE ENERGY AND BET CONSTANTS CALCULATED FROM SORPTION AND DESORPTION MOISTURE ISOTHERMS

Sample		ΔF_{25} (cal./mole)	$(a_s)_{25}$	a_1	c
L51	Desorption	−1520	78	10.2	16.4
	Sorption			8.3	20.2
804	Desorption	−1620	72	9.1	11.4
L64	Desorption	−1630	76	10.3	16.2
	Sorption			9.5	9.1
L37P	Desorption	−1590	82	10.6	11.1
	Sorption			9.1	7.3
L81	Desorption	−1650	72	10.1	19.8
	Sorption			9.8	7.8
805	Desorption	−1680	72	10.5	15.8
L67	Desorption	−1700	84	10.6	18.9
	Sorption			9.5	19.2
619	Desorption	−1540	56	10.3	14.8
L69	Desorption	−1670	70	9.8	20.4
	Sorption			10.0	6.6

The saturation values, $(a_s)_{25}$, are quite large but appear to be reasonable in view of the high water contents observed at 95% relative humidity.

Stuewer[23] states that ultrafiltration experiments show that an apple pectin in aqueous solution was hydrated to the extent of about one-third of its weight. The values obtained by extrapolation from alcohol solutions indicated hydration to the extent of only about 25%. Both of these values are very much lower than those recorded in Table III.

The application of the adsorption theory of Brunauer, Emmett and Teller (BET)[24] to the observed moisture isotherms of the pectinic and pectic acids has been made in order that the results can be compared with similar analyses on other hydrophilic materials.[10,25]

Plots of $p/a(p_0 - p)$ as a function of x give reasonably straight lines for values of x between 0.15 and 0.45, where a is the grams of water sorbed per 100 g. of dry sample at water vapor pressure p, and p_0 is the water vapor pressure at saturation. The intercept on the ordinate is $1/a_1c$ and the slope is $(c - 1)/a_1c$, where c is approximately

---

(22) G. E. Boyd and H. K. Livingston, THIS JOURNAL, **64**, 2383 (1942).

(23) R. F. Stuewer, *J. Phys. Chem.*, **42**, 305 (1938).

(24) S. Brunauer, P. H. Emmett and E. Teller, THIS JOURNAL, **60**, 309 (1938).

(25) L. Pauling, *ibid.*, **67**, 555 (1945); T. M. Shaw, *J. Chem. Physics*, **12**, 391 (1944).

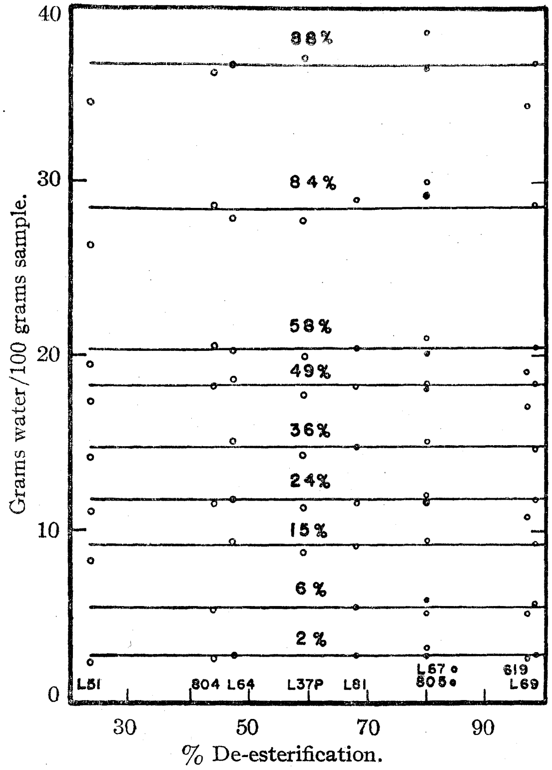


Fig. 6.—Variation of equilibrium moisture content (desorption) with per cent. de-esterification at the nine relative humidities shown on the curves.

equal to $e^{(E_1 - E_e)/RT}$. In the usual application of the BET theory to non-swelling sorbents, E_1 is taken as the heat of adsorption on the first layer, E_e the heat of liquefaction of the sorbate, and a_1 as the grams of sorbate necessary to cover the available surface in 100 grams of sorbent with a monolayer. The values of a_1 and c calculated from the BET plots are given in columns five and six of Table III, respectively.

It is interesting that the magnitude of a_1 is not only approximately constant for all the pectinic acids, but corresponds to about one water molecule per galacturonide unit. This amounts to one water molecule per three polar groups if equal weight is given to the hydroxyl, carboxyl, and esterified carboxyl groups.

X-Ray Spacings.—The X-ray spacing plotted in Figs. 3, 4 and 5 has been shown[12] to arise from planes which are parallel to the polygalacturonide chains. The variation in this spacing, therefore, reflects a change in interchain distance. The curves shown in Figs. 3, 4 and 5 give the variation of this reflection with water content at constant methoxyl content. The variation of this reflection with methoxyl content at constant moisture content can also be deduced from these curves.

It is interesting that when completely dry all but two samples have spacings that fall between 6.05 and 6.22 Å. This difference in spacing is approximately maintained for these same samples throughout the entire moisture range investigated. Of the two anomalous samples, L51 and 804, the pectinic acid sample L51 shows the most striking deviation. As shown in Fig. 3, the X-ray reflection does not appear to change appreciably with water content. This sample has a methoxyl content of 10.9% or about three methyl ester groups per four galacturonide units. The chains in this case evidently cannot coalesce when water is removed because of the prevalence of the methyl ester side chains. The diffuseness of the inner X-ray reflection obtained from L51 increases markedly with decrease in water content, indicating that a very irregular arrangement of the chains occurs when water is removed. At high relative humidities the X-ray reflection under discussion becomes much sharper, and in addition several new rings appear. It is apparent, therefore, that the chains assume a much more regular arrangement when hydrated than when dry. The reason why the interchain distance in L51 does not increase with increase in water content is not known, but may be due to the prevalence along the chain of the hydrophobic methyl groups.

The reason for the slightly different behavior of sample 804 as compared to the other samples may be due to the fact that this sample was acid de-esterified, while L64, which contains a comparable methyl ester content, was enzymatically de-esterified. It has been suggested[4b] that the acid treatment demethoxylates at random, while the enzyme removes the methyl ester groups continuously along the chain with which it is reacting. This results in a significantly different distribution of methyl ester groups after partial demethoxylation and may account for the observed difference in behavior between samples 804 and L64.

The X-ray spacing plotted in Figs. 3, 4 and 5 deviates in a significant way from the similar X-ray spacing of sodium pectate. In the case of sodium pectate, the analogous X-ray spacing increases with water content up to a water content of about 24% and then remains constant.[19] As shown in Figs. 3, 4 and 5, the crystallites in the pectinic and pectic acids, except L51, continue to sorb water throughout the entire range investigated. Swelling in the crystallites appears to be reaching a maximum value in some cases, notably 804, L64 and L67, but at a higher water content than 24%.

This difference in swelling behavior of the crystallites in the pectinic and pectic acids on the one hand, and sodium pectate on the other, is probably due to the higher degree of regularity which exists in the crystallites of sodium pectate as compared to those of the pectinic and pectic acids. The difference in crystallinity is readily apparent from a visual inspection of the X-ray photographs.

It is interesting that the two samples (sodium pectate and L51) in which the crystallites do not swell in the high moisture region are both water soluble, whereas the low methyl ester pectinic acids and pectic acid are not. Evidently the resistance to swelling at high relative humidities at 25° exhibited by the crystallites of sodium pectate and L51 is not related to the behavior of the sample when placed in contact with liquid water.

Acknowledgments.—We wish to express our appreciation to W. D. Maclay, H. S. Owens and R. M. McCready for generously furnishing us with the samples used in this investigation, as well as the analytical data given in Table I. We also wish to thank D. E. Jamison for his help in making some of the BET calculations.

Summary

The equilibrium moisture content at ten relative humidities between zero and 95% are given for seven pectinic and two pectic acids. The moisture content was found to be essentially independent of the methoxyl content.

The free energy change (average about 1600 cal./mole) is considerably higher than found for most proteins.

The BET constants have been calculated. The value of a_1 is nearly the same for all samples and corresponds to approximately one water molecule per galacturonic acid unit.

The variation of the equatorially accentuated X-ray reflection with water content has been determined. These results show that the interchain distance within the crystalline regions increases with increase in water content for all samples, except that having the highest methyl ester content (10.9%). In this latter sample the interchain separation appears to be independent of the water content.

ALBANY, CALIFORNIA RECEIVED JUNE 2, 1947

[CONTRIBUTION FROM THE COATES LABORATORIES, LOUISIANA STATE UNIVERSITY]

The Near Ultraviolet Absorption Spectra of the Vapors of the Monodeuterated Toluenes

BY A. R. CHOPPIN AND C. H. SMITH[1]

The study of the spectra of compounds in which hydrogen is partially or entirely replaced by deuterium is of importance in that it provides data on molecules having the same force constants but different masses and mass distributions. Such data are of assistance in identifying the vibrational forms corresponding to particular frequencies, and provide the additional frequencies which are often needed for the solution of secular equations and the calculation of numerical values for force constants.

Spectral data on deuterium substituted benzene derivatives are rather meager, although such data on benzene itself is extensive.[2,3,4,5] The infrared[6] and ultraviolet[7] absorption spectra of phenol-*d* and aniline-d_2 have been determined, but no report of work on benzene derivatives with nuclear deuteration has been found. This paper presents the results of a study of the near ultraviolet absorption spectra of the vapors of the following compounds: toluene, toluene-α-*d*, toluene-2-*d*, toluene-3-*d*, and toluene-4-*d*.[8] The spectrum of toluene vapor has been extensively investigated by many workers. The latest study is that of Ginsburg, Robertson and Matsen.[9] Such studies of the deuterated toluenes have not been reported.

Experimental

Preparation of Compounds.—Merck "Reagent Grade" toluene was purified by sulfonation, recrystallization of the sodium *p*-toluenesulfonate from saturated sodium chloride solution and regeneration of the toluene by steam distillation of a solution of the sodium *p*-toluenesulfonate in 80% sulfuric acid. The toluene layer was thoroughly washed with sodium hydroxide solution, cold concentrated sulfuric acid and with water. After drying over sodium and distilling over sodium, the middle fraction of the toluene boiled at 110.6 and had a refractive index (n^{20}D) of 1.4965.

Each of the deuterated toluenes was prepared by treating the Grignard reagent, made from the appropriate halogenated toluene, with an equivalent amount of 99.9% deuterium oxide. Volatile components of the reaction mixture were removed by distillation, using an oil-bath. The temperature of the bath was not allowed to rise above 150°. The distillate was fractionated, using a packed eight-inch column, until the temperature of the vapors had risen to 50°. The distillate from the fractionation contained most of the ether and was discarded. The residue from the fractionation was thoroughly extracted with cold concentrated hydrochloric acid in order to remove the remainder of the ether. Then it was

---

[1] Ethyl Corporation Research Fellow at Louisiana State University during this research.

[2] Langseth and Lord, *Det. Kgl. Danske Videnskabernes Selskab*, **16**, no. 6 (1938).

[3] Bailey, Hale, Ingold and Thompson, *J. Chem. Soc.*, 931 (1936).

[4] Miller and Crawford, *J. Chem. Phys.*, **14**, 292 (1946).

[5] Bailey, Hale, Herzfeld, Ingold, Leckie and Poole, *J. Chem. Soc.*, 255 (1946).

[6] Williams, Hofstadter and Herman, *J. Chem. Phys.*, **7**, 802 (1939).

[7] Ginsburg, Symposium on "Color and the Electronic Structure of Complex Molecules," Northwestern University, December, 1946.

[8] The nomenclature of the deuterated compounds corresponds to that recommended by the American Chemical Society Committee on Nomenclature, Spelling and Pronunciation, *Ind. Eng. Chem.*, *News Ed.*, **13**, 200 (1935). This is a modification of the nomenclature suggested by Boughton, *Science*, **79**, 159 (1934).

[9] Ginsburg, Robertson and Matsen, *J. Chem. Phys.*, **14**, 511 (1946).

washed, dried and distilled to obtain the deuterated toluene. The deuterated compounds were prepared from the following halogenated compounds: toluene-*α*-*d* from benzyl chloride; toluene-2-*d* from *o*-bromotoluene; toluene-3-*d* from *m*-bromotoluene; toluene-4-*d* from *p*-bromotoluene. When the spectra of these compounds were determined it was evident that toluene-2-*d*, toluene-3-*d* and toluene-4-*d* contained some ordinary toluene. The spectrum of toluene-*α*-*d* was so similar to that of ordinary toluene that it was impossible to detect any small amounts of toluene that may have been present. From the intensities of the 0,0 bands of toluene in the spectra of the three ring deuterated toluenes, it was estimated that the latter contained from 5 to 10% toluene.[10,11]

Spectroscopic Procedure.—The spectra were determined using a Bausch and Lomb Large Littrow Spectrograph with a Hanovia Hydrogen Discharge Tube as the source of the ultraviolet continuum. Absorption cells, varying in length from 20 to 100 cm., were constructed of Pyrex with optically flat quartz end pieces. Spectra were determined at temperatures varying from 20 to 150°. The cells were heated by liquids circulating in an outer jacket. A slit width of two microns and an exposure time of three minutes were used. Eastman Spectroscopic Plates, Type IV-O, developed for five minutes in Eastman D-19 at 18°, proved most satisfactory. Positions of the absorption maxima were determined using a visual wave length comparator equipped with a Variac to control the intensity of the light source. Wave numbers were determined by interpolation between the wave numbers of lines of the iron arc. The iron arc was photographed along with the absorption spectrum by means of a Hartmann diaphragm. Wave lengths of the iron lines were determined by comparison with standard prints.[12] Wave numbers of the iron lines were calculated from these wave lengths using the data of Kösters and Lampe on the refractive index of air.[13]

Intensities were determined by means of a Leeds and Northrup Recording Photoelectric Microphotometer. The absorption does not follow Beer's law; the bands are widened and flattened as the pressure increases. Intensities are reported on a logarithmic scale giving the strongest line of each compound a value of 1000. In determining intensities, account was taken of the presence of continuous absorption and of the overlapping of bands, thus giving the individual bands an intensity more nearly what they would have if they were not overlapped by other bands. Since all of the bands could not be photographed on a single plate or at the same pressure, it was necessary to adopt secondary standards of intensity from among the bands which could be compared directly with the strongest band. The *relative* intensity of the bands is not greatly changed by a change in pressure. In this way a much better approximation to the intensities was obtained than could have been gotten by the use of Beer's law.

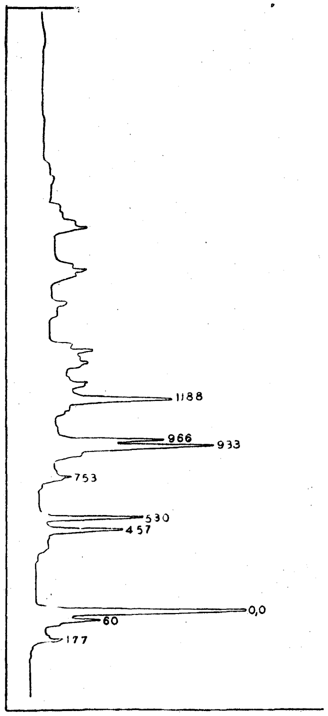


Fig. 1.—Microphotometer trace of the absorption spectrum of toluene.

Experimental Results.—Tables showing the wave numbers, intensities, and wave number differences (from the 0,0 band) and giving a partial analysis of the bands will be available from the American Documentation Institute.[13a] Figures 1 through 5 give microphotometer tracings of the spectra taken at 5 mm. pressure in a 30 cm. cell. Finer details of the spectra are not visible on these small tracings.

The 0,0 Bands.—The position of the vibrationless transition in toluene is fixed at the

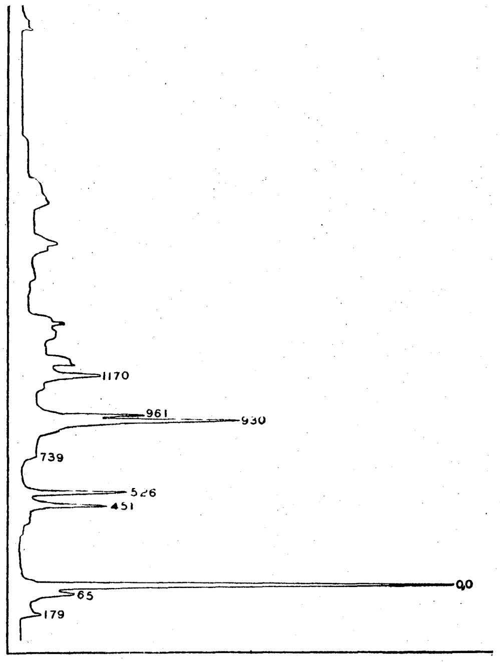


Fig. 2.—Microphotometer trace of the absorption spectrum of toluene-*α*-*d*.

---

[10] Due to the small amount of deuterium oxide that was available it was not considered advisable to use up this material in perfecting the experimental technique so as to eliminate the presence of ordinary toluene in the products. The situation is greatly improved now that the United States Atomic Energy Commission has made deuterium oxide more available.

[11] Since these compounds were prepared a technique for preparing pure deuterated benzenes using the Grignard reaction has been published in detail: see Weldon and Wilson, *J. Chem. Soc.*, 235 1946).

[12] Purchased from Adam Hilger, Ltd.

[13] Kösters and Lampe, *Physik. Z.*, **35**, 223 (1934).

[13a] Address American Documentation Institute, 1719 N St., N.W., remitting for Document 2485 $2.40 for photoprints or $0.50 for microfilm.

TABLE I

OBSERVED FUNDAMENTALS

Toluene		Toluene-α-*d*		Toluene-4-d		Toluene-3-d		Toluene-2-d	
Ground	Excited	Ground	Excited	Ground	Excited	Ground	Excited	Ground	Excited
520[a]	457[a]	514[a]	451[a]	516[a]	452[a]	521	458	515	455
624[a]	530[a]	626[a]	526[a]	618[a]	523[a]	620	526	618	526
787[a]	753[a]	776[a]	739[a]	784[a]	744[a]	770	719	786	745
1003[a]	933[a]	1005[a]	930[a]	987[a]	909[a]	816	799?	821?	784?
	966[a]		961[a]		932[a]	875	841	846?	831
1210[a]	1188[a]	1200[a]	1170[a]		961	939	902	955?	900
	979?		978?	1211[a]	1190[a]	1001	967	994	946
1581	1572		1566		1568	1206	1172		953
	3075?		3067?		3071?		1572	1215	1184
							3051?		1572
									3072?

[a] According to the interpretation developed in this article, these frequencies correspond to Class A_1 carbon vibrations.

37478 cm.$^{-1}$ band (strongest of spectrum) by a comparison with the Raman spectrum,[14,15] according to Masaki[16] and Ginsburg, Robertson and Matsen.[17] The corresponding bands in all of the toluenes are as follows (in cm.$^{-1}$)

Toluene	37478
Toluene-α-*d*	37487
Toluene-2-*d*	37513
Toluene-3-*d*	37511
Toluene-4-*d*	37511

The shifts in the position of the 0,0 band are ascribed to the existence of zero-point vibrational energy.

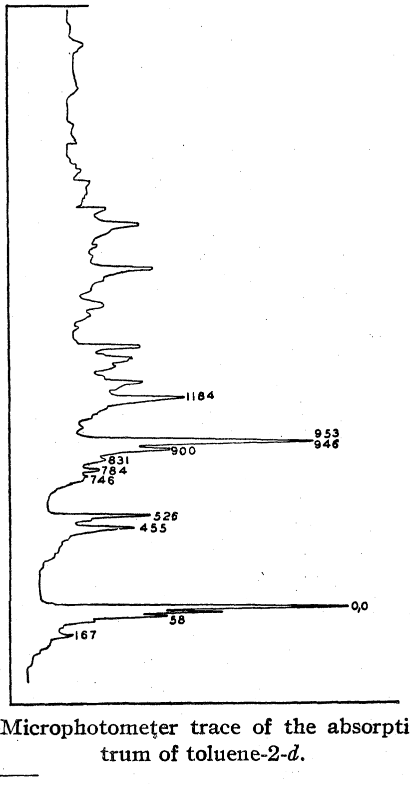


Fig. 3.—Microphotometer trace of the absorption spectrum of toluene-2-*d*.

Difference Frequencies.—On the low frequency side of the 0,0 band of each of the compounds is found a group of strong bands. These bands are interpreted as difference frequencies (1–1 transitions), in agreement with the interpretation of Ginsburg, Robertson and Matsen[17] for toluene.

Fundamental Vibrational Frequencies.—The presence of difference, overtone and combination frequencies renders the identification of fundamentals somewhat difficult. Therefore, the following list must be considered tentative and subject to revision when the Raman and infrared spectra have been studied. Doubtful fundamentals are marked with a question mark. Corresponding lines in the ground and excited states of each compound have been placed on the same line.

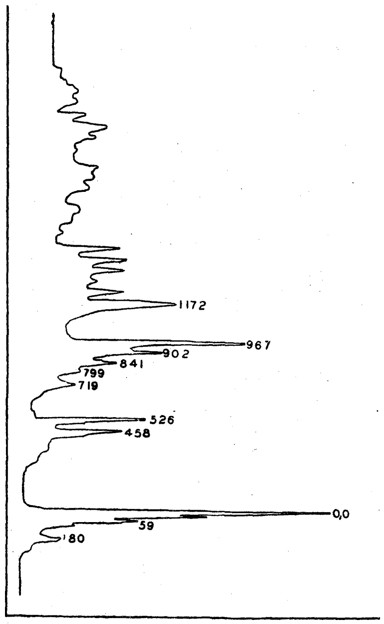


Fig. 4.—Microphotometer trace of the absorption spectrum of toluene-3-*d*.

---

(14) Howlett, *Can. J. Res.*, **5**, 572 (1931).

(15) Kohlrausch and Wittek, *Monatsh.*, **74**, 1 (1941).

(16) Masaki, *Bull. Chem. Soc. Japan*, **11**, 346 (1936).

(17) Ginsburg, Robertson and Matsen, *J. Chem. Phys.*, **14**, 511 (1946).

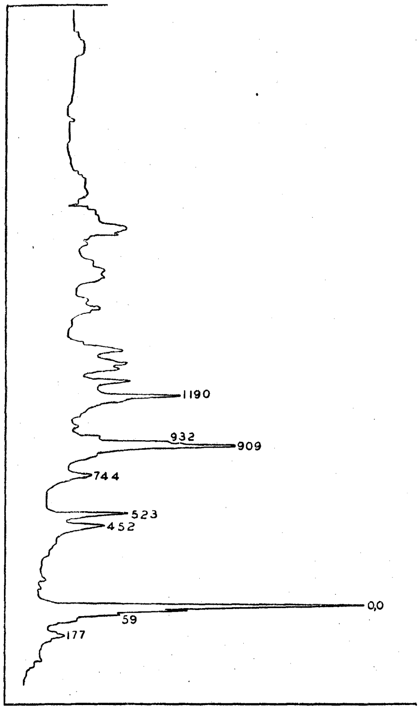


Fig. 5.—Microphotometer trace of the absorption spectrum of toluene-4-*d*.

Theory.—From heat capacity measurements Pitzer and Scott[18] concluded that in toluene the potential hindering methyl group rotation must be extremely small, so that at ordinary temperatures this group has essentially free rotation. In this case, at most positions of the methyl group, the molecule has no symmetry elements. However, on a time average the hydrogens on the methyl group would be smeared out in a cone and the molecule would have C_{2v} symmetry, and at no time would its symmetry vary greatly from C_{2v}. For the following discussion, C_{2v} symmetry is assumed for toluene,[18] toluene-α-*d* and toluene-4-*d*, and C_s symmetry for toluene-2-*d* and toluene-3-*d*.

Herzberg and Teller[19] applied the Franck–Condon Principle to the vibrations of polyatomic molecules during an electronic transition and concluded that, for an allowed transition taking place from the vibrationless ground state, the absorption is intense only when totally symmetrical vibrations are excited in the upper electronic state (the 0,0 band is also intense). For the toluenes of C_{2v} symmetry only the vibrations of class A_1 should appear strongly in the near ultraviolet absorption. However, Ginsburg, Robertson and Matsen[17] assigned one of the stronger lines of the spectrum of toluene (624 cm.$^{-1}$ in the ground state and 530 cm.$^{-1}$ in the excited state) to a Class B_1 vibration. This assignment is supported by the observation of Cleveland[20] that the 624 cm.$^{-1}$ line in the Raman spectrum is depolarized. It agrees with the interpretations of the spectra of fluorobenzene,[21] chlorobenzene,[22] phenol,[23] and aniline.[24] Pitzer and Scott[18] made a complete assignment of the toluene vibrations and assigned the 624 cm.$^{-1}$ line to class B_1.

The authors have developed a different assignment for the toluene vibrations by way of the following steps:

An examination of the spectra of the toluenes shows that, for the excited state, there are no *strong* fundamentals in the region of the hydrogen valence-stretching vibrations. This leads to the assumption that *no hydrogen vibrations appear strongly in the near ultraviolet absorption spectra of the toluenes*. Presumably this statement would hold for other benzene derivatives also. The assumption is reasonable since the absorption largely involves the electrons of the ring carbon atoms.

According to group theory there should be *six* carbon vibrations of class A_1 for each of the toluenes of symmetry C_{2v}. Six strong fundamentals are observed in the excited state of these compounds. This leads to the assumption that *the six strong fundamentals in the excited state of the toluenes of symmetry C_{2v} correspond to the six carbon vibrations of class A_1*. These frequencies are given in Table I. The corresponding ground state frequencies are also given. This assignment differs from the usual one in that the 624 cm.$^{-1}$ line in toluene is assigned to class A_1 instead of Class B_1. Theoretically, the degree of polarization of a Raman line produced by a totally symmetric vibration may vary from total polarization to depolarization. Therefore, the observation that the 624 cm.$^{-1}$ line is depolarized does not exclude the possibility of its belonging to a totally symmetric vibration.

Vibrational Forms.—By a consideration of the frequency changes upon the introduction of deuterium, it is possible to arrive at certain rather hypothetical vibrational forms.

The vibrations at 520 cm.$^{-1}$ and 624 cm.$^{-1}$ in the ground state of toluene are recognized as being due to planar bending of the ring by a comparison with the benzene assignments.[25] The 520 cm.$^{-1}$ frequency is reduced almost equally by substitution of deuterium on the methyl group or on the para carbon atom. This indicates that the methyl group and the para carbon atom form parts of vibrating groups whose amplitudes along the two-fold axis are about the same. The only way that this can happen so as to preserve the center of gravity of the molecule is for the ortho and meta carbon atoms to possess a component of vibration in the same direction as the para carbon atom.

---

[18] Pitzer and Scott, This Journal, **65**, 803 (1943).

[19] Herzberg and Teller, *Z. physik. Chem.*, **B21**, 410 (1933).

[20] Cleveland, *J. Chem. Phys.*, **13**, 101 (1945).

[21] Wollman, *ibid.*, **14**, 123–130 (1946).

[22] Sponer and Wollman, *ibid.*, **9**, 816 (1941).

[23] Matsen, Ginsburg and Robertson, *ibid.*, **13**, 309 (1945).

[24] Ginsburg and Matsen, *ibid.*, **13**, 167 (1945).

[25] Angus, Bailey, Hale, Ingold, Leckie, Raisin, Thompson and Wilson, *J. Chem. Soc.*, **971** (1936).

The mode of vibration must be very similar to that indicated in 1 of Fig. 6.

The 624 cm.$^{-1}$ frequency in toluene is very little affected by substitution of deuterium on the methyl group but is more affected by substitution of deuterium on the para carbon atom. This indicates that the amplitude of the methyl group is very small but that of the para carbon atom is rather large. The mode of vibration must be similar to 2 of Fig. 6.

The frequency at 1003 cm.$^{-1}$ in the ground state of toluene is recognized by its high intensity, high polarization in the Raman spectrum and by its frequency value, as corresponding to the carbon-to-carbon valence-stretching vibration which is totally symmetric in benzene. Agreeing with this mode of vibration, its frequency is little changed in toluene-*α-d* but is reduced in toluene-4-*d*. The vibrational mode corresponds to 3 of Fig. 6.

In studies with vibrating mechanical models, Teets and Andrews[26] observed a mode in which the methyl group vibrated against the remainder of the molecule. Now Lewis and Houston[27] observed the C–C valence-stretching vibration of ethane in the Raman spectrum at 993 cm.$^{-1}$. If the single C–C bond in toluene has the same force constant, the vibrational frequency of the methyl group against the remainder of the molecule is calculated to be 770 cm.$^{-1}$, taking the change in mass into account. This value is very close to the observed frequency of 787 cm.$^{-1}$ in the ground state of toluene. Furthermore this frequency is reduced much more in toluene-*α-d* than it is in toluene-4-*d*, agreeing with the idea that this vibration chiefly involves the methyl group against the ring, as is shown in 4 of Fig. 6.

The 1188 cm.$^{-1}$ frequency in the excited state of toluene is strongly reduced by substitution of deuterium on the methyl group but not by deuterium on the para carbon atom, indicating that the methyl group has a large amplitude but the para carbon atom does not. Form 5 of Fig. 6 gives a satisfactory mode of vibration.

The 966 cm.$^{-1}$ frequency in the excited state of toluene is reduced much more by substitution on the para carbon atom than it is by substitution on the methyl group, indicating a form similar to 6 of Fig. 6.

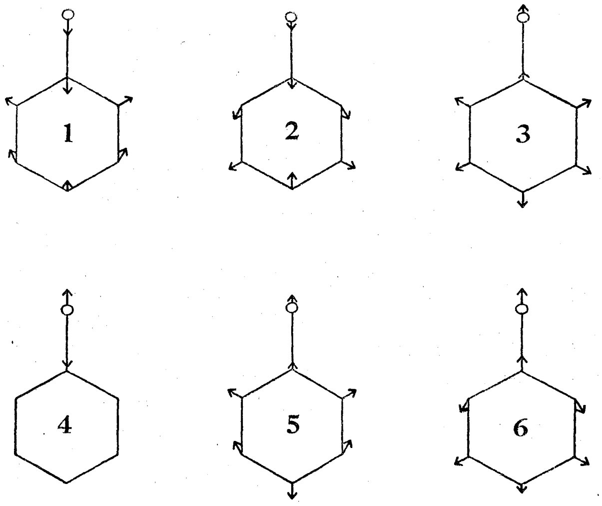


Fig. 6.—Approximate vibrational forms of the toluenes of C_{2v} symmetry. Carbon vibrations of class A_1.

It is realized that these modes of vibration are highly hypothetical. They afford, however, a satisfactory and logical explanation of the data. Both the assumptions and the vibrational forms are to be taken as working ideas, pending further investigations now in progress in this Laboratory.

Toluene-2-d and Toluene-3-d.—These compounds have C_s symmetry and should have eleven totally symmetric carbon vibrations. However, the perturbing effect of deuterium is so slight that the five new vibrations do not appear with such intensity as the six which are totally symmetric in the compounds of C_{2v} symmetry. A greater number of fairly strong fundamentals were found. Additional studies are now being made and will be reported in a subsequent publication.

Summary

The near ultraviolet absorption spectra of the vapors of toluene, toluene-*α-d*, toluene-2-*d*, toluene-3-*d* and toluene-4-*d* have been determined and partially analyzed. It is postulated that the six strong fundamentals in the excited states of the toluenes of C_{2v} symmetry correspond to the six totally symmetric carbon vibrations. The frequencies are correlated with certain hypothetical modes of vibration.

BATON ROUGE, LOUISIANA

RECEIVED JUNE 30, 1947

---

[26] Teets and Andrews, *J. Chem. Phys.*, **3**, 175 (1935).

[27] Lewis and Houston, *Phys. Rev.*, **44**, 903 (1933).

[Contribution from the Department of Chemistry and Chemical Engineering, Case Institute of Technology]

The Electrophoretic Mobility of Type II GR-S Latex[1,2]

By S. H. Maron, D. Turnbull[3] and M. E. Elder

Type II GR-S latex is a negatively charged colloidal dispersion of rubber polymer in an aqueous medium and like any such colloid, it can be made to migrate in an electric field toward the anode. By application of the moving boundary technique it is possible to measure the rate of this electrophoretic migration. Since the electrophoretic mobility is related to the charge on the colloidal particles, and since the charge in turn is responsible to a large degree for the stability of the colloid, such measurements can lead to a better understanding of the factors responsible for latex stability and of the way in which these factors are influenced by various modifications of the latex.

In this paper are presented results obtained on the mobility of Type II latex as a function of solids content, *p*H, temperature, ionic strength and electrolyte type. Also described are some studies made on the effects of creaming and redispersion, and of freezing and thawing of a latex on the mobility. From the mobilities have been calculated also the *zeta* potentials of the latex and the manner in which these potentials vary with temperature, *p*H and ionic strength.

Experimental

The assembly employed for measuring electrophoretic mobility consisted merely of the electrophoretic cell in series with a source of potential, a variable resistance and a milliammeter. The source of potential was a 90–180 volt B-battery bank whose output was regulated by means of the variable resistance. The milliammeter served to indicate the magnitude and constancy of current flow through the cell. Since latex solutions are turbid, the motion of the boundaries could be followed with a cathetometer positioned in front of the cell, which was kept immersed in a thermostat controlled to better than ±0.1°.

The details of the cell construction are shown in Fig. 1. Two microscope slides, S, each about 1.6 mm. thick, were ground to serve as sliding surfaces for formation of the sharp sheared boundaries. Holes about 8 mm. in diameter were drilled on each side of the slides as shown. A Pyrex U-tube, A, with vertical arms and flatly ground ends was then sealed with deKhotinsky or glycerine–litharge cement to the upper slide in such a manner as to make the tube ends flush with the sliding surface. To the lower slide were sealed in like fashion the lower arms, B, of the cell, due attention being given that the tubes be vertical and that their ground ends be flush with the lower sliding surface. These lower tubes were connected by thick gum rubber tubing to the two vessels, E, containing the electrodes. The electrodes consisted of coils of pure silver wire which were converted into thick silver–silver chloride electrodes by electrodeposition of chlorine upon them. Light copper leads were then hard-soldered to the electrodes for external circuit connection.

The cell was supported in the thermostat in the position shown in the figure by a special brass holder which was slotted horizontally to permit the sliding past each other of the surfaces S. With this arrangement the general procedure for making a run was as follows. Tube A was first inverted and filled completely with the latex dispersion to be studied. Next unit B of the cell was slid over the slide connected to the U-tube, shearing off thus the protruding drops of latex solution and enclosing the latex in the U-tube. In this operation slide B was always so displaced that the tube ends of A and B were closed off. To prevent leakage the ground surfaces of the slides were greased with purified vaseline before each experiment. Finally the electrode vessels E were attached to B, the vessels and tubes filled with enough leading and following solution to cover the electrodes, the center portion of the cell inverted and the entire assembly mounted in the thermostat in the position shown in Fig. 1. The latex portion A of the cell had to be kept in the position shown because the latex solutions were less dense than the electrolyte used for leading and following solutions.

The cell thus assembled was allowed to remain undisturbed in the thermostat until thermal equilibrium had been established. When temperature constancy was attained slide A was pushed manually along slide B until the tubes in A and B were continuous. In this manner two sharp sheared boundaries were obtained between the latex in A and the solutions in the two arms of B. After the boundaries were formed the current was turned on, adjusted to the desired value and kept there thereafter. With a high resistance in the circuit the current could be kept constant without any difficulty and any minor variations in resistance of the solution were not enough to upset the current setting. At various time intervals the positions of the two latex-solution boundaries were measured with the cathetometer.

To keep the potential gradient constant throughout the cell it was necessary to adjust the conductances of the leading and following solutions to those of the latex solution. This adjustment was made by using the same electrolyte for making up the latex as was used for the leading and following solutions and by making the concentrations of the latter such as to be identical with conductances of the latex–electrolyte mixtures. This procedure worked well with electrolytes containing chloride and gave no trouble with gassing at or fouling up of the electrodes. However, when electrolytes which did not contain chloride were used, considerable gassing occurred at the anode and a deposit frequently formed on the electrode. To overcome these difficulties enough sodium chloride was added to such electrolytes to make the concentration of chloride about 0.0002 molar. This small quantity of chloride was sufficient to eliminate the gassing entirely at low currents and to prevent the formation of any deposits on the silver–silver chloride anode.

Before initiating systematic measurements, a study was made to ascertain the most favorable currents for mobility determination. For this purpose the mobilities of latex solutions in 0.05 molar disodium phosphate were measured at currents of 5.0 and 1.5 milliamperes. At the latter current strength both ascending and descending boundaries were sharp and the mobilities calculated from their motion checked each other within the experimental uncertainty. When the higher current was used, however, the descending boundary was sharp and gave the same mobility as with a current of 1.5 milliamperes, but the ascending boundary was diffuse and the mobility calculated from its motion did not agree with that for the other boundary. Consequently in all the measurements reported here the current was kept sufficiently low to make both boundaries sharply defined. The optimum current for use with 0.05

---

[1] This research was sponsored by the Office of Rubber Reserve, Reconstruction Finance Corporation, as part of the Government Synthetic Rubber Program, and was first reported in December, 1943.

[2] Type II GR-S latex is prepared from butadiene–styrene charged in 3:1 proportions by weight, and with fatty acid soap as emulsifier. No antioxidant is added to this latex.

[3] Present address: General Electric Company, Schenectady, New York.

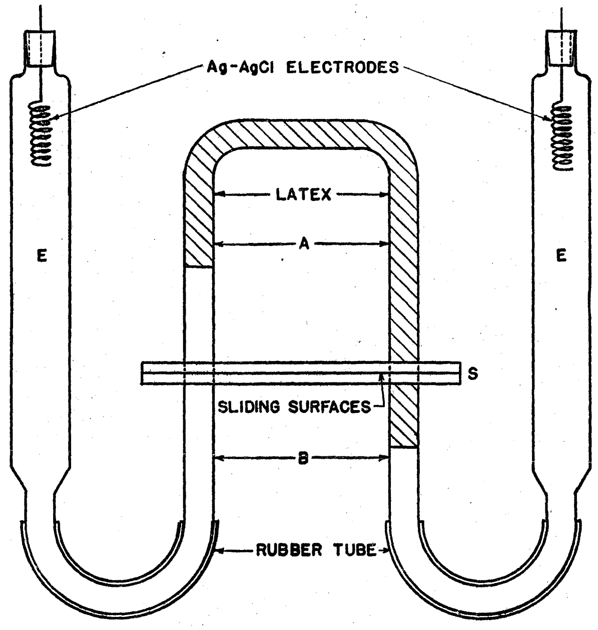


Fig. 1.—Latex electrophoretic mobility cell.

molar disodium phosphate was taken as 1.5 milliamperes and in all other cases the current was varied as the square root of the specific conductance of the solutions, giving thus approximately equal heating values due to current passage in all determinations.

The consistency of the data within a run was judged in all cases by the uniformity of the motion of the two boundaries. The distances which the boundaries traversed were plotted against time and the plots inspected. Any determinations in which the movements of the boundaries were not uniform or in which the boundaries were diffuse were discarded. Actually not many runs had to be eliminated for the reasons stated and these involved generally quite concentrated solutions of electrolyte or latex. A typical plot of migration distance *vs.* time is shown in Fig. 2. The plot is linear and very nearly identical for both boundaries.

The slopes of plots such as Fig. 2 give directly the actual rate of migration. To obtain from these the mobility the potential gradient under which the migration takes place must be known. This gradient follows readily from the specific conductance of the latex–electrolyte solution, L_s, the cross-sectional area of the tubes, S, and the current i, as i/L_sS, and hence the mobility, v, is given by

$$v = (l/t)/(i/L_sS) = lSL_s/it \qquad (1)$$

where l is the distance traversed by the boundaries in time t. In the present work the cross-sectional areas of the migration tubes were determined by calibration with mercury at various heights. In the cells used these areas were uniformly constant within experimental error.

In all experiments except those where the effect of temperature was studied, the temperature was kept constant at 30.0 ± 0.1°. Again, except where mobility as a function of *p*H was investigated, the latter was generally held within the range 8.4–9.0 by addition of disodium phosphate. As will be shown below, in this *p*H range the mobility is very little affected by *p*H change. In fact, over this entire range the variation in mobility amounts to only 0.1 micron/second. Finally, since it was found that the total solids content of the latex had practically no effect on the mobility in the concentration interval 9–15 g. per liter, all measurements were confined to lattices falling within this concentration range.

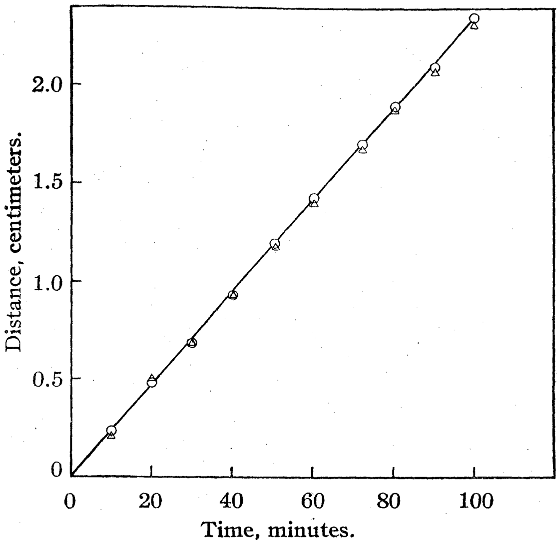


Fig. 2.—Plot of migration distance *vs.* time for Type II Latex no. 3: ○, ascending boundary; △, descending boundary.

The lattices employed in this study were polymerization products stripped of excess butadiene and styrene, and short-stopped. Latex no. 3 had an initial total solids content of 24.2% and a soap content 0.0362 normal, while Latex no. 7 had a solids content of 28.8% and a soap content 0.0474 normal.

All *p*H measurements were made with a Model G Beckman glass electrode assembly.

Effect of Various Factors on Latex Mobility.—In initiating this study it was assumed *a priori* that the mobility of a latex may depend upon (a) the total solids content, (b) the *p*H of the latex–electrolyte solution, (c) the ionic strength of the solution, (d) the temperature and (e) the type of electrolyte used to adjust the latex. In order to check the effects of these possible variables, experiments were designed to vary one variable at a time and to ascertain its effect on mobility.

(a) Effect of Total Solids Content.—Table I shows some results for mobility measurements in 0.05 molar disodium phosphate solutions at 30° on three concentrations of latex ranging from 9.4 to 29.4 g. per liter total solids. These relatively dilute lattices had to be used in the electrophoretic studies because of density difficulties with either much more concentrated or more dilute dispersions. From Table I it may be seen that between 9 and 15 g. per liter total latex solids the mobility is independent of concentration. However, at 29 g. per liter the mobility is already not constant and, hence, all measurements were limited to the lower concentration interval.

Table I

Effect of Total Solids Content on Mobility of Type II Latex No. 3 at 30°

Electrolyte: 0.05 Molar Na_2HPO_4

Total solids, grams/liter	Mobility (microns-cm./volt-sec.) Descending boundary	Ascending boundary	Average
9.4	5.58	5.58	5.58
14.7	5.59	5.62	5.61
29.4	5.38	5.49	5.44

(b) **Effect of *p*H.**—The effect of *p*H on latex mobility was studied at 30° at a constant ionic strength of 0.150. The *p*H's were adjusted to the desired values by addition of appropriate quantities of sodium hydroxide or hydrochloric acid to the disodium phosphate solutions used. The results obtained are summarized in Table II and are shown graphically in Fig. 3.

Table II

Effect of *p*H on Mobility of Type II Latex No. 3 at 30° and $\mu = 0.150$

*p*H	Mobility microns-cm./volt-sec.
5.10	3.1
5.95	4.1
6.37	4.9
6.85	5.4
7.90	5.6
8.60	5.6
10.5	5.8
11.6	6.0

From this figure it may be seen that the mobility decreases slowly and linearly as the *p*H is decreased from about 12 to *p*H 6.85. At the latter *p*H, however, a sharp and again linear drop in mobility sets in. The measurements along the latter branch of the curve could not be carried below the *p*H of 5.10 because at the given ionic strength any further decrease in *p*H resulted in coagulation of rubber. If it be assumed that the course of mobility variation with *p*H below 5.10 is continuous with the curve shown, then the extrapolation of this plot to zero mobility yields a *p*H of 2.7 for the isoelectric point of the latex at $\mu = 0.150$.

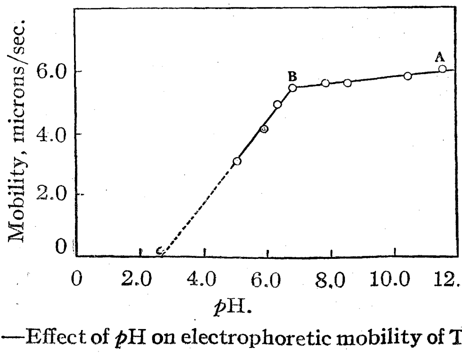


Fig. 3.—Effect of *p*H on electrophoretic mobility of Type II Latex no. 3 at 30° and $\mu = 0.150$.

At *p*H's above about ten the emulsifier in Type II latex is present entirely as the sodium soap of the fatty acids used in polymerization. When the *p*H is lowered progressively below 10 conversion of the soap into a mixture of soap and fatty acid takes place until eventually all the soap is transformed into fatty acid. The slow decrease in mobility along curve AB in Fig. 3 is in all probability to be ascribed to the gradual change of soap into fatty acid, with consequent gradual decrease in the charge on the polymer particles. As the *p*H of 6.9 is reached this transformation of soap into acid is quite advanced and, hence, thereafter mostly fatty acid is present to give the latex stability. It is known that fatty acids are not so strongly adsorbed by the rubber as soap. Further, since fatty acids are weak acids their ionization is small. Consequently, appreciable conversion of soap into fatty acid leads to a decided decrease in charge of the latex particles and hence also to a decided decrease in their mobility. With still further decrease in *p*H all soap is removed and the ionization of the fatty acids is strongly repressed. Hence, the charge and mobility drop rapidly and the latex system becomes sufficiently destabilized to precipitate rubber. From what has been experienced with coagulation difficulties below a *p*H of 5.1 it would appear that it is not necessary to reduce the charge or mobility to zero in order to precipitate rubber. Rather, it is only necessary to reduce the charge and hence mobility to a low critical value, which in this case lies at a *p*H of about 5 at $\mu = 0.150$.

(c) **Effect of Temperature.**—The effect of temperature on Type II latex mobility was studied in disodium phosphate solutions of $\mu = 0.144$ and *p*H 7.9–9.0 over the temperature range 1–35°. The results obtained are summarized in Table III. They can be represented by the linear equation

$$v = 2.40 + 0.107t \qquad (2)$$

as may be seen from the comparison of the observed and calculated mobilities given in the last two columns of the table. This rate of change of mobility with temperature corresponds to an in-

Table III

Effect of Temperature on Electrophoretic Mobility of Type II Latex No. 3 at $\mu = 0.144$

Temp., °C.	Number of determinations	Mobility (microns-cm./volt-sec.) Observed	Calculated equation (2)
1.0	2	2.54 ± 0.03	2.51
20.0	2	4.48 ± .07	4.54
30.0	4	5.62 ± .06	5.61
35.0	1	6.13	6.15

crease of *ca.* 2% per degree at 25° which is of the same order of magnitude as the rate of change of mobility with temperature of ordinary ions.

(d) Effect of Ionic Strength and Electrolyte Type.—To obtain the effect of ionic strength on latex mobility measurements were made at 30° in disodium phosphate solutions ranging from 0.0077 to 0.240 molar, *i. e.*, μ = 0.023–0.720. The mobilities of Latex no. 3 thus obtained as a function of μ are shown in curve 2 of Fig. 4. From this curve it is seen that between $\mu = 0.023$ and $\mu = 0.058$ the mobility increases with ionic strength to go through a maximum at the latter value of μ. Beginning at $\mu = 0.058$ and up to about $\mu = 0.43$ the mobility decreases practically linearly with ionic strength. Thereafter the mobility becomes essentially independent of μ until an ionic strength of *ca.* 0.65 is reached. Beyond the latter value of ionic strength measurements of mobility become very difficult due to particle aggregation and consequent rubber segregation from the latex. However, the result obtained at μ = 0.72 shows, as might be expected, that at salt concentrations very near to those causing rubber separation a very sharp drop in mobility takes place. This particular result was obtained on a latex dispersion in disodium phosphate which did not segregate in the electrophoretic cell but separated on standing for several hours after completion of the run.

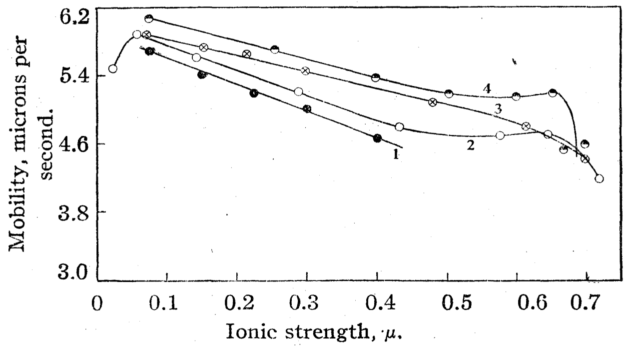


Fig. 4.—Effect of ionic strength on mobility of Latex no. 3 at 30° (*p*H range 8.2–9.0): ○, Na_2HPO_4; ⊗, Na_2HPO_4–Na_2SO_4 (1:3 moles); ●, Na_2HPO_4–NaCl (1:4.5 moles); ◓, Na_2HPO_4–KCl (1:4.5 moles).

Similar data for Latex no. 7 are shown in curve 2 of Fig. 5. These data indicate in essence a similar dependence of mobility on ionic strength except that the maximum appears at a higher value of μ.

In order to ascertain whether ionic strength alone or electrolyte specificity as well are factors determining mobility variation a series of experiments were carried out on latex dispersions in Na_2HPO_4–NaCl, Na_2HPO_4–Na_2SO_4 and Na_2HPO_4–KCl mixtures. These electrolytes were used in presence of Na_2HPO_4 because the desired *p*H control could not be obtained with NaCl, Na_2SO_4 and KCl alone. In using these salts the molar ratio of Na_2HPO_4 to the second salt was kept constant in each series but the over-all concentration of the solution was varied to obtain different ionic strengths. The results obtained are depicted in curves 1, 3 and 4 of Fig. 4 and curves 1 and 3 of Fig. 5. In both figures the measurements on the Na_2HPO_4–NaCl solutions could not be carried to higher ionic strengths than those shown due to rubber segregation from the latex–salt mixtures.

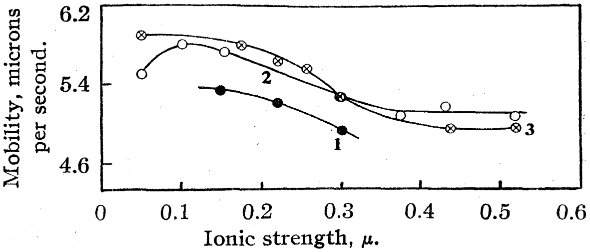


Fig. 5.—Effect of ionic strength on mobility of Latex no. 7 at 30° (*p*H range 7.9–8.7): ○, Na_2HPO_4; ⊗, Na_2HPO_4–Na_2SO_4 (1:3 moles); ●, Na_2HPO_4–NaCl (1:4.5 moles).

From the positions of the various curves in the two figures it is quite evident that ionic strength alone is not the factor responsible for mobility variation, but that the nature of the electrolyte as well is significant. At any given ionic strength NaCl is most effective in lowering mobility, followed in turn by Na_2HPO_4, Na_2SO_4 and KCl. This order is the same as that observed in this laboratory for the effectiveness of the various electrolytes as precipitating agents for rubber from Type II latex. However, the specificity of electrolyte action is not as pronounced as Figs. 4 and 5 would tend to suggest. If the data in Fig. 4 for Latex no. 3 be replotted to show mobility as a function of total cation concentration in equivalents per liter we obtain Fig. 6. Plotted in this manner the data for Na_2HPO_4 and Na_2HPO_4–NaCl can be made to fall along the same curve but the data for Na_2HPO_4–Na_2SO_4 and Na_2HPO_4–KCl mixtures still remain displaced. Essentially the same picture is given by a replot of the data for Latex no. 7 except that here the Na_2HPO_4–

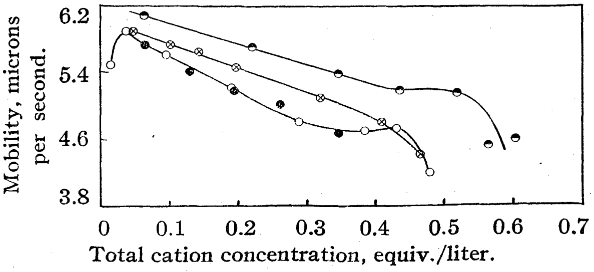


Fig. 6.—Mobility of Latex no. 3 as a function of total cation concentration at 30° (*p*H range 8.9–9.0): ○, Na_2HPO_4; ⊗, Na_2HPO_4–Na_2SO_4 (1:3 moles); ●, Na_2HPO_4–NaCl (1:4.5 moles); ◓, Na_2HPO_4–KCl (1:4.5 moles).

Na_2SO_4 data lie closer to those for Na_2HPO_4 and Na_2HPO_4–NaCl. These observations suggest, at least in the case of the electrolytes containing sodium only, that to a large degree the lowering in mobility is a function of the total cation concentration present but that this action of the sodium ions is modified by the nature of the particular co-ion with which it is associated.

The less effective action of potassium chloride in lowering mobility is in all probability due to exchange of sodium ions in the adsorbed soap layer for potassium. Potassium soaps are much more difficult to salt out from a latex than sodium soaps and this fact may be taken to indicate that electrolytes are less effective in desorbing potassium than sodium soaps. Consequently, the charge on latex particles in presence of potassium ions is preserved more effectively and the mobility does not fall as rapidly with ionic strength as in presence of sodium ions alone.

It is to be expected that all the curves in Fig. 4 and those in Fig. 5 should extrapolate to common values of mobility at zero ionic strength. The course of curves 1, 3 and 4 in Fig. 4 and of curves 1 and 3 in Fig. 5 is such as to suggest that the common extrapolation limit cannot be obtained by prolongation of these curves to $\mu = 0$. Instead, curves 2 in these figures suggest that the extrapolation limit may be obtained by passage of the v–μ curves through a maximum followed by a drop in mobility as $\mu = 0$ is approached. In other words, in all probability the effect of ionic strength is first to increase the mobility at low values of ionic strength up to a maximum value for each electrolyte, followed thereafter by a decrease along the lines shown in the figures.

The initial rise in mobility at low ionic strengths may be due primarily to adsorption of anions. It is felt that the ionic strengths at which this increase takes place are still too low to lead to any significant desolvation of the soap. At the same time the effect of the ionic atmosphere and possible cation adsorption, which would operate to decrease the mobility, come into play, and hence the mobility goes through a maximum and then decreases. The levelling off in this decrease, setting in at μ values of 0.3–0.4, may be due to the counterbalancing action of desolvation, which would tend to increase charge density and hence mobility. The final sharp drops in mobility are definitely due to desorption of soap with attendant discharge of the latex particles. Surface tension studies have shown that near the coagulation point this desorption of soap takes place quite sharply and, hence, the drop in mobility should also be quite sharp near the rubber precipitation point as is actually the case.

Mobility of Creamed and Redispersed Latex.—On addition of a large quantity of sodium chloride to a latex, the rubber precipitated out is highly aggregated and cannot be redispersed. However, by controlled addition of salt it is possible to "cream" a latex, remove part of the serum and then to redisperse the "cream" in water or an electrolyte solution. In such a redispersion the soap which was desorbed in the creaming is not entirely readsorbed, as is evidenced by the comparatively low surface tension of the redispersed latex. It is also quite probable that the mean particle size of the redispersed latex is larger than that present in the original colloid. It is of some interest, therefore, to ascertain how the mobility of the latex is modified by the changes accompanying creaming and redispersion.

A sample of latex was creamed with sodium chloride and after filtering off serum the rubber was redispersed in a disodium phosphate solution of $\mu = 0.145$. The total solids content of the redispersion was about that of the original latex, although some of the rubber did not redisperse. The mobility was then measured again at 30°. It was thus found that the mobility of the redispersed latex was 6.10 microns/second as against 5.62 for the untreated latex; *i. e.*, the mobility of the redispersed latex was about 8.5% higher than the untreated latex at the same ionic strength, temperature and *p*H.

Mobility of Frozen Latex.—Previous work in this Laboratory[4] has indicated that latex may be destabilized and even coagulated by freezing. If the latex is frozen and then rewarmed before any appreciable coagulation occurs, a large number of particles of microscopic size can be detected in the dispersion and the surface tension is found to have dropped to 30–40 dynes/cm. These observations indicate that in the freezing and rewarming operation the particle size is increased and that part of the soap is desorbed.

To ascertain what effect these changes have on mobility latex solutions were frozen, rewarmed and then made up in disodium phosphate solutions of $\mu = 0.145$ as described. A number of mobility determinations were then carried out at 30° on different frozen samples of the same latex. The results thus obtained in ten separate determinations gave for the mobility $v = 6.24 \pm 2.7\%$ as against 5.62 microns/second for the unfrozen samples. This 11% increase in mobility here and the 8.5% increase in the mobility of creamed and redispersed latex are off-hand surprising. However, they may be accounted for by the increase in the particle size attending the above manipulations. Although both creaming and redispersion and freezing and rewarming result in loss of soap by the rubber, nevertheless the higher mobility of the resulting particles indicates that these carry upon them more soap and, hence, a higher charge. By increasing the size of the particles at total constant concentration the number of these is considerably decreased, and apparently whatever soap is available is sufficient to yield a higher surface soap concentration per particle than in the original latex. To test this supposition it would be of in-

---

(4) Results to be published at a future date.

terest to investigate the mobility of latex dispersions with added soap.

Mobility of Soap.—Since latex owes its mobility primarily to the charge imparted to it by the adsorbed soap it is of considerable interest to see how the mobility of soap itself compares with that of the latex particles. To obtain the mobility of soap a single measurement was made upon a 0.01 molar solution of RS soap chips in 0.004 molar sodium chloride at 30° with phenolphthalein as an indicator. The moving boundaries were not as sharp here as with latex; however, the experiment could be carried out to yield for the mobility of the soap 6.31 microns per second. Although the experimental conditions were quite different in the measurements of the latex and soap mobilities, nevertheless it is of importance that the mobilities of the soap and the latex are of the same order of magnitude. In fact, it would not be too surprising to find that they are more or less identical under comparable experimental conditions since it has been shown that the mobilities of proteins and various materials coated with proteins are the same.

The *Zeta* Potentials of Latex.—Type II GR-S latex particles are known to be spherical in shape and of the order of 800–1000 Å. in diameter. For such particles the *zeta* potential, Z, is related to the mobility by the expression[5] at 30° for v in

$$Z = 4\pi\eta v/D = -1.18 \times 10^{-2}\, v \qquad (3)$$

microns per second and where η is the viscosity coefficient of the medium and D is the dielectric constant. The minus sign is included since in fact v is negative. In view of the direct proportionality between Z and v all the conclusions drawn with respect to variation of mobility at 30° with respect to solids, *p*H, ionic strength and type of electrolyte apply equally well to the effect of these on *zeta* potentials.

The effect of temperature on *zeta* potentials of Latex no. 3 at $\mu = 0.144$ and average *p*H of about 8.5, can be obtained from the combination of the mobility data summarized by equation (2) and the effect of temperature on viscosity and dielectric constant. For lattices as dilute as those used here the viscosity is essentially the same as that of pure water. The dielectric constants of water as a function of temperature have been given by Wyman.[6] The *zeta* potentials thus calculated at various temperatures from 0 to 40° are shown in Fig. 7. From this plot it may be seen that the *zeta* potentials of the latex increase continually over the entire temperature range. The increase is quite rapid between 0 and 20°, and then becomes much more gradual thereafter. This increase in *zeta* potentials with temperature is again in accord with the observations in this laboratory, to be published later, that Type II latex shows increased stability in presence of added electrolytes at higher temperatures than at lower ones.

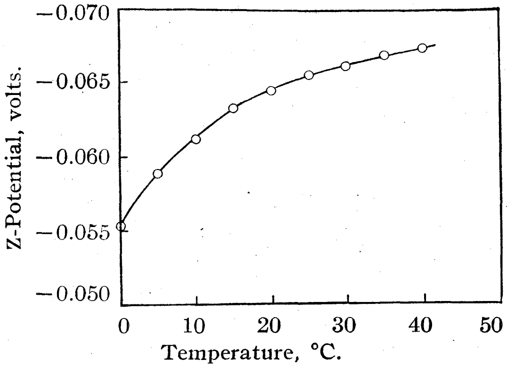


Fig. 7.—Effect of temperature on Z-potentials of Latex no. 3 at $\mu = 0.144$ and *p*H 7.9–9.0.

Summary

A very simple procedure is described for measuring the electrophoretic mobility of latex by the moving boundary method. This method has been applied to the determination of the mobilities of Type II GR-S latex as a function of total solids, *p*H, ionic strength, electrolyte type at 30° and of temperature between 0 and 35°.

The effects of creaming and redispersion and of freezing and thawing of lattices on mobility have also been determined.

The above data were used to estimate the isoelectric point of latex and to calculate the *zeta* potentials as a function of the various variables.

CLEVELAND, OHIO RECEIVED AUGUST 29, 1947

---

[5] H. A. Abramson, L. S. Moyer and M. H. Gorin, "Electrophoresis of Proteins," Reinhold Publishing Corporation, New York, N. Y., 1942, p. 109.

[6] J. Wyman, *Phys. Rev.*, **35**, 623 (1930).

[CONTRIBUTION FROM THE CARNEGIE INSTITUTION OF WASHINGTON, DIVISION OF PLANT BIOLOGY]

Molecular Structure and Adsorption Sequences of Carotenoid Pigments

BY HAROLD H. STRAIN

The sequence in which carotenoid pigments form bands in Tswett adsorption columns depends upon the adsorbent and the solvent.[1,2,3] This dependence of the relative adsorbability of carotenoid pigments upon the different conditions in the columns indicates that there is a complex relationship between adsorbability and molecular structure.

From the viewpoint of kinetics, separation of mixtures in Tswett columns is contingent upon a reversible distribution of the solutes between the solvent and the adsorbent. Variation of the adsorption sequence with different conditions must result from disproportionate variation of the attractive forces among the adsorbent, the solvent and the solutes. In one instance, the adsorption of fucoxanthin and zeaxanthin in columns of sugar, variation of the attraction between solvent and solutes, as indicated by variation of solubility, has seemed responsible for alteration of the adsorption sequence.[2] Other conditions that might alter the adsorption sequence are variation of the adsorbability of particular structural groups of the carotenoid molecules with different solvents or adsorbents; changes in the structure of the carotenoid molecules induced by adsorbents or solvents; variation in the tendency of the solvents to combine with the adsorbent and thus to displace the adsorbed molecules or particular groups of the adsorbed molecules; etc.

In order to gain further insight into the relationship between the structure and the relative adsorbability of organic molecules, adsorption sequences of several carotenoid pigments have been determined under different conditions. These adsorption sequences have then been compared with the principal structural features of the pigment molecules, with the properties of the adsorbents and solvents and with spectral absorption properties of the pigments. In this way clues to the relative adsorbability of various structural groups have been obtained. Conversely, conditions that determine relative adsorbability and separability of similar organic compounds have been more accurately defined.

Materials and Methods

Natural polyene hydrocarbons, the carotenes, and their hydroxy and oxo derivatives, the xanthophylls, were isolated from common sources by means of partition and chromatographic adsorption methods. These polyene pigments, their sources and the method of preparation, most of which have been described previously,[1,2,4,5] are summarized in Table I.

TABLE I

CAROTENOID PIGMENTS, THEIR SOURCES AND METHOD OF PURIFICATION

Pigments	Sources	Adsorbents	Solvents
	Xanthophylls		
Rhodoxanthin	*Cryptomeria japonica*	Sugar	Pet. ether + 4% acetone
Zeaxanthin	Calyx of *Physalis*	Magnesia	Dichloroethane
Lutein	Leaves of barley	Magnesia	Pet. ether + 25% acetone
Cryptoxanthin	Calyx of *Physalis*	Magnesia	Dichloroethane
	Carotenes		
Lycopene	Tomatoes	Magnesia	Pet. ether + 4% acetone
β-Carotene	Carrots	Magnesia	Pet. ether + 4% acetone
α-Carotene	Carrots	Magnesia	Pet. ether + 4% acetone

Rhodoxanthin, a diketo-dehydro-β-carotene was prepared from the red, winter needles of *Cryptomeria japonica*.[6] It was purified by adsorption from petroleum ether solution in columns of sugar and in columns of Celite 501.

Molecules of each of these carotenoids have many features in common.[7,8] Each pigment contains forty carbon atoms which form similar skeletal structures. The chromophoric group of each pigment consists of eleven or more double bonds at least ten of which occur in conjugation. Oxygen atoms in the four xanthophylls occupy the same relative positions in the molecule; hence, variation of the adsorption sequences due to differences in the location of the oxygen atoms in the molecule was avoided.

Except for lycopene, which has aliphatic instead of cyclic terminal structures, molecules of the several carotenoid pigments differ from one another only in the number and arrangement of the double bonds and in the number and function of the oxygen atoms. A summary of the principal structural features of the pigments is presented in Table II.

TABLE II

PRINCIPAL STRUCTURAL FEATURES OF THE CAROTENOID PIGMENTS

Double bonds are indicated by "="; conjugated double bonds by "conj. ="

Pigment	Formula	=	Conj. =	Conj. C=O	—OH	Rings
Rhodoxanthin	$C_{40}H_{50}O_2$	14	12	2	0	2
Zeaxanthin	$C_{40}H_{56}O_2$	11	11	0	2	2
Lutein	$C_{40}H_{56}O_2$	11	10	0	2	2
Cryptoxanthin	$C_{40}H_{56}O$	11	11	0	1	2
Lycopene	$C_{40}H_{56}$	13	11	0	0	0
β-Carotene	$C_{40}H_{56}$	11	11	0	0	2
α-Carotene	$C_{40}H_{56}$	11	10	0	0	2

Adsorbents employed for determination of the adsorption sequences of the carotenoid pigments were powdered sugar (confectioners powdered sugar with 3% starch to prevent caking, grade XXXXXX[2]), heat-treated siliceous earth (Celite 501) and activated magnesium oxide (Micron

---

(1) Strain, "Chromatographic Adsorption Analysis," Interscience Publishers, Inc., New York, N. Y., 1942.

(2) Strain, Manning and Hardin, *Biol. Bull.*, **86**, 169 (1944).

(3) Strain, *Ind. Eng. Chem., Anal. Ed.*, **18**, 605 (1946).

(4) Strain, *J. Biol. Chem.*, **105**, 523 (1934).

(5) Strain, "Leaf Xanthophylls," Carnegie Inst. of Washington, Publ. No. 490, 1938.

(6) Lippmaa, "Das Rhodoxanthin, seine Eigenschaften, Bildungsbedingungen und seine Funktion in der Pflanze," K. Mattiesen'i trükikoda, Tartru, 1925.

(7) Mayer and Cook, "The Chemistry of the Natural Coloring Matters," Reinhold Publishing Corp., New York, N. Y., 1943.

(8) Zechmeister, "Carotinoide," J. Springer, Berlin, 1934.

Brand No. 2641) which was usually mixed with twice its weight of Celite in order to accelerate filtration.[1,3,4]

Adsorption columns were prepared by pressing successive portions of the dry adsorbent into the adsorption tubes (1.3 × 25 cm.). Usually a dilute solution of two or more of the pigments in petroleum ether (about 1 mg. per 100 ml.) was filtered through the adsorption column until the uppermost 3 to 5 mm. of the adsorbent was saturated with the pigments (suction about 0.5 atmosphere). Then fresh solvent or the appropriate solvent mixture was filtered through the column until the bands of adsorbed pigment had migrated from 3 to 15 or 20 cm. Comparison of the chromatograms developed in this way revealed the adsorption sequences of the pigments.

Results

Effect of Different Adsorbents on the Adsorption Sequence.—In columns of different adsorbents, mixtures of carotenes and xanthophylls yielded dissimilar adsorption sequences as is shown in Table III. In all the experiments summarized in this table, the major variable was the adsorbent; hence, the several adsorption sequences must be attributed to selective attraction between the adsorbents and the pigments.

TABLE III

ADSORPTION SEQUENCES OF CAROTENOID PIGMENTS IN COLUMNS OF SUGAR, OF CELITE AND OF MAGNESIA

The solvent was petroleum ether plus 4 to 25% acetone. The most adsorbed pigment is listed at the top of each column and the least adsorbed pigment at the bottom. Brackets indicate pigments that were incompletely separated.

Sugar	Celite	Magnesia
(*top of column*)	(*top of column*)	(*top of column*)
Zeaxanthin	Zeaxanthin	Rhodoxanthin
Lutein	Lutein	Lycopene
Cryptoxanthin	Rhodoxanthin	Zeaxanthin
Rhodoxanthin	Cryptoxanthin	Lutein
Lycopene	Lycopene	Cryptoxanthin
β-Carotene	β-Carotene	β-Carotene
α-Carotene	α-Carotene	α-Carotene

Inseparability of the carotenes in columns of sugar and in columns of Celite as indicated in Table III is due, in part, to their weak adsorbability relative to their concentration. At extremely low concentration carotenes are very weakly adsorbed on Celite from petroleum ether solution. Comparison of the amount of colorless solvent obtained by adsorption of equally dilute solutions of each pigment in separate columns revealed lycopene to be more adsorbed than β-carotene and α-carotene. In order to observe this separation one must adsorb the pigments from petroleum ether solutions so dilute that the bands in the columns are barely visible.

Effect of Different Solvents on the Adsorption Sequence.—Use of different solvents for development of the chromatograms in columns of a given adsorbent also gave different adsorption sequences. Results obtained in columns of powdered sugar are summarized in Table IV. Except for the variation of the adsorbability of rhodoxanthin, the different solvents had little effect upon the relative adsorbabilities of the pigments.

TABLE IV

ADSORPTION SEQUENCES OF CAROTENOID PIGMENTS IN COLUMNS OF SUGAR WHEN DIFFERENT SOLVENTS WERE EMPLOYED FOR DEVELOPMENT OF THE CHROMATOGRAMS

Petroleum ether	Petroleum ether plus 4% acetone	Petroleum ether plus 0.5% propanol
(*top of column*)	(*top of column*)	(*top of column*)
Rhodoxanthin	Zeaxanthin	Zeaxanthin
Zeaxanthin	Lutein	Lutein
Lutein	Cryptoxanthin	Cryptoxanthin
Cryptoxanthin	Rhodoxanthin	Rhodoxanthin
Lycopene	Lycopene	Lycopene
β-Carotene	β-Carotene	β-Carotene
α-Carotene	α-Carotene	α-Carotene

Use of different solvents for development of the chromatograms in columns of Celite yielded the results summarized in Table V. With minor exceptions these results are similar to those observed in columns of sugar. In the columns of Celite the presence of propanol in petroleum ether had an unusual effect upon the adsorbability of rhodoxanthin relative to the adsorbability of zeaxanthin and lutein. When these pigments were adsorbed from solution in petroleum ether rhodoxanthin formed a band above the zeaxanthin and lutein. Then as the chromatogram was developed with petroleum ether containing 0.5% propanol the rhodoxanthin appeared below the zeaxanthin and lutein, but upon continued washing of the column with the petroleum ether plus propanol the rhodoxanthin band widened and migrated more slowly so that the zeaxanthin and lutein moved below it.

TABLE V

ADSORPTION SEQUENCES OF CAROTENOID PIGMENTS IN COLUMNS OF CELITE 501 WHEN DIFFERENT SOLVENTS WERE EMPLOYED FOR DEVELOPMENT OF THE CHROMATOGRAMS

Petroleum ether	Petroleum ether plus 4% acetone	Petroleum ether plus 0.5% propanol
(*top of column*)	(*top of column*)	(*top of column*)
Rhodoxanthin	Zeaxanthin	Rhodoxanthin
Zeaxanthin	Lutein	Zeaxanthin
Lutein	Rhodoxanthin	Lutein
Cryptoxanthin	Cryptoxanthin	Cryptoxanthin
Lycopene	Lycopene	Lycopene
β-Carotene	β-Carotene	β-Carotene
α-Carotene	α-Carotene	α-Carotene

In columns of magnesia polar solvents in petroleum ether did not alter the adsorbability of rhodoxanthin relative to the other carotenoid pigments as is shown by the results presented in Table VI.

Effect of Solvents and Adsorbents on Molecular Structure.—Dissolved in polar solvents, many ketonic carotenoid pigments exhibit spectral absorption maxima that are less distinct than the absorption bands of the same pigments

TABLE VI

ADSORPTION SEQUENCES OF CAROTENOID PIGMENTS IN COLUMNS OF MAGNESIA WHEN DIFFERENT SOLVENTS WERE EMPLOYED FOR DEVELOPMENT OF THE CHROMATOGRAMS

Petroleum ether	Petroleum ether plus 25% acetone	Petroleum ether plus 4% propanol
(*top of column*)	(*top of column*)	(*top of column*)
⎡Rhodoxanthin	Rhodoxanthin	Rhodoxanthin
⎢Lycopene	Lycopene	⎡Zeaxanthin
⎣Zeaxanthin	Zeaxanthin	⎣Lycopene
Lutein	Lutein	Lutein
Cryptoxanthin	Cryptoxanthin	Cryptoxanthin
β-Carotene	⎡β-Carotene	⎡β-Carotene
α-Carotene	⎣α-Carotene	⎣α-Carotene

dissolved in nonpolar solvents. This effect, which is not pronounced with carotenes or with hydroxy carotenes,[5] indicates an alteration of the chromophoric structure of the ketonic pigments by the polar solvents.[2,9,10] Analogous effects of polar solvents upon the spectral absorption properties of rhodoxanthin are shown by the characteristic spectral absorption curves of Fig. 1. Compared to the characteristic absorption curves of other xanthophylls plotted on the same scale[2,5] the absorption curves of rhodoxanthin exhibit remarkably indistinct absorption maxima which are shifted to longer wave lengths by the polar solvent.

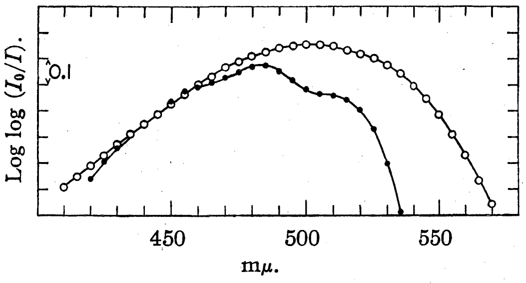


Fig. 1.—Characteristic spectral absorption curves of rhodoxanthin measured at the same concentration in petroleum ether and in 95% ethanol: ●, in petroleum ether; O, in ethanol.

Adsorption of rhodoxanthin either on solids or on liquids also alters the spectral properties of the pigment. Adsorbed on sugar or Celite or magnesia from solution in petroleum ether the keto carotenoid forms a violet-red band; the other carotenoids form orange or orange-red bands. Adsorbed on water droplets by shaking a yellow petroleum ether solution with water, rhodoxanthin causes the emulsion to appear pink. As the emulsion separates, the adsorbed rhodoxanthin liberated at the interface again forms a yellow solution in the petroleum ether.

Discussion

Variation of the adsorbability of the carotenoid pigments in columns of different adsorbents (Table III) can be related to the preferential attraction of the adsorbents for particular structural units in these organic molecules. In columns of sugar adsorbability of the carotenoids is determined to a very limited extent by the conjugated double bonds. Comparison of the structural characteristics of the carotenoids (Table II) with the adsorption sequence observed in columns of sugar (Table III) shows that the single hydroxyl group of cryptoxanthin causes this pigment to be much more adsorbed than the parent hydrocarbon, β-carotene, or the related hydrocarbon lycopene, which contains two additional double bonds. This single hydroxyl group also causes the cryptoxanthin to be much more adsorbed than rhodoxanthin which has three additional unsaturated linkages. Zeaxanthin and lutein, which differ only in the arrangement of one double bond in the molecule, are separable with difficulty in columns of sugar. On the basis of these results sugar is useful as an adsorbent for the separation of carotenoids which differ in the number of hydroxyl or keto groups; it is less useful for separation of pigments which differ only in total unsaturation or in the arrangement of the double bonds.

In columns of magnesia adsorbability of the carotenoids is determined to a large degree by the conjugated double bonds. Comparison of the molecular characteristics of the carotenoids (Table II) with the adsorption sequences (Table III) shows that with magnesia adsorbability of the carotenes increases markedly with the number and with the arrangement of the double bonds, even a small difference in the conjugation of the double bonds being reflected in an appreciable difference in adsorbability as with β-carotene and α-carotene. By contrast with the results obtained in columns of sugar, the two non-conjugated double bonds in lycopene cause this pigment to be more adsorbed than zeaxanthin. These two double bonds in lycopene have, therefore, a slightly greater influence on adsorbability than the two hydroxyl groups in zeaxanthin. Rhodoxanthin with fourteen conjugated, unsaturated linkages is even more adsorbed than lycopene. The small difference between the arrangement of one double bond in zeaxanthin and lutein which has little effect upon the adsorbability of these two pigments in columns of sugar has, by contrast, a great effect upon their adsorbability in columns of magnesia in which they are readily separable. From these experiments, magnesia is much more effective than sugar as an adsorbent for separation of carotenoid pigments which differ principally in the number and arrangement of their double bonds. With respect to adsorption capacity and to the specificity of the adsorption Celite is intermediate between sugar and magnesia (Table III).

Differences between the relative adsorbabilities of carotenoids on sugar and on magnesia must depend upon the nature or quality of the attractive forces of these two adsorbents. Strongly polar, neutral powdered sugar (with eight hydroxyl

---

[9] Heilbron and Lythgoe, *J. Chem. Soc.*, 1376 (1936).

[10] Polgar and Zechmeister, THIS JOURNAL, **66**, 186 (1944).

groups and three additional oxygen atoms comprising more than 50% of the molecule) probably attracts the polar hydroxyl groups of the xanthophylls and repels the large, non-polar hydrocarbon portions. Strongly alkaline magnesia, on the other hand, must attract the conjugated polyene system of the xanthophylls as well as the hydroxyl groups.

Polar solvents, which affect the relative adsorbability and the spectral absorption properties of rhodoxanthin, may alter the molecular structure of this pigment, probably through variation of the proportions of the enolic and ketonic modifications. Decrease of the relative adsorbability of rhodoxanthin in columns of sugar by polar solvents (Table IV) corresponds to a decrease in the enolic properties of the keto carotenoid. The slight effect of polar solvents on the relative adsorbability of rhodoxanthin in columns of magnesia (Table VI) indicates that a decrease in enolic properties must be accompanied by an increase in ketonic or polyene properties. This latter conclusion is supported by the effect of polar solvents on the spectral absorption properties of rhodoxanthin as shown already in Fig. 1. Increase in the spectral absorption capacity and shift of the spectral absorption maxima to longer wave lengths by polar solvents are equivalent to an intensification of the ketonic or polyene properties.

In view of the affinity of adsorbents for particular molecular structures, the adsorbability of a complex molecule, as represented by the adsorption isotherm, may be the sum of the adsorbabilities of all the reactive groups. Prediction of the effect of any one group upon the adsorbability of a complex molecule will require some knowledge of the relation between this group and the other reactive centers in the molecule. But it must be remembered that the adsorbability may be influenced by the effect of solvents upon the molecular structure of the adsorbed substance and by the affinity among the solvent, the solute and the adsorbent. Solvents that increase the proportion of those structural groups for which the adsorbent has greatest affinity intensify the adsorbability and *vice versa.* Adsorbability is, as a rule, inversely proportional to solubility. Pronounced affinity between solvent and adsorbent tends to diminish adsorbability of the solute.

These effects of solvents and adsorbents upon the adsorbability of different groups in an organic molecule point the way to new improvements and applications of the chromatographic adsorption method. Information about the adsorbability of particular molecular structures serves as a guide in the selection of solvents and adsorbents for separation of mixtures of various organic compounds and aids prediction of the adsorbability of complex molecules. Solvents and adsorbents may be varied so that adsorption of similar molecules involves the structural features in which the greatest differences reside. Under these conditions, maximum separation of similar substances may be expected.

Summary

Relative adsorbability of seven carotenoid pigments was determined by observation of the adsorption sequence of these polyene compounds in Tswett columns of powdered sugar, of Celite and of magnesia. Petroleum ether, petroleum ether plus acetone and petroleum ether plus propanol were used for development of the chromatograms.

The seven carotenoid pigments, rhodoxanthin, zeaxanthin, lutein, cryptoxanthin, lycopene, β-carotene and α-carotene, are related structurally in such a way that certain molecular features may be regarded as constant while others vary. Comparison of the observed adsorption sequences with the molecular structures of the pigments indicated that the relative adsorbability is determined to a large extent by the selective affinity of the adsorbents for different groups or portions of the pigment molecules. Powdered sugar attracts preferentially the polar hydroxyl groups of the xanthophylls; it has little affinity for the unsaturated hydrocarbon portions of carotenes or xanthophylls. Magnesia, on the other hand, attracts the unsaturated portions of both carotenes and xanthophylls as well as the hydroxyl groups of the xanthophylls. Adsorbents that are most effective for the separation of mixtures of similar carotenoid pigments in Tswett columns attract preferentially those portions of the pigment molecules which contain the greatest structural differences.

Solvents that have a pronounced effect upon the absorption spectrum of the diketonic rhodoxanthin also have a great effect upon the relative adsorbability of this pigment.

STANFORD, CALIFORNIA RECEIVED JUNE 3, 1947

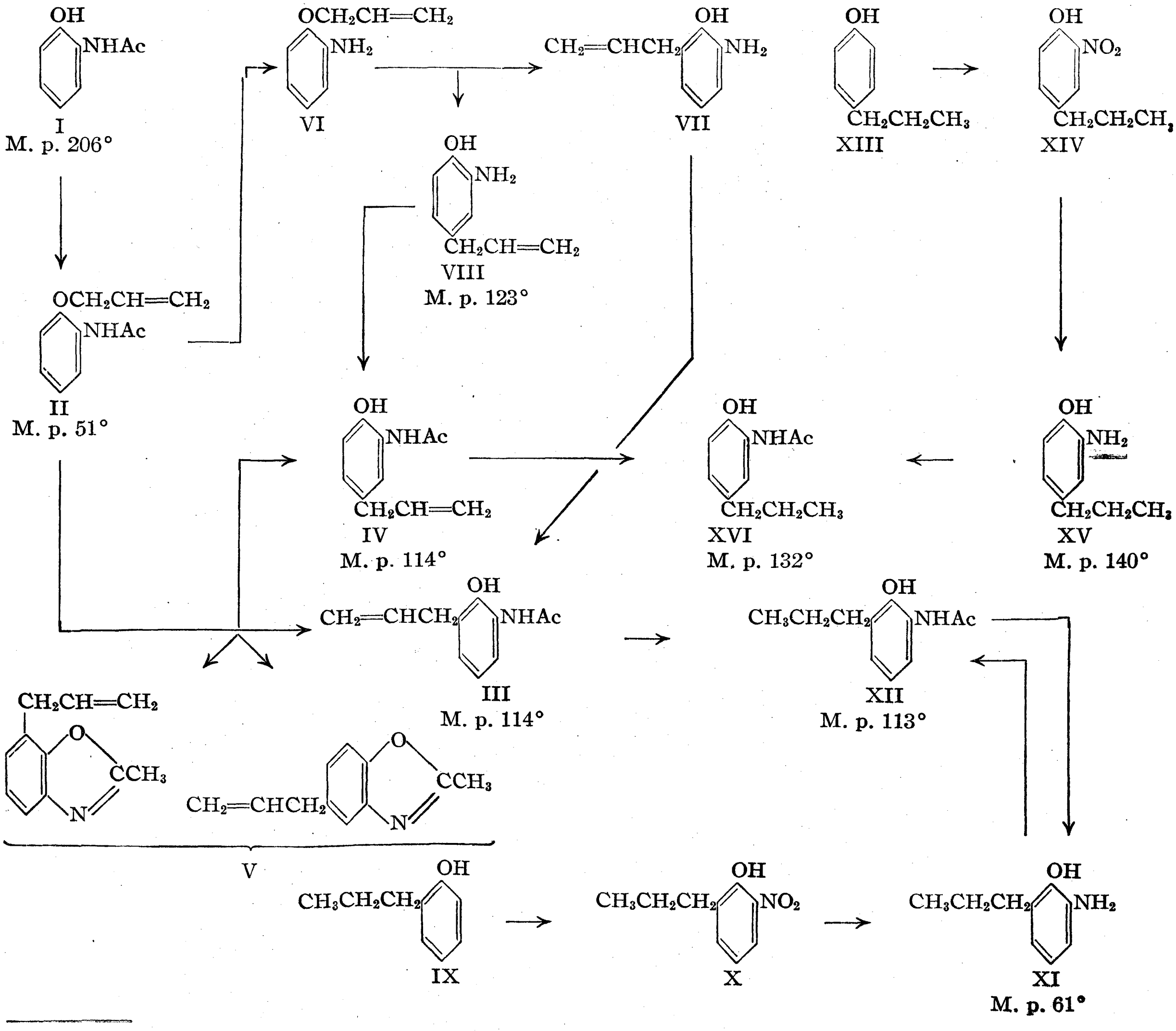
[CONTRIBUTION FROM ABBOTT LABORATORIES]

Partial *para*-Migration in the Allylic Rearrangement of *o*-Acetamidophenyl Allyl Ether and of *o*-Aminophenyl Allyl Ether

BY BURRIS D. TIFFANY[1]

In the rearrangement of allyl ethers of phenolic compounds, the allyl group usually migrates exclusively to the *ortho* position if one is free, and the product is obtained generally in good yield.[2] The allylic rearrangement seemed, therefore, to provide a likely avenue for the synthesis of 2-amino-6-propylphenol (XI) which was required in connection with another problem. It was found, however, that the rearrangement of both *o*-acetamidophenyl allyl ether (II) and *o*-aminophenyl allyl ether (VI) gave products which were mixtures of the *ortho*- and *para*-rearranged isomers. Other examples of partial rearrangement to the *para* position are known[2] and it may be significant that each of these involves compounds containing strongly *ortho–para* directing groups, adjacent to the hydroxyl.

When *o*-acetamidophenyl allyl ether (II) was heated in dimethylaniline at 190° for thirty minutes, it was possible to isolate 50% of 2-acetamido-6-allylphenol (III) and 7.6% of the *para* isomer (IV) (*o* to *p* ratio = 6.5:1). Treatment of the acetamido compound at such elevated temperatures, however, also caused the loss of at least 10% of the product, probably by cyclization to 2-methyl-5-allyl-benzoxazole and/or the 7-allyl isomer (V).



---

[1] Present address: Department of Chemistry, University of Wisconsin, Madison, Wisconsin.

[2] Tarbell, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 8.

To avoid the loss through cyclization when the acetyl group was present, *o*-aminophenyl allyl ether (VI) was rearranged. When it was heated in diphenyl ether at 190° for forty minutes and the resulting mixture of aminophenols acetylated, 42% of III and 21% of IV were isolated (*o* to *p* ratio = 2:1). The acetylation of the amino group before the separation of the isomers could be carried out was made necessary by the extreme sensitivity of the aminophenols to air oxidation.

The isomeric acetamido allylphenols (III) and (IV) were reduced to their corresponding propyl derivatives (XII) and (XVI) and the structures of these two compounds proved by synthesis. *o*-Propylphenol (IX) was nitrated *ortho* to the hydroxyl to give X. The nitro group was reduced and the resulting aminophenol (XI) acetylated. The product was shown by mixed m. p. determinations to be identical with XII prepared through the allylic rearrangement. The same procedure beginning with *p*-propylphenol was used to confirm the structure of 2-acetamido-4-propylphenol (XVI).

Acknowledgments.—The author is indebted to Doctors M. A. Spielman and W. J. Close for their assistance and encouragement and to Mr. M. Freifelder for the hydrogenations reported. Furthermore, he wishes to thank Mr. E. F. Shelberg, Mrs. Jane Wood, and Messrs. B. F. Claeboe and R. H. Berg of the Microanalytical Laboratory for their coöperation in providing he microanalytical data.

Experimental Part

***o*-Acetamidophenyl Allyl Ether (II).**—A mixture of 125 g. (0.82 mole) of *o*-acetamidophenol (I), 116 g. (0.82 mole) of anhydrous potassium carbonate, and 300 ml. of acetone was stirred vigorously to ensure intimate mixing. Then 100 g. (0.82 mole) of allyl bromide was added cautiously with stirring at a gentle reflux temperature. Refluxing and stirring was continued eight hours. About 800 ml. of water was added and the resulting mixture extracted with ether. The ether extract was washed with 10% aqueous sodium hydroxide, rinsed with water, dried, and concentrated to yield 156 g. (100%) of brown oil which crystallized completely, m. p. 49–51°. A sample recrystallized from pentane yielded white chalky crystals, m. p. 50–51.5°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.27; H, 6.57; N, 7.24.

2-Acetamido-6-allylphenol (III) and 2-Acetamido-4-allylphenol (IV). Method A. Rearrangement of *o*-Acetamidophenyl Allyl Ether.—A solution of 95.5 g. (0.50 mole) of *o*-acetamidophenyl allyl ether (II) in 200 ml. of dimethylaniline was heated at 190° for thirty minutes.[3] The reaction mixture was dissolved in ether and extracted with excess 20% aqueous sodium hydroxide. The alkaline extract was neutralized and extracted with ether. The ether extract was washed with dilute hydrochloric acid, rinsed with water, treated with Norit, dried, and evaporated under reduced pressure. A light brown solid weighing 69.1 g. resulted. By repeated fractional recrystallization from benzene about 35 g. of III, m. p. 112–114°, was obtained. The filtrates were concentrated, seeded with IV and allowed to crystallize slowly. The solution yielded a mixture of dense granular crystals (IV) dispersed among light fluffy needles (III). These were collected, dried, mixed with pentane, and shaken vigorously. The needles (III) were largely held in suspension and were decanted from the denser crystals (IV). Shaking and decanting was repeated several times. The whole process was repeated until the separation of III and IV was essentially complete.

A total of 47.5 g. (50%) of III, m. p. 112–114°, was obtained. Recrystallization from benzene yielded fine white needles, m. p. 113–114°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.17; H, 7.01; N, 7.25.

A total of 7.3 g. (7.6%) of IV, m. p. 112–114°, was obtained. Treatment with Norit and recrystallization from 2:1 benzene–cyclohexane yielded white platelets, m. p. 113–114°; mixed m. p. with III, 85–100°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.15; H, 6.54; N, 7.33.

By fractionating the oil isolated from the original ether solution, 8.4 g. (10%) of material boiling at 94–96° (1.7 mm.), n^{25}D 1.5444, was obtained. The analysis suggested that this was **2-methyl-5-allylbenzoxazole** and/or the **7-allyl isomer**.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.41; N, 8.10. Found: C, 76.07; H, 6.40; N, 8.29.

Method B. Rearrangement of *o*-Aminophenyl Allyl Ether (VI).—A solution of 14.9 g. (0.100 mole) of freshly distilled *o*-aminophenyl allyl ether (VI) (see below) in 30 ml. of diphenyl ether was heated to 190° in an oil-bath during fifteen minutes and maintained at 190–195° for thirty minutes under nitrogen. The reaction mixture was then dissolved in ether, extracted with 120 ml. of 1 *N* hydrochloric acid, and rinsed with water. The acid solution was treated with Norit, filtered and placed in a 1-liter three-necked flask equipped with a mechanical stirrer, two dropping funnels and a thermometer. With stirring and cooling to 20–25°, 15.3 g. (14.2 ml., 0.150 mole) of acetic anhydride and a solution of 17.6 g. (0.13 mole) of sodium acetate trihydrate in 20 ml. of water were added simultaneously over fifteen minutes so that the acetic anhydride was always in excess. Stirring was continued thirty minutes. The precipitate was collected, dissolved in ether, extracted with 40 ml. of 10% aqueous sodium hydroxide, and rinsed with water. The alkaline solution was made strongly acid and the brown oil which separated was extracted with ether. The ether solution was treated with Norit, dried, concentrated, diluted with Skelly B, and the precipitate collected. When dried it weighed 14.8 g. (77%). The two isomeric products were isolated in a manner similar to that described in Method A.

A total of 8.0 g. (42%) of III, m. p. 112–114°, was obtained. Recrystallization from benzene gave fine white needles, m. p. 113–114° and mixed m. p. with III from Method A, 113–114°.

A total of 4.1 g. (21%) of IV, m. p. 112–114°, was obtained. Treatment with Norit and recrystallization from 2:1 benzene–cyclohexane gave white platelets, m. p. 113–114° and mixed m. p. with IV from Method B, 113–114°.

***o*-Aminophenyl Allyl Ether (VI).**—A mixture of 114.6 g. (109.5 ml., 0.600 mole) of *o*-acetamidophenyl allyl ether (II) and 120 ml. of 6 *N* hydrochloric acid was refluxed for seventy minutes. The resulting solution was made alkaline with 20% sodium hydroxide solution and the red oil which separated was extracted with benzene. The benzene extract was washed with 10% sodium hydroxide solution, rinsed with water, dried, concentrated and fractionated to yield 81 g. (91%) of colorless oil, b. p. 84–85° at 0.6 mm., n^{25}D 1.5628, which darkened on standing.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.44; N, 9.40. Found: C, 72.57, 72.70; H, 6.91, 6.99; N, 9.52.

2-Amino-4-allylphenol (VIII).—A solution of 18.0 g. (0.120 mole) of freshly distilled *o*-aminophenyl allyl ether (VI) in 100 ml. of diphenyl ether was heated at 185–190° for six hours under nitrogen. The precipitate which formed on cooling was collected and recrystallized repeatedly from an ether–Skelly B mixture. Only about 1 g. of product, m. p. 121.5–123°, was obtained. It was very sensitive to air oxidation.

---

[3] Water distilled out during this heating period. Such a loss of water supports the structure proposed for V.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.44; N, 9.40. Found: C, 72.80; H, 7.34; N, 9.54.

The acetyl derivative of VIII was prepared in the usual manner. Its m. p. was 112–113°, its mixed m. p. with III was 85–100°, and its mixed m. p. with IV was 112–113°.

2-Acetamido-6-propylphenol (XII).—To 19.1 g. (0.100 mole) of 2-acetamido-6-allylphenol (III) in 250 ml. of 95% ethanol was added 0.2 g. of platinum oxide. The mixture was reduced in twenty minutes at 25° and 2 atmospheres pressure, filtered, diluted with 800 ml. water and the product, 18 g. (94%), collected. Recrystallized from 50% ethanol, its m. p. was 112–113° and its mixed m. p. with XII prepared by the acetylation of 2-amino-6-propylphenol was 112–113°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.36; H, 7.69; N, 7.24.

2-Acetamido-4-propylphenol (XVI).—About 0.02 g. of platinum oxide in 75 ml. of 95% ethanol was reduced to platinum black. Then 1.91 g. (0.010 mole) of 2-acetamido-4-allylphenol was added and reduced in thirty minutes at 25° and 2 atmospheres pressure. The reaction mixture was filtered and evaporated to dryness and the residue was recrystallized from benzene, 1.6 g. (83%), m. p. 129–131°. Recrystallized from 60% ethanol, it yielded white needles, m. p. 130.5–132°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.42; H, 7.78; N, 7.16.

2-Amino-6-propylphenol (XI).—A mixture of 1.93 g. (0.010 mole) of 2-acetamido-6-propylphenol (XII) in 3 ml. of 6 *N* hydrochloric acid was refluxed for ninety minutes and the product worked up in the usual manner to yield 1.45 g. (77%) of pink platelets of the hydrochloride. The free base was liberated from 0.50 g. of the hydrochloride yielding 0.40 g. (99%) of white platelets, m. p. 60–61°, after recrystallization from ether and Skelly B. The product was very sensitive to air oxidation and was collected under nitrogen.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.54; H, 8.67; N, 9.27. Found: C, 71.48; H, 8.50; N, 9.47.

2-Nitro-6-propylphenol (X).—A solution of 20.4 g. (0.150 mole) of *o*-propylphenol in 20.4 g. (0.34 mole) of glacial acetic acid was added to a mixture of 40.8 g. (0.46 mole) of nitric acid (d. 1.42) and 61.2 g. (1.02 mole) of glacial acetic acid at −4 to −6° with stirring over a period of two hours. The reaction mixture was immediately poured with stirring onto 300 g. of ice. It was then extracted with benzene and the extract washed with water, 5% sodium bicarbonate, and finally with water. The brown benzene solution was steam distilled and the 3 liters of distillate extracted with benzene, dried, concentrated and vacuum distilled twice. The product was an orange oil, 7.0 g. (39%), b. p. 84–89° at 1.2 mm., $n^{25}D$ 1.5542.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.74. Found: C, 59.80; H, 6.03; N, 7.66.

2-Amino-6-propylphenol Hydrochloride (XIa).—A solution of 7.0 g. of 2-nitro-6-propylphenol in 150 ml. of absolute ethanol was hydrogenated over 1.5 g. of Raney nickel in one hour at 2 atmospheres pressure and at room temperature. The product was isolated in the usual manner. It weighed 6 g. (83%), m. p. 208° (dec.). A sample was converted in 91% yield to 2-acetamido-6-propylphenol (XII), m. p. 111–112°. The mixed m. p. with XII prepared by the reduction of 2-acetamido-6-allylphenol (III) was 111–112°.

2-Acetamido-4-propylphenol (XVI).—To a solution of 9.4 g. (0.050 mole) of 2-amino-4-propylphenol hydrochloride[4] in 15 ml. of water, 6.1 g. (0.060 mole) of acetic anhydride and a solution of 7.5 g. (0.055 mole) of sodium acetate trihydrate in 9 ml. of water, were added simultaneously over five minutes with stirring and cooling. Stirring was continued ten minutes and the product, 9.4 g. (97%), m. p. 130–133°, was collected and dried. A sample recrystallized several times from 60% ethanol melted at 131–132°. Its mixed m. p. with XVI prepared by the reduction of 2-acetamido-4-allylphenol (IV) was 130.5–132°.

Summary

1. The thermal rearrangement of *o*-acetamidophenyl allyl ether has been shown to yield 2-acetamido-6-allylphenol and 2-acetamido-4-allylphenol in the ratio of 6.5 to 1.

2. The thermal rearrangement of *o*-aminophenyl allyl ether has been shown to yield 2-amino-6-allylphenol and 2-amino-4-allylphenol in the ratio of 2 to 1.

3. Several *o*-amino and *o*-acetamido alkyl phenols have been prepared and their structures proved by synthesis.

(4) Baranger, *Bull. soc. chim.*, [4] **49**, 1213 (1931).

NORTH CHICAGO, ILLINOIS RECEIVED SEPTEMBER 8, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

The Synthesis of D-Fructomethylose by Biochemical Oxidation[1]

BY LAURENS ANDERSON[2] AND HENRY A. LARDY

Two organisms of the genus *Acetobacter*, *A. xylinum* and *A. suboxydans*, have been widely used in the carbohydrate field for the oxidation of the grouping —CHOHCHOHCH$_2$OH to —CHOHCOCH$_2$OH. By this method a considerable number of ketose sugars have been prepared from the corresponding alcohols. As is the case with many biochemical procedures the application of the method is limited to compounds of proper steric makeup. According to "Bertrand's rule,"[3] *A. xylinum* will attack those alcohols in which the configurations about carbons two and three are the same. Hann, Tilden and Hudson[4] suggested that *A. suboxydans* is specific in its ability to oxidize polyalcohols of D-configuration. While these generalizations appear to hold for "normal" sugar alcohols ($C_nH_{n+2}(OH)_n$) of five or more carbon atoms, the results obtained with alcohols having a terminal methyl group have been anomalous. Thus Votoček, Valentin and Rác[5] were unable to oxidize L-rhamnitol (I) with *A. xylinum*, and Müller and Reichstein[6] obtained only slight oxi-

---

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. This work was supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

(2) Wisconsin Alumni Research Foundation Fellow, 1946–1947.

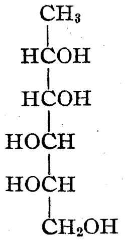
(3) Bertrand, *Compt. rend.*, **126**, 762 (1898); *Ann. chim. phys.*, [8] **3**, 181 (1904).

(4) Hann, Tilden and Hudson, THIS JOURNAL, **60**, 1201 (1938).

(5) Votoček, Valentin and Rác, *Coll. Czech. Chem. Commun.*, **2**, 402 (1930).

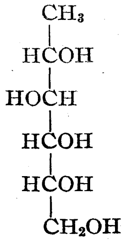
(6) Müller and Reichstein, *Helv. Chim. Acta*, **21**, 271 (1938).

dation of L-gulomethylitol (II), while Hann, Tilden and Hudson unexpectedly found that L-fucitol (III) was attacked by *A. suboxydans*.



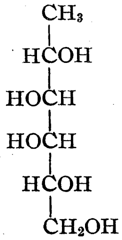
$$\begin{array}{c}CH_3\\ |\\ HCOH\\ |\\ HCOH\\ |\\ HOCH\\ |\\ HOCH\\ |\\ CH_2OH\end{array}$$

I



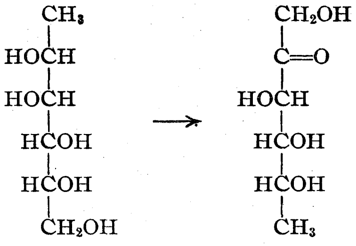
$$\begin{array}{c}CH_3\\ |\\ HCOH\\ |\\ HOCH\\ |\\ HCOH\\ |\\ HCOH\\ |\\ CH_2OH\end{array}$$

II



$$\begin{array}{c}CH_3\\ |\\ HCOH\\ |\\ HOCH\\ |\\ HOCH\\ |\\ HCOH\\ |\\ CH_2OH\end{array}$$

III



$$\begin{array}{c}CH_3\\ |\\ HOCH\\ |\\ HOCH\\ |\\ HCOH\\ |\\ HCOH\\ |\\ CH_2OH\end{array} \longrightarrow \begin{array}{c}CH_2OH\\ |\\ C{=}O\\ |\\ HOCH\\ |\\ HCOH\\ |\\ HCOH\\ |\\ CH_3\end{array}$$

IV V

An opportunity to obtain further information about the action of *A. suboxydans* on this type of alcohol was afforded when in connection with research being carried out in this Laboratory on intermediates in glycolysis it was decided to study the properties of D-fructomethylose (V). This sugar was prepared by Morgan and Reichstein[7] in 12% over-all yield from D-fructose by a procedure involving a Freudenberg–Raschig desoxydation. Since it is the expected product of an *Acetobacter* oxidation of D-rhamnitol (IV) which recently became readily available through a synthesis worked out by Haskins, Hann and Hudson,[8] the possibility of preparing it in this way was investigated. It was found that in contrast to the desoxyhexitols previously cited D-rhamnitol is oxidized by *A. suboxydans* according to the "rules." The yield of ketose in this process is 80%; D-rhamnitol is obtained in 28% yield from methyl α-D-mannoside, the starting material, making the over-all yield 22%. The product has not been obtained in a state of purity comparable to that of the chemically prepared material but could be purified by standard methods. The chief difficulty stems from the fact that the sugar is a sirup which offers little hope of crystallization. The two processes are of about equal length (six steps) and difficulty.

The oxidation proceeded very rapidly, reaching completion in three days. The yield quoted is based on copper reduction analyses of the liquor. The results of these analyses were calculated in terms of glucose since no quantitative data are available for the fructomethyloses. The tagatomethyloses are said to have about 90% of the reducing power of glucose[9]; if the fructomethyloses behave similarly the calculated yield is somewhat low.

In view of the erratic behavior of other methyl hexitols in *Acetobacter* oxidations, it was necessary to obtain rigorous proof that the compound obtained was the anticipated D-fructomethylose. Although Reichstein and collaborators[7] prepared four of the eight possible 6-desoxy-2-ketohexoses, little information as to the properties of these sugars was published by this group. It was noted that they reduced Fehling solution in the cold and were otherwise very reactive.

The sirupy sugar obtained in this investigation caused the appearance of cuprous oxide in a few seconds on being treated with Fehling solution at room temperature and in general had the characteristic reactivity of its class. Thus, in contrast to other ketohexoses, it was about 50% oxidized by hypoiodite in fifteen minutes. It is interesting to note that similar results have been obtained with D-*threo*-pentulose[10] ("D-xyloketose").[11,12] It would seem that the 6-desoxyketohexoses and the ketopentoses closely resemble each other in their behavior with a variety of reagents. This behavior undoubtedly arises from a structural feature common to both types of sugars; *i. e.*, the lack of a hydroxyl more distant from the keto group than the γ carbon atom. This precludes the existence of pyranose rings, leaving as possible structures the more reactive furanose and open chain forms.

The substitution of a methyl for a hydroxymethyl group in the six position apparently alters the susceptibility of a sugar to the Selivanov test. Although definitely positive, the response of D-fructomethylose to this test was weak. Classification of the sugar as a ketose follows from the above considerations and from its reaction with α-methyl-α-phenylhydrazine which is regarded[13,13a] as a ketose reagent. Upon treatment under the prescribed conditions the sirup gave a positive reaction.

In performing the qualitative tests listed samples of D-rhamnose were treated simultaneously with the reagent being used and in all cases the results were completely negative.

The configuration of the sugar was established by converting it to 6-desoxy-D-*arabo*-hexose phenylosazone,[14] phenylosotriazole and *p*-bromophenylosazone, obtainable only from D-fructomethylose and the aldoses D-rhamnose and D-quinovose; D-quinovose would be a very unlikely result of the *Acetobacter* oxidation of D-rhamnitol;

---

(7) Morgan and Reichstein, *Helv. Chim. Acta*, **21**, 1023 (1938). References to preceding papers are given in this article.

(8) Haskins, Hann and Hudson, THIS JOURNAL, **68**, 628 (1946).

(9) Barnett and Reichstein, *Helv. Chim. Acta*, **20**, 1529 (1937).

(10) See Wolfrom, Thompson and Evans, THIS JOURNAL, **67**, 1794 (1945), for a discussion of the nomenclature of ketoses.

(11) Schmidt and Treiber, *Ber.*, **66**, 1765 (1933).

(12) Hassid, private communication.

(13) Van der Haar, "Nachweis, etc.," Berlin, 1920, p. 221 ff.

(13a) Neuberg, *Ber.*, **35**, 960 (1902); Neuberg and Mandl, *Arch. Biochem.*, **11**, 451 (1946).

(14) *Cf.* note 10. The recent suggestion of Sowden, THIS JOURNAL, **69**, 1047 (1947), with reference to the nomenclature of sugar derivatives with fewer asymmetric carbon atoms than the parent compound is followed in this paper.

moreover, its reactions are very similar to those of D-rhamnose which is excluded as a possibility by the results of the qualitative tests. The product must therefore be D-fructomethylose. The quantities of the precipitates obtained with all reagents giving them were much greater than could be accounted for by possible impurities in the preparation.

The osotriazole of this series had not been reported in the literature at the time that this work was done. Both antipodes have since been prepared, the D-form by Hardegger and El Khadem[15] and the L-form by Haskins, Hann and Hudson.[16] The results published by these investigators are in good agreement with those obtained in this work as regards both melting point and specific rotation.

Attempts to prepare derivatives characteristic of D-fructomethylose only were not successful. The *o*-nitrophenylhydrazone described in the original paper of Morgan and Reichstein was not obtained, possibly because of impurities in the sugar. It is believed that crystals of the *p*-bromophenylhydrazone appeared at one stage of the reaction with *p*-bromophenylhydrazine but that further reaction to give the osazone occurred during the working up of the reaction mixture. The hydrazone, if it could be prepared, would serve for the preparation of the pure sugar. Acetonation and acetylation of the sugar were both tried. The former gave negative results but the sirupy acetate might be subject to purification, perhaps by vacuum distillation, after which the pure sugar could be obtained by catalytic saponification. Sufficient material to test this possibility was not obtained.

Experimental

D-Rhamnitol (IV) was synthesized from methyl α-D-mannoside according to Haskins, Hann and Hudson.[8] It was found convenient to use refluxing methyl isobutyl ketone in place of acetone in a pressure bottle as the solvent in the tosyl–iodine exchange reaction. Excess sodium iodide is not required when the higher boiling ketone is used. In the last step the D-rhamnose solution obtained from the hydrolysis of the methyl α-D-rhamnoside was hydrogenated directly after treatment with silver carbonate and concentration to a smaller volume.

D-Fructomethylose (V).—The bacterial oxidation was carried out in a cotton stoppered 2-liter Erlenmeyer flask containing 4.5 g. of D-rhamnitol, 0.5 g. of Difco yeast extract, 0.075 g. of potassium acid phosphate and 0.1 g. of glycerol dissolved in 100 ml. of water. After sterilization for fifteen minutes at 15 pounds the medium was inoculated with 1 ml. of a culture of *A. suboxydans* from an original stock maintained by the Department of Agricultural Bacteriology.[17] After incubation for three days at 30° the medium was well covered with pellicle. An aliquot withdrawn at this time and analyzed by the Shaffer–Hartmann method assayed 40.6 mg. reducing sugar per ml., calculated as glucose. One day later the value was 38.4 mg. per ml. After an initial filtration to remove the bacterial cells the liquor was treated with Norite, filtered and evaporated under reduced pressure to a volume of 15 ml. The Norite treatment was repeated twice and the final filtrate was concentrated to a brown sirup. This was taken up in absolute ethanol; the insoluble material was centrifuged off and washed twice with ethanol and the washings combined with the original solution. Samples of the sugar for further experiments were obtained by evaporating the ethanol from aliquots of this solution.

Reaction with Hypoiodite (Willstätter–Schudel Titration).—A sample (0.099 g.) of the sirup was dissolved in a mixture of 40 ml. of 0.05 *N* iodine, 35 ml. of 0.1 *N* sodium hydroxide and 10 ml. of water and allowed to stand fifteen minutes after which it was acidified and the remaining iodine was titrated with standard thiosulfate. The consumption of iodine was 0.662 g. per g. of sugar or 47% of the amount consumed by an equal weight of glucose under identical conditions.

The Selivanov Test was carried out according to Roe[18] except that only qualitative comparisons were made. D-Fructomethylose gave about one-tenth of the amount of color given by an equal quantity of D-fructose. The rhamnose control remained colorless.

6-Desoxy-D-*arabo*-hexose Phenylosazone from D-Fructomethylose.—The osazone was prepared according to directions given by Fieser.[19] After two recrystallizations from ethanol–water the compound melted at 183° (rapid heating) and showed no depression when mixed with 6-desoxy-D-*arabo*-hexose phenylosazone prepared from D-rhamnose. Fischer and Zach[20] found m. p. 185° for "d-rhamnosazon," while Van der Haar[21] gives 182° for the L-isomer and Freudenberg and Raschig[22] reported melting points from 187 to 191° for these osazones depending on the sugar from which they were made.

Anal. Calcd. for $C_{18}H_{22}N_4O_3$ (342.39): N, 16.37. Found: N, 16.17.

It was noted that the addition of the phenylhydrazine reagent to a solution of the crude sirup caused the immediate formation of a small amount of a bright yellow precipitate which did not increase on standing. The material had the same nitrogen content as that obtained by heating. This observation suggests the possibility that a small amount of D-fructomethylosone or other dicarbonyl compound was formed by the bacteria.

6-Desoxy-D-*arabo*-hexose Phenylosotriazole.—The methods described by Haskins, Hann and Hudson[23,24] were followed in preparing this compound from samples of 6-desoxy-D-*arabo*-hexose phenylosazone prepared from D-rhamnose and D-fructomethylose, respectively. For detailed directions the reader is referred to the recent paper[16] by the same authors. Our compound had the following constants: From D-rhamnose, m. p. 137–138°, $[\alpha]^{24}D$ −99.4° (in pyridine, *c* 0.805). *Anal.* Calcd. for $C_{12}H_{15}N_3O_3$ (249.26): N, 16.86. Found: N, 16.80, 16.71. From D-fructomethylose, m. p. 137–138°, $[\alpha]^{26}D$ 98.5° (in pyridine, *c* 0.63). *Anal.* Found: N, 16.79, 16.90.

A mixture of the two samples showed no depression in melting point. Haskins, Hann and Hudson[16] give m. p. 136–137° and $[\alpha]^{20}D$ + 101.5° for 6-desoxy-L-*arabo* hexose phenylosotriazole ("L-rhamnose phenylosotriazole"), and Hardegger and El Khadem[15] give m. p. 140° for the D-isomer ("*d*-chinovose-phenylosotriazole"). The latter workers distilled their material in high vacuum for analysis.

Attempted Preparation of D-Fructomethylose *p*-Bromophenylhydrazone.[25] **6-Desoxy-D-*arabo*-hexose *p*-Bromophenylosazone.**—A solution of 0.5 g. of sirup in 1 ml.

---

[15] Hardegger and El Khadem, *Helv. Chim. Acta*, **30**, 900 (1947).

[16] Haskins, Hann and Hudson, THIS JOURNAL, **69**, 1461 (1947).

[17] Thanks are due Dr. Elizabeth McCoy who kindly supplied his culture.

[18] Roe, *J. Biol. Chem.*, **107**, 15 (1934).

[19] Fieser, "Experiments in Organic Chemistry," 2nd ed., New York, N. Y., 1941, p. 126. The quantity of water recommended by Fieser for dissolving the solid reagents was found insufficient. Two and a half times the amount given was required.

[20] Fischer and Zach, *Ber.*, **45**, 3770 (1912).

[21] Van der Haar, *op. cit.*, p. 212.

[22] Freudenberg and Raschig, *Ber.*, **62**, 373 (1929).

[23] Haskins, Hann and Hudson, THIS JOURNAL, **67**, 939 (1945).

[24] Hann and Hudson, *ibid.*, **66**, 735 (1944).

[25] The procedure was adapted from that used by Schmidt and Treiber to prepare the *p*-bromophenylhydrazone of D-*threo*-pentulose.

of water and 2 ml. of ethanol was warmed with 0.6 g. of *p*-bromophenylhydrazine until the reagent dissolved, then placed in a vacuum desiccator over sulfuric acid and potassium hydroxide. After three days apparently colorless crystals which may have been the hydrazone were deposited. After an unsuccessful attempt to dissolve the crystals in warm ethanol the adhering gum was washed from them with liberal quantities of cold ethanol. The product which was now yellow melted at 224° after two recrystallizations from ethyl acetate. Votoček and Valentin[26] give 222–223° as the melting point of "*d*-rhamnose *p*-bromophenylosazone" and Freudenberg and Raschig[22] quote 225° for "*d*-chinovose-*p*-bromophenylosazon."

Anal. Calcd. for $C_{18}H_{20}N_4O_3Br_2$ (500.21): N, 11.20. Found: N, 11.14, 11.22.

Acetylation of a small sample of the sugar with acetic anhydride in pyridine at 0° furnished only a water-insoluble oil which has so far not yielded crystalline material.

We are indebted to Prof. Homer Adkins for providing facilities for the high pressure hydrogenation of the D-rhamnose.

Summary

The oxidation of D-rhamnitol by *Acetobacter suboxydans* was found to proceed normally to give crude D-fructomethylose sirup in 80% yield.

The behavior of the sugar with some standard carbohydrate reagents is described.

Recently reported physical constants of 6-desoxy-D-*arabo*-hexose phenylosotriazole are confirmed.

Methods are indicated by which purification of the crude sugar might be effected.

MADISON 6, WISCONSIN RECEIVED OCTOBER 6, 1947

---

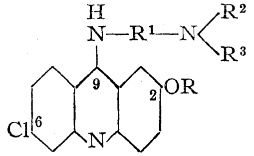
[26] Votoček and Valentin, *Compt. rend.*, **183**, 62 (1926).

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE]

The Hydroxyethyl Analog of Quinacrine

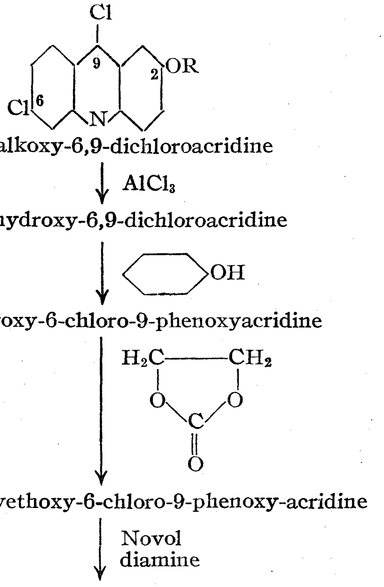
BY WARNER W. CARLSON AND LEONARD H. CRETCHER

Modification of the host toxicity of quinacrine (I) was attempted by hydroxyalkylation at the 2-position of the acridine ring. Literature reports were found of the introduction of the hydroxyl group into (a) the R_1 residue of the aliphatic side-chain,[1] (b) the terminal dialkylamino grouping,[2] and (c) one instance of hydroxylation of both R_1 and R_2 or R_3.[3] Introduction of a hydroxyl grouping into the R_1 residue was somewhat variable in effect, although generally there was a lowering of antimalarial activity unaccompanied by a compensating decrease in host toxicity.[1a,c] The presence of a hydroxyl group in the terminal dialkylamino grouping, either alone or in conjunction with another such radical in the R_1 residue, uniformly lowered antimalarial activity.[2b,3] No previous study was found of the effect of a hydroxyalkyl group at position 2.



I. For quinacrine, R = CH_3—; $R^1{}_2$ = —$CH(CH_3)(CH_2)_3$—; $R^2 = R^3 = C_2H_5$—

The synthesis of the hydroxyethyl analog of quinacrine (VI) was accomplished as outlined in the accompanying diagram. The necessary intermediate II customarily is obtained by ring closure of an appropriately substituted diphenylamine carboxylic acid by means of phosphorus oxychloride,[4] this procedure precluding the presence of a hydroxyalkyl radical at this stage. Direct synthesis of the phenol III was unsatisfactory, while preparation of this compound by the action of various hydrolytic agents on II failed because of the lability of the 9-chloro substituent. Dealkylation of II by anhydrous aluminum chloride afforded the phenol III in good yield. Hydroxyethylation of III, or the 9-phenoxy derivative IV, was difficult because of the ease with which the 9-substituent split off to form an acridone



II. 2-alkoxy-6,9-dichloroacridine

III. 2-hydroxy-6,9-dichloroacridine

IV. 2-hydroxy-6-chloro-9-phenoxyacridine

V. 2-β-hydroxyethoxy-6-chloro-9-phenoxy-acridine

VI. 2-β-hydroxyethoxy-6-chloro-9-[(α-methyl-γ-diethylaminobutyl)-amino]-acridine

---

[1] (a) Cherntsov and Drozdov, *J. Gen. Chem.* (*U. S. S. R.*) **9**, 1435 (1939); (b) Magidson and Grigorovskii, *Ber.*, **69B**, 396 (1936); (c) Wiselogle, "Survey of Antimalarial Drugs," Vol. II, Part 2, J. W. Edwards, Ann Arbor, 1946, Compounds SN186, 5557, 5559, 5578 and 5545.

[2] (a) Burckhalter, Jones, Holcomb, and Sweet, THIS JOURNAL, **65**, 2012 (1943); (b) ref. 1(c), Compounds SN189, 845, 856, and 9616.

[3] Ref. 1(c), Compound SN5588.

[4] Mietzsch and Mauss, *Angew. Chem.*, **47**, 633 (1934).

VII. However, alkylation of IV with ethylene carbonate[5] proceeded smoothly, and the hydroxy ethyl ether V was obtained in good yield. Condensation of V with 1-diethylamino-4-aminopentane then gave the hydroxyethyl analog of quinacrine VI.

The chronic toxicity to white mice of quinacrine and its hydroxyethyl analog was determined by the drug-diet method.[6] The results obtained are listed in Table I, from which it is estimated that the 2-hydroxyethoxy derivative is approximately one-third as toxic as the parent 2-methoxy compound. Determined in another laboratory, the chronic toxicity of VI to white mice has been estimated to be one-half that of quinacrine.[7] In regard to antimalarial activity, the hydroxyethyl derivative has been assigned a quinine equivalent of two[7]; in the same test (F-1), quinacrine was given a quinine equivalent of three.[8]

Experimental

2-Ethoxy-6,9-dichloroacridine (II), as well as the **2-methoxy** derivative, was prepared according to Magidson and Grigorovskii[1b]; over-all yield, 76%.

2-Hydroxy-6,9-dichloroacridine (III).—De-alkylation of II, the 2-ethoxy derivative being preferred, was accomplished by a modification of the method of Magidson, Grigorovskii and Gal'perin.[9] One hundred grams of anhydrous aluminum chloride and 20 g. of II were dissolved and suspended in 300 cc. of xylene in a flask equipped for reflux and stirring. The mixture was heated at 135° (oil-bath temperature) for three-quarters of an hour, cooled, and poured (two liquid layers) into 1.5 liters of ice water containing 60 cc. of concentrated hydrochloric acid, the hydrochloride salt of III precipitating. The product was filtered, washed with ice water, then ether, and dried; yield, 95%. The hydrochloride was ground in aqueous-alcoholic ammonia and crystallized from alcohol, giving the free base (III), m. p. 222°; Magidson, *et al.*,[9] give m. p. 220–222°.

2-Hydroxy-6-chloro-9-phenoxy-acridine (IV).—In a few cases III was hydroxyethylated, but in general better yields were obtained with the 9-phenoxy derivative IV. Conversion of III into IV was accomplished by two methods: (a) by heating III free base in excess phenol at 100° for one hour, adding ether and then precipitating IV hydrochloride; (b) by heating III hydrochloride in phenol containing one mole equivalent of potassium hydroxide, yielding IV free base. Method (a) gave yields of 70–80%, (b) of 85–93%. In a typical reaction (b), 12 g. of III hydrochloride was dissolved in 60 g. of hot phenol containing 3.9 g. of 85% potassium hydroxide. The mixture was heated for one hour at 100°, cooled slightly, 100 cc. of toluene added, and the solution extracted with 500 cc. of 10% sodium hydroxide. The aqueous layer was filtered and treated with carbon dioxide until neutral to phenolphthalein. The precipitated IV was dissolved in acetone, the solution filtered, the IV free base reprecipitated by addition of water: m. p. 219–20°, yield 92%.

Anal. Calcd. for $C_{19}H_{12}O_2NCl$: C, 70.90; H, 3.76; N, 4.36; Cl, 11.03. Found: C, 70.72; H, 3.80; N, 4.25; Cl, 10.94.

2-β-Hydroxyethoxy-6-chloro-9-phenoxyacridine (V).—Because of the sensitivity of the 9-substituent an excess of the hydroxyethylating agent was used as solvent.[5] In a typical experiment a mixture of 8 g. of IV, 10.3 g. of potassium carbonate and 44 g. of ethylene carbonate[5] was heated with stirring for one and one-half hours at 95°, cooled slightly and poured into 200 cc. of ice water containing 40 cc. of concentrated hydrochloric acid, V partly separating as a gum. The acid solution was decanted from the gum and poured into excess cold alkali, precipitating 2.9 g. of V; a trace of IV was recovered from the filtrate by treatment with carbon dioxide. The gummy product from above was taken up in 50% alcohol–acetone, the solution filtered, made alkaline to phenolphthalein and diluted with water, precipitating the hydroxyalkylated base V. The two crops of V were combined and crystallized from aqueous acetone, giving 8.4 g. of yellow needles, m. p. 153°, yield 89%.

Anal. Calcd. for $C_{21}H_{16}O_3NCl$: C, 68.93; H, 4.41; N, 3.83; Cl, 9.70. Found: C, 68.74; H, 4.35; N, 3.71; Cl, 9.78.

2-β-Hydroxyethoxy-6-chloro-9-[(α-methyl-γ-diethylaminobutyl)-aminoacridine] (VI), **SN3055**.—In a typical preparation 3.65 g. (0.01 mole) of V was dissolved in 12 g. of hot phenol, 2.37 g. (0.015 mole) of 1-diethylamino-4-aminopentane was added, the solution was heated with stirring for two hours at 100°, then cooled to 40° and 10 cc. of ethanol added, followed by concentrated hydrochloric acid to congo red. Addition of 100 cc. of 50% acetone–ether precipitated a gum which was dissolved in alcohol; the solution was treated with acetone to turbidity and chilled, VI dihydrochloride separating as a light yellow powder, m. p. 250°; 3.8 g., 82%. From alcohol–ether it was obtained as clusters of pale yellow needles, m. p. 250°.

Anal. Calcd. for $C_{24}H_{34}O_2N_3Cl_3$: C, 57.30; H, 6.82; N, 8.36; Cl, 21.16. Found: C, 57.12; H, 6.75; N, 8.19; Cl, 20.98.

2-β-Hydroxyethoxy-6-chloro-9-acridone (VII).—This compound was obtained both as a by-product in the preparation of V and by the treatment of V for fifteen minutes with boiling 3 *N* alcoholic alkali, VII precipitating from solution upon dilution with water; crystallized from alcohol, m. p. >300°.

Anal. Calcd. for $C_{15}H_{12}NO_3Cl$: C, 62.16; H, 4.18; N, 4.83; Cl, 12.24. Found: C, 62.02; H, 4.15; N, 4.71; Cl, 12.29.

Toxicity of Atebrin and VI.—Estimation of the chronic toxicity to white mice of atebrin and its hydroxyethyl analog (VI) was carried out essentially as described by Bratton.[6b] The two drugs as dihydrochlorides were prepared in powdered Purina dog chow. The drug-diets were placed in the inner member of a double food cup; spilled food thus could be recovered. After being air-dried and sifted from extraneous material recovered diet was weighed and allowance accordingly made in estimating food intake. Male white mice in the weight range 15–20 g. were employed, and the experiment continued for

TABLE I

CHRONIC TOXICITY TO MICE OF QUINACRINE AND ITS HYDROXYETHYL ANALOG

No. mice	Drug in diet, %	Diet intake, g./kg./day	Drug intake, g./kg./day	Dead/total in two weeks	Average day of death	Weight change, %
			Atebrin			
10	0.15	153	0.230[a]	1/10	13	−20
10	.30	135	.405	5/10	11.6	−34
			Hydroxyethyl Analog			
10	0.30	163	0.489	0/10		−14
10	.45	151	.680[a]	1/10	9	−24
			Controls			
5		201		0/10		+18

[a] Maximum tolerated intake.

---

(5) Carlson and Cretcher, THIS JOURNAL, **69**, 1952 (1947).

(6) (a) Litchfield, White and Marshall, *J. Pharmacol.*, **67**, 441 (1939); (b) Bratton, *ibid.*, **85**, 111 (1945).

(7) Ref. 1(c), Compound SN3055.

(8) Ref. 1(c), Compound SN390.

(9) Magidson, Grigorovskii and Gal'perin, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 56 (1938).

two weeks, the animals being weighed at frequent intervals. The results are given in Table I.

Summary

The 2-β-hydroxyethyl analog of quinacrine was synthesized and its chronic toxicity to white mice, as determined by the drug diet method, found to be one-third that of the parent drug.

PITTSBURGH 13, PA. RECEIVED SEPTEMBER 22, 1947

[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Synthesis of Chromans from Phenols and from ortho-Hydroxy Aromatic Aldehydes[1,2]

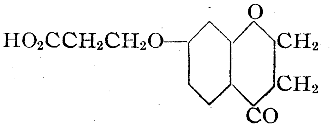
BY G. BRYANT BACHMAN AND HAROLD A. LEVINE[3]

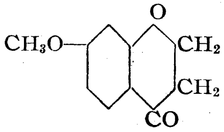
The success of the recently developed synthesis of benzo[f]chromanones by cyclization of β-naphthoxypropionitriles obtained from addition of β-naphthols to acrylonitrile[4] suggested a study of the application of this method to other phenols, especially those in the benzene series. From phenol itself 3-phenoxypropionitrile[5] was obtained in good yield, but a series of cyclization experiments gave only traces of impure ketonic material or no reaction. *p*-Nitrophenol and methyl salicylate did not add, and *o*- and *p*-chlorophenols added only slowly to acrylonitrile. Apparently, electron-withdrawing groups on the benzene nucleus hinder the addition. Even 6-bromo-2-naphthol gave poor yields (10%) of 3-(6′-bromo-2′-naphthoxy)-propionitrile. This cyclized satisfactorily, however, in the presence of sulfuric acid to 8-bromo-1-benzo[f]chromone.

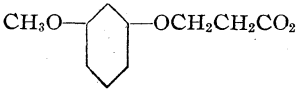
The presence of electron-supplying groups on the benzene ring apparently increases the ease of addition of phenolic hydroxyl groups to acrylonitrile but does not necessarily increase the ease of cyclization of the product because of an increased tendency of such compounds to sulfonate. Resorcinol gives a dinitrile[5] in 40% yields, but treatment with cyclizing agents gives poor yields of a monocyclized product, 7-(2′-carboxy-ethoxy)-chromanone (I). Resorcinol monomethyl ether gives a nitrile in 76% yield. With 85% sulfuric acid this cyclizes to the expected 7-methoxychromanone (II),[6] while with 85% phosphoric acid the uncyclized 3-(3′-methoxyphenoxy)-propionic acid (III)[6] is obtained.

In all of these reactions sulfonation and phosphorylation led to considerable amounts of water-soluble, ether-insoluble products which were not investigated. The desired products were obtained in poor yields.

An alternative preparation of derivatives of chroman based on the addition of the hydroxyl group of salicylaldehyde to acrylonitrile followed by an aldol cyclization was also investigated.


I


II


III

When salicylaldehyde was heated in an excess of acrylonitrile in the presence of dimethylbenzylcetyl-ammonium hydroxide (Triton B) as a catalyst, reaction proceeded to only a limited extent. Three crystalline products were isolated from the alkali-insoluble fraction of the reaction mixture in yields of 1–2%. These compounds were identified by qualitative tests and analytical data as 2-(β-cyanoethoxy)-benzaldehyde (IV), 3-cyano-4-chromanol (V), and 3-cyano-1,2-benzopyran (VI). Attempts to increase the yield of V by the use of other condensation catalysts were unsuccessful. When the condensation was carried out at 100° with Triton B as a catalyst, there was a marked increase in the amount of alkali-insoluble product, but pure V could not be isolated. 3-Aminomethyl-4-chromanol (VII) was prepared by reduction of V in acetic anhydride with platinum oxide catalyst,[7] followed by hydrolysis with methanolic sodium hydroxide.

A second synthesis of derivatives of chroman from salicylaldehyde was also developed. The base catalyzed addition of salicylaldehyde to an aliphatic primary nitroölefin followed by an aldol-type of cyclization gives both the nitroalcohol (VIII) and the nitroölefin (IX) of the expected structures. β-Chloronitroparaffins prepared according to the method of Riley[8] were used as sources of the nitroölefins. The two reactions may be accomplished in one step by condensing the chloronitroparaffin with the sodium salt of salicylaldehyde. Of the three chloronitroparaffins tried, 2-chloro-1-nitroethane, 1-chloro-2-nitropropane and 2-chloro-1-nitropropane, only the last gave the desired products. The others gave polymeric material. This result was not unexpected since the intermediate nitroölefins of the type

---

[1] From the Ph.D. thesis of H. A. Levine, Purdue University, February, 1947.

[2] The assistance of Mr. A. Karler in many of these experiments is gratefully acknowledged.

[3] Present address: Neurological Institute of New York, New York, N. Y.

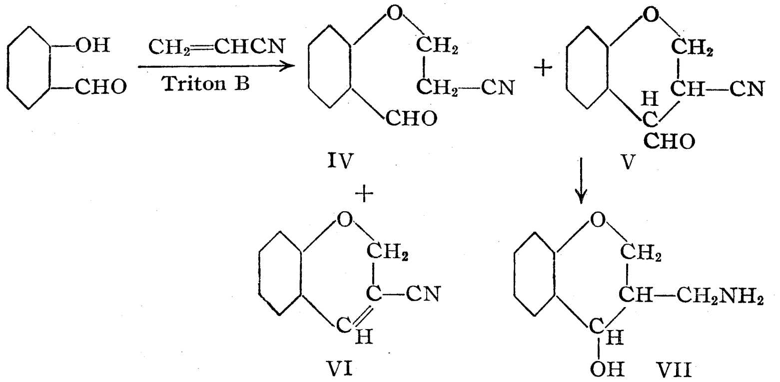
[4] Bachman and Levine, THIS JOURNAL, **69**, 2341 (1947).

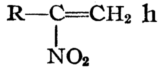
[5] Cook and Reed, *J. Chem. Soc.*, 920 (1945).

[6] Pfeiffer and Oberlin, *Ber.*, **57**, 208 (1924).

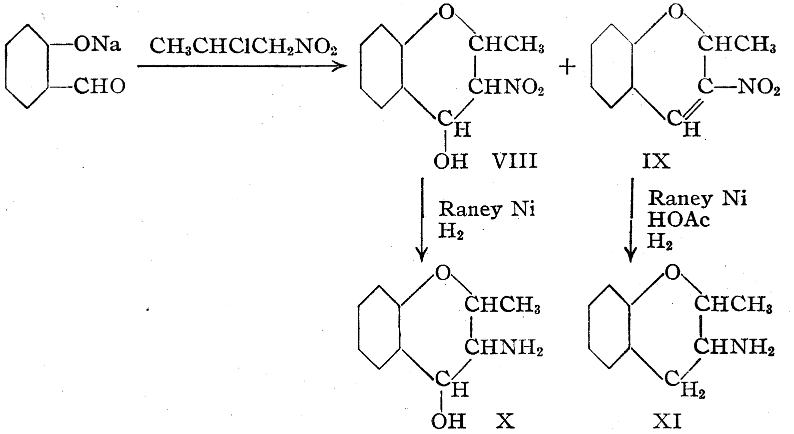
[7] Carothers and Jones, THIS JOURNAL, **47**, 3051 (1925).

[8] McBee and Riley, U. S. Patent 2,337,912 (Dec. 28, 1943).





$\mathrm{R{-}\underset{NO_2}{C}{=}CH_2}$ have been reported to polymerize very readily.[9] Since 3-aminochromans structurally resemble known sympathomimetic phenylethylamine derivatives,[10] VIII and IX were converted to the corresponding amines for testing. Catalytic hydrogenation of 2-methyl-3-nitro-4-chromanol (VIII) proceeds smoothly to give the corresponding amino alcohol (X). The preparation of 2-methyl-3-aminochroman (XI) proved to be more difficult. Reduction of IX to the oxime catalytically,[11] or with iron filings and hydrochloric acid,[11] was unsuccessful. Tarry products were obtained. However catalytic hydrogenation with Raney nickel gave the desired amine in low yield.



Pharmacological Testing.—The aminochromans tested as sympathomimetics showed no pressor activity (VII), slight pressor activity (XI) or slight depressor activity (X). In addition X showed no antimalarial, slight antihistaminic, and no analgesic action.

Acknowledgment.—The authors wish to express their appreciation to Eli Lilly and Company and the Purdue Research Foundation for the financial support which made this investigation possible.

Experimental

Reactions of Acrylonitrile with Phenols.—The phenol (0.25 mole) was refluxed with acrylonitrile (2–4 moles) and *Triton B* (dimethylbenzylacetylammonium hydroxide) (2–5 ml.) for about twenty hours. The reaction mixture was diluted with two volumes of a solvent (ether or chloroform), filtered, and washed successively with several portions of 5% aqueous sodium hydroxide, dilute hydrochloric acid and then water. Evaporation of the solvent and distillation or recrystallization of the residue gave the desired product. The yields and physical properties are as follows: (a) 3-phenoxypropionitrile,[5] 67.5%, m. p. 59–60° from benzene–petroleum ether (reported,[5] 70%, m. p. 61–62°); (b) 3-(7′-bromo-2′-naphthoxy)-propionitrile, 10%, m. p. 120° from ethanol. *Anal.* Calcd. for $C_{13}H_{10}NOBr$: N, 5.07. Found: N, 5.03, 4.98. (c) 1,3-Di-(2′-cyanoethoxy)-benzene, 40%, m. p. 110–111° (reported,[5] 53%, m. p. 112°). (d) 3-(3′-methoxyphenoxy)-propionitrile 76.5%, b. p. 145–146° (3 mm.), m. p. 29.5–30.5°. *Anal.* Calcd. for $C_{10}H_{11}NO_2$: C, 67.77; H, 6.26; N, 7.91. Found: C, 67.75, 67.89; H, 6.18, 6.12; N, 8.00, 7.73.

Cyclizations of 3-Aryloxypropionitriles.—No success attended efforts to cyclize 3-phenoxypropionitrile with concd. or 85% sulfuric acid, 85% phosphoric acid, stannic chloride, phosphorus oxychloride, or acetic anhydride and sodium acetate at various temperatures. Either no reaction occurred or water-soluble, ether-insoluble products were formed. The remaining nitriles were treated as follows: 3-(7′-bromo-2′-naphthoxy)-propionitrile, 17.0 g., was mixed with 200 ml. of 85% sulfuric acid, stirred till dissolved, and poured into 2 liters of ice and water. The yellowish-white solid was recrystallized from 50% aqueous ethanol; yield 13.6 g., 80%, m. p. 123°, of 8-bromo-1-benzo(f)-chromanone.

Anal. Calcd. for $C_{13}H_9O_2Br$: Br, 28.48. Found: Br, 28.96, 28.98.

1,3-Di-(2′-cyanoethoxy)-benzene, 5 g., and 85% sulfuric acid, 25 ml., were mixed and stirred at room temperature for three hours, poured into 200 ml. of water and let stand five days. The precipitated solid, collected and recrystallized from water, gave tan needles, 0.7 g. (12.8%) m. p. 171–173°. They were soluble in dilute solutions of sodium bicarbonate and gave a positive ketone test with 2,4-dinitrophenylhydrazine. The analytical data indicate the product to be 7-(2′-carboxyethoxy)-chromanone (I).

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 60.92, 60.86; H, 5.17, 5.21.

3-(3′-Methoxyphenoxy)-propionitrile, 5 g., and 85% sulfuric acid, 25 ml. were mixed and stirred at room temperature for three hours and then heated on a steam-bath for one hour. The cooled mixture was poured into 200 ml. of water and extracted with ether. The ether extract was evaporated and the oily residue was recrystallized from water. The product, 7-methoxychromanone (II), was obtained in 0.1 g. yield (2%) as colorless needles m. p. 52–54° (reported,[6] m. p. 50–56°, yield 18–40%).

The product when 85% phosphoric acid was used instead of 85% sulfuric acid was 3-(3′-methoxyphenoxy)-propionic acid[6] (III). The ether extract of the reaction mixture was itself extracted with 5% aqueous sodium hydroxide. This latter extract was acidified and the solid precipitate was recrystallized from water (Norit decolorization). The product, 1.4 g. (25.3% yield), was obtained as colorless plates, m. p. 80–82° (reported[6] m. p. 81–83°, 15% yield).

---

(9) Wieland and Sakellarios, *Ber.*, **52**, 898 (1919).

(10) Hartung, *Ind. Eng. Chem.*, **37**, 126 (1945).

(11) Reichert and Koch, *Archiv. Pharm.*, **273**, 265 (1935).

Reaction of Acrylonitrile with Salicylaldehyde.—A mixture of 61 g. of salicylaldehyde (0.5 mole), 133 g. of acrylonitrile (2.5 mole), and 5 ml. of 40% Triton B was heated at reflux for thirty hours, cooled, poured into a mixture of 40 ml. of concd. hydrochloric acid and 500 ml. of ether, and filtered. The ether layer was extracted with three 200-ml. portions of 5% sodium hydroxide, dried, and evaporated under vacuum to yield 16.0 g. of at an oil. Fractional precipitation from benzene by the addition of petroleum ether (b. p. 90–100°) gave 2.0 g. of a crystalline solid. Recrystallization from benzene gave 1.7 g. (2% yield) of 3-cyano-4-chromanol (V), m. p. 141–142.5°.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. Found: C, 68.58, 68.52; H, 5.18, 5.25.

The crystallization mother liquors were evaporated and distilled. Fraction I, b. p. 105–137°, 2.9 g., partially crystallized on cooling to give 1.0 g. (1.3% yield) of 3-cyano-1,2-benzopyran (VI), colorless plates (from methanol), m. p. 48–49°.

Anal. Calcd. for $C_{10}H_7NO$: N, 8.81. Found: N, 8.84, 8.96.

Fraction II, b. p. (2 mm.) 137–170°, 5.5 g., partially crystallized on cooling to give 1.2 g. (1.3% yield) of 2-(2′-cyanoethoxy)-benzaldehyde (IV), m. p. 73–75° (from benzene).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. Found: C, 68.69, 68.56; H, 5.12, 5.17.

3-Aminomethyl-4-chromanol (VII) Hydrochloride.—A mixture of 7.0 g. of 3-cyano-4-chromanol (V), 50 ml. of acetic anhydride, and 0.3 g. of platinum oxide catalyst was hydrogenated for nine hours, filtered, and vacuum-evaporated to yield 9.0 g. of the diacetylated amino alcohol, m. p. 160–165°. Eight grams of this material in 50 ml. of methanol and 100 ml. of 15% sodium hydroxide was heated at reflux for twenty-four hours. The hydrolysis mixture was extracted with ether. Addition of anhydrous hydrogen chloride to the dried ether extract followed by recrystallization of the solid product from ethanol-butyl ether gave 4.0 g. (52% yield) of VII hydrochloride, m. p. 175–176° (d).

Anal. Calcd. for $C_{10}H_{13}NO_2 \cdot HCl$: C, 55.68; H, 6.54. Found: C, 55.88, 55.77; H, 6.64, 6.61.

Reaction of 2-Chloro-1-nitropropane with Salicylaldehyde.—A solution of 1 mole of sodium ethoxide in 500 ml. of absolute ethanol was added to a cooled, stirred mixture of 122 g. of salicylaldehyde (1 mole) and 100 ml. of absolute ethanol. The stirred suspension was kept at 10° while 123.5 g. of 2-chloro-1-nitropropane (1 mole) was added dropwise during one hour. The yellow reaction mixture was stirred for five hours at 5–10° and then overnight at room temperature, filtered, and the filtrate evaporated under vacuum. The residual oil partially solidified on cooling. Filtration followed by washing with 500 ml. of 1:4 ethylene dichloride-petroleum ether (b. p. 90–100°) gave 65.0 g. of Solid A, m. p. 98–100°. The filtrate and washings were evaporated and distilled at 3 mm. The fraction of b. p. 135–145° was recrystallized from 75 ml. of methanol; yield 29.5 g. of yellow crystals, m. p. 72–75° Solid B, Crop 1.

Solid A was dissolved in 500 ml. of hot acetic acid, refluxed for thirty minutes, poured into 1500 ml. of water, filtered, and the solid recrystallized from 1 l. of 1:4 ethylene dichloride-petroleum ether (90–100°); yield, 22.4 g. (10.7%) of pure 2-methyl-3-nitro-4-chromanol (VIII), m. p. 135–137°.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.44; H, 5.26; N, 6.70. Found: C, 57.57, 57.48; H, 5.37, 5.32; N, 6.79, 6.71.

The dilute acetic acid mother liquors were evaporated to 1 liter, cooled and filtered. The yellow residue was combined with the methanol filtrates from Solid B, Crop 1. Evaporation followed by rectification gave an orange oil, b. p. 120–123° (2 mm.). This material was crystallized from 50 ml. of methanol to give 38.0 g. of yellow crystals, m. p. 72–75°; Solid B, Crop 2; total yield 77.5 g. (35.2%). Pure 2-methyl-3-nitro-1,2-benzopyran (IX), m. p. 75.0–75.5°, was obtained by recrystallization from methanol.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.85; H, 4.71; N, 7.33. Found: C, 62.63, 62.69; H, 4.79, 4.71; N, 7.48, 7.40.

2-Methyl-3-amino-4-chromanol (X).—A mixture of 18.2 g. of 2-methyl-3-nitro-4-chromanol (VIII), 200 ml. of absolute ethanol, and 5 g. of Raney nickel catalyst was hydrogenated under a pressure of 1400 lb. for seven hours at 40–50°. Recovery of the product and recrystallization from 475 ml. of benzene gave 7.5 g. of colorless needles, m. p. 155–159°. The benzene mother liquors were extracted with four 50-ml. portions of 5% hydrochloric acid. Addition of an excess of sodium hydroxide to this extract gave 4.2 g. of a tan solid, m. p. 146–156°. This material was recrystallized from benzene, combined with the first crop of crystals, and recrystallized again. A total of 9.9 g. (63.6% yield) of pure 2-methyl-3-amino-4-chromanol, m. p. 158–159°, was obtained. Which of the several possible racemic pairs this represents was not determined.

Addition of isopropyl ether to a solution of 2-methyl-3-amino-4-chromanol in methanolic hydrogen chloride precipitated the crystalline hydrochloride, m. p. 229–230°.

Anal. Calcd. for $C_{10}H_{13}NO_2 \cdot HCl$: N, 6.50. Found: N, 6.67, 6.71.

2-Methyl-3-aminochroman (XI).—A mixture of 19.1 g. (0.1 mole) of 2-methyl-3-nitro-1,2-benzopyran (IX), 6.0 g. of acetic acid (0.1 mole), 75 ml. of methanol, and 5 g. of Raney nickel catalyst was hydrogenated at 1400 lb. pressure, first at 40–50° then at 90–100°, filtered, treated with 9 ml. of concd. hydrochloric acid, and evaporated under vacuum. The residue was successively extracted with 125 ml. of water and 100 ml. of 5% hydrochloric acid. The extracts were made basic and extracted with benzene. The red benzene extracts were dried over potassium hydroxide and evaporated. Vacuum distillation of the dark residual oil gave 3.9 g. of a colorless liquid, b. p. 101–105° (4 mm.).

The crude hydrochloride of this product was recrystallized from isopropyl alcohol–isopropyl ether and then twice from purified nitromethane to obtain colorless needles, m.p. 216.0–217.5°.

Anal. Calcd. for $C_{10}H_{13}NO \cdot HCl$: N, 7.02. Found: N, 7.22, 7.28.

Summary

New syntheses of chroman derivatives based on the cyclizations of phenol–acrylonitrile addition products and salicylaldehyde–nitroölefin addition products have been investigated.

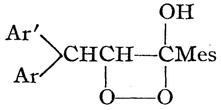
LAFAYETTE, INDIANA RECEIVED MAY 29, 1947

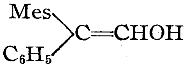
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Vinyl Alcohols. XIX.[1] Mesitylphenylacetaldehyde

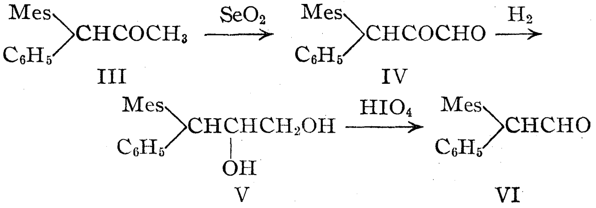
BY REYNOLD C. FUSON AND TZI-LIEH TAN

Although a number of stable 2,2-diarylvinyl alcohols are known, efforts to synthesize the corresponding diarylacetaldehydes have been unavailing. In particular, attempts to form the aldehydes by isomerization of the vinyl alcohols have failed; treatment with alcoholic hydrogen chloride, a method that had been used to convert several trisubstituted vinyl alcohols to the corresponding ketones,[2] yielded only vinyl ethers.[3] Attempts to synthesize highly hindered diarylacetaldehydes by the decomposition of peroxides of type I produced the corresponding vinyl alcohols.[4] The only evidence for the existence of such aldehydes was the fact that mesitylphenylvinyl alcohol (II) formed a semicarbazone.[4]


I

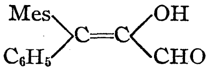

II

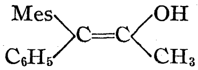
We have now tried various other methods of synthesis and have been successful in preparing an aldehyde of the desired type—mesitylphenylacetaldehyde (VI). It was made first by the oxidative cleavage of 3-mesityl-3-phenyl-1,2-propanediol (V), a hydrogenation product of mesitylphenylpyruvaldehyde (IV), which in turn was prepared by selenium dioxide oxidation of 1-mesityl-1-phenylpropanone (III).[5]

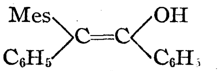


The oxidation of the propanone (III) afforded a very low yield of the glyoxal and produced in addition mesityl phenyl diketone. This benzyl could be made also by oxidation of the glyoxal (IV) with nitric acid. Oxidation with hydrogen peroxide, however, cleaved the glyoxal, yielding mesitylphenylacetic acid.

Certain reactions of the glyoxal did not correspond entirely with those to be expected of an α-keto aldehyde. It formed only a mono-oxime and a monosemicarbazone; with acetic anhydride in pyridine it gave an acetate. The glyoxal failed to yield mesitylphenyllactic acid when treated with alkali and could be regenerated by alkaline hydrolysis of the acetate. Moreover, the compound was colorless. In view of these observations it seemed probable that it was to be classed with benzyl phenyl diketone[6] and benzyl mesityl diketone[7] and to be ascribed the enol form, VII. The infrared spectrum of this compound in hexane solution showed absorption maxima at 2.94μ and 6.02μ indicating the presence of a hydroxyl and a conjugated carbonyl group, respectively.[8]

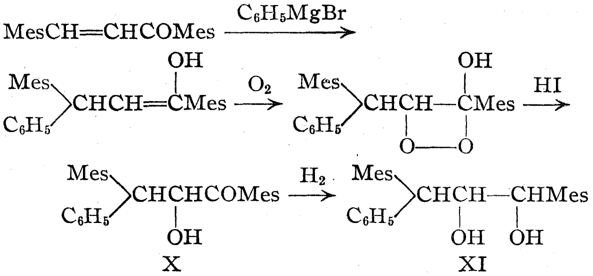

VII


VIII


IX

This enol is an interesting addition to the list of stable trisubstituted vinyl alcohols, especially in view of the fact that the corresponding enols in which the aldehyde group has been replaced by a methyl (VIII) or a phenyl group (IX)[5] are known to be unstable.

Because of the unsatisfactory yields of glyoxal (IV) other methods of preparation of mesitylphenylacetaldehyde were sought. The only attempt to be brought to a successful conclusion involved the oxidative cleavage of 1,3-dimesityl-3-phenyl-1,2-propanediol (XI) with periodic acid. The glycol was prepared from mesitalacetomesitylene by the following series of changes. The hydroxy ketone (X) failed to be cleaved by periodic acid.



A by-product of the cleavage of the glycol (XI) was 2,4,6-trimethylbenzoin. Since this benzoin is known to be produced by the action of ozone on 2-mesityl-2-phenylvinyl alcohol[3] it seems probable that it was formed from mesitylphenylacetaldehyde, perhaps by way of the vinyl alcohol. Attempts were made to extend the synthetic method

---

[1] For the preceding article in this series see Fuson, Chadwick and Ward, THIS JOURNAL, **68**, 389 (1946).

[2] Fuson, Byers and Rabjohn, *ibid.*, **63**, 2639 (1941).

[3] Fuson, Rabjohn and Byers, *ibid.*, **66**, 1272 (1944).

[4] Fuson, Maynert and Shenk, *ibid.*, **67**, 1939 (1945).

[5] Fuson, Armstrong, Chadwick, Kneisley, Rowland, Shenk and Soper, *ibid.*, **66**, 1464 (1944).

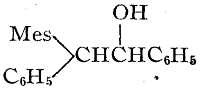
[6] Kohler and Barnes, *ibid.*, **56**, 211 (1934).

[7] Barnes, *ibid.*, **57**, 937 (1935).

[8] The authors are indebted to Dr. F. A. Miller and Mrs. J. L. Johnson for the measurement and interpretation of the infrared spectrum.

to other aldehydes but without success. When 1,3-dimesityl-3-*p*-tolyl-1,2-propanediol was treated with periodic acid, mesityl *p*-tolylacetic acid was formed.

Mesitylphenylacetaldehyde gave a positive Tollens test and yielded a semicarbazone identical with that prepared earlier from 2-mesityl-2-phenylvinyl alcohol.[4] The structure of the aldehyde was established by its reaction with phenylmagnesium bromide which converted it to 2-mesityl-1,2-diphenylethanol (XII). The carbinol yielded an acetate which proved to be identical with the known compound.[5]



$(\mathrm{Mes})(C_6H_5)CHCH(OH)C_6H_5$

XII

The aldehyde structure was confirmed by the infrared absorption spectrum which showed a maximum at 5.77μ.

Mesitylphenylacetaldehyde showed a pronounced tendency to undergo enolization. The enol form could be produced by treatment with alkali or by heating at 150° for two hours. The rearrangement under the influence of heat offers an explanation of the fact that vinyl alcohols rather than aldehydes were obtained by the thermal decomposition of peroxides of Type I.[4] Heating with acetic anhydride in the presence of sodium acetate converted the aldehyde to the acetate of the enol.[3] However, the aldehyde like the vinyl alcohol did not undergo spontaneous rearrangement, *i. e.*, the tautomeric shift appeared to be inhibited. In this respect the behavior of these compounds is similar to that of the stable trisubstituted vinyl alcohols and the corresponding ketones.[5] In this connection it is interesting to recall the behavior of benzhydryl mesityl diketone which was isolated in both the enol and keto forms by Kohler and Thompson,[9] who ascribed the sluggishness of the tautomeric shift to steric hindrance.

Experimental

Oxidation of 1-Mesityl-1-phenylpropanone with Selenium Dioxide.—A number of runs were made in which the reaction conditions were varied in an attempt to improve the yield. The procedure which gave the best result was as follows:

A mixture of 20 g. of 1-mesityl-1-phenylpropanone, 10 g. of selenium dioxide, 300 ml. of dioxane and 20 ml. of water was stirred and refluxed for six hours. The solution was decanted from the free selenium formed in the oxidation and the solvent was removed by distillation. The residue was distilled *in vacuo,* the fraction boiling at 165–175° (3 mm.) being collected. Addition of hexane caused the precipitation of a brown solid which was fractionally crystallized from hexane and separated by mechanical manipulation into two components. The glyoxal, a white crystalline compound which separated preferentially from hexane, was recrystallized from the same solvent; m. p. 134–135°, yield 2 g.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.18; H, 6.81. Found: C, 81.31; H, 7.06.

The infrared spectrum of this compound in hexane solution showed absorption maxima at 2.94 μ and 6.02 μ indicating the presence of a hydroxyl and a carbonyl (conjugated) group, respectively.

The other component of the mixture, a yellow compound, was recrystallized from ethanol; m. p. 136–137°. A mixed melting point determination with mesityl phenyl diketone showed no depression.

Distillation of the filtrate left after the separation of the brown solid gave a red oil boiling at 149–150° (1 mm.); n^{20}_D 1.5791 (*anal.* Found: C, 82.53; H, 7.50). It was shown by a color test with codeine sulfate solution to be a selenium compound. When treated with sodium ethoxide it was converted in low yield to mesitylphenylacetic acid.

In one run in which dry dioxane was used as solvent no mesitylphenylpyruvaldehyde was formed. Mesityl phenyl diketone and the selenium compound were isolated, however.

Reactions of Mesitylphenylpyruvaldehyde. (A) With Nitric Acid.—A mixture of 0.5 g. of mesitylphenylpyruvaldehyde, 5 ml. of concentrated nitric acid and 15 ml. of water was heated under reflux for forty minutes. The acid solution was decanted and the residue dissolved in hexane. The yellow compound which had separated at the end of two weeks melted at 135–137° and was shown by a mixed melting point determination to be mesityl phenyl diketone.

(B) **With Hydrogen Peroxide.**—A mixture of 0.2 g. of mesitylphenylpyruvaldehyde, 20 ml. of dioxane and 10 ml. of hydrogen peroxide (30%) was heated under reflux for four hours. It was diluted with water and extracted with ether. The ether solution in turn was extracted with sodium hydroxide solution (10%). Acidification of the alkaline extract with hydrochloric acid precipitated a substance which was recrystallized from high-boiling petroleum ether; m. p. 166–168°. A mixed melting point determination with mesitylphenylacetic acid showed no depression.

(C) **With Semicarbazide.**—A mixture of 0.2 g. of mesitylphenylpyruvaldehyde, 1 g. of semicarbazide hydrochloride, 1.5 g. of sodium acetate, 10 ml. of ethanol and 1 ml. of water was boiled for ten minutes and allowed to stand in the cold. The semicarbazone was recrystallized from acetone; m. p. 140–145°.

Anal. Calcd. for $C_{19}H_{21}O_2N_3$: C, 70.55; H, 6.56; N, 13.00. Found: C, 70.21; H, 6.86; N, 13.25.

(D) **With Hydroxylamine.**—A mixture of 0.2 g. of mesitylphenylpyruvaldehyde, 0.5 g. of hydroxylamine hydrochloride, 3 ml. of water, 2 ml. of sodium hydroxide solution (10%) and 20 ml. of ethanol was heated on a steam-bath for twenty minutes. The resulting mixture was filtered to remove the sodium chloride, diluted with water and allowed to stand in the cold. The oxime which separated was recrystallized from hexane; m. p. 142–143°.

Anal. Calcd. for $C_{18}H_{19}O_2N$: C, 76.89; H, 6.82; N, 4.98. Found: C, 77.21; H, 6.96; N, 4.97.

(E) **With Alkali.**—A suspension of 0.2 g. of mesitylphenylpyruvaldehyde in 10 ml. of sodium hydroxide solution (10%) was heated under reflux for thirty minutes, diluted with water and extracted with ether. The aqueous layer was acidified with hydrochloric acid and the acidified solution again extracted with ether. Evaporation of the ether left an oil which could not be induced to crystallize.

(F) **With Acetic Anhydride.**—An acetate was formed by allowing a mixture of 1 g. of mesitylphenylpyruvaldehyde, 4 ml. of acetic anhydride and 6 ml. of pyridine to stand at room temperature overnight. It crystallized from low-boiling petroleum ether in colorless cubes; m. p. 100–101°, yield 0.9 g.

Anal. $C_{20}H_{20}O_3$: C, 77.78; H, 6.54. Found: C, 77.79; H, 6.78.

When the acetate was heated with ethanolic sodium hydroxide for twenty minutes, it was hydrolyzed to

---

[9] Kohler and Thompson, THIS JOURNAL, **59**, 887 (1937).

mesitylphenylpyruvaldehyde. Treatment of the acetate with semicarbazide gave the semicarbazone of the original pyruvaldehyde.

3-Mesityl-3-phenyl-1,2-propanediol.—A mixture of 1 g. of mesitylphenylpyruvaldehyde, 0.02 g. of platinum oxide and 50 ml. of ethanol was treated with hydrogen at atmospheric pressure until two molecular equivalents of hydrogen was absorbed. The catalyst was removed by filtration and the solvent evaporated. The propanediol was crystallized from benzene; yield 0.89 g., m. p. 147–148°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.99; H, 8.21. Found: C, 79.97; H, 8.41.

The **diacetate** was prepared by allowing a mixture of 0.5 g. of the glycol, 4 ml. of acetic anhydride and 6 ml. of pyridine to stand overnight. It was recrystallized from hexane; m. p. 80–81°.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.40. Found: C, 74.33; H, 7.45.

Mesitylphenylacetaldehyde.—To a solution of 1 g. of 3-mesityl-3-phenyl-1,2-propanediol in 50 ml. of ethanol was added a solution of 1 g. of potassium periodate in 50 ml. of sulfuric acid (1 *N*). The mixture was stirred for one-half hour at 18° and an additional hour at 33°. Water was then added to dilute the mixture and the precipitate which separated was collected on a filter and dried in the air. It weighed 0.89 g. and melted at 66–72°. Several crystallizations of the aldehyde from low-boiling petroleum ether raised its melting point to 73–74°.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 7.62. Found: C, 85.92; H, 7.85.

The aldehyde gave a positive test with Tollens reagent. Its infrared spectrum showed a peak at 5.77 (presence of an aldehyde group) and no absorption in the hydroxyl and olefinic regions. It was stable under ordinary conditions. However, after standing one year in air it was found to have undergone extensive decomposition.

Reactions of Mesitylphenylacetaldehyde. (A) **With Semicarbazide.**—A mixture of 0.21 g. of mesitylphenylacetaldehyde, 0.15 g. of semicarbazide hydrochloride, 0.25 g. of sodium acetate, 8 ml. of ethanol (aldehyde-free) and 8 ml. of water was heated to boiling. Dilution of the solution with water caused the slow precipitation of the semicarbazone. It melted at 203–205° and did not depress the melting point of the known semicarbazone prepared from 2-mesityl-2-phenylvinyl alcohol.[4]

(B) **With Acetic Anhydride.**—A mixture of 0.1 g. of mesitylphenylacetaldehyde, 0.15 g. of fused sodium acetate and 1.5 ml. of acetic anhydride was heated on a steam-bath for two hours and poured with vigorous stirring into 20 ml. of ice water. The precipitate was collected on a filter, washed with water and recrystallized from dilute ethanol; m. p. 89–90°. A mixed melting point determination with the acetate prepared from 2-mesityl-2-phenylvinyl alcohol[3] showed no depression.

(C) **With Phenylmagnesium Bromide.**—A solution of 0.5 g. of the aldehyde in 12 ml. of absolute ether was added in fifteen minutes to a Grignard reagent prepared from 0.063 g. of magnesium turnings, 0.505 g. of bromobenzene and 10 ml. of absolute ether. Stirring was continued for two hours during which time nitrogen was passed over the reaction mixture and the solution was decomposed with cold hydrochloric acid. The ether layer was removed, washed successively with water, sodium bicarbonate solution and water and dried over magnesium sulfate. Removal of the ether left the 2-mesityl-1,2-diphenylethanol as a white solid which was recrystallized from high-boiling petroleum ether; m. p. 133–134°.

Anal. Calcd. for $C_{23}H_{24}O$: C, 87.29; H, 7.66. Found: C, 87.02; H, 7.65.

When the 2-mesityl-1,2-diphenylethanol was treated with acetic anhydride and pyridine an acetate (m. p. 125–126°) was formed. It did not depress the melting point of an authentic sample of 2-mesityl-1,2-diphenylethyl acetate prepared previously by the reduction of α-mesityldesoxybenzoin with isopropylmagnesium bromide and treatment of the product with acetyl chloride.[5]

(D) **Enolization.**—1. A sample of 0.1 g. of mesitylphenylacetaldehyde was dissolved in a solution of 0.35 g. of potassium hydroxide in 5 ml. of ethanol. The solution was allowed to stand at room temperature overnight, diluted with water and neutralized with hydrochloric acid. The precipitate was collected on a filter and recrystallized from low-boiling petroleum ether; m. p. 112–113°. It was shown by a mixed melting point determination to be 2-mesityl-2-phenylvinyl alcohol.

2. Enolization of the aldehyde was also effected by heating at 150° for two hours. The vinyl alcohol was recrystallized from low-boiling petroleum ether; m. p. 112–113°.

α-Hydroxy-β-mesityl-β-phenylpropiomesitylene.—A mixture of 4 g. of 1,3-dimesityl-3-phenyl-1-propen-1-ol peroxide (m. p. 132–134°),[4] 6.7 g. of potassium iodide and 40 ml. of glacial acetic acid was shaken at room temperature for six hours. It was diluted with 60 ml. of water and the precipitate was collected on a filter. The pure α-hydroxy-β-mesityl-β-phenylpropiomesitylene obtained by recrystallization from ethanol melted at 160–162° and weighed 2 g.

Anal. Calcd. for $C_{27}H_{30}O_2$: C, 83.88; H, 7.83. Found: C, 83.84; H, 7.82.

The **acetate** prepared by treatment with acetic anhydride and pyridine was recrystallized from ethanol; m. p. 195–196°.

Anal. Calcd. for $C_{29}H_{32}O_3$: C, 81.25; H, 7.54. Found: C, 81.14; H, 7.56.

An attempt was made to cleave α-hydroxy-β-mesityl-β-phenylpropiomesitylene with periodic acid. To a solution of 1 g. of the hydroxy ketone in 100 ml. of ethanol was added a solution of 0.6 g. of potassium periodate in 30 ml. of sulfuric acid (1 *N*). The mixture was shaken at room temperature for six hours and then diluted with water. The starting material was recovered.

1,3-Dimesityl-3-phenyl-1,2-propanediol.—A solution of 4 g. of α-hydroxy-β-mesityl-β-phenylpropiomesitylene in 20 ml. of ethanol was heated to 150° and subjected to a pressure of 2200 lb. of hydrogen for two hours in the presence of a copper chromite catalyst. After removal of the catalyst the solution was concentrated to a small volume. The white propanediol which separated when the solution was allowed to stand in the cold was recrystallized from ethanol; m. p. 134–135°, yield 2.9 g.

Anal. Calcd. for $C_{27}H_{32}O_2$: C, 83.45; H, 8.32. Found: C, 83.35; H, 8.58.

The **diacetate** prepared by the use of acetic anhydride and pyridine was recrystallized from ethanol; m. p. 187–188°.

Anal. Calcd. for $C_{31}H_{36}O_4$: C, 78.76; H, 7.69. Found: C, 78.36; H, 7.63.

Oxidative Cleavage of 1,3-Dimesityl-3-phenyl-1,2-propanediol with Periodic Acid.—To a solution of 10 g. of 1,3-dimesityl-3-phenyl-1,2-propanediol in 1000 ml. of ethanol was added a solution of 6 g. of potassium periodate in 300 ml. of sulfuric acid (1 *N*). The mixture was stirred at room temperature for seven hours and diluted with 2 l. of water. The brown oily substance which separated from the water solution was collected and dissolved in 10 ml. of ethanol. The white needles which separated when the solution was allowed to stand in the cold were recrystallized from low-boiling petroleum ether; m. p. 73–74°. A mixed melting point determination with the sample of mesitylphenylacetaldehyde prepared by cleavage of 3-mesityl-3-phenyl-1,2-propanediol with periodic acid showed no depression.

The filtrate remaining after removal of mesitylphenylacetaldehyde was evaporated under diminished pressure and the residue distilled *in vacuo*. The fractions boiling at 89–90° (5 mm.) and 186–187° (5 mm.) were collected separately.

The lower-boiling fraction was identified as mesitaldehyde. Its dinitro derivative was formed by nitration with equal volumes of nitric acid and concentrated sulfuric acid; m. p. 166–167°. The dinitromesitaldehyde formed a phenylhydrazone which melted at 208–209°.[10]

The higher-boiling fraction was dissolved in 2 ml. of low-boiling petroleum ether. The white compound which had separated at the end of two days was recrystallized from low-boiling petroleum ether; m. p. 103–105°. A mixed melting point determination with 2,4,6-trimethylbenzoin showed no depression.

1,3-Dimesityl-3-*p*-tolyl-1-propen-1-ol Peroxide.—The procedure for the preparation of this compound was based on the directions used in the preparation of 1,3-dimesityl-3-phenyl-1-propen-1-ol peroxide.[4] To a Grignard reagent prepared from 14.8 g. of magnesium turnings, 105 g. of *p*-bromotoluene and 400 ml. of absolute ether was added a solution of 116 g. of mesitylacetomesitylene in 300 ml. of dry benzene. The mixture was stirred and heated for two hours and decomposed with cold dilute hydrochloric acid. The organic layer was washed with ice water and placed in a 1-liter Erlenmeyer flask held in an ice-bath. Oxygen was bubbled rapidly through the solution for six hours. The solvent was removed by a stream of air leaving 137 g. of white powder melting at 130–131°. The enol peroxide was recrystallized from a mixture of ether, benzene and low-boiling petroleum ether; m. p. 130.5–131.5°.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 80.73; H, 7.76. Found: C, 80.92; H, 7.92.

α-Hydroxy-β-mesityl-β-*p*-tolylpropiomesitylene.—A mixture of 8 g. of 1,3-dimesityl-3-*p*-tolyl-1-propen-1-ol peroxide, 14 g. of potassium iodide and 100 ml. of glacial acetic acid was shaken at room temperature for eight hours. It was diluted with 150 ml. of water and the precipitate was collected on a filter. The yield of the crude α-hydroxy-β-mesityl-β-*p*-tolylpropiomesitylene was 7 g.; m. p. 134–136°. After recrystallization from ethanol the compound melted at 136–138°.

Anal. Calcd. for $C_{28}H_{32}O_2$: C, 83.96; H, 8.07. Found: C, 83.96; H, 8.13.

The **acetate**, prepared by treatment with acetic anhydride and pyridine, was recrystallized from ethanol; m. p. 170–171°.

Anal. Calcd. for $C_{30}H_{34}O_3$: C, 81.41; H, 7.76. Found: C, 81.48; H, 7.84.

1,3-Dimesityl-3-*p*-tolyl-1,2-propanediol.—A solution of 4 g. of α-hydroxy-β-mesityl-β-*p*-tolylpropiomesitylene in 20 ml. of ethanol was subjected for three hours to a hydrogen pressure of 2000 pounds and a temperature of 150° in the presence of a copper chromite catalyst. The catalyst was removed by filtration and the solvent evaporated. The 1,3-dimesityl-3-*p*-tolyl-1,2-propanediol crystallized from ethanol in white plates which melted at 147–148°.

Anal. Calcd. for $C_{28}H_{34}O_2$: C, 83.53; H, 8.52. Found C, 83.28; H, 8.73.

The **diacetate** of the glycol, prepared by the use of acetic anhydride and pyridine, was recrystallized from dilute ethanol; m. p. 163–165°.

Anal. Calcd. for $C_{32}H_{38}O_4$: C, 78.98; H, 7.87. Found: C, 79.17; H, 8.01.

Oxidative Cleavage of 1,3-Dimesityl-3-*p*-tolyl-1,2-propanediol with Periodic Acid.—To a solution of 5 g. of 1,3-dimesityl-3-*p*-tolyl-1,2-propanediol in 250 ml. of pure dioxane was added a solution of 3 g. of potassium periodate in 150 ml. of sulfuric acid (1 *N*). The mixture was stirred at room temperature for eight hours, diluted with 600 ml. of water and extracted twice with ether. Evaporation of the ether extract left an oil which could not be induced to crystallize.

When the oil was distilled *in vacuo* fractions boiling at 85–86° (3 mm.) and 163–165° (3 mm.) were collected. The residue that remained in the distilling flask was dissolved in ethanol and the solution allowed to stand in the cold; white crystals separated slowly. When recrystallized from ethanol they formed fine needles; m. p. 116–117°.

Anal. Calcd. for $C_{28}H_{32}O$: C, 87.45; H, 8.39. Found: C, 87.94; H, 8.59.

This compound had the composition of the glycol minus the elements of water and may be a ketone.

The lower-boiling portion of the distillate was identified as mesitaldehyde by nitration, which converted it to the known dinitromesitaldehyde; m. p. 166–167°.[10]

The higher-boiling portion was dissolved in 5 ml. of low-boiling petroleum ether and allowed to stand in the cold. White crystals which separated after several days were recrystallized from high-boiling petroleum ether; m. p. 211–212°. A mixed melting point determination with mesityl-*p*-tolylacetic acid showed no depression.

Summary

Mesitylphenylacetaldehyde has been prepared by the oxidative cleavage of 3-mesityl-3-phenyl-1,2-propanediol and of 1,3-dimesityl-3-phenyl-1,2-propanediol. It rearranged to 2-mesityl-2-phenylvinyl alcohol when heated at 150° or when treated with alkali.

Evidence is presented indicating that mesitylphenylpyruvaldehyde exists in the enol form.

URBANA, ILLINOIS RECEIVED SEPTEMBER 8, 1947

---

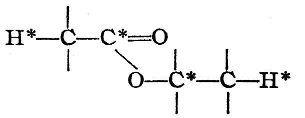
[10] Hinkel, Ayling and Morgan, *J. Chem. Soc.*, 1170 (1931).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Types of Reaction of Carboxylic Esters with Grignard Reagents[1]

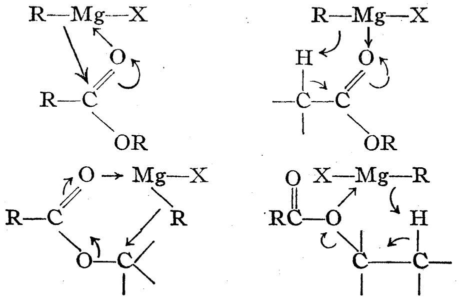
BY CHARLES R. HAUSER, PASSIE O. SAPERSTEIN AND JOSEPH C. SHIVERS

A strong base such as the amide ion[2] is capable of reacting with carboxylic esters at any of the four positions indicated by asterisks in the following general formula: at the carbonyl carbon, the α-hydrogen in the acyl portion, the α-carbon or the β-hydrogen in the alkoxy portion.



Since the strongly basic alkyl or aryl anion is potentially present in Grignard reagents these reagents should be capable of reacting at any of the four vulnerable positions of esters. Actually, reactions at three of these positions have been observed previously; reaction at the fourth position, the β-hydrogen, has been realized in this investigation.

The reactions of the potential alkyl or aryl anions of Grignard reagents at the four vulnerable positions of esters are of different types. Addition occurs at the carbonyl carbon to form a ketone or more often a tertiary alcohol[3]; the α-hydrogen is removed to form the magnesium halide derivative (enolate) of the ester which condenses with unchanged ester to form a β-keto ester (acetoacetic ester condensation); substitution takes place at the α-carbon to form a hydrocarbon; and the β-hydrogen is removed, accompanied by the elimination of the carboxylate group, to form an olefin (β-elimination). Because the magnesium atoms of Grignard reagents probably first coördinate with the carbonyl or alkoxy oxygen atoms of esters it is possible that these four types of reaction take place within the resulting coördination complexes. Indeed, the formation of the coördination complex should activate both the potential alkyl or aryl anion of the Grignard reagent and the electron accepting atom of the ester; moreover, these reactive centers should be brought in close contact within the coördination complex.[4] The electronic changes that may occur within the coördination complexes leading to the four types of reaction may be indicated as



It is well known that ethyl acetate and higher aliphatic homologs as well as ordinary aromatic esters such as ethyl benzoate exhibit mainly the carbonyl carbon reaction with most Grignard reagents. However, t-butyl acetate,[5] which has a relatively unreactive carbonyl carbon, and especially ethyl phenylacetate,[6] which has a relatively reactive α-hydrogen, are self-condensed by isopropylmagnesium bromide. With the more complex Grignard reagent, t-butylmagnesium chloride,[7] ethyl propionate mainly self-condenses, while with mesitylmagnesium bromide[8] even ethyl isovalerate and ethyl isobutyrate self-condense.

In this investigation ethylmagnesium bromide was found to effect the self-condensation of ethyl phenylacetate to the extent of only 8% under the conditions that have produced a 94% yield of the condensation product in the presence of the more complex isopropylmagnesium bromide.[6] Ethyl diphenylacetate was found to react to some extent with isopropylmagensium bromide in refluxing ethyl ether but neither the self-condensation product of the ester nor the carbonyl carbon product was obtained. Since treatment of the reaction mixture with benzoyl chloride gave some ethyl benzoyldiphenylacetate whereas none was obtained from the ester alone with benzoyl chloride, part of the ester must have been converted to its magnesium derivative by the Grignard reagent, thus

$$(C_6H_5)_2CHCO_2C_2H_5 \xrightarrow{(CH_3)_2CHMgBr} [(C_6H_5)_2CCO_2C_2H_5]MgBr \xrightarrow{C_6H_5COCl} C_6H_5COC(C_6H_5)_2CO_2C_2H_5$$

This appears to be the first case in which the magnesium derivative of an ester has been condensed with a component other than the original ester[9];

---

[1] This work was supported in part by a grant from the Duke University Research Council.

[2] Hauser, Shivers and Skell, THIS JOURNAL, **67**, 409 (1945).

[3] Obviously, the tertiary alcohol results from reaction with a second molecule of the Grignard but it is not clear whether the ketone is formed as an intermediate; see Gilman, "Organic Chemistry," Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 502–504.

[4] See Johnson, *ibid.*, Vol. II, pp. 1866, 1880; Young and Roberts, THIS JOURNAL, **68**, 649 (1946); Whitmore and George, Abstracts, Division of Organic Chemistry, Meeting of the American Chemical Society, Atlantic City, September, 1941.

[5] Hudson, Shivers and Hauser, THIS JOURNAL, **65**, 2051 (1943).

[6] Conant and Blatt, *ibid.*, **51**, 1227 (1929); see also Ivanov and Spassov, *Bull. soc. chim.*, [4] **49**, 375 (1931).

[7] Zook, McAleer and Horwin, THIS JOURNAL, **68**, 2404 (1946).

[8] Spielman and Schmidt, *ibid.*, **59**, 2009 (1937).

[9] An unsuccessful attempt to benzoylate the magnesium derivative of ethyl isobutyrate, prepared by means of mesitylmagnesium bromide, was made previously in this laboratory; Hudson and Hauser, *ibid.*, **63**, 3157 (1941), note 8.

judging from previous results with diethylaminomagnesium bromide[10] the magnesium derivative of most esters condense very rapidly with the original ester. An attempt to carbonate the magnesium derivative of ethyl diphenylacetate failed, presumably because of the instability of the carbonation product.[11]

Substitution at the α-carbon in the alkoxy portion of esters has been observed with certain esters in which the carbonyl carbon is hindered and the α-carbon is attached to relatively strong electron releasing groups. Arnold and co-workers[12] have realized this type of reaction with certain allyl esters, for example allyl mesitoate, with which phenylmagnesium bromide gave a 70% yield of allylbenzene.[13] Fieser and Heymann[14] found that triphenylmethyl acetate reacts with methylmagnesium iodide to form α,α,α-triphenylethane in good yield. In the present investigation triphenylmethyl benzoate has been found to react similarly.

$$C_6H_5CO_2C(C_6H_5)_3 + CH_3MgI \longrightarrow (C_6H_5)_3CCH_3 + C_6H_5CO_2MgI$$

β-Elimination of esters with Grignards has apparently not been reported previously.[15] This type of reaction has been realized in the present investigation with α,β-diphenylethyl mesitoate in which the carbonyl carbon is hindered and the β-hydrogen is activated. With phenylmagnesium bromide in refluxing n-butyl ether this ester yielded the elimination products stilbene and mesitoic acid in yields of 80–90%; this was shown not to be merely a thermal elimination.

$$\text{Mes-}CO_2CH(C_6H_5)CH_2C_6H_5 + C_6H_5MgBr \longrightarrow C_6H_5CH{=}CHC_6H_5 + \text{Mes-}CO_2MgBr$$

With methylmagnesium iodide or ethylmagnesium bromide under similar conditions the yield of stilbene was only 30–40% and another product, 1,2,3,4-tetraphenylbutane, was obtained in 8–9% yield. The latter substance might be accounted for by the dimerization of the intermediate free α,β-diphenylethyl radical.[16] This type of reaction appears to have been observed by Stadnikoff[17] who found that benzhydryl acetate reacts with n-propyl- or n-butyl-magnesium iodide to form partly (6–10%) *sym*-tetraphenylethane along with the corresponding alkane and alkene from the Grignard. Since Kharasch and co-workers[18] have found that cobaltous chloride increases the free radical nature of certain Grignard reactions, α,β-diphenylethyl mesitoate and methylmagnesium iodide have been allowed to react in the presence of a catalytic amount of this salt. In agreement with the radical mechanism, the yield of the dimer was increased from 9% to 16% and no stilbene was found. However, the reaction of the ester with phenylmagnesium bromide and cobaltous chloride produced none of the dimer, although the yield of stilbene was reduced considerably. Actually the best yield (22%) of the dimer was obtained when the reaction was carried out with methylmagnesium iodide using a metal stirrer; no cobaltous chloride was added in this experiment. It might appear that the stilbene could be accounted for by the radical mechanism in which the α,β-diphenylethyl radical underwent disproportionation, but the other product of this reaction, dibenzyl, has not been found. Moreover, the yield of stilbene decreased as the conditions were made more favorable for the radical reaction.

Experimental[19]

Esters.—Ethyl diphenylacetate (m. p. 57°) was synthesized by the carbethoxylation of diphenylmethylpotassium as described previously.[20]

Triphenylmethyl benzoate was prepared by a modification of the method of Gomberg and Davis[21] for triphenylmethyl acetate. A mixture of 43.2 g. (0.15 mole) of triphenylchloromethane and 40.0 g. (0.15 mole) of silver benzoate in 500 ml. of dry benzene was stirred and heated on the steam-bath for six hours, filtered hot and the filtrate concentrated. The precipitate obtained on cooling was filtered off and recrystallized from ethyl acetate yielding 25 g. (50%) of the ester, melting at 162–163°.

Anal. Calcd. for $C_{25}H_{20}O_2$: C, 85.69; H, 5.53. Found: C, 85.35; H, 5.67.

α,β-Diphenylethyl mesitoate was prepared by stirring for four hours a mixture of 37 g. (0.22 mole) of phenylbenzylcarbinol and 40 g. (0.22 mole) of mesitoyl chloride[22] in 200 ml. of dry benzene. The benzene solution was extracted with sodium bicarbonate solution, dried with Drierite and the solvent distilled. The oily residue was recrystallized from 50% ethanol yielding 60 g. (82%) of the ester, melting at 55–57°.

Anal. Calcd. for $C_{24}H_{24}O_2$: C, 83.71; H, 7.03. Found: C, 83.36; H, 7.11.

Grignards.—These reagents were prepared under nitrogen in absolute ethyl or n-butyl ether. The solutions were decanted from unreacted magnesium and analyzed; when not used immediately they were stored under nitrogen in well stoppered flasks in the dark.

Apparatus.—The reactions of esters with Grignards were carried out in three necked round bottomed flasks (of suitable capacity) equipped through ground glass joints with a dropping funnel, a mercury sealed stirrer and a reflux condenser to which was attached a drying tube.

---

[10] Hauser and Walker, THIS JOURNAL, **69**, 295 (1947).

[11] This half acid ester should be about as unstable as diphenylmalonic acid which is unknown in the free state; see Heilbron, "Dictionary of Organic Compounds," Vol. I, Oxford University Press, New York, N. Y., 1943, p. 1033.

[12] Arnold, Bank and Liggett, THIS JOURNAL, **63**, 3444 (1941); Arnold and Liggett, *ibid.*, **64**, 2875 (1942). See also, Arnold and Liggett, *ibid.*, **67**, 337 (1945).

[13] Fuson, Bottorf and Speck *ibid.*, **64**, 1450 (1942)) found that with methyl, butyl or benzyl mesitoate in refluxing n-butyl ether Grignards produce methyl, butyl or benzyl halide instead of the alkylation product.

[14] Fieser and Heymann, THIS JOURNAL, **64**, 376 (1942).

[15] Although t-butyl halides exhibit β-elimination relatively readily, t-butyl benzoate has failed to exhibit this type of reaction with phenylmagnesium bromide to form isobutylene; instead, the carbonyl carbon reaction occurred to form triphenylcarbinol (unpublished results of F. C. Frostick and Erwin Baumgarten in this Laboratory).

[16] See Waters, "Chemistry of Free Radicals," Oxford University Press, London, 1946, pp. 211–213.

[17] Stadnikoff, *Ber.*, **47**, 2135 (1914).

[18] See Kharasch and Fuchs, THIS JOURNAL, **65**, 504 (1943).

[19] Microanalyses are by Oakwold Laboratories, Alexandria, Va.

[20] Yost and Hauser, THIS JOURNAL, **69**, 2325 (1947).

[21] Gomberg and Davis, *Ber.*, **36**, 3926 (1903).

[22] See Fuson, Corse and McKeever, THIS JOURNAL, **61**, 2010 (1939).

Ethyl Diphenylacetate with Isopropylmagnesium Bromide and Benzoyl Chloride.—To 143 ml. of the stirred ethyl ether solution containing 0.073 moles of isopropylmagnesium bromide was added 17.5 g. (0.073 mole) of ethyl diphenylacetate in 100 ml. of dry ether. Some gas was evolved. On stirring and refluxing for two days the solution became yellow and deposited a few crystals on the sides of the flask. Benzoyl chloride (14 g., 0.1 mole) was then added and the stirring continued for one-half hour. The mixture was decomposed with hydrochloric acid and crushed ice and the ether phase washed with water, dried and the solvent distilled. The brown oily residue was refluxed with 60 ml. of 47% hydriodic acid and 30 ml. of glacial acetic acid for three hours (to hydrolyze the benzoyl chloride and original ester but not the β-keto ester).[20] The resulting mixture was shaken with ether and the ether phase extracted with 2 *M* sodium hydroxide, dried and the solvent distilled. The white crystalline residue was recrystallized from 95% ethanol yielding 3.5 g. (14%) of ethyl benzoyldiphenylacetate, melting at 146° (and at 147° when mixed with an authentic sample,[20] m. p. 148°). Some (5 g., 29%) of ethyl diphenylacetate (m. p. 57°) was recovered from the ethanol filtrate; no attempt was made to recover the diphenylacetic acid that was undoubtedly present in the alkaline extract. The self-condensation product of the ester was not found.

A blank experiment with ethyl diphenylacetate and benzoyl chloride in ether yielded no ethyl benzoyldiphenylacetate. Some (30%) of the original ester was recovered; most of it was probably hydrolyzed in the hydriodic-acetic acid treatment.

In an attempt to effect carbonation the ether solution of equivalents of the Grignard and ester, after stirring and refluxing for two hours, was poured onto excess Dry Ice but no ethyl hydrogen diphenylmalonate was found; most (83%) of the original ester was recovered.

Triphenylmethyl Benzoate with Methylmagnesium Iodide.—To the stirred reagent from 13.5 g. (0.098 mole) of methyl iodide and 2.4 g. (0.098 g. at.) of magnesium in 400 ml. of ethyl ether, was added 6.0 g. (0.015 mole) of triphenylmethyl benzoate (partly as a suspension) in 350 ml. of dry ether. The resulting solution was stirred and refluxed for eight hours (producing a precipitate) and decomposed with ice and acid. The ether phase was extracted with sodium bicarbonate solution, dried and the solvent distilled. The residue (3.8 g.) melted at 65–75°. Recrystallization from 95% ethanol yielded 2.3 g. (45%) of α,α,α-triphenylethane, m. p. 93–94.5° (reported m. p. 93.8–95°).[14] Acidification of the bicarbonate extract yielded 1 g. (85%) of benzoic acid, m. p. 121°.

When triphenylmethyl benzoate was treated with excess diethylamino-magnesium bromide in ether[10] or with potassium amide in liquid ammonia, amines appeared to be formed but their hydrochlorides soon decomposed.

α,β-Diphenylethyl Mesitoate with Grignards. (A). With Phenyl-magnesium Bromide.—Since 75% of the ester was recovered when it was refluxed with the Grignard in ethyl ether for one hour and then allowed to stand overnight, the reaction was carried out in refluxing *n*-butyl ether (b. p. 142–143°). It was first shown that the ester may be refluxed alone in *n*-butyl ether for four hours and most (89%) of it recovered unchanged.

To 100 ml. of the stirred *n*-butyl ether solution containing 0.1 mole of phenylmagnesium bromide (prepared from an ethyl ether solution of the reagent by adding the butyl ether in an atmosphere of nitrogen and distilling off the ethyl ether) was added 13 g. (0.05 mole) of α,β-diphenylethyl mesitoate in 100 ml. of butyl ether. The mixture was stirred and refluxed for four hours and then hydrolyzed with ice and acid. The ether phase was extracted with bicarbonate, washed with water, dried and the solvent distilled. The oily residue on recrystallization from ethanol yielded 5.5 g. (68%) of *trans*-stilbene, m. p. and mixed m. p. 124°. From the ethanol filtrate there was obtained 1.1 g. (13%) of *cis*-stilbene, b. p. 148° (14 mm.) (reported b. p. 148–9° (17 mm.), 145° (13 mm.)).[23] The *trans*- and *cis*-stilbene gave the same dibromide, m. p. 237°.[24] Acidification of the bicarbonate extract yielded 7.3 g. (90%) of mesitoic acid, m. p. 151°.

When the reaction was carried out in the presence of 3 mole per cent. of anhydrous cobaltous chloride[18] (which was first refluxed with the Grignard before adding the ester) the yields of stilbene and mesitoic acid were only 38–40% but other products were not found.

(B) **With Methylmagnesium Iodide.**—The reaction of 35 ml. of a *n*-butyl ether solution containing 0.045 mole of methylmagnesium iodide (prepared in the butyl ether) with 5 g. (0.02 mole) of α,β-diphenylethyl mesitoate in 100 ml. of butyl ether was carried out as in (A). The residue obtained on distilling the solvent consisted of 2 g. of yellow solid from which two products were isolated by fractional crystallization from 95% ethanol. The more soluble substance (1.0 g., 30%) was *trans*-stilbene (m. p. and mixed m. p. 124°). The less soluble substance (0.3 g., 9%) was 1,2,3,4-tetraphenylbutane, m. p. 177–179°,[25] which after treatment with chromic anhydride in glacial acetic acid for five hours was recovered unchanged.

Anal. Calcd. for $C_{28}H_{26}$: C, 92.85; H, 7.18. Found: C, 92.52; H, 7.21.

Acidification of the bicarbonate extract gave 2.6 g. (78%) of mesitoic acid, m. p. 152°.

When the reaction was carried out in the presence of 3 mole per cent. of anhydrous cobaltous chloride[18] the yield of 1,2,3,4-tetraphenylbutane (m. p. 178°) was increased to 16%, a 40% yield of mesitoic acid was obtained but no stilbene or dibenzyl was found. Some (25%) of the original ester was recovered.

(C) **With Ethylmagnesium Bromide.**—The reaction of 22 ml. of a *n*-butyl ether solution containing 0.04 mole of ethylmagnesium bromide (prepared in the butyl ether) with 6.8 g. (0.028 mole) of α,β-diphenylethyl mesitoate in 100 ml. of butyl ether was carried out as in (A). The residue obtained on distillation of the solvent consisted of 2.5 g. of yellow solid from which was isolated 0.3 g. (8%) of 1,2,3,4-tetraphenylbutane (m. p. 178°) and 1.5 g. (45%) of a mixture of *cis*- and *trans*-stilbene (in approximately equal proportions) each of which was converted to the dibromide (m. p. 237°).[24] A 76% yield of mesitoic acid, m. p. 151°, was obtained.

Summary

1. Any of four positions of a carboxylic ester may react with the Grignard reagent. Reaction at one of these, the β-hydrogen in the alkoxy portion of an ester, has been realized for the first time. New examples of reactions at two other positions have also been described.

2. The influence of structure on the four courses of reaction and mechanisms have been considered.

3. Dimerization of the alkyl group in the alkoxy portion of an ester (apparently by a radical mechanism) has been realized.

DURHAM, NORTH CAROLINA RECEIVED AUGUST 25, 1947

---

[23] Ref. 11, Vol. III, 1938, p. 640.

[24] Huntress and Mulliken, "Identification of Pure Organic Compounds," Order I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 514.

[25] Smith and Hoehn, THIS JOURNAL, **63**, 1184 (1941).

[CONTRIBUTION FROM THE BANTING–BEST DEPARTMENT OF MEDICAL RESEARCH, BANTING INSTITUTE, UNIVERSITY OF TORONTO]

L(+)Propylene Glycol

BY ERICH BAER AND HERMANN O. L. FISCHER

The preparation and the properties of both enantiomers of propylene glycol have been previously described. The levo-rotatory form has been obtained (a) by reduction of ethyl D-lactate with sodium in ethanol and toluene,[1] (b) by desamination of the levo-rotatory 1-aminopropanol-2 hydrochloride with potassium nitrite[2] or silver nitrite,[3,4] (c) by hydrolysis of dextro-rotatory propylene oxide with sodium hydroxide[5] or hydrolysis of levo-rotatory propylene oxide with formic acid and hydrochloric acid[6] and (d) by phytochemical reduction of acetol.[7,8] The dextro-rotatory form of propylene glycol has been obtained by hydrolysis of dextro-rotatory propylene oxide with formic and hydrochloric acid.[5,6] The specific rotations of both enantiomers obtained by the above methods vary greatly. It is obvious that most of these procedures produce mixtures of the dextro- and levo-rotatory propylene glycol, the ratio depending on the optical purity of the starting material and the prevailing experimental conditions.

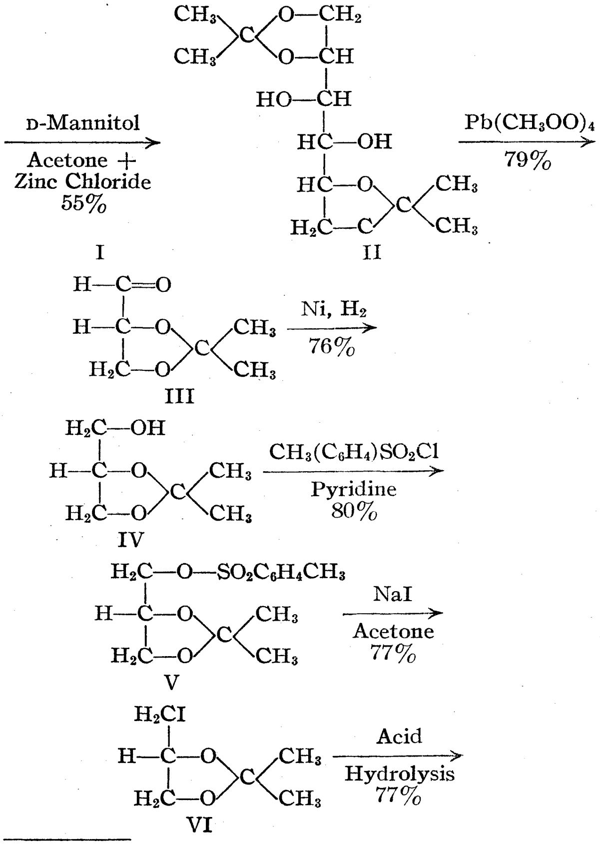
We had at our disposal a method which was expected to yield the pure enantiomers of propylene glycol and to reveal their steric relationship to glyceraldehyde, the accepted compound of reference in stereochemistry. It was decided to prepare by means of this method the dextro-rotatory propylene glycol because this isomer had not yet been obtained in as pure an optical state as the levo-rotatory compound for which an excellent biochemical method of preparation already existed.[7] Incidentally, this choice also permitted the use of the much more readily available D-mannitol as starting material. The sequence of reactions employed in the synthesis of L(+)propylene glycol and the steric interrelationship of the various compounds concerned are outlined in the reaction scheme.

The L(+)propylene glycol, obtained from D-mannitol in seven steps and with an over-all yield of approximately 11% of the theory, was in all respects identical with D(−)propylene glycol prepared by the phytochemical reduction of acetol[7] except that its rotation was opposite in sign. The D(−)propylene glycol can be obtained by the same sequence of reactions starting the synthesis with L-mannitol.

With regard to the steric classification of the dextro-rotatory propylene glycol, it should be noted that the transformation of the acetone D-glyceraldehyde into the dextro-rotatory propylene glycol is accompanied by a reversal in configuration. If one were to oxidize the primary hydroxyl group of the dextro-rotatory propylene glycol the result would be either L-lactic aldehyde or L-lactic acid. Thus the dextro-rotatory propylene glycol belongs to the L-series and the levo-rotatory form to the D-series.[9]

This result is in agreement with the fact that the reduction of ethyl D-lactate IX yields the levo-rotatory D-propylene glycol X.

This optical classification of the propylene glycols seemed to be of interest because recently propylene glycol in the form of its phosphate has been isolated from a natural source, cattle brain, where it constitutes about 5% of the acid soluble phosphorus.[10]



---

[1] P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **67**, 331 (1926).

[2] P. A. Levene and A. Walti, *ibid.*, **68**, 423 (1926).

[3] P. A. Levene and H. L. Haller, *ibid.*, **65**, 49 (1925).

[4] P. Karrer and W. Klarer, *Helv. Chim. Acta*, **8**, 393 (1925).

[5] P. A. Levene and A. Walti, *J. Biol. Chem.*, **73**, 269 (1927).

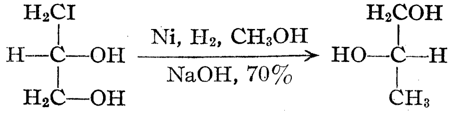
[6] E. Abderhalden and E. Eichwald, *Ber.*, **51**, 1312 (1918).

[7] E. Färber and F. F. Nord, *Biochem. Z.*, **112**, 313 (1920).

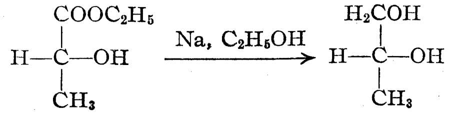
[8] "Organic Syntheses," Coll. Vol. II, p. 545.

[9] The guiding principles in establishing the steric classification of the enantiomeric glycerides and related compounds are outlined in "Preparation and Properties of Optically Active Derivatives of Glycerol" by H. O. L. Fischer and E. Baer, *Chem. Rev.*, **29**, 287 (1941), and *J. Biol. Chem.*, **128**, 475 (1939).

[10] O. Lindberg, *Arkiv. Kemi. Mineral Geol.*, **A23**, 1–45 (1946).



VII L(+)Propylene glycol VIII



IX Ethyl D-lactate X D(−)Propylene glycol

Experimental Part

α-(*p*-Toluenesulfonyl) D-Acetone Glycerol (V).—To a gently agitated and cooled mixture of 38.0 g. of *p*-toluene sulfonylchloride and 20 ml. of dry pyridine was added 26.4 g. of freshly prepared D(+)acetone glycerol ($[\alpha]_D$+ 13.9°). The reaction mixture was kept in an ice-bath until the reaction had subsided (approximately one hour). After standing forty-eight hours at room temperature a crystalline sludge had formed which was poured with stirring into 500 ml. of ice-water. The supernatant liquid was immediately decanted and the heavy oil, dissolved in ether, washed with sodium carbonate solution. The ether solution was dried with anhydrous sodium sulfate and concentrated *in vacuo* to a thick sirup. The residue (48.4 g.) was dissolved in a mixture of 300 ml. of dry ether and 600 ml. of petroleum ether (b. p. 30–60°), the solution cooled to −70° and the thick sludge filtered with suction on a cooled Büchner funnel. The substance, which liquifies at room temperature, was freed *in vacuo* from adhering solvent. The yield of α-(*p*-toluenesulfonyl) D-acetone glycerol (V) was 46.0 g. (80.2%), n^{22}_D 1.5054; d^{24} 1.208. $[\alpha]^{34}_D$ −6.7° in substance; $[\alpha]^{24}_D$ −4.6° in dry ethanol (*c*, 13).

Anal. Calcd. for $C_{13}H_{18}O_5S$ (286.2): C, 54.51; H, 6.29; acetone, 20.3. Found: C, 54.60; H, 6.28; acetone, 20.6, 20.0.

α-Iodo Acetone L-Propylene Glycol (VI).—A solution of 46.0 g. of α-(*p*-toluenesulfonyl) D-acetone glycerol and 65 g. of sodium iodide in 300 ml. of dry acetone was kept in a pressure bottle at 90° for ten hours. The sodium *p*-toluenesulfonate was collected on a Büchner funnel and thoroughly washed with dry acetone. The combined filtrates were brought to dryness at reduced pressure and the reddish-brown solid extracted with four 100-ml. portions of ether. The ether-extract was washed twice with 30-ml. portions of a dilute sodium thiosulfate solution, dried with anhydrous sodium sulfate and concentrated under diminished pressure (bath to 35°). The fractional vacuum distillation of the residue yielded 30.0 g. (77.4%) of pure α-iodo acetone L-propylene glycol (VI), b. p. (6 mm.) 68–69°; n^{25}_D 1.5022; $d^{20.5}$ 1.644; $[\alpha]^{23}_D$ + 54.0° in substance; $[\alpha]^{23}_D$ + 35.5° in dry ethanol (*c*, 12.7).

Anal. Calcd. for $C_6H_{11}O_2I$ (241.9): I, 52.46; acetone, 23.97. Found: I, 52.63; acetone, 24.3.

α-Iodo L-Propylene Glycol (VII).—A solution of 30.0 g. of α-iodoacetone L-propylene glycol in 75 ml. of 85% ethanol was prepared and after the addition of 2.5 ml. of 5 *N* sulfuric acid kept for twenty hours at room temperature. In order to ensure a complete hydrolysis the solution was diluted with 10 ml. of water and refluxed for a period of five minutes. The cold solution was made neutral to litmus with aqueous baryta and concentrated *in vacuo* to a dry sirup at a bath temperature of 35 to 45°. The residue was extracted with four 75-ml. portions of ether and the combined extracts, after drying with anhydrous sodium sulfate, brought to dryness under reduced pressure. The residue (20.2 g., m. p. 47–49°) was recrystallized from chloroform–petroleum ether (b. p. 30–60°) and yielded 19.3 g. (77%) of analytically pure α-iodo-L-propylene glycol (VII). Platelets, m. p. 48.5–49.5°, $[\alpha]_D$ −5.5° in dry ethanol (*c*, 9.5).

Anal. Calcd. for $C_3H_7O_2I$ (201.9): C, 17.83; H, 3.46; I, 62.85. Found: C, 18.09, 18.07; H, 3.79, 3.74; I, 62.70.

L(+)Propylene Glycol (VIII).—A solution of 19.3 g. of α-iodo-L-propylene glycol (VII) and 15 ml. of 10 *N* sodium hydroxide in 300 ml. of 95% ethanol was shaken with 10 g. of Raney nickel catalyst in a hydrogen atmosphere of slightly positive pressure until the absorption of hydrogen ceased. Within thirty minutes 1906 ml. of dry hydrogen (N.P.T.) or 89% of the theoretical amount had been consumed. The solution was freed from the catalyst, treated with carbon dioxide, filtered and the filtrate evaporated to dryness under diminished pressure and a bath temperature of 35–45°. The residue was dissolved in 60 ml. of dry ethanol and 200 ml. of dry ether and the solution dried with approximately 40 g. of anhydrous sodium sulfate. The ether solution was decanted and concentrated under normal pressure. The rest of the solvent was removed under reduced pressure raising the temperature of the bath to 60°. The remaining mixture of propylene glycol and sodium iodide was gradually heated *in vacuo* to 160° and the colorless distillate purified by fractional distillation either at normal pressure or *in vacuo*. The yield of pure L(+)propylene glycol (VIII) was 4.32 g. (70%), b.p. (765 mm.) 186–188°; b. p. (6 mm.) 76–78°, $n^{23.5}_D$ 1.4312, d^{20} 1.04, $[\alpha]^{23}_D$ + 15.4° in substance; $[\alpha]^{23}_D$ + 20.1° in water (*c*, 7.5), $[\alpha]^{22}_D$ + 4.2° in dry ethanol (*c*, 6.6).

Anal. Calcd. for $C_3H_8O_2$(76): C, 47.36; H, 10.52. Found: C, 47.84; H, 10.38.

Summary

Dextro-rotatory propylene glycol was prepared and its L-configuration established by means of the following sequence of reactions: D-acetone glyceraldehyde → D-acetone glycerol → α-(*p*-toluenesulfonyl) D-acetone glycerol → α-iodo acetone L-propylene glycol → α-iodo-L-propylene glycol → L(+)propylene glycol.

TORONTO 5, CANADA RECEIVED SEPTEMBER 26, 1947

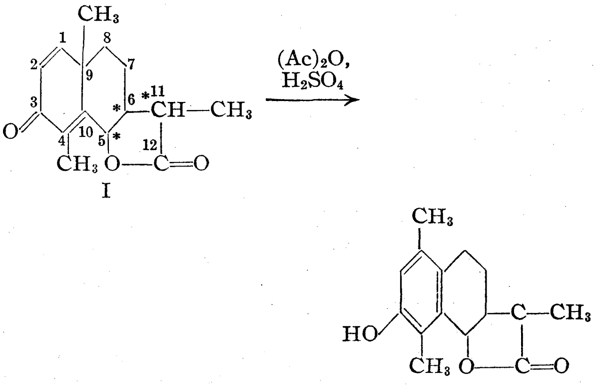
[CONTRIBUTION OF THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

Studies in the Santonin Series. IV.[1,2,3] The Stereochemistry of Santonin and its Derivatives

BY HUANG-MINLON[3a]

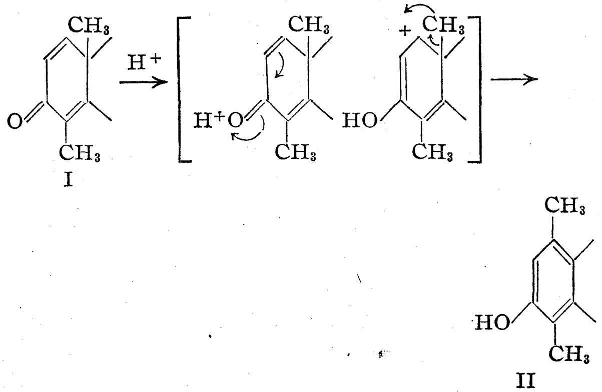
The relative configuration of santonin and of various transformation products has been discussed briefly in an earlier paper.[1] In the meantime sufficient experimental facts have accumulated to extend this discussion.

The almost quantitative rearrangement of santonin (I) into the aromatic *l*-α-desmotroposantonin (II)[3b] induced by acetic anhydride and a trace of sulfuric acid was originally considered as an enol acylation reaction.[1] The enolization, however, is unusual in that, in addition to the prototropic change, an alkylotropy occurs also. This acid-catalyzed rearrangement is similar to a Wagner–Meerwein rearrangement and the mechanism can be formulated as



I

II

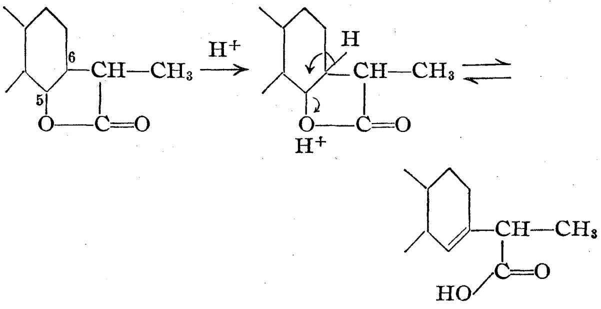


I

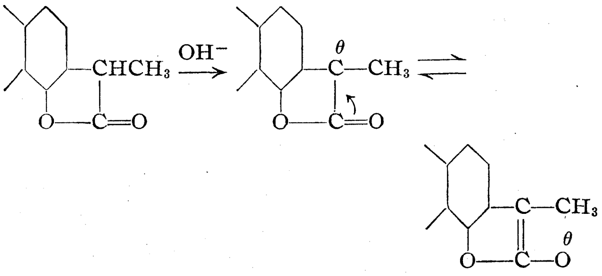
II

Of particular interest is the interconversion of the four isomeric desmotroposantonins by successive treatment with acid and with alkali[1] (see chart[3c]), since this is probably the first instance of a cycle in which the configurations of three asymmetric carbon atoms are changed and then restored to the original state.

(a) Acid conversion:



(b) Alkaline conversion



Plausible mechanisms for the conversions observed with acid and with alkali can now be advanced. Support for the postulated acid-catalyzed reaction is furnished by the formation of the ethyl ester of dihydrosantinic acid (IV) from isohyposantonin (III) by the action of alcoholic hydrochloric acid.[6] Isohyposantonin is *levo*-rotatory; it contains three asymmetric carbon atoms that have the same configuration as that of *l*-α-desmotroposantonin, A (see conversion of III into A, below). The β,γ-unsaturated ester, which contains only one asymmetric carbon atom, is dextrorotatory. The reaction is comparable to the transformation of A to B, but in this case the β,γ-un-

---

(1) Huang-Minlon, Lo and Chu, THIS JOURNAL, **65**, 1780 (1943); for experimental part see: *J. Chinese Chem. Soc.*, **10**, 126 (1943).

(2) Huang-Minlon, Lo and Chu, THIS JOURNAL, **66**, 1954 (1944).

(3) Huang-Minlon and Cheng, *ibid.*, **70**, 449 (1948).

(3a) On leave of absence from the National Research Institute of Chemistry, Academia Sinica.

(3b) The nomenclature is discussed in Paper I.[1]

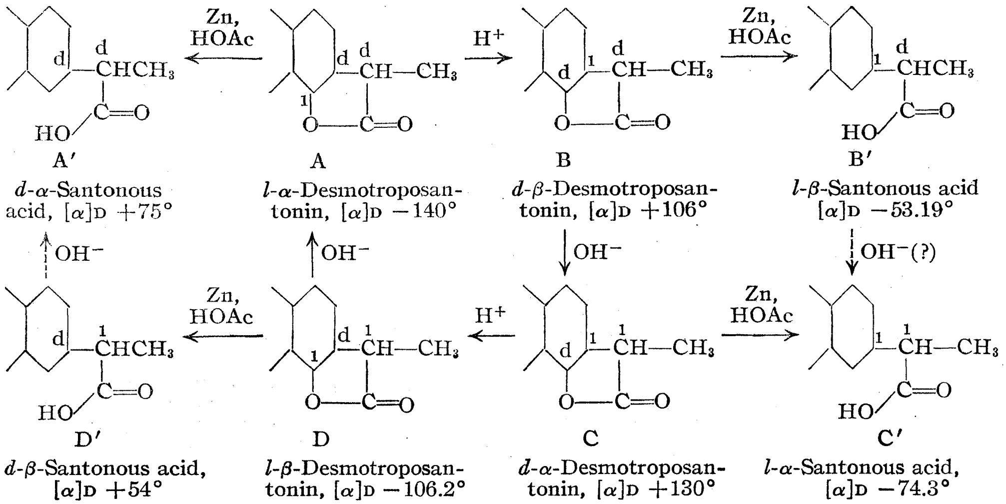
(3c) The transformations indicated by the dotted lines in the chart, D′ → A′ and B′ → C′, have probably been accomplished. In the latter case, the experimental conditions have not been clearly defined[4]; in the former, the investigators[5] did not realize the true nature of the observed change. They did observe, however, that treatment of *d*-β-santonous acid (D′) with barium hydroxide followed by alkali. fusion led to a more dextrorotatory acid ($[\alpha]_D$ +64), undoubtedly A′

(4) Andreocci, *Atti R. Accad. dei Lincei Roma*, [5] **4**, 259 (1894); *Chem. Zentr.*, **66**, I, 1069 (1895).

(5) Clemo, *J. Chem. Soc.*, 1343 (1934).

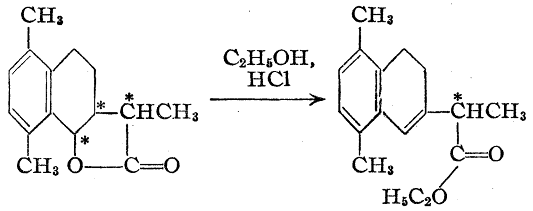
(6) Gucci and Grassi-Cristaldi, *Gazz. chim. ital.*, **22**, I, 24 (1892).

CHART[a]



[a] All data of the specific rotations given in this paper are taken from the work of: (a) Huang-Minlon, see refs. 1 and 3; (b) Clemo, see ref. 5; (c) Asahina, see ref. 10; (d) Andreocci, *Gazz. chim. ital.*, **23**, II 477, 478 (1893); **25**, I, 486 (1895); (e) Grassi-Cristaldi, see refs. 6, 13 and 14.

saturated acid postulated in the acid-catalyzed reaction above is tied down by esterification.



III IV

According to the postulated reactions with acid and with base the configurations of C-5 and of C-6 are inverted by acid treatment, whereas the configuration of C-11 is inverted by alkali. Unfortunately, the rule of optical superposition[7] is not obeyed strictly in the case under discussion because the asymmetric centers are adjacent to one another and conseqently vicinal effects are to be expected.[7] However, the [α]D values do correspond with proposed formulations with the exception of B → C and D → A. Furthermore, it is assumed in the following discussion that inversion of one asymmetric center does not cause inversion of another asymmetric center.

The reduction of each optically active desmotroposantonin results in an optically active santonous acid[8] of opposite optical rotation[1] as shown above. In the reduction one center of asymmetry is destroyed (C-5) and, since this loss results in a marked change in the optical rotatory power in all four cases, it can be assumed that this asymmetric center (C-5) makes the largest contribution to the total rotatory power. For this reason the asymmetric center C-5 in 1-α-desmotroposantonin (A) for example, must be levorotatory; the two remaining asymmetric centers (C-6 and C-11) must be dextrorotatory since the corresponding santonous acid (A') is the most dextrorotatory of the four possible santonous acids. Since treatment with acid and then with alkali (for example, A → B → C) or treatment with alkali and then with acid (B → C → D) converts a desmotroposantonin into the antipode, either acid or alkali must change simultaneously the configuration of two carbon atoms. Acid converts one desmotroposantonin into an isomer of opposite rotation (A → B or C → D); when the asymmetry (C-5) of the isomer (B or D) is destroyed by reduction (*e. g.*, B → B') an acid is obtained that is not identical with the acid obtained from the starting material (*i. e.*, B' ≠ A'). These facts are explainable only on the assumption that acid treatment changes the direction of rotation of two asymmetric centers. The postulated acid reaction (a) results in inversion at C-5 and at C-6 and the alkaline reaction (b) results in inversion at C-11, and thus they fit the experimental facts.

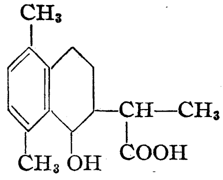
According to the above formulation the desmotroposantonins are all either *cis* or *trans* compounds with reference to the linkage of the lactone ring to the cyclohexyl ring, and are not *cis–trans* isomers. Various experimental facts indicate that the linkage is *cis*. When the lactone ring of a desmotroposantonin is opened by dilute alkali and the basic solution is acidified, the starting material is recovered immediately. The equally instantaneous ring closure of either the α- or the β-form suggests a *cis*-configuration of both forms. From a consideration of molecular models Clemo[5] concludes that the *cis* linkage is the more stable. The physical and chemical properties of the open compounds, (V), of the lactone, (III), hyposanto-

---

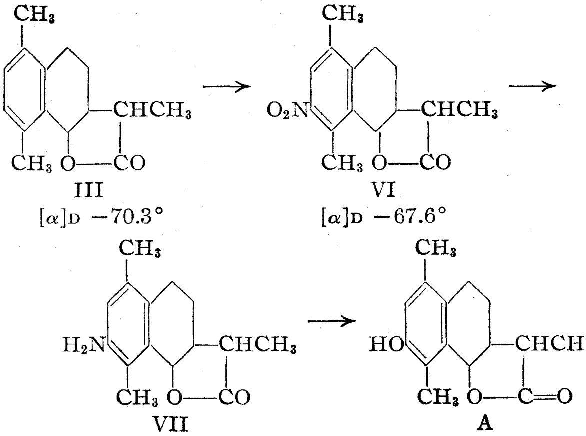
(7) For a discussion of the modern theories of optical rotatory power see Kauzmann, Walter and Eyring, *Chem. Rev.*, **26**, 339 (1940).

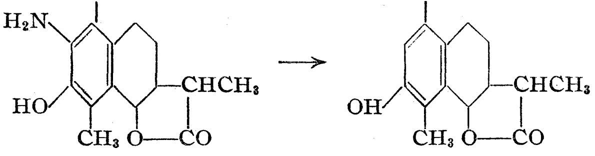
(8) For the sake of convenience the desmotroposantonous acids are named simply santonous acids.

ninic acid (*trans*) and isohyposantoninic acid (*cis*), indicate that the isomerism is geometrical.[9]


V

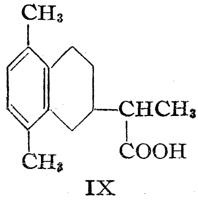
Accordingly, hyposantonin (III) is probably the *trans* form because the lactone ring opens readily with the formation of hyposantoninic acid. Isohyposantoninic acid is not stable and even on standing reverts to the lactone, isohyposantonin[9] (III). This *cis* lactone can be converted into *l*-α-desmotroposantonin (A) by the procedure of Asahina,[10] who converted the *trans* lactone in A. The series of transformations, shown in the formulas, do not involve the lactone ring and probably do not affect the mode of juncture. This assumption is supported by the fact that the optical rotation is not affected to any significant extent by the transformation. Furthermore, the transformation of 2-amino-*d*-β-desmotroposantonin (VIII), which is prepared by analogous reaction, into *d*-β-desmotroposantonin (B)[3] demonstrates unequivocally that nitro and amino derivatives retain the configuration of the parent desmotroposantonin. It follows then that *l*-α-desmotroposantonin must also possess the same *cis* linkage as in isohyposantonin and that the other desmotroposantonins are also *cis*.


III $[\alpha]_D$ −70.3°
VI $[\alpha]_D$ −67.6°
VII $[\alpha]_D$ −165.7°
A $[\alpha]_D$ −140°


VIII $[\alpha]_D$ +113.8°
B $[\alpha]_D$ +106.2°

The assumption that the so-called *l*-desmotropo-β-santonin[11] prepared by Clemo[1] from β-santonin is identical with *l*-β-desmotroposantonin (D)[1] has now been established by a direct comparison of crystalline form, of solubility, and of melting point (m. p. 259–260°). The two substances show no depression of melting point on admixture. Equal quantities of Clemo's material and of *d*-β-desmotroposantonin (B) form a racemic product which exhibits no optical activity, melts at 230–231°, and shows no depression in melting point on admixture with *dl*-β-desmotroposantonin.[1] The acetate of the racemic product was likewise compared with the known *dl*-compound[1] and found to be identical. The racemic product on zinc and acetic acid reduction yields an inactive acid (m. p. 181°), which is identical with *dl*-β-santonous acid.[1] The identity of Clemo's compound and D was further confirmed by transformation of both substances into the same santonous acid (D′) (m. p. 175–176°).

Santonin (I) itself probably does not have the *cis* configuration of the lactone ring, even though the aromatization reaction proceeds so readily as to suggest[1] that the steric arrangement is not affected in the transformation into 1-α-desmotroposantonin (A). Santonin oxime is transformed by mild reducing agents mainly into hyposantonin,[12] which has a *trans* configuration and which changes readily into isohyposantonin (*cis*).[13] Hyposantonin and isohyposantonin frequently produce the same reaction products, and many of the derivatives obtained by chemical treatment of hyposantonin, particularly in the presence of acids, are probably in reality derivatives of isohyposantonin. For example, hyposantonin and isohyposantonin form the same nitro product (VI).[10] The rotation of VI and of the amino derivative (VII) is comparable to that of isohyposantonin ($[\alpha]_D$ −70.3°) and not to that of hyposantonin ($[\alpha]_D$ + 32.7°), and therefore nitric acid treatment probably induces isomerization of hyposantonin. Furthermore the so-called aminohyposantonous acid[10] obtained by reduction of the amino derivative (VII) ($[\alpha]_D$ −165.7°) is dextrorotatory ($[\alpha]_D$ + 62.5°) and in this respect is comparable to the changes observed in the reduction of the desmotroposantonins (A $\rightarrow$ A′, etc.). Similarly, the so-called hyposantonous acid (IX)[14] obtained from


IX
$[\alpha]_D$ +75.95°

---

[9] Grassi-Cristaldi, *Gazz. chim. ital.*, **23,** I, 67 (1893).

[10] Asahina and Momose, *Ber.*, **71,** 1421 (1938).

[11] I am indebted to Prof. Clemo for a sample of this material and of *d*-β-santonous acid.

[12] Gucci, *Gazz. chim. ital.*, **19,** 378 (1889).

[13] Grassi-Cristaldi, *ibid.*, **19,** 393 (1889).

[14] Grassi-Cristaldi, *ibid.*, **26,** II, 456 (1896).

both hyposantonin and isohyposantonin by reduction should be designated isohyposantonous acid because it is dextrorotatory, and reductive opening of the lactone ring causes reversal in the direction of rotation.

I am indebted to Prof. L. F. Fieser for his encouragement in the persuance of this investigation and to Mrs. Mary Fieser for help in the preparation of this manuscript.

Summary

The mechanism of the acid-catalyzed rearrangement of santonin to desmotroposantonin and that of the interconversion of the four isomers of desmotroposantonins by acid and alkali has been postulated. The relative configurations of all the known desmotroposantonins have been formulated. *l*-Desmotropo-β-santonin of Clemo has been found to be identical with *l*-β-desmotroposantonin. The spacial configurations of santonin, hyposantonin and isohyposantonin have also been discussed.

CAMBRIDGE 38, MASS. RECEIVED AUGUST 15, 1947

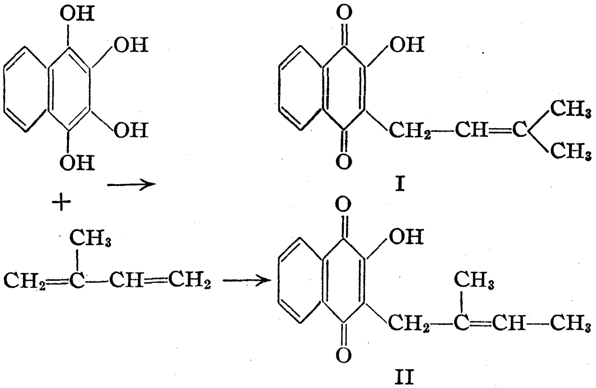
[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY, BRYN MAWR COLLEGE, AND THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

Syntheses in the Lapachol Series

BY MARSHALL GATES AND DOROTHY L. MOESTA[1]

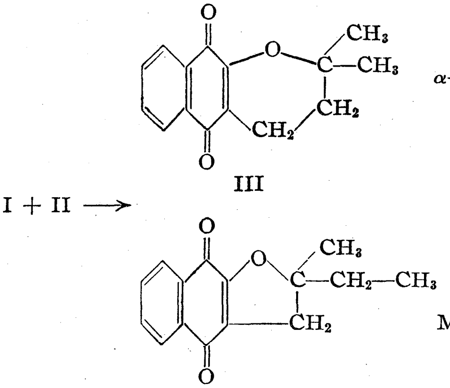
In an extension of the condensation reaction between allylic alcohols and hydroxyhydroquinones reported by Fieser and Gates,[2] we have investigated the condensation of leucoisonaphthazarin with isoprene and with several allylic alcohols related to isoprene. As in earlier examples[2] yields are low, but the inaccessibility of the products by other methods may warrant consideration of this method for the preparation of small amounts.

Isoprene condenses with leucoisonaphthazarin in the presence of oxalic acid to yield, after oxidation, a mixture of lapachol (I)[3] and an isomer of lapachol, presumably 2-hydroxy-3-(2′-methyl-2′-butenyl)-1,4-naphthoquinone (II), in roughly equal parts.


I

II

Separation of the two was achieved by fractional crystallization, although the more soluble isomer II was obtained pure only in small amounts by this method. Additional material containing the side-chain carbon skeleton of II could be obtained from the filtrate by cyclization to a mixture of the α-lapachone type isomers III and IV in which the solubility relationships are reversed.


α-Lapachone, m. p. 117°

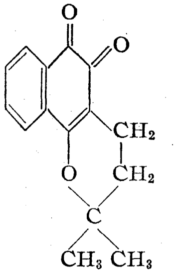
III

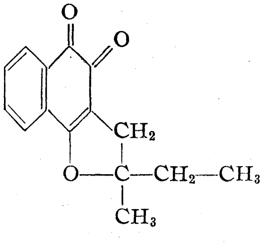
I + II →

M. p. 149–150°

IX

The hydroxynaphthoquinones I and II were further characterized by cyclization with concentrated sulfuric acid to β-lapachone (V) and its isomer, α-methyl-α-ethyldihydrofurano-1,2-naphthoquinone (VI),[4] respectively.


V


VI

2-Hydroxy-3-(2′-methyl-2′-butenyl)-1,4-naphthoquinone (II) also results from the condensation

---

[1] Mrs. George Hain.

[2] Fieser and Gates, THIS JOURNAL, **63**, 2948 (1941).

[3] Earlier syntheses of lapachol have been reported by Fieser, *ibid.*, **49**, 857 (1927), and by Hooker, *ibid.*, **58**, 1181 (1936).

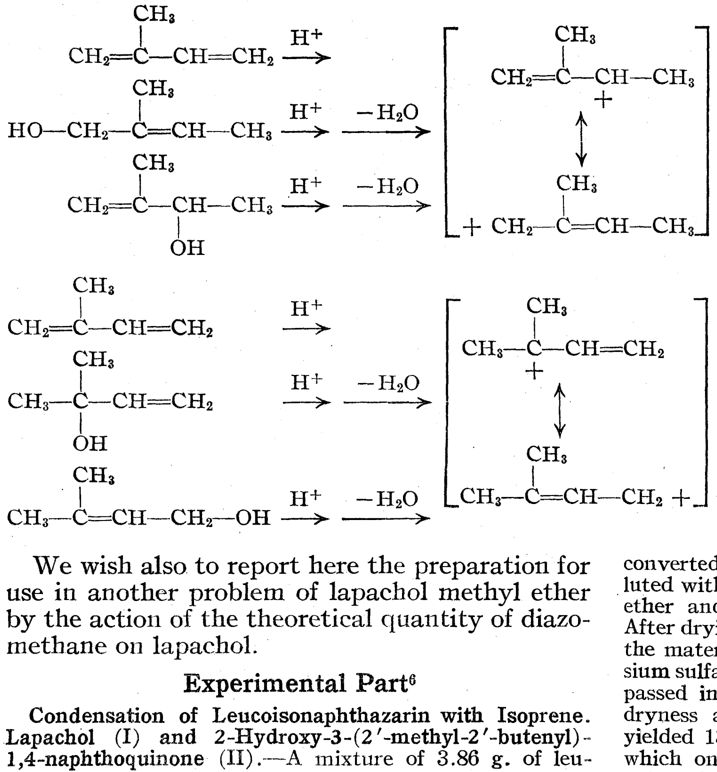
[4] Structure VI is one, although not the preferred one, of three structures originally considered possible for dunnione by Price and Robinson (*J. Chem. Soc.*, 1525 (1939)). If the structure assigned above is correct, VI is eliminated as a possible structure for dunnione since its physical properties do not agree with those of dunnione. Later work by Price and Robinson (*J. Chem. Soc.*, 1493 (1940)) continues to support their original preference (α,α,β-trimethyldihydrofurano-1,2-naphthoquinone) for the structure of this substance.

of 2-methylbutene-2-ol-1 with leucoisonaphthazarin in the presence of oxalic acid. In this case it is the sole hydroxynaphthoquinone isolated and its structure has been assigned on this basis.

Dimethylvinylcarbinol condenses with leucoisonaphthazarin in the presence of oxalic acid to yield lapachol as the sole hydroxynaphthoquinone.

The secondary alcohol 2-methylbutene-1-ol-3 does not yield any hydroxynaphthoquinone when allowed to react with leucoisonaphthazarin under the conditions used in the above condensations.

Any comment on the mechanism of this condensation at present must necessarily, in view of the paucity of data bearing on the question, be largely speculation. It may be noted, however, that the simple postulation of an attack on leucoisonaphthazarin by a carbonium ion produced by the action of acid on either isoprene or the allylic type alcohols used followed by the necessary eliminations[5] is not entirely adequate. For example, an identical resonating carbonium ion should result from isoprene, 2-methylbutene-2-ol-1 and 2-methylbutene-1-ol-3, but only the first two of these give the same product (II), whereas the condensation fails with the third. Isoprene can, in addition, yield the same resonating carbonium ion as dimethylvinylcarbinol and 3-methylbutene-2-ol-1 (not investigated in this work). The first two of these yield lapachol.



We wish also to report here the preparation for use in another problem of lapachol methyl ether by the action of the theoretical quantity of diazomethane on lapachol.

Experimental Part[6]

Condensation of Leucoisonaphthazarin with Isoprene. Lapachol (I) and 2-Hydroxy-3-(2′-methyl-2′-butenyl)-1,4-naphthoquinone (II).—A mixture of 3.86 g. of leucoisonaphthazarin (prepared by hydrosulfite reduction of an ether suspension of isonaphthazarin), 12 cc. of isoprene, 2.5 g. of anhydrous oxalic acid and 50 cc. of dioxane (refluxed and distilled over sodium) was heated at 90 to 100° for sixty hours under nitrogen in a capped bottle. After filtration from some crystalline isonaphthazarin (0.73 g.) the solvent was completely removed by a current of dry air and the residue was taken into ether and extracted four times with dilute sodium carbonate solution. The red-black carbonate extract on acidification with glacial acetic acid and extraction with ether yielded an orange-yellow ethereal solution which was further processed by an additional extraction into carbonate and acidification followed by two chromatographic adsorptions from benzene–hexane onto anhydrous magnesium sulfate. During the second of these a bright yellow band (45 mm. on an 18-mm. diameter column) passed readily into the filtrate and on concentration yielded 446 mg. of bright yellow plates, m. p. 111–126°. Several distinct more strongly adsorbed bands remained on the column and from the two adsorptions a further 0.13 g. of unchanged isonaphthazarin was recovered.

The solid material from the filtrate was subjected to a systematic fractional crystallization from ether–petroleum ether and after numerous crystallizations 156 mg. of lapachol (I) of m. p. 139–140° and 15 mg. of an additional substance (II), m. p. 123–124.5°, were obtained. The lapachol did not depress the melting point of an authentic sample, m. p. 139–140.5°, from the collection of the late Dr. Samuel Cox Hooker, and was further characterized by conversion to β-lapachone, m. p. 154–155°, which likewise did not depress the melting point of an authentic sample from Dr. Hooker's collection. The samples from this collection were kindly placed at our disposal by Professor Louis F. Fieser of Harvard University.

The substance (II) of m. p. 123.5–124.5° crystallizes from ether–petroleum ether in long bright yellow needles and gives a scarlet solution with dilute potassium hydroxide, the color of which can be completely extracted by amyl alcohol.[7] It is isomeric with lapachol.

Anal.[8] Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.04; H, 5.57.

As the following example demonstrates it may be converted into an isomer (VI) of β-lapachone by the action of concentrated sulfuric acid: 8.6 mg. was dissolved in about 0.3 cc. of concentrated sulfuric acid, and after standing for five minutes the deep orange-red solution was diluted with water and the precipitated red solid was collected, washed with water and crystallized twice from dilute alcohol to give 3.5 mg. of beautiful scarlet-orange needles, m. p. 118.5–119°.

Anal.[8] Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.29; H, 5.78.

Selected filtrates from the fractional crystallization described above were concentrated to dryness, taken into 2 cc. of glacial acetic acid, treated with 0.5 cc. of concentrated hydrochloric acid and heated on the steam-bath for one hour. Under these conditions lapachol is converted to α-lapachone.[9] The reaction mixture was diluted with water and the resultant dark oil was taken into ether and washed with sodium bicarbonate and water. After drying the ether was replaced by benzene–hexane and the material was chromatographed on anhydrous magnesium sulfate. A poorly adsorbed broad canary yellow band passed into the filtrate rapidly and on concentration to dryness and crystallization from ether–petroleum ether yielded 130 mg. of canary yellow plates, m. p. 131–140°, which on two further crystallizations from this solvent pair and a final crystallization from alcohol afforded 72 mg.

---

[5] Bondhus (Dissertation, Bryn Mawr College, 1947) has discussed the mechanism of this reaction as well as the silver salt alkylation used by Fieser[3] for the synthesis of lapachol.

[6] All melting points are corrected.

[7] Price and Robinson, *J. Chem. Soc.*, 1522 (1939).

[8] Microanalysis by Miss Eleanor Werbel.

[9] Hooker, *J. Chem. Soc.*, **61**, 611 (1892).

of yellow leaves of IV, m. p. 149.4–150.2°. It does not dissolve immediately in dilute aqueous potassium hydroxide, but the suspension on standing slowly acquires a red color.

Anal.[8] Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.29; H, 5.79.

This material (15 mg.) on standing in concentrated sulfuric acid solution for fifteen minutes yields, on dilution with water and crystallization from dilute alcohol, the isomer VI of β-lapachone described above (9 mg.), m. p. 118.5–119°, mixed melting point not depressed.

Condensation of Leucoisonaphthazarin with Dimethylvinylcarbinol. Lapachol (I).—Dimethylvinylcarbinol[10] (4 cc.) was condensed with 2.77 g. of leucoisonaphthazarin under approximately the conditions outlined above. The reaction mixture, filtered from 0.70 g. of isonaphthazarin, was made alkaline, aerated, extracted with ether and the acidic material taken into ether after acidification with glacial acetic acid. Further processing included extraction by dilute potassium carbonate and chromatographic adsorption on magnesium sulfate from benzene–hexane of the material recovered from the deep red carbonate solution by acidification. Elution of a homogeneous bright yellow band by absolute ether and concentration yielded a yellow residue of impure lapachol (I) (186 mg.) which readily solidified, m. p. 132–136°. One crystallization from petroleum ether raised its melting point to 139–140.5°. The material did not depress the melting point of an authentic sample of lapachol.

Condensation of Leucoisonaphthazarin with 2-Methylbutene-2-ol-1. 2-Hydroxy-3-(2′-methyl-2′-butenyl)-1,4-naphthoquinone (II).—2-Methylbutene-2-ol-1[11] (4 g.) was condensed with leucoisonaphthazarin (from 4 g. of isonaphthazarin) under approximately the conditions outlined above. A processing scheme similar to those described above yielded bright yellow platelets of II, 175 mg., m. p. 120–121°. Recrystallization from ether–petroleum ether gave 160 mg., m. p. 120.5–121.5°.

α-Methyl-α-ethyldihydrofurano-1,4-naphthoquinone (IV) was prepared by stirring the above substance (28 mg.) into a mixture of 8 cc. of glacial acetic acid and 1.5 cc. of concentrated hydrochloric acid and heating on the steam-bath for one hour. Dilution of the reaction mixture with 30 cc. of water at the end of this time resulted in the separation of bright yellow needles which, after recrystallization from alcohol, melted at 147.5–148°; yield 12 mg. The isomeric **α-methyl-α-ethyldihydrofurano-1,2-naphthoquinone (VI)** was prepared by stirring the above isomer of lapachol (29 mg.) into 2 cc. of concentrated sulfuric acid and diluting the orange-brown solution with 35 cc. of water. Recrystallization from alcohol of the precipitated red solid afforded 13 mg. of dark red needles, m. p. 113–114°.

Although a direct comparison was not made, the methods of preparation and the correspondence in melting points of the hydroxyquinones and of the derivatives of the α- and β-lapachone types make the identity of the above isomer of lapachol and that isolated from the isoprene reaction highly probable.

Attempted Condensation of Leucoisonaphthazarin and 2 Methylbutene-1-ol-3.—2-Methylbutene-1-ol-3[12] was treated with leucoisonaphthazarin (from 4 g. of isonaphthazarin) as described for earlier examples. On working up the reaction mixture by the same general scheme used above only isonaphthazarin was recovered. A similar reaction carried out at 65–80° over a period of nine days was also unsuccessful.

Lapachol Methyl Ether.—To 121 mg. of lapachol in a few cc. of ether at 0° was added 1.50 cc. of cold freshly prepared and standardized 0.334 *N* diazomethane solution. The resulting deep orange solution was allowed to stand for several hours during which time the color lightened to yellow. The solution was extracted several times with dilute carbonate solution (acidification of the crimson carbonate extracts gave 11 mg. of unchanged lapachol, m. p. 138–140.5°), washed with water and brine and then filtered and concentrated to dryness. The residual orange oil (116 mg.) solidified on manipulation and was crystallized several times from methanol, in which it is quite soluble, to give 50 mg., m. p. 51–51.8°, of beautiful bright yellow needles. A sample was crystallized once again for analysis and dried at 10^{-4} mm. for several hours, m. p. 52–52.4°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.51; H, 6.14.

The material is readily hydrolyzed to lapachol on warming with dilute potassium hydroxide in water and methanol.

Summary

Leucoisonaphthazarin has been shown to condense with isoprene, dimethylvinylcarbinol and 2-methylbutene-2-ol-1 in the presence of anhydrous oxalic acid to give low yields of 2-hydroxy-3-alkenyl-1,4-naphthoquinones. Dimethylvinylcarbinol gives rise to lapachol, 2-methylbutene-2-ol-1 gives 2-hydroxy-3-(2′-methyl-2′-butenyl)-1,4 naphthoquinone, and isoprene yields a mixture of these products.

BRYN MAWR, PENNSYLVANIA, AND
CAMBRIDGE, MASSACHUSETTS

RECEIVED SEPTEMBER 18, 1947

---

(10) We are indebted to Mr. Edward F. Greene of Harvard University for this sample, which was prepared by catalytic reduction over Raney nickel of dimethylethynylcarbinol, prepared by the method of Newman, Fones and Booth, THIS JOURNAL, **67**, 1053 (1945).

(11) Prepared from trimethylethylene by the method of Guillemonat, *Ann. chim.*, [11] **11**, 154 (1939).

(12) Kondakow, *J. Russ. Phys.-Chem. Soc.*, **17**, 296 (1885). Our sample was prepared by the action of methylmagnesium bromide on methacrolein.

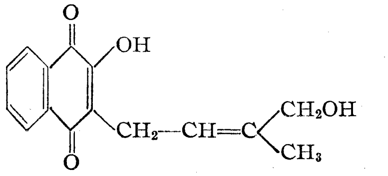
[CONTRIBUTION FROM THE MARIAN EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

A Synthesis of Lomatiol

BY MARSHALL GATES

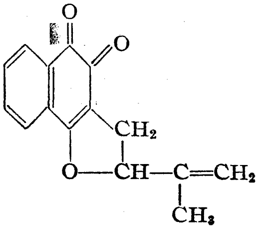
Lomatiol, the yellow coloring matter surrounding the seeds of several Australian species of *Lomatia*, was first investigated by Rennie[1] who, after demonstrating its close relationship to lapachol, left further investigation of the pigment to Samuel Cox Hooker. Hooker,[2] in a series of papers closely integrated with those describing his elegant work in the lapachol field, was able to show that the structure 2-hydroxy-3-(3′-hydroxymethyl-2′-butenyl)-1,4-naphthoquinone (I) is in complete harmony with the experimental facts. In the course of this work Hooker accomplished the conversion of lomatiol into lapachol.

We have now achieved the reverse transformation of lapachol into lomatiol, and, since lapachol has been prepared synthetically by several methods,[3,2b] this constitutes a synthesis of lomatiol. Our conversion made use of selenium dioxide oxidation of leucolapachol triacetate in the presence of acetic anhydride, essentially as described by Guillemonat,[4] to give a mixture containing both leucolomatiol tetraacetate and unchanged leucolapachol triacetate.[5] This crude product on saponification and air oxidation yielded a mixture from which lomatiol and lapachol were easily separated by chromatographic adsorption on magnesium sulfate. The lomatiol was fully identified by comparison with an authentic sample,[6] by conversion to its highly characteristic barium salts,[2b] and by conversion to dehydroiso-β-lapachone (II)[2b] which was compared with a sample prepared from authentic lomatiol.



I

Lomatiol



II

Dehydroiso-β-lapachone

Experimental Part[7]

Lomatiol.—Leucolapachol triacetate[8] (119 mg., m. p. 141–142.5°) dissolved in a mixture of 5 cc. of C. P. acetic anhydride and 3 cc. of glacial acetic acid (refluxed and distilled over chromium trioxide) was treated with 15 mg. of freshly sublimed selenium dioxide. There was no apparent action at room temperature, but on warming gradually to reflux during fifteen minutes the mixture darkened, the selenium dioxide began to go into solution and selenium, at first red, later black, began to separate. The mixture was held at reflux for twenty-five minutes, cooled and diluted with water. The precipitated oil was taken into peroxide-free ether, washed twice with water, twice with 2% sodium hydroxide, again with water, dried and concentrated. The residual clear pale-yellow very viscous oil (134 mg.) was dissolved in 5 cc. of methanol and treated with 5 cc. of water containing 2 g. of potassium hydroxide. The solution, which immediately became deep brown but quickly changed to deep red, was heated to reflux for ten minutes during which it was necessary to dilute with a small amount of water to redissolve some dark red oily sodium salt which had separated. After cooling the mixture was carefully acidified with 5% hydrochloric acid and the precipitated brown gummy solid was taken into peroxide-free ether, filtered from a small amount of insoluble material, washed twice with water, once with saturated brine, filtered through anhydrous sodium sulfate and concentrated. The residual brown very viscous oil (64 mg.) was taken into hot benzene (not entirely soluble), cooled and chromatographed on ignited magnesium sulfate. Development with benzene caused a broad yellow-tan band (1) followed by a thin, faint yellow band (2) to pass rapidly into the filtrate, and left three distinct bands on the column—toward the bottom a thin reddish band (3) overlain by a broad yellow band (4) and at the top a reddish-brown band (5)—which were sectioned out and eluted, (3) and (4) with ether, (5) with alcohol. Fractions 2 and 5 were discarded, fractions 1, 3 and 4 were concentrated and pumped out.

Fraction 1 (orange solid, 17 mg.) proved to be crude lapachol, and after three crystallizations from benzene–hexane, the final one with the aid of norite, yielded 5 mg. of beautiful bright yellow leaves, m. p. 139.2–139.8°, which did not depress the melting point of an authentic sample of lapachol of m. p. 139–140.3°.

Fraction 3 (yellow solid, 8 mg.) was sparingly soluble in benzene and gave no immediate red color with dilute aqueous potassium hydroxide, although on standing or fairly rapidly on heating a crimson color was produced with alkali. After boiling up twice with benzene the bright yellow material remaining insoluble melted with decomposition and the production of a blue-green color at 186–188°. It was not investigated further, although its properties indicate that it may be of the α-lapachone type.

Fraction 4 (orange solid, 21 mg.) was crystallized four times, once with the aid of norite, from benzene, in which it was rather sparingly soluble, to yield 11.5 mg. of beautiful bright yellow needles m. p. 127.3–128.5°, which did not

---

(1) Rennie, *J. Chem. Soc.*, **67**, 784 (1895).

(2) Hooker, (a) *ibid.*, **69**, 1381 (1896); (b) THIS JOURNAL, **58**, 1181 (1936); (c) **58**, 1198 (1936); (d) **58**, 1207 (1936).

(3) Fieser, (a) THIS JOURNAL, **49**, 857 (1927); (b) Gates and Moesta, *ibid.*, **70**, 614 (1948).

(4) Guillemonat, *Ann. chim.*, [11] **11**, 147 (1939).

(5) It is of interest to note that even with the relatively complicated olefin represented by leucolapachol triacetate, the conditions recommended by Guillemonat (approximately 0.35 mole of selenium dioxide to 1 mole of ethylene) lead to much the same result obtained by him with simple ethylenes, *i. e.*, yields in the neighborhood of 30% for both product and unchanged ethylene.

(6) We are indebted to Professor Louis F. Fieser of Harvard University for a sample of lomatiol from the collection of the late Dr. Samuel Cox Hooker.

(7) All melting points are corrected.

(8) Monti, *Gazz. chim. ital.*, **45**, II, 53 (1915).

depress the melting point of an authentic sample[6] of lomatiol of m. p. 127.7–129°. It dissolved in dilute potassium hydroxide with a deep crimson color, and a drop of a solution of its barium salt, prepared as described by Hooker,[2b] allowed to evaporate on a microscope slide, exhibited the two characteristic forms and the highly characteristic behavior on rubbing described by him.

Dehydroiso-β-lapachone was prepared from a sample (7.1 mg.) of the synthetic lomatiol described above by the method of Hooker.[2b] After two crystallizations from dilute alcohol 3 mg. of orange-red needles were obtained which exhibited the following very characteristic melting point behavior. An initial melting point of 110–112° was observed (*cf.* refs. 1 and 2b) but if the capillary was held for some time at about 113° the material resolidified and then remelted at 115.2–116.2°. Likewise, if a freshly melted sample of the needles (m. p. 110–112°) was caused to solidify by brief removal from the bath it remelted at 115.2–116.2°. A precisely similar behavior was exhibited both by a sample of dehydroiso-β-lapachone prepared from an authentic sample[6] of lomatiol and by a mixture of the two. The lower of the two melting points corresponds to the metastable needles observed by Rennie,[1] whereas the higher corresponds to the stable prisms reported by Hooker. We have observed both forms, but have not had a sample composed exclusively of the prismatic form.

Summary

A conversion of lapachol to lomatiol has been accomplished.

BRYN MAWR, PENNSYLVANIA
RECEIVED SEPTEMBER 18, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

Symmetrical Morpholinium Alkyl Sulfates

BY J. B. NIEDERL, H. W. SALZBERG AND J. J. SHATYNSKI[1]

Studies in the morpholinium type of "Invert Soaps"[2] have now been extended to those derived from symmetrical dialkyl sulfates and morpholines containing a long chain alkyl substituent on nitrogen.

Experimental

Dialkyl Sulfates.—Dimethyl and diethyl sulfates were commercial products; the others were prepared using the method of Barkenbus and Owen.[3]

N-Alkyl morpholines were prepared by refluxing equimolar quantities of morpholine and the appropriate alkyl bromide in absolute ethyl alcohol with anhydrous potassium carbonate for six hours. The solvent was distilled off, the residue washed with distilled water and the product distilled under reduced pressure.

Morpholinium sulfates were obtained by mixing equimolecular quantities of the alkyl morpholine and the dialkyl sulfate. With methyl sulfate the reaction was quantitative in the cold; with ethyl sulfate slight heating on a steam-bath was necessary; with *n*-butyl and *n*-hexyl sulfates prolonged heating in sealed ampules on a steam-bath was needed; and with hexadecyl sulfate prolonged refluxing of the reactants in toluene was required. The methyl sulfates were recrystallized from water in form of crystalline hydrates while the others were recrystallized from ethyl acetate.

Physiological.—In the phenol coefficient determinations using the U. S. Bureau of Standards technique toward *S. aureus*, the N-hexadecyl morpholinium series exhibited the maximum activity, reaching phenol coefficients of 500 to 600 depending on the *p*H of the solutions tested, with hardly any difference in the methyl, ethyl and *n*-butyl or *n*-hexyl sulfate series. Toward *E. typhosa*, the N-tetradecyl compounds showed the higher activity, the phenol coefficients being about 200. Equal activities toward both Gram-positive as well as Gram-negative microörganisms was reached with the hexyl sulfate compounds.

TABLE I

N-ALKYL MORPHOLINES AND MORPHOLINIUM SULFATES

R	R′	Formula	M. p., °C., (uncor.)	Analyses, % N Calcd.	Found
		$O(CH_2CH_2)_2NR$			
Dodecyl	...	$C_{16}H_{23}NO$	15	5.72	5.70
Tetradecyl	...	$C_{18}H_{27}NO$	17	5.12	5.15
Hexadecyl	...	$C_{20}H_{31}NO$	40	4.65	4.68
Octadecyl	...	$C_{22}H_{35}NO$	25	4.25	4.31
		$[O(CH_2CH_2)_2NRR']SO_4R'$			
Dodecyl	Methyl[a]	$C_{18}H_{31}NSO_6$	47	3.59	3.52
Dodecyl	Ethyl	$C_{20}H_{33}NSO_5$	43	3.53	3.45
Dodecyl	*n*-Butyl	$C_{24}H_{47}NSO_5$	41	3.03	2.68
Dodecyl	*n*-Hexyl	$C_{28}H_{49}NSO_5$	160	2.74	2.93
Dodecyl	Hexadecyl	$C_{48}H_{99}NSO_5$	93	2.37	2.31
Tetradecyl	Methyl[a]	$C_{20}H_{35}NSO_6$	57	3.35	3.33
Tetradecyl	Ethyl	$C_{22}H_{37}NSO_5$	50	3.27	3.16
Tetradecyl	*n*-Butyl	$C_{26}H_{51}NSO_5$	90	2.86	2.52
Tetradecyl	*n*-Hexyl	$C_{30}H_{53}NSO_5$	167	2.59	2.71
Tetradecyl	Hexadecyl	$C_{50}H_{103}NSO_5$	127	2.26	1.88
Hexadecyl	Methyl[a]	$C_{22}H_{39}NSO_6$	68	3.19	3.21
Hexadecyl	Ethyl	$C_{24}H_{41}NSO_5$	64	3.08	3.03
Hexadecyl	*n*-Butyl	$C_{28}H_{55}NSO_5$	142	2.70	2.77
Hexadecyl	*n*-Hexyl	$C_{32}H_{57}NSO_5$	173	2.47	2.83
Hexadecyl	Hexadecyl	$C_{52}H_{107}NSO_5$	104	2.17	2.14
Octadecyl	Methyl[a]	$C_{24}H_{43}NSO_6$	81	2.96	2.88
Octadecyl	Ethyl	$C_{26}H_{45}NSO_5$	75	2.89	2.81

[a] Hydrate.

Acknowledgments.—The authors wish to express their appreciation for the phenol coefficient work involved in this investigation to Dr. C. T. Van Meter of Reed and Carnrick, Jersey City, N. J., and to Drs. F. E. Stirn and A. J. Weil of the Lederle Laboratories, Pearl River, N. Y.

Summary

A series of new symmetrical morpholium alkyl sulfates has been prepared and their phenol coefficients determined.

NEW YORK, N. Y. RECEIVED JUNE 11, 1947

---

[1] Abstracted from the theses of Hugh W. Salzberg and John J. Shatynski presented to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Master of Science, 1946. Presented before the Division of Organic Chemistry at the Atlantic City meeting of the American Chemical Society, April 16, 1947.

[2] J. B. Niederl and co-workers, THIS JOURNAL, **63**, 1476 (1941); **66**, 840 (1944); **67**, 1227 (1945).

[3] Barkenbus and Owen, *ibid.*, **56**, 1204 (1934).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

Synthetic Estrogens. Phenyl and Benzyl Hexestrols and Dienestrols[1,2]

BY J. B. NIEDERL AND R. M. SILVERSTEIN

Studies in the introduction of alkyl radicals into the benzene rings of synthetic estrogens, with subsequent enhancement of therapeutic properties in at least two cases,[3] have now been extended to include phenyl and benzyl substituted hexestrols and dienestrols.

3,4-bis-(*m*-Phenyl-*p*-hydroxyphenyl)-2,4-hexadiene and 3,4-(*m*-benzyl-*p*-hydroxyphenyl)-2,4-hexadiene were prepared from *o*-phenylphenol and *o*-benzylphenol, respectively, using the following method of synthesis.[4] The phenols were esterified with propionic anhydride. The resulting esters were subjected to a Fries rearrangement to yield the 3-phenyl-4-hydroxy- and the 3-benzyl-4-hydroxy-propiophenones which were then esterified. These ketones were reduced to the corresponding pinacols which in turn were dehydrated and saponified to the desired dienestrols. Catalytic hydrogenation yielded the corresponding hexestrols.

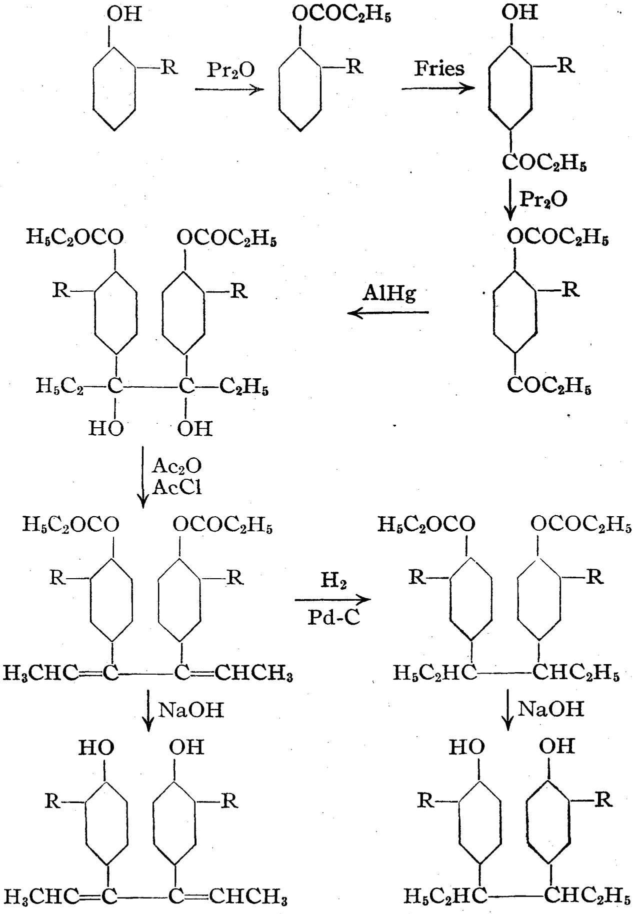
Experimental

***o*-Phenylphenylpropionate (I) and *o*-Benzylphenylpropionate (II).**—*o*-Phenylphenola nd *o*-benzylphenol were esterified with propionic anhydride. The propionic acid formed and the unreacted anhydride were removed under reduced pressure and the residue used without further purification.

3-Phenyl-4-hydroxypropiophenone (III) and 3-Benzyl-4-hydroxypropiophenone (IV).—These compounds were obtained by a Fries rearrangement[5] of (I) and (II). One and one-half moles of anhydrous aluminum chloride was dissolved in 400 ml. of nitrobenzene. When the solution cooled to room temperature one mole of the ester (I, II) was added dropwise with constant stirring at such a rate that the temperature did not rise above 30°. The flask was protected with a calcium chloride tube, allowed to stand overnight, then heated to 50° for three hours. The solution was poured into about three times its volume of an ice–water mixture and allowed to stand for several hours until the aluminum chloride complex was hydrolyzed. The aqueous layer was separated and extracted with ether which was then combined with the nitrobenzene layer. The ether–nitrobenzene mixture was extracted with 10% sodium hydroxide. After washing with several portions of ether to remove traces of nitrobenzene, the alkaline extract was acidified with dilute hydrochloric acid. The precipitate was filtered, washed, dried and used in the next step without further purification.

3-Phenyl-4-propionoxypropiophenone (V) and 3-Benzyl-4-propionoxypropiophenone (VI).—(III) and (IV) were esterified with propionic anhydride. After removing the propionic acid and anhydride and a forerun probably consisting of the ortho rearranged isomer, the esters distilled at 190–192° (3 mm.) and 208–209° (3 mm.), respectively, and crystallized on standing.

FLOW SHEET



R = phenyl, benzyl

3,4-bis-(*m*-Phenyl-*p*-propionoxyphenyl)-3,4-hexanediol (VII) and 3,4-bis-(*m*-Benzyl-*p*-propionoxyphenyl)-3,4-hexanediol (VIII).—Two moles of aluminum foil were cut into strips, crumpled loosely, amalgamated with mercuric chloride, washed rapidly with water, ethanol and ether, then covered with 500 ml. of ether in a 2-liter 3-necked flask. The flask was fitted with a sealed stirrer, a dropping funnel and a reflux condenser. One third of a mole of the ketone (V, VI) was added in one batch. Water was added dropwise through the dropping funnel at such a rate that a gentle reflux of ether was maintained. The reaction took about eight hours until the aluminum was exhausted. The mass was filtered and the residue extracted with ether which was then combined with the filtrate. The ether was removed and the viscous residue used in the next step. Neither of the reaction products could be crystallized.

3,4-bis-(*m*-Phenyl-*p*-propionoxyphenyl)-2,4-hexadiene (IX) and 3,4-bis-(*m*-Benzyl-*p*-propionoxyphenyl)-2,4-hexadiene (X).—Fifty grams of the hexanediol (VII, VIII)

---

[1] This material has been abstracted from the Ph.D. Thesis to be presented by R. M. Silverstein to the faculty of the Graduate School of New York University.

[2] Presented before the Medicinal Chemistry Division at the Atlantic City meeting of the American Chemical Society, April, 1947.

[3] C. A. Siconalfi and C. T. Van Meter, Chicago Meeting, September, 1946, and J. B. Niederl and co-workers, New York Meeting, September, 1947, of the American Chemical Society.

[4] E. C. Dodds and co-workers, *Proc. Roy. Soc.* (*London*), **B127**, 140 (1939).

[5] H. Wojahn, *Arch. Pharm.*, **271**, 417 (1933).

TABLE OF COMPOUNDS

	Formula	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Over-all yields, %
3-Phenyl-4-propionoxypropiophenone	$C_{18}H_{18}O_3$	46	76.57	6.43	76.86	6.19	70
3,4-bis-(*m*-Phenyl-*p*-hydroxyphenyl)-2,4-hexadiene							
Free phenol	$C_{30}H_{26}O_2$	202–204d	86.14	6.23	86.40	6.36	9.5
Diacetate	$C_{34}H_{30}O_4$	170–171	81.25	6.02	81.35	6.10	9.5
Dipropionate	$C_{36}H_{34}O_4$	125–126	81.47	6.40	81.29	6.77	10
Dibenzoate	$C_{44}H_{34}O_4$	212–214	84.32	5.47	84.54	5.20	9.3
3,4-bis-(*m*-Phenyl-*p*-hydroxyphenyl)-hexane							
Free phenol	$C_{30}H_{30}O_2$	219–221d	85.27	7.16	85.52	7.32	7.0
Diacetate	$C_{34}H_{34}O_4$	188–190	80.60	6.76	80.40	6.72	7.0
Dipropionate	$C_{36}H_{38}O_4$	135–137	80.86	7.16	80.81	7.25	7.0
Dibenzoate	$C_{44}H_{38}O_4$	154–157	83.77	6.07	83.95	6.13	6.9
3-Benzyl-4-propionoxypropiophenone	$C_{19}H_{20}O_3$	88–89	77.00	6.80	77.25	6.96	70
3,4-bis-(*m*-Benzyl-*p*-hydroxyphenyl)-2,4-hexadiene							
Free phenol	$C_{32}H_{30}O_2$	150–152	86.06	6.77	85.94	6.82	5.3
Diacetate	$C_{36}H_{34}O_4$	122–124	81.48	6.46	81.43	6.40	5.3
Dipropionate	$C_{38}H_{38}O_4$	115–117	81.68	6.85	81.41	6.83	5.6
Dibenzoate	$C_{46}H_{38}O_4$	173	84.37	5.85	84.34	5.85	5.2
3,4-bis-(*m*-Benzyl-*p*-hydroxyphenyl)-hexane							
Free phenol	$C_{32}H_{34}O_2$	169–171	85.29	7.60	85.28	7.38	4.0
Diacetate	$C_{36}H_{38}O_4$	122–123	80.87	7.16	80.72	7.21	4.0
Dipropionate	$C_{38}H_{42}O_4$	119–121	81.13	7.52	80.73	6.96	4.0
Dibenzoate	$C_{46}H_{42}O_4$	148–149	83.86	6.42	83.95	6.40	3.9

was refluxed for twenty minutes with 150 ml. of acetic anhydride and 100 ml. of acetyl chloride. The solution was poured into a large volume of ice–water mixture in an Erlenmeyer flask, shaken vigorously and allowed to stand for several hours. The semi-solid mass which separated was shaken with several changes of water, then triturated with a small amount of cold methanol until solidification was effected. The flaky solid was filtered, washed with methanol and recrystallized from the same solvent.

3,4-bis-(*m*-Phenyl-*p*-hydroxyphenyl)-2,4-hexadiene (XI) and **3,4-bis(*m*-Benzyl-*p*-hydroxyphenyl)-2,4-hexadiene** (XII).—Saponification of (IX, X) was effected by heating at 60° for two hours with Claisen solution and allowing to stand overnight at room temperature. The solution was diluted with water, filtered, the filtrate acidified, and the precipitate filtered, washed and recrystallized from dilute ethanol.

3,4-bis-(*m*-Phenyl-*p*-hydroxyphenyl)-hexane (XIII), and 3,4-bis-(*m*-Benzyl-*p*-hydroxyphenyl)-hexane (XIV).—These compounds were obtained by hydrogenation of (IX, X) in acetone with palladium on carbon at 3 atmospheres and room temperature for one hour. The solvent was removed but in neither case could the viscous residue be crystallized. Saponification was effected as under (XI, XII) and the compounds were recrystallized from dilute ethanol.

Esters.—The diacetates of (XI, XII) and (XIII, XIV) and the propionates of (XIII, XIV) were prepared by refluxing with acetic and propionic anhydrides, respectively, and recrystallizing from dilute ethanol. The dibenzoates were prepared from (XI, XII) and (XIII, XIV) by the Schotten–Baumann method and recrystallized from an absolute ethanol–ethyl acetate mixture.

Physiological.—Assays were performed according to standard procedure by subcutaneous injection into rats of oil solutions of the compounds. At the 50 gamma dose level 3,4-bis-(*m*-benzyl-*p*-hydroxy)-hexane showed no estrogenic activity. At the same dose level 3,4-bis-(*m*-phenyl-*p*-hydroxy)-hexane elicited estrogenic response in 10% of the animals tested.

Acknowledgment.—The authors desire to express their appreciation to Dr. C. T. Van Meter of Reed and Carnrick, Jersey City, N. J., for the estrogenic assays.

Summary

In continuation of the work done in this Laboratory in the field of synthetic estrogens the phenyl and benzyl hexestrols and dienestrols have been prepared. The introduction of the phenyl or benzyl group resulted in considerable diminution of estrogenic activity.

NEW YORK 3, N. Y. RECEIVED OCTOBER 10, 1947

[CONTRIBUTION FROM THE LABORATORIES OF COMPAGNIE PARENTO, INC.]

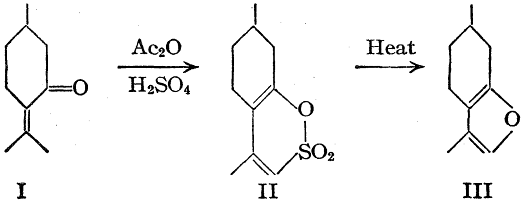
Occurrence of Menthofuran in Oil of Peppermint (Mentha piperita vulgaris S.)

BY PAUL Z. BEDOUKIAN

In 1904, Charabot[1] obtained from the flowering heads of the peppermint plant an oil which was found to have a rotation of +19° whereas the oil obtained from the whole plant was known to have a rotation of −19 to −22°. Further investigation of this oil by Carles[2] in 1929 showed that the positive rotation was due to the presence of an unidentified substance. This substance could not be isolated in the pure state but repeated distillations gave a fraction rich in the unknown substance with a rotation of +81°. Carles studied the properties of this substance and although he was unable to elucidate its structure his studies led him to believe it to be an oxide. The dextrorotatory substance was present in both French and Italian peppermint oils. It is noteworthy to mention a report of the occurrence of a dextrorotatory fraction in American peppermint oil which the investigator[3] attributed to the possible presence of *d*-menthone.

In 1934 Wienhaus and Dewein[4] deduced the structure of this dextro-rotatory compound to be tetrahydro-4,5,6,7-dimethyl-3,5-coumarane (menthofuran). Their deduction was based on experimental facts such as its complete reduction to *p*-menthane and oxidation to β-methyladipic acid. On hydrogenation it gave a product identical to the oxide derived from isopulegol which possessed an oxygen between the carbon atoms 3 and 9.

The syntheses of this unusual compound was successfully carried out by Treibs.[5] On treating pulegone (I) with cold acetic anhydride–sulfuric acid mixture by Reychler's method[6] Treibs obtained the cyclic ester of pulegenol sulfonic acid (II). When this compound was heated with an inert filler such as zinc oxide it lost one molecule of sulfur dioxide, giving a liquid of a composition $C_{10}H_{14}O$ (III).



I II III

The product was found to contain two double bonds which were conjugated, since the compound combined readily with maleic anhydride giving an addition product $C_{14}H_{16}O_4$. The conjugated double bonds were present in the furan ring because the vapor of menthofuran gave a deep red pine splinter reaction. Further evidence of the structure of synthetic menthofuran was obtained by degradation experiments.

The purpose of the present investigation was to establish conclusive proof of the presence of menthofuran in peppermint oil by direct comparison of the synthetic compound with the naturally occurring oxide.

In the examination of essential oils it is imperative to start with material of unquestionable purity. The peppermint oil investigated was obtained from plants grown in southern Ontario, the plants, *Mentha piperita vulgaris S.*, having been originally imported from Indiana. The writer was present during the harvesting and distillation period and acquired several drums of oil on the spot. The harvesting of the plant was begun as usual with the flowering of the plant and was continued for about two weeks. The fields were free from weeds and foreign plants. During the analysis of these oils which involved fractionation it was noted that a small fraction had a positive rotation, an unusual occurrence with peppermint oils. The properties of this oil were reported in a publication.[7] The dextro-rotatory fraction was separated and subjected to a study.[8] It was found impossible to obtain it in the pure state even after the removal by chemical means of menthone and menthol which have boiling points close to menthofuran. The purest fraction obtained had a rotation of +61° and exhibited properties similar to menthofuran as described in the literature. Its identity was established by the fact that its addition product with maleic anhydride did not give a depression in melting point when mixed with the addition product of synthetic menthofuran. The occurrence of menthofuran in oil of peppermint (*Mentha piperita vulgaris S.*) was thus definitely established.

Since menthofuran is present in relatively large quantities in the oil of flowering heads of *Mentha piperita vulgaris S.* and only in traces in oil of peppermint obtained from the whole plant, it is quite probable that the source of menthofuran in peppermint is the flower of the plant.

Menthofuran, in common with other furans, exhibits some interesting color reactions. On exposure to air both the natural and synthetic menthofuran turn purplish. This color, apparently due to the formation of an oxidation product, is completely removed by filtering the oil with magnesium carbonate powder. Menthofuran gives an intense blue–violet color on adding bro-

---

(1) Charabot, *Bull. soc. chim.*, **31**, 402 (1904).

(2) Carles, *Parf. Moderne*, **22**, 615 (1929).

(3) Gordon, *Am. J. Pharm.*, **99**, 524 (1927)

(4) Wienhaus and Dewein, *Z. angew. Chem.*, **47**, 415 (1934).

(5) Treibs, *Ber.*, **70B**, 85 (1937).

(6) Reychler, *Bull. soc. chim.*, **19**, 129 (1898).

(7) Bedoukian, *Am. Perfumer*, **46**, No. 2, 59 (1944).

(8) Part of this work was carried out in the laboratories of W. J. Bush & Co., Ltd., Montreal, Canada.

mine to its solution of carbon tetrachloride. This reaction recalls the behavior of azulenes. Similar color reactions of many essential oils may be due to the presence of such compounds of unknown structure.

Experimental

Separation of Natural Menthofuran.—The fraction of peppermint oil possessing a slight dextro-rotation was subjected to several fractionations and the fractions having a rotation of +15 to +20° were collected. The menthone present in these fractions was removed by means of semicarbazide hydrochloride. On fractionation the unreacted oil gave a product having a rotation of +61°, $d^{20}{}_{25}$ 0.930, $n^{25}{}_D$ 1.4657, b. p. (17 mm.) 92–94°. Carles[2] obtained a purer sample of natural menthofuran with the following constants: rot. +81°, b. p. (20 mm.) 95°, d^{15} 0.965, $n^{20}{}_D$ 1.4807.

Maleic Anhydride Addition Product of Natural Menthofuran.—The above impure menthofuran (5 g.) was added to 15 ml. of benzene containing 5 g. of maleic anhydride. There was a noticeable rise in temperature and the mixture was allowed to stand for two hours. The crystals obtained after several recrystallizations from benzene had a m. p. of 133–133.5°. The mixed m. p. with the synthetic product showed no depression (m. p. 133°).

Preparation of Pulegenol Sulfonic Ester.—Oil of pennyroyal (100 g.) was fractionated and the fraction having a b. p. of 100–101° (17 mm.), rot. +21.50, $d^{25}{}_{25}$ 0.939, $n^{20}{}_D$ 1.4850, was taken as pure pulegone. Forty grams of pulegone was treated with 80 g. of an ice cold mixture of 2 moles of acetic anhydride and 1 mole of sulfuric acid. The temperature rose to 25° and the mixture was allowed to stand for two hours. The crystals obtained were filtered, washed and recrystallized from methyl alcohol, m. p. 86°. Treibs reports m. p. 85° for pulegenol sulfonic acid cyclic ester.

Formation of Menthofuran.—The above product (20 g.) was mixed with 20 g. of zinc oxide and heated at atmospheric pressure. When the oil-bath reached 280–290° strong fumes of sulfur dioxide came off followed by an oil of bluish color. The oil (13 g.) was first washed with water, then with a 5% solution of sodium carbonate, redistilled and the fraction (8 g.) of b. p. 205–206°, rot. +92° $n^{20}{}_D$ 1.4855, $d^{25}{}_{25}$ 0.966, was taken as menthofuran. It was a colorless oil which turned purplish on exposure to air. Treibs gives the following constants for synthetic menthofuran: b. p. 80° (18 mm.), d^{15} 0.972, n_D 1.4890, rot. +92°.

Maleic Anhydride Addition Product.—The same procedure was followed as with natural menthofuran. The maleic anhydride addition product had a m. p. of 133–133.5°. Treibs reports 138° for the m. p. of the addition product of menthofuran. Both the natural and synthetic menthofuran exhibited a greenish coloration and fluorescence in benzene solution although the crystals themselves were colorless.

Summary

A dextro-rotatory substance occurring in oil of peppermint (*Mentha piperita vulgaris S.*) was shown to be menthofuran (tetrahydro-4,5,6,7-dimethyl-3,6-coumarane). Its identity was established by the fact that its maleic anhydride addition product did not give a depression in m. p. when mixed with the maleic anhydride addition product of synthetic menthofuran.

CROTON-ON-HUDSON, N. Y.
RECEIVED SEPTEMBER 29, 1947

[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Monomers and Polymers. II. α-Methylstyrenes and the Steric Hindrance of *ortho*-Substituents[1]

BY G. BRYANT BACHMAN AND R. W. FINHOLT[2]

Although styrene (S) itself polymerizes readily in the presence of peroxides, α-methylstyrene (AMS) resists polymerization with peroxides and forms high polymers only in conjunction with other vinyl compounds.[2a] This is in part advantageous since the AMS may be stored even in the presence of air without loss (except by partial oxidation to acetophenone), and may be recovered from reaction mixtures with ease. The copolymers of AMS do not appear to differ markedly in physical properties from the analogous copolymers of S.

In undertaking a study of synthetic rubbers prepared by copolymerizing substituted α-methylstyrenes with butadiene we soon became aware of the importance of the relative positions of the substituent groups. Thus, 3,4-dichloro-AMS gave good rubbers with butadiene while 2,4-dichloro-AMS did not copolymerize. Construction of molecular models showed that the isopropenyl group is not free to rotate through 360° in the 2,4-isomer because of the hindering effect of the *ortho* chlorine atom. Such hindrance is not apparent in the S series, and there are numerous references in the literature to the polymerization of ortho substituted S's.[3] Models of the polymers of 2-chloro-AMS show that the phenyl groups are forced to lie at right angles to the direction of prop-

---

(1) From the Ph.D. thesis of R. W. Finholt, Purdue University, June, 1947.

(2) Present address: Department of Chemistry, Union College, Schenectady, New York.

(2a) Note, however, that acid and ionic catalysts cause polymerization of α-methylstyrenes. Staudinger and Breusch, *Ber.*, **62**, 442 (1929); Bergmann, Tanbadel and Weiss, *Ber.*, **64**, 1493 (1931); Hershberger, Reid and Heiligmann, *Ind. Eng. Chem.*, **37**, 1073 (1945).

(3) *o*-F-S, Brooks, THIS JOURNAL, **66**, 1295 (1944), and private communication. 2-CH_3O-S, Walling and Wolfstirn, *ibid.*, **69**, 852 (1947), and private communication; Pschorr and Einbeck, *Ber.*, **38**, 2076 (1905); Klages and Eppelsheim, *ibid.*, **36**, 3590 (1903). 2,3-, 2,4-, 2,5- and 2,6-diCl-S's, British Patent 564,828 (Oct. 16, 1944); Marvel, Overberger, Allen, Johnston, Saunders and Young, THIS JOURNAL, **68**, 861 (1946); Michalek and Clark, *Chem. Eng. News*, **22**, 1559 (1944). 2-CH_3-S, v. Auwers, *Ann.*, **413**, 295 (1917). 2,4-diCH_3 and 2,5-diCH_3-S's, Marvel, Saunders and Overberger, THIS JOURNAL, **68**, 1085 (1946). 2-OH-S, Fries and Fickewirth, *Ber.*, **41**, 369 (1908). 2,4-di(OH)-S, Flood and Nieuwland, THIS JOURNAL, **50**, 2568 (1918); etc.

agation of the chain, like pennies strung on a wire through a small hole in their centers.

While the above-described steric hindrance is not great enough to preclude ordinary reactions of AMS's, it does effectively prevent polymerization reactions, probably because of the small free energy changes (about 8 cal./mole) involved in going from a monomer to a polymer. An *ortho* fluorine atom, which is about midway in size between a hydrogen and a chlorine atom, is apparently just small enough to permit copolymerizations. This is evident in the models and corresponds with our experience. On the other hand, an *o*-methoxy group prevents copolymerization of AMS. The CH_3O- group is larger than the F atom but may, through restricted rotation, assume a position that is not in interference with the isopropenyl group. It is apparent, however, that rotation of the methoxy group is not restricted sufficiently to permit copolymers to form.

2,3-Dimethoxy- and 3,4,5-trimethoxy-AMS's not only did not copolymerize but also inhibited the polymerization of butadiene. This is not the result of steric hindrance, but is probably associated with the well-known inhibiting action of *o*- and *p*-dihydroxy aromatic compounds in polymerizations catalyzed by peroxides. It is even possible that traces of these methoxy compounds were hydrolyzed to the corresponding hydroxy compounds during their purification or polymerization.

The substituted AMS's, like AMS itself, did not polymerize on standing alone or in the presence of peroxides.

In Table I are summarized the results obtained with eleven AMS's. The rubbers from the unhindered AMS's were about equal to GR-S in their properties except for those from 4-chloro- and 3,4-dichloro-A7S which were superior. Table II compares the properties of these rubbers with a GR-S control.

Acknowledgment.—The authors are indebted to the Purdue Research Foundation and the General Tire and Rubber Company for financial support in the form of a fellowship and to the latter for testing the synthetic rubbers prepared.

Experimental

Known Styrenes.—The following were prepared in the indicated yields by published procedures: 2-methoxy-AMS[4], 64% yield from methyl 2-methoxybenzoate; 2-fluoro-AMS[4] (d^{25}_{25} 1.004), 65% yield from methyl 2-fluorobenzoate; 4-methoxy-AMS,[5] 73% yield from 4-methoxyacetophenone; 4-ethoxy-AMS,[5] 65% yield from 4-ethoxyacetophenone; 3,4,5-trimethoxy-AMS.[6] (m. p. 34°), 66% yield from methyl 3,4,5-trimethoxybenzoate.

2,4-Dichloro-AMS.—A solution of 110 g. (0.5 mole) of ethyl 2,4-dichlorobenzoate in 300 ml. of ether was added slowly with cooling to 9.1 moles of methylmagnesium iodide in 750 ml. of ether. After refluxing for half an hour, the mixture was hydrolyzed with aqueous ammonium chloride and the ether extract was dried and evaporated. Without further treatment the residue was slowly distilled at 70 mm. pressure from 0.5 g. of phosphorus pentoxide and 6 g. of sodium acid sulfate. Rectification of the dried distillate gave 64 g. (68% yield) of the desired AMS, b.p. (15 mm.) 103–104°, d^{25}_{25} 1.182, n^{25}_D 1.5460.

Anal. Calcd. for $C_9H_8Cl_2$: Cl, 37.91. Found: Cl, 37.85, 37.72.

3,4-Dichloro-AMS.—Saturation of a solution of 382 g. of 3,4-dichlorobenzoic acid in 2 l. of ethanol with dry hydrogen chloride followed by neutralization and distillation gave 410 g. (95% yield) of the ester. Reaction of this with an excess of methylmagnesium iodide and conversion to the AMS as described in the preceding preparation gave 248 g. (70% yield) of product, b. p. (3 mm.) 94°, d^{25}_{25} 1.224, n^{25}_D 1.5732.

Anal. Calcd. for $C_9H_8Cl_2$: Cl, 37.91. Found: Cl, 37.69, 37.61.

2-Chloro-AMS.—From 313 g. of *o*-chlorobenzoic acid was obtained 317 g. (87% yield) of the ethyl ester. This was reacted with methylmagnesium iodide, the resulting crude alcohol was dehydrated and the styrene was obtained in 60% yield, b. p. (14 mm.) 75°, d^{25}_{25} 1.057, n^{25}_D 1.5329.

Anal. Calcd. for C_9H_9Cl: Cl, 23.23. Found: Cl, 22.92, 22.82.

TABLE I

COPOLYMERIZATION OF SUBSTITUTED α-METHYLSTYRENES WITH BUTADIENE[a] AT 40°

Substituents	Copolymerization	Yield	Hr.	Quality of rubber
2-Cl[c]	No	70	20	Dry[b]
2-F	Yes	75	25	Good
2-MeO	No	60	40	Dry[b]
4-Cl[c]	Yes	76	20	Good
4-MeO	Yes	80	38	Good
4-EtO	Yes	75	30	Good
2,4-Cl_2[c]	No	78	24	Dry[b]
3,4-Cl_2[c]	Yes	78	20	Good
3,5-Br_2[c]	Yes	100	44	Good
2,3-$(MeO)_2$[c]	No	...	..	Inhibits
3,4,5-$(MeO)_3$	No	...	..	Inhibits

[a] Butadiene 75%, α-methylstyrene 25%. [b] These rubbers were dry and brittle polybutadienes. [c] New compound.

TABLE II

PHYSICAL PROPERTIES[a] OF RUBBERS FROM BUTADIENE WITH 4-CHLORO- AND 3,4-DICHLORO-α-METHYLSTYRENES

Comonomer	3,4-Cl_2[b]	4-Cl[b]	GR-S control[c]
% Conversion	82	84	75
Modulus at 300%[d]	930 (705)	1260 (930)	800 (200)
Elongation[d]	705 (520)	613 (415)	600 (320)
Tensile[d]	4440 (1570)	4600 (1755)	3000 (800)
Durometer hardness	64	65	62
Bashore	37	37	36
Goodrich flexometer			
Change in *T*, °F.	68	63	65
Static compression, %	15.5	14.3	16.1
Change in height	4.4	3.9	2.6
Permanent set	2.0	1.4	3.3

[a] Physical tests were determined by the General Tire and Rubber Company. [b] Butadiene 70%, α-methylstyrene 30%. [c] Butadiene 75%, styrene 25%. [d] The figures in parentheses were obtained with the sample immersed in hot water (*ca.* 95°).

---

[4] Bergman and Weizman, *Trans. Far. Soc.*, **32**, 1327 (1931).

[5] Behal and Tiffeneau, *Bull. soc. chim.*, [4] **3**, 321 (1908).

[6] Bogert and Isham, THIS JOURNAL, **36**, 516 (1914).

4-Chloro-AMS.—A solution of 154.5 g. of *p*-chloroacetophenone in 700 ml. of ether was added slowly with cooling and stirring to 1.2 moles of methylmagnesium iodide in 1200 ml. of ether. The crude tertiary alcohol obtained as a product was dehydrated at 15 mm. pressure by heating with 2 g. of sodium acid sulfate. Rectification gave 110 g. (71% yield) of the desired AMS, b. p. (10 mm.) 86°, d^{25}_{25} 1.073, n^{25}_{D} 1.5540.

Anal. Calcd. for C_9H_9Cl: Cl, 23.23. Found: Cl, 23.09. 22.90.

2,3-Dimethoxy-AMS.—A solution of 77 g. (0.4 mole) of methyl 2,3-dimethoxybenzoate in 300 ml. of ether was reacted with 0.8 mole of methylmagnesium iodide in 700 ml. of ether to obtain the tertiary alcohol which was dehydrated by slow distillation at normal pressure from 5 g. of phosphorus pentoxide. The resulting AMS was obtained in 28.5 g. (42% yield); b. p. (3 mm.) 78°, d^{25}_{25} 1.026, n^{30}_{D} 1.5237.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.89, 73,80; H, 7.89, 7.76.

3,5-Dibromo-AMS.—A solution of 200 g. of anthranilic acid in 2 l. of methanol was saturated with hydrogen chloride and refluxed for twenty hours. The ester solution was treated with 160 ml. of bromine in 400 ml. of concentrated aqueous potassium bromide maintaining the temperature at 25–30°. After three hours the dibromo ester (376 g., 83% yield) was precipitated in 25 liters of water. A solution of 154.5 g. of the ester in a mixture of 50 ml. of water, 50 ml. of acetic acid and 300 ml. of 95% ethanol was heated to boiling and treated with 85 g. of isopropyl nitrite added slowly over a period of three hours. The deaminated acid (88 g., 62% yield) was precipitated by pouring into 2 liters of water. It was esterified by saturating the solution in 1 l. of methanol with hydrogen chloride and refluxing for eight hours. The ester (86.5 g., 94% yield) separated on cooling as long white needles, m. p. 62–63°.

A solution of 99 g. (0.34 mole) of methyl 3,5-dibromobenzoate in 300 ml. of benzene was reacted with 0.7 mole of methylmagnesium bromide in 650 ml. of ether. Distillation of the resulting tertiary alcohol from 4 g. of phosphorus pentoxide at 20 mm. pressure and rectification of the product gave 65 g. (70.3%) yield of the desired AMS; b. p. (3 mm.) 98°, d^{25}_{25} 1.750, n^{30}_{D} 1.6097.

Anal. Calcd. for $C_9H_8Br_2$: C, 39.16; H, 2.92. Found: C, 39.33, 39.40; H, 2.78, 2.85.

Polymerization Experiments.—Each monomer was copolymerized with butadiene on a small scale (2.5 g. of AMS) to approximate the rate, then on a larger scale (50 g. or more of AMS) to compound, cure and test the rubber. The polymerization recipe was: butadiene 75 parts, AMS 25 parts, soap 5 parts, OEI (a mercaptan mixture from the Naugatuck Chemical Company) 0.6 part, a peroxide salt 0.3 part, water 175 parts by weight. The polymerizations were done in small sealed Pyrex tubes or quart size soda water bottles immersed and rotated in a thermostat bath. The conditions and results are summarized in Tables I and II.

Summary

The copolymerizations of eleven different nuclearly substituted α-methylstyrenes with butadiene have been studied. The effects of the natures and positions of the substituents on the rates of copolymerization have been discussed and the hindrance of *ortho* substituents has been indicated. Six new α-methylstyrenes have been prepared and characterized.

LAFAYETTE, INDIANA RECEIVED JULY 23, 1947

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Some Properties of Phenanthrene Semiquinone

BY L. MICHAELIS AND S. GRANICK

It has been shown in previous papers[1,2,3,4] that phenanthrenequinone or its sulfonate on partial reduction establishes a compound intermediate between the quinone and the hydroquinone. This intermediate compound, when in the dissolved state, is in equilibrium with the two "parent substances" and furthermore exists in two modifications which also are in equilibrium with each other, namely, the free paramagnetic semiquinone radical and its diamagnetic, quinhydrone-like dimerization product. All of the equilibrium constants for an aqueous solution at 30° and at different acidities have been determined. The equilibrium between the free radical, the quinone and the hydroquinone is displaced in favor of the radical by increase of *p*H up to about 11, and remains constant at its maximum value on further increase of *p*H. The percentage of dimerization of the free radical is increased with increasing total concentration, as expected for a bimolecular reaction. Two more properties of that intermediate compound will be described in this paper.

(1) The dimerization of the free radical is counteracted by water-miscible organic solvents such as ethanol or pyridine. Even at a very high concentration of potassium phenanthrenequinone-3-sulfonate, 0.05 *M*, no noticeable dimerization of the free radical takes place if the solvent is 50% pyridine instead of pure water. Evidence for this statement is produced by the measurement of the change of magnetic susceptibility of the quinone in alkaline solution during the slow reduction by glucose using the method described previously.[5] In the three experiments plotted in Fig. 1 the alkalinity is always great enough to make the semiquinone formation constant maximal and independent of minor variations of *p*H. In a purely aqueous solution, at the very high concentration of the substance used in this experiment, the change of susceptibility in time is such as to indicate *in maximo* not more than about 16% (3) of the substance in the state of a free radical. Such

---

(1) L. Michaelis and M. P. Schubert, *J. Biol. Chem.*, **119**, 133 (1927).

(2) L. Michaelis and E. S. Fetcher, THIS JOURNAL, **59**, 2460 (1937).

(3) L. Michaelis, G. B. Boeker and R. K. Reber, *ibid.*, **60**, 202 (1938).

(4) L. Michaelis, R. K. Reber and J. A. Kuck, *ibid.*, **60**, 214 (1938).

(5) L. Michaelis, *ibid.*, **63**, 2446 (1941). (1) Calculated as shown in (5).

a value is compatible with results obtained previously with different initial concentrations of the substance. When the same experiment is carried out with 50% pyridine as a solvent, the change of susceptibility in time is much larger and indicates, at the maximum point, the presence of 64% of the substance as a free radical. There is no evidence, either spectrophotometrically or otherwise, for any appreciable, measurable amount of the dimer.

(2) The free radical disappears both for solutions in water and in 50% pyridine (or alcohol) on addition of a small amount of a salt of calcium (or strontium or barium, but not magnesium or zinc or nickel). Instead of the brown radical an intensely emerald-green calcium compound of it is formed which is diamagnetic. During the reduction of the quinone by glucose in the presence of calcium no change of susceptibility is observed but the color changes observed during the reduction go from light yellow through green to light yellow (Fig. 1).

It is desirable to confirm the existence of the three modifications of the intermediate reduction product spectrophotometrically. In fact, they can be distinguished. Figure 2 shows first of all that the absorption of the quinone and the hydroquinone above 400 mμ is almost negligible. It is worth while mentioning that in such an alkaline solution the yellow color of the hydroquinone is more intense than that of the quinone, as can also be inferred from the graph. Figure 2 shows the molar absorption curve of the free radical. The relative values are quite reliable although the absolute values may be in error by 10 or perhaps even 20% because of the uncertainties involved in the calculation of the concentration of the free radical, as described in the legend of Fig. 2. Anyhow, it is obvious that the molar absorption coefficient of the free radical is much smaller than that of a "good" dyestuff such as methylene blue. This seems to be true for most of the free semiquinone radicals.

Curve O—O shows, as well as possible, the molar absorption curve for the dimer as it arises in purely aqueous alkaline solution of high concentration of the quinone on partial reduction. The calculations may be much more in error than for curve ·—·, especially for the absolute values, but the fact that this spectrum represents a compound which is different from the free radical is established without doubt.

The absorption curve for the green calcium complex, curve ×—×, is quite reliable for the relative values although the absolute values may be somewhat in error.

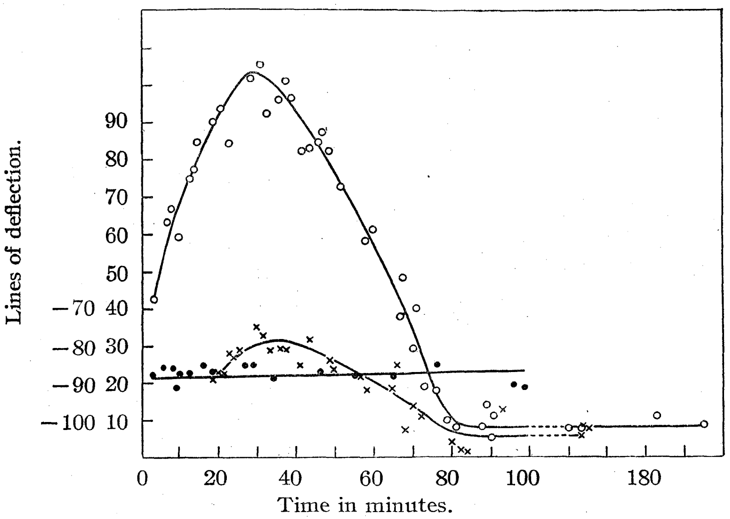
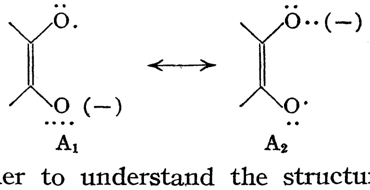


Fig. 1.—Change of magnetic susceptibility of potassium phenanthrenequinone-3-sulfonate during the reduction by glucose in an alkaline solution. The solution of the substance is contained in the upper compartment of the "double vessel" (or "compensation vessel"); the lower compartment is permanently filled with an agar gel. The ordinate is magnetic pull in terms of lines of deflection, measured always at an amperage close to 8.5 and recalculated for 10 amperes. One line of deflection corresponds to an increment of susceptibility 4.20×10^{-10} c. g. s. u. The solution is made up of 0.0407 g. of potassium phenanthrenequinone-3-sulfonate, 0.150 g. of glucose, and brought to a volume of 2.5 cc.: 1, for O—O by a solution made from 25 cc. of pyridine, 25 cc. of water and 1 cc. of 7.3 *N* NaOH; 2, for ×—× by a solution made from 50 cc. of water + 1 cc. of 7.3 *N* NaOH; 3, for ●—● by an aqueous solution of $Ca(OH)_2$, 0.047 *N*. At time "O" the reduction has started already. The intermediate color is: red-brown for O—O; brown for ×—×; green for ●—●.

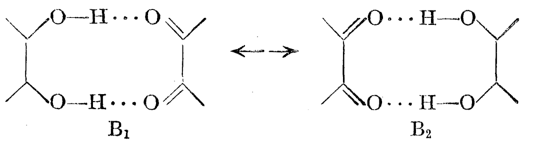
Discussion

The structure of the three molecular species, intermediate in oxidation between quinone and hydroquinone, may now be considered. It is easy to account for the structure of the free radical. It may be in analogy to the structure previously proposed for the semiquinone of duroquinone, symbolized by a structure resonating essentially between two equivalent "limiting structures," A_1 and A_2.



A_1 A_2

In order to understand the structure of the dimer one has to keep in mind the fact that the dimerization constant d/s^2, where d is the concentration of the dimer and s that of the free radical, was found (2) to be $= 2 \times 10^6$ at *p*H 4.6, but as low as 70 at *p*H 12. Such a high dependence on *p*H is compatible only with the assumption that the dimer does not consist of two negatively charged semiquinone ions as represented by the structure A_1, A_2, but that it consists of two uncharged molecules of the free radical with protons attached. So the dimer may be symbolized as B_1 in resonance with B_2. This formula is analogous to the one suggested for the diamagnetic benzoquinhydrone as it exists in the solid state, and to a minute extent also in solution[6] probably with the difference that for this ortho-quinoid compound both moieties lie in one plane, *i. e.*, the dimer is coplanar, whereas there was reason to assume that for the para-quinonoid compounds such as benzoquinhydrone in the dissolved state, the two rings lie stacked upon each other. The bond that holds together the two moieties may be classified among the "dimeric resonance bonds."[8] This resonance differs from most other cases of resonance in so far as it represents the only force holding together the two moieties, whereas usually resonance only increases the stability of a molecule which may be imagined to form a molecular unit even without that resonance.


B_1 B_2

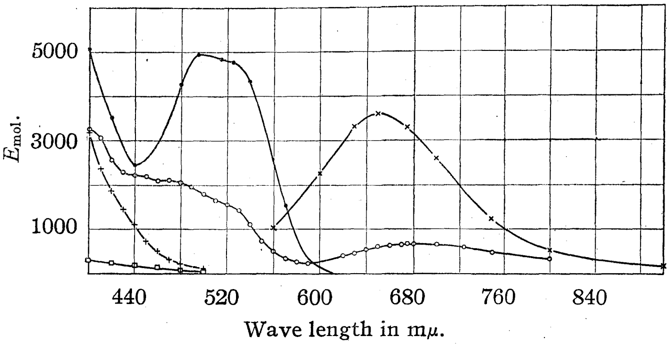
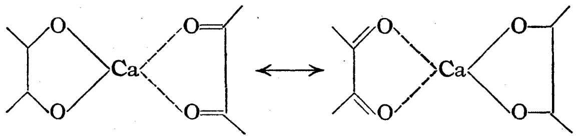


Fig. 2.—The ordinate is molar absorption coefficient, $1/(cd)$ log (I_0/I), where I_0 is light transmitted through blank, I that transmitted by the solution; c is concentration in gram moles per liter; d is light path through the absorption cell in centimeters. All solutions are 0.073 N in sodium hydroxide and 1.048×10^{-4} molar in potassium phenanthrene-quinone-3-sulfonate, unless otherwise stated. O—O Solution of the quinone itself in 50% pyridine in a 1-cm. absorption cell; x—x, same, after complete reduction by glucose to the hydroquinone; +, the free semiquinone radical. (The two maxima at 490 and at 525 mμ are distinctly visible also in the hand spectroscope.) This curve has been obtained as follows. The alkaline solution of the dye in 50% pyridine was completely reduced by $Na_2S_2O_4$, slightly reoxidized by air, transferred to the absorption cell and sealed with mineral oil to keep the level of oxidation constant for a sufficiently long time. Readings of optical density at various wave lengths were taken. These values were translated into molar absorption coefficients as follows. The alkaline solution of the quinone plus some glucose was transferred to the absorption cell and the optical density for one particular wave length was watched while the reduction proceeded. After a certain time the optical density passes through a maximum. It is known from previous potentiometric measurements that *in maximo* 64% of the dye exists in the form of the free radical. This is true for any solution of pH > 11. These data are sufficient to convert the optical densities observed into molar absorption coefficients. There may be an error of 10% or even 20% with respect to the absolute values, but there is no appreciable error in the relative values. Since the hydroquinone, at least at the left hand of this curve, also absorbs somewhat, the curve has been slightly corrected by subtracting the absorption due to the hydroquinone which at 50% reduction of the quinone was supposed to be present to the extent of 18% of the total dye. × is the diamagnetic dimer of the radical, or the "quinhydrone." The solvent contains no pyridine. A 0.0193 M solution of the dye in 0.05 M sodium hydroxide is prepared. This concentration of the dye in the alkaline, aqueous solution is high enough to have the intermediate form to a very large extent in the dimeric form. The absorption cell had a diameter of 0.00578 cm. as described previously.[7] In principle the curve was obtained in the same way as for +, so no corrections for the presence of some free radical and of the quinone and the hydroquinone were applied. The absolute values may be considered as reliable only as to the order of magnitude, the relative values somewhat better, but no accuracy is claimed. Nevertheless, it is obvious that the absorption is much more diffuse than that of the free radical. The essential result is that the difference between two forms, the free radical and its dimeric "quinhydrone," is substantiated also spectrophotometrically. × is the green calcium complex of the radical, measured in a 1-cm. cell: 1 cc. of 2.47×10^{-3} M stock solution of the dye in 0.05 N NaOH + 9 cc. of 0.05 N NaOH + 0.4 cc. of saturated solution of $Ca(OH)_2$. The curve is obtained in the same way as in +. (Since a slight cloud of colorless precipitate appears, a corresponding solution in the completely oxidized, practically colorless state, was chosen as a blank for the readings. The dye was completely reduced with $Na_2S_2O_4$, and during the reoxidation by air the maximum point of absorption at any one wave length was watched.) It is assumed that *in maximo* practically all of the dye exists as the calcium quinhydrone. This may involve an error perhaps up to 20% or even more in the absolute values, but no essential error as to the relative values of the extinction coefficients.

For the calcium complex we may imagine the two H atoms replaced by Ca:


C_1 C_2

The fact that a structure can hardly be imagined otherwise than in coplanar configuration is in favor of the coplanarity, also of the calcium-free

---

[6] L. Michaelis and S. Granick, THIS JOURNAL, **66**, 1023 (1944).

[7] L. Michaelis and S. Granick, *ibid.*, **67**, 1212 (1945).

[8] L. Michaelis and S. Granick, *ibid.*, **65**, 1747 (1943).

dimer. It may be mentioned that a comparable effect of calcium was not observed with quinone, duroquinone, or 1,4-or 1,2-naphthoquinone.

The fact that organic solvents prevent the dimerization, at least in the absence of calcium, is not easy to explain. This effect is quite analogous to the effect of organic solvents on the dimerization of regular (quinonoid, not semiquinone) dyestuffs, such as methylene blue, recognizable by spectrophotometric methods. Here also alcohol prevents dimerization. In alcohol such dyestuffs obey Beer's law: in water they do not because there is an equilibrium established between the monomer and the dimer, depending on concentration and temperature. Furthermore, it may be added that according to preliminary experiments the dimerization of the free radicals of the "Wurster's dye" type, obtained by partial oxidation of aromatic *para*-diamines, is counteracted also by alcohol to a certain extent.

Summary

The semiquinone radical of phenanthrene-quinone-3-sulfonate is paramagnetic. In aqueous solution it is in equilibrium with its quinhydrone-like, diamagnetic dimer. The dimerization is prevented by pyridine or alcohol. In presence of calcium ion the radical forms a diamagnetic calcium complex of green color.

NEW YORK, N. Y. RECEIVED MAY 15, 1947

[CONTRIBUTION FROM THE AMERICAN CYANAMID COMPANY, STAMFORD RESEARCH LABORATORIES]

The Dipole Moments of Diazines

BY WILLIAM C. SCHNEIDER

During the course of an investigation of the dipole moments of some thiouracil derivatives,[1] it was deemed desirable to determine the dipole moments of some simpler pyrimidine derivatives and other similar heterocyclic nitrogen compounds in order to obtain a value for the carbon–nitrogen bond moment in this type of molecule which could be used in calculating the electric moments of the more complex thiouracils. Although these thiouracil derivatives later proved to be too complicated for a detailed analysis, the simpler heterocyclic compounds were found to be of sufficient interest in themselves to warrant discussion.

Experimental

The apparatus and measuring technique will be described in another article.[1] Dioxane used as solvent was purified as follows: Commercial dioxane was partially frozen, and the liquid portion discarded. The remaining solid after remelting was refluxed over sodium to remove water and finally distilled through an efficient fractionating column to remove any remaining impurities. The best dioxane obtained in this manner had the following properties: b. p. (uncor.), 100.5°, $d^{35}{}_4$ 1.01690, ϵ_{35} 2.1874, n^{35} 1.4150.

TABLE I

Compound	M. p., °C.
Pyridazine[a]	......
Pyrimidine[a]	18–20
Pyrazine[b]	52–53
4-Oxypyrimidine[b]	163–164
2,5-Dichloropyrimidine[c]	57–57.5
2-Mercapto-5-chloropyrimidine[c]	221–222
2-Methoxy-5-chloropyrimidine[c]	53–54

[a] Furnished by Dr. R. C. Lord, The Johns Hopkins University. [b] Furnished by Dr. I. F. Halverstadt, these Laboratories. [c] Furnished by Dr. J. P. English, these Laboratories.

The compounds investigated are listed in Table I. Table II gives the experimental values of ϵ, dielectric constant, d density and w, weight fraction for dioxane solutions at 35°. Dipole moments were calculated by a modified Hedestrand method similar to that introduced by Halverstadt and Kumler,[2] differing in that densities were used rather than specific volumes. The empirical equation used may be written as

$$ {}_{\infty}p_{\mathrm{T}} = \frac{\epsilon_0 - 1}{\epsilon_0 + 2} \times \frac{1}{d_0}\left[1 - \beta/d_0\right] + \frac{3\alpha}{(\epsilon_0 + 2)^2 d_0} \qquad (3) $$

where ϵ_0 = extrapolated dielectric constant of solvent
d_0 = extrapolated density of solvent
${}_{\infty}p_{\mathrm{T}}$ = specific polarization at infinite dilution
α = slope of dielectric constant *vs.* weight fraction curve
β = slope of density *vs.* weight fraction curve.

The total molar polarization at infinite dilution, ${}_{\infty}P_{\mathrm{T}}$, is obtained from the specific polarization by multiplying by the molecular weight. Atomic polarization was neglected, and molecular refractions were calculated from the atomic refractions listed in the "Landolt–Börnstein Tabellen." The values obtained from these calculations are listed in Table III, where P_{D} and P_0 refer to the distortion and orientation polarizations, respectively.

Discussion

To determine whether or not the carbon–nitrogen linkage can be adequately represented by a single constant in heterocyclic ring systems, its moment was calculated from the observed moment of pyridine, 2.3*D*,[3] assuming a value of 0.4*D* for the carbon–hydrogen link and a plane hexagonal structure for the pyridine ring. A value of 1.9*D*

---

(1) Paper to be published shortly.

(2) Halverstadt and Kumler, THIS JOURNAL, **64**, 2988 (1942).

(3) Goethals, *Rec. trav. chim.*, **54**, 299 (1935).

TABLE II

w	ε	d	w	ε	d
	Pyridazine			Pyrimidine	
0.0	(2.2090)[a]	(1.01491)	0.0	2.2134	(1.01689)
.0009217	2.2348	1.01496	.0001612	2.2149	1.01691
.001915	2.2499	.....	.0003038	2.2164	1.10694
.002854	2.2819	1.01506	.0006735	2.2195	1.01699
.003656	2.2908	.....			
	Pyrazine (benzene)			2,5-Dichloropyrimidine	
0.0	2.2525	(0.86283)	0.0	2.2016	(1.01612)
.0007764	2.2529	.86304	.001232	2.2059	1.01649
.001540	2.2533	.86320	.002387	2.2134	1.01691
.001945	2.2528	.86335	.003834	2.2190	1.01728
.002823	2.2526	.86365	.005288	2.2248	1.01773
	Pyrazine (dioxine)			2-Mercapto-5-chloropyrimidine	
0.0	(2.1989)	1.01623	0.0	(2.2046)	.....
.0005494	2.1993	1.01630	.0001938	2.2047	.....
.0009504	2.1998	1.01638	.0003652	2.2051	.....
.001548	2.2005	1.01640	.0005124	2.2043	.....
.002069	2.2009	1.01646	.0006109	2.2040	.....
	4-Oxypyrimidine			2-Methoxy-5-chloropyrimidine	
0.0	2.2057	1.01530	0.0	(2.2040)	.....
.0004479	....	.....	.0004794	2.2045	.....
.0005520	2.2119	1.01547	.0007872	2.2036	.....
.001062	2.2152	1.01568	.0009427	2.2043	.....
.001294	2.2179	1.01566			

[a] Values in parentheses obtained by extrapolation.

TABLE III

Compound	α	β	$_\infty p_T$	Mol. wt.	$_\infty P_T$	P_D	P_0	$\mu \times 10^{18}$
Pyridazine	23.523	0.1149	4.1712	80	333.7	22.1	311.6	3.94
Pyrimidine	9.057	.1485	1.7469	80	139.8	22.3	117.5	2.42
Pyrazine (benzene)	0.0	.2650	0.2366	80	18.9	22.3	(−3.4)	(0)
Pyrazine (dioxane)	.9666	.1112	.4120	80	32.96	22.3	10.7	0.66
4-Oxypyrimidine	9.505	.2937	1.788	95	169.9	23.5	146.4	2.70
2,5-Dichloropyrimidine	4.4062	.3082	0.9330	149	138.9	35.7	103.2	2.27
2-Mercapto-5-chloropyrimidine	0.0	....	....	...	....	..		(0.0)
2-Methoxy-5-chloropyrimidine	.0	....	....	...	....	..		(0.0)

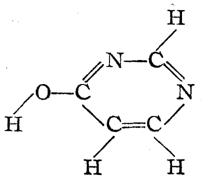
was obtained. Using this value, the dipole moments of pyridazine, pyrimidine and pyrazine were calculated, assuming again a plane hexagonal structure for the heterocyclic ring. Table IV lists these calculated values together with experimental values.

TABLE IV

Compound	$\mu_{\text{obs.}} \times 10^{18}$	$\mu_{\text{calcd.}} \times 10^{18}$
Pyridine (benzene)	2.3	...
Pyridazine (dioxane)	3.9	4.0
Pyrimidine (dioxane)	2.4	2.3
Pyrizine (dioxane)	0.6	0.0
(benzene)	.0	.0
Quinoline (benzene)	2.2	2.3

These data allow three important conclusions to be drawn: (1) the carbon–nitrogen electric moment apparently has a constant value in these heterocyclic compounds; (2) a heterocyclic ring of the pyridine type can be represented by a plane, regular hexagon; and (3) in the compounds investigated, all bonds between nitrogen and carbon seem to be electrically[4] equivalent.

To obtain an additional check upon the carbon–nitrogen bond moment obtained above, the dipole moment of 4-oxypyrimidine was calculated and compared with the experimental value. This compound may be represented as



where the hydrogen–oxygen linkage exhibits free rotation about the carbon–oxygen axis. Since the resultant moment of the ring acts at an angle to the direction of the carbon–oxygen moment, it is necessary to take into consideration the free ro-

---

(4) So far as dipolar characteristics are concerned.

tation of the hydrogen–oxygen linkage when calculating a moment for the molecule.

At any given instant the vector diagram for the resultant moment, μ, of the molecule may be represented by Fig. 1. Fuchs[5] has developed an expression for calculating the average value, $\bar{\mu}$, of the resultant moment which in the present case may be written as

$$\bar{\mu}^2 = \mu_1^2 + \mu_2^2 + 2\mu_1\mu_2 \cos \varphi \cos \theta \qquad (2)$$

Using equation (2) and the following assumptions: (1) $\mu_{H-O} = 1.7D$, (2) $\mu_{C-O} = 0.7D$, (3) $\mu_{C-N} = 1.9D$ and (4) an oxygen valency angle of 110°, the dipole moment of 4-oxypyrimidine is calculated to be $2.6D$, which gives satisfactory agreement with the experimental value, $2.7D$.

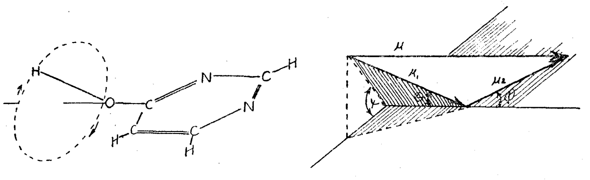


Fig. 1.—Vector representation of the resultant moment of a molecule which has a freely rotating group.

Several additional pyrimidine derivatives were investigated, yielding rather interesting results. Table V lists these compounds and their moments, together with the corresponding benzene derivatives. Presumably, the moment of 2,5-dichloropyrimidine is identical with the moment of the pyrimidine ring. The observed moment of pyrimidine, $2.4D$, supports this assumption. Since the moment of 2-methoxy-5-chloropyrimidine can be considered as the resultant of the ring moment and the moment of p-chloroanisole, and since these last two moments are essentially identical, the observed zero moment forces one to the conclusion that the resultant of the carbon–chlorine and methyl–oxygen moment exactly opposes the moment of the ring. A similar argument can be used to account for the moment of 2-mercapto-5-chloropyrimidine.

TABLE V

Compound	$\mu \times 10^{18}$
2,5-Dichloropyrimidine	2.27
2-Mercapto-5-chloropyrimidine	(0.0)
2-Methoxy-5-chloropyrimidine	(.0)
p-Dichlorobenzene	0.0[a]
p-Chlorophenol	2.22[a]
p-Chloroanisole	2.24[a]

[a] Values taken from *Annual Tables of Constants and Numerical Data*, "Dielectric Constants and Dipole Moments," Vol. 11 Sect. 22 (1931–1934), Hermann and Co., Paris, 1937.

Unless resonance effects in all of the above compounds are identical or the agreement merely fortuitous, the two opposing moments must lie on the same straight line since neither pyrimidine derivative possesses a center of symmetry. The vector representation for the resultant moment of the carbon–chlorine and hydrogen–sulfur–carbon groups is given in Fig. 2. Initially, the hydrogen–sulfur bond is assumed to be in the plane of the paper; the dotted vectors indicate the situation after rotation through 180°. Since the resultant moment always intersects the axis of rotation at the constant angle φ regardless of the position of the freely rotating hydrogen–sulfur vector, it cannot exactly cancel the ring moment unless the valence angle is 180° for then φ will be zero.

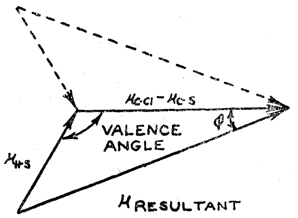
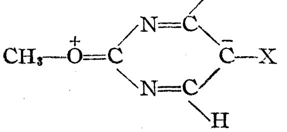
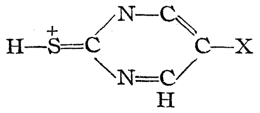


Fig. 2.—Vector representation of the resultant moment of a freely rotating group.

However, in any real molecule the distortion of the valency angle is probably much less than that predicted above for exact cancellation. In para substituted anisoles Bergmann and collaborators in Germany[6] and Hampson and Sutton in England[7] concluded that the oxygen valency angle is greater than 110°, the latter authors reporting a value of 142 ± 8°.[8] Opposing this point of view Bennett[9] concludes that induced moments in the molecule could introduce errors in the method used by the above investigators, and that it is more logical to assume a constant valency angle of 110° and calculate induced moments rather than assume constant bond moments and calculate deviations in the valency angle.

The data are perhaps best interpreted by assuming that an unknown but significant distortion in the valence angle combined with resonance effects causes the hydrogen–oxygen, hydrogen–sulfur or methyl–oxygen link moments to contribute as though they were acting at 180° to the para substituted ring moment. Resonance effects would tend to spread the valence angle slightly and reduce the link moment between the aromatic carbon and oxygen or sulfur atoms due to resonance structures of the type





Using this assumption satisfactory agreement can be obtained between calculated and observed

---

[5] Fuchs, *Z. physik. Chem.*, **14B**, 339 (1931).

[6] Bergmann, Engel and Sandor, *ibid.*, **10B**, 397 (1930).

[7] Hampson and Sutton, *Proc. Roy. Soc.* (*London*), **140A**, 552 (1933).

[8] Hampson, Farmer and Sutton, *ibid.*, **143A**, 147 (1933).

[9] Bennett, *Trans. Faraday Soc.*, 853–858 (1934).

moments for all of the above mentioned compounds and for most of the para substituted anisoles whose moment values are in the literature. Table VI lists observed and calculated moments for several compounds of the type discussed above; Table VII gives the values used for the various bond moments.

The dipole moment of 4-methoxypyridine gives further evidence in support of an abnormal valency angle of oxygen in para substituted derivatives and a constant value of the carbon–nitrogen linkage. Curran and Leis[10] found this compound to have a moment of 2.94D in benzene solution. The calculated value obtained using the above assumptions is 3.0D.

It must be emphasized that the speculations concerning the valency angle of oxygen and the carbon–oxygen link moment are valid only in the case of *para* substituted derivatives. This fact is immediately obvious if one considers anisole where the observed moment is identical for all practical purposes with that of diethyl ether, thereby requiring a normal carbon–oxygen link moment and an oxygen valency angle of 110°. This viewpoint is further substantiated if one considers the meta substituted isomers. Table VIII compares observed and calculated values for various meta substituted derivatives. The calculated values were obtained by use of equation (2) assuming an oxygen valency angle of 110°, and a carbon–oxygen link moment of 0.7D and the link moments listed in Table VII. Here again, the agreement is satisfactory considering that the observed values were obtained from solution measurements by different workers.

TABLE VI

Compound	$\mu_{\text{obs.}}$ × 10^{18}	$\mu_{\text{calcd.}}$ × 10^{18}
2,5-Dichloropyrimidine	2.27	2.3
2-Mercapto-5-chloropyrimidine	0	0
2-Methoxy-5-chloropyrimidine	0	0
p-Chloroanisole	2.24[a]	2.3
p-Bromoanisole	2.25	2.2
p-Iodoanisole	2.12	2.0
p-Fluoroanisole	2.09	2.1
p-Nitroanisole	4.76	4.6
p-Chlorophenol	2.40	2.9
p-Bromophenol	2.6	2.8
p-Nitrophenol	5.03	5.2
p-Nitrodiphenyl ether	4.3	4.6
p-Nitrosophenol	4.72	4.5

[a] All observed values not obtained in this investigation were taken from the Appendix in the *Trans. Faraday Soc.*, "Discussion of Dipole Moments" (1934).

TABLE VII

$\mu_{C-N} = 1.9D$ $\mu_{C-Cl} = 1.2D$ $\mu_{C-F} = 1.0D$

$\mu_{H-C} = 0.4D$ $\mu_{C-NO_2} = 3.5D$ $\mu_{C-I} = 0.9D$

$\mu_{H-O} = 1.7D$ $\mu_{C-Br} = 1.1D$ $\mu_{H-S} = 1.3D$

TABLE VIII

Compound	$\mu_{\text{obs.}}$ × 10^{18}	$\mu_{\text{calcd.}}$ × 10^{18}
m-Chlorophenol	2.14[a]	2.1
m-Nitrophenol	3.90	4.0
m-Nitroanisole	3.86	3.7

[a] See footnote Table VI.

Acknowledgment.—The author wishes to express here his indebtedness to Doctors I. F. Halverstadt and P. H. Bell for many helpful discussions and to the American Cyanamid Company for permission to publish these results.

Summary

1. The dipole moments in dioxane solution at 35° have been determined for the following compounds: pyridazine (3.94), pyrimidine (2.42), pyrazine (0.6), 2,5-dichloropyrimidine (2.27), 2-mercapto-5-chloropyrimidine (0), 2-methoxy-5-chloropyrimidine (0) and 4-oxypyrimidine (2.70).

2. The diazine rings may be represented as plane, regular hexagons.

3. In pyridine and the diazines the carbon–nitrogen linkage has a bond moment of 1.9D compared to 0.5D in aliphatic compounds.

4. The observed fact that 2-methoxy-5-chloropyrimidine and 2-mercapto-5-chloropyrimidine have zero electric moments is best interpreted by assuming that an unknown distortion in the valence angle combined with resonance effects reduces the link moment between the aromatic carbon and oxygen or sulfur atoms and causes the CH_3–O and H–S link moments to contribute as though they were acting at an angle of 180° to the para substituted ring moment.

5. An analogous situation is assumed to exist in several para substituted phenols and anisoles.

STAMFORD, CONN. RECEIVED MAY 6, 1947

---

[10] Curran and Leis, THIS JOURNAL, **67**, 79–81 (1945).

[CONTRIBUTION FROM THE UNIVERSITY OF CHICAGO TOXICITY LABORATORY]

The Volatility and Vapor Pressure of Eight 2-Chloroethyl Alkyl (or Cycloalkyl) Sulfides[1]

BY C. ERNST REDEMANN,[2] SAUL W. CHAIKIN AND RALPH B. FEARING[3]

In conjunction with other studies in progress in this Laboratory it was necessary to determine the volatility[4] and vapor pressure of several 2-chloroethyl alkyl (or cycloalkyl) sulfides over the temperature range 0 to 60°. One of these compounds, bis-(2-chloroethyl) sulfide,[5] has been studied before, but other observations had indicated that there might be some considerable error in these data and that a re-evaluation of its volatility was desirable.

The static method of measuring the vapor pressure was unsatisfactory, since for some of these compounds the vapor pressure is only a few thousandths of a millimeter of mercury at 20° and its value needed to be known with considerable accuracy. Of the several dynamic methods the one known as the transpiration method, first described by Regnault[6] but frequently referred to as the method of Walker,[7] was chosen as most suitable. The direct measurement of volatility given by the Regnault procedure was especially desirable for the problem in hand. The apparatus used in these studies was patterned after that of Bent and Francel[8] and will not be described in this report except where important differences are present.

Experimental

Dried tank nitrogen was used as the entrainment gas for all compounds since it avoids possible oxidation of sensitive compounds and is less soluble in most organic compounds than is the oxygen of the air. Six sizes of bottles were used to meter this dry nitrogen before it was passed through the saturator. These bottles were of 1, 2.5, 4, 9, 20 and 50 liters capacity and their volume was determined to closer than ±0.1% by weighing the bottles empty and then filled with distilled water at a known temperature, from which the corrected volume of the bottle was computed.

The spiral condensation traps were cooled by a mixture of solid carbon dioxide and acetone rather than by liquid air as used by Bent and co-workers,[8] since computation indicated that even for a volatile liquid like water under equilibrium conditions at the temperature of solid carbon dioxide the amount of water vapor escaping uncondensed from the trap was far less than the error in weighing the trap when 100–200 mg. of water had been collected. A second cold trap was used in over-night runs, which might finish before the return of the operator, to avoid diffusion of moisture from the atmosphere back into the trap to be weighed.

The 20, 40 and 60° thermostats were of a conventional type with the necessary precautions observed for careful temperature regulation. The temperature was maintained constant to ±0.008° as measured at different points in the bath with a Beckmann thermometer over an extended interval of time. The 0° thermostat was a 1-gallon silvered Pyrex Dewar flask filled with crushed ice and distilled water. In some runs a small electrically driven stirrer was added to this bath, but since it was found to add nothing to the constancy of the temperature it was omitted in later runs.

Vaporizer.—The vaporizer shown in Fig. 1 was patterned after the one described by Bent.[8] It was modified to give more rapid saturation with less liquid[9] by using a coarse sintered glass disk at (A) and indentations at (B). For successful operation the inner spiral should be made from tubing having a bore of 3.5 to 4.0 mm. Both larger and smaller bore tubing are less satisfactory. The vaporizer required 6 to 8 ml. of compound for proper operation. When the vaporizer had been freshly filled with a compound, dry nitrogen was bubbled through the liquid for some hours to remove traces of moisture which may have been picked up during the filling operation. This also served to remove traces of lower boiling impurities in certain cases.

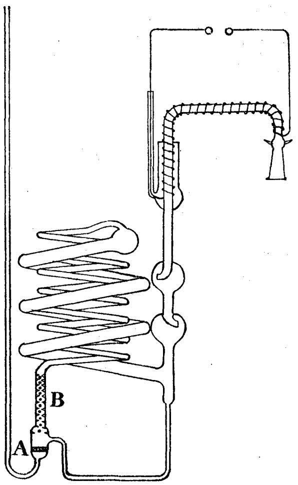


Fig. 1.—Vaporizer.

Presaturator.—In some runs it was considered desirable to approach saturation from both sides. The presaturator shown in Fig. 2 was used to accomplish this. It was connected to the inlet of a regular vaporizer just above the thermostated bath by means of a ground glass joint lightly lubricated on the outer 10 mm. of ground surface. The temperature of the presaturator was maintained about 20° higher than the thermostat bath surrounding the regular vaporizer by applying the proper voltage to the ends of the electrically heated coil by means of a variable transformer.

Results were the same when equilibrium was approached from both sides only if the rate of gas flow was sufficiently low when approaching equilibrium from the unsaturated side. This required rates of flow as low as 0.5 to 1.5 liters/hr. for those compounds which reached equilibrium most slowly. In general the compounds of low viscosity produced more rapid saturation of the nitrogen stream than was produced by the more viscous liquids.

Flow Regulator.—The needle valve used by Bent[8] to regulate the rate of flow of water from the reservoir into the metering bottle, displacing the contained nitrogen,

---

[1] This work was carried out under contract with the National Defense Research Committee of the Office of Scientific Research and Development.

[2] Present address: 770 S. Arroyo Parkway, Pasadena 2, California.

[3] Present address: 622 N. East Ave., Oak Park, Illinois.

[4] Volatility is defined as the mass of the volatile substance per unit volume of air (or nitrogen) saturated with the substance. In this report the unit of volatility is milligrams per liter.

[5] (a) Lamb, Carleton, Hughes and Nichols, THIS JOURNAL, **42**, 79 (1920); (b) Herbst, *Kolloidchem. Beih.*, **23**, 313 (1926); (c) Mumford, Phillips and Ball, *J. Chem. Soc.*, 589 (1932); (d) Jackson, *Chem. Rev.*, **15**, 425 (1934); (e) Holst and Melander, *Svensk Kem. Tid.*, **55**, 131 (1943).

[6] Regnault, *Ann. chim. phys.*, [3] **15**, 129 (1845).

[7] Walker, *Z. physik. Chem.*, **2**, 602 (1888).

[8] Bent and Francel, THIS JOURNAL, **70**, 634 (1948).

[9] A saturator requiring only a very small amount of liquid was necessary since for certain of the compounds studied only very small samples were submitted.

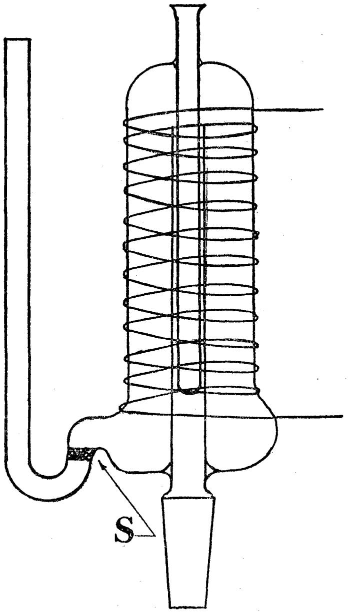


Fig. 2.—Presaturator: S, sintered glass disk.

was advantageously replaced by a calibrated flow regulator of the form shown in Fig. 3. The by-pass on the side of the regulator was opened when the water was forced back into the reservoir from the metering bottle. A series of these regulators was prepared having flow rates varying from 0.8 l./hr. to 6.0 l./hr. It was customary to use a different flow rate for each determination at a given temperature. If the results with different rates of flow checked, equilibrium was assumed to have been established; if the higher rate of flow gave a lower volatility than the slower rate of flow, it was assumed that the higher flow rate was too great and that saturation had not been secured. Only rates of flow slow enough to give concordant results were used.

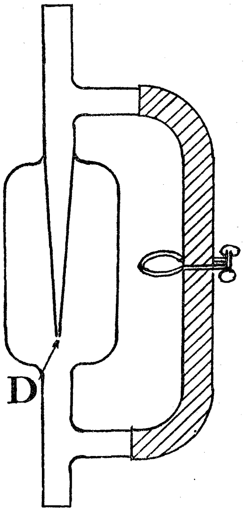


Fig. 3.—Flow regulator: D, diameter 0.5 to 0.1 mm.

Purification of Compounds.—As indicated in Table I all compounds studied were prepared in laboratories other than that of the authors. Samples were generally furnished in a purified form. Nevertheless, each sample was carefully fractionally distilled under reduced pressure from all-glass apparatus just prior to use. A fraction having an essentially constant boiling point was used for these measurements. The boiling range, refractive index and density of the fraction used are recorded in Table I. The refractive index of the material in the vaporizer was checked at the completion of a series of runs, in some cases, to make certain that no change in composition had occurred during the determination. Two samples of bis-(2-chloroethyl) sulfide, one made by the Levinstein[10] and one by the thiodiglycol[11] process, were each purified highly and run separately, thus giving an indication of the reproducibility of the method and the purity of the samples.

Treatment of Results

In the interest of economy of space the experimental points are not given, three to twelve measurements having been made at each temperature for each compound. Values agreeing within 1 to 3%, the lower limit for moderately volatile compounds and the upper limit for compounds of very low volatility, were used. The study of 2-chloroethyl 2-chlorocyclohexyl sulfide was made with somewhat less precision, but is included here for completeness. Exceptionally large values at the beginning of a run, due to traces of more volatile impurities, and points of obvious experimental error were discarded. Measurements were made for each compound at 20, 40 and 60° wherever possible, in some cases at 0, 20 and 40°, and in a few instances at 40 and 60° only because of the very low vapor pressure of the compound. The arithmetic mean of all points at any given temperature was taken for each compound. A smoothed curve was fitted to these mean points by the method of least squares.

The Clausius–Clapeyron equation was used in deriving appropriate relationships between the several variables since it was believed that over the small temperature range 0 to 60° these assumptions were justified: (1) the molal latent heat of vaporization remains essentially constant, (2) the vapor at these low partial pressures obeys the laws of ideal gases and (3) the volume of unit mass of the liquid phase is negligible in comparison with the volume of the same mass of the vapor at these temperatures and pressures. These assumptions allow the three equations used to be related quantitatively.

$$W = \frac{wT_1(p_2 - p)}{vT_2p_1} \qquad (1)$$

W = volatility expressed in mg./liter of nitrogen (or air) saturated with the compound.
w = increase in the weight of the trap in mg.
v = corrected volume, in liters, of the bottle metering out the dry nitrogen
T_1 = initial temperature of the gas in the metering bottle °K.
T_2 = temperature of the thermostat bath, °K.
p = vapor pressure of liquid under study, found by successive approximations, mm.
p_1 = barometric pressure when the bottle was closed after filling with dry nitrogen and equalizing to atmospheric pressure, mm.
p_2 = mean barometric pressure during the determination of mm.

$$\log p = A - B/T \qquad (2)$$

$$\log WT = A' - B/T \qquad (3)$$

in which $A' = A + \log M + 1.20520$. A, A', and B are constants and M is the molecular weight of the compound under study. In equations (2) and (3) pressure was expressed in mm., and temperature in ° K.

In Table II are shown the mean and the maxi-

---

[10] M. Sartori, "The War Gases," 1st English ed., J. and A. Churchill, Ltd., London, 1939, p. 223.

[11] *Ibid.*, p. 220.

TABLE I

CONSTANTS OF THE 2-CHLOROETHYL ALKYL SULFIDES USED

Alkyl group	Formula	Boiling point °C.	Mm.	Refractive index n_D	°C.	Density G./cc.	°C.	Constants for equations A	A'	B
Methyl[a]	$ClC_2H_4SCH_3$	138.0–138.7	744			1.1155[e]	20	8.28937	11.53837	2215.7
Ethyl[a]	$ClC_2H_4SC_2H_5$	71–72	40	1.4878	20	1.0664[g]	20	8.29455	11.59502	2318.8
2-Chloroethyl[b] (Levinstein)	$(ClC_2H_4)_2S$	105, M. p. 14.2–14.4	14	1.5220[d]	30	1.2684[d]	25	9.31448	12.72119	3061.5
2-Chloroethyl[c] (Thiodiglycol)	$(ClC_2H_4)_2S$	110 M. p. 14.4	20	1.5220[d]	30	1.2681[d]	25	9.31768	12.72439	3062.5
Allyl[a]	$ClC_2H_4SCH_2CH{=}CH_2$	66–67[h]	14	1.5071	20	1.0761[h]	20	8.88346	12.22408	2619.9
Benzyl[a,f]	$ClC_2H_4SCH_2C_6H_5$	145	13	1.571	20	1.1477[g]	25	7.37666	10.85044	2733.4
2-Chlorocyclopentyl[a]	$ClC_2H_4SC_5H_8Cl$	125–127	10	1.5322	25	1.2370	25	9.72886	13.23306	3444.6
2-Chlorocyclohexyl[a]	$ClC_2H_4SC_6H_{10}Cl$	139–143	7	1.5369	25	1.2168	20	8.7460	12.28018	3265.5
Bis-(2-chloroethyl) trisulfide[a,i]	$(ClC_2H_4)_2S_3$	M. p. 28–29		1.6050	30	1.3940	30	9.23029	12.78410	3565.7

[a] Supplied by Dr. R. C. Fuson. [b] Supplied by Edgewood Arsenal. [c] Supplied by Dr. R. Norris Shreve. [d] According to Mumford's equations (ref. 5c) the refractive index at 30° is 1.5226 and at 25° the density is 1.2693. [e] Kirner (THIS JOURNAL, **50**, 2446 (1928)) gives d^{20}_{20} 1.1245. [f] This compound behaved as if it were undergoing decomposition during the determination. Results may not be closer than ±10% for this compound. However, Kilmer and du Vigneaud (*J. Biol. Chem.*, **154**, 247 (1944)) report the b. p. as 105–108° (1.5 mm.). The value calculated from our equation is 106.6° (1.5 mm.). [g] Dawson (THIS JOURNAL, **55**, 2070 (1933)) gives d^{25}_4 1.0663 for the ethyl derivative and d^{25}_4 1.1479 for the benzyl compound. [h] Sherlin and Vasilevksii (*J. prakt. Chem.*, **121** 173 (1929)) report the boiling point as 67.5–69° (12 mm.) and the density as d^{20}_{20} 1.0768. [i] R. C. Fuson, *et al.*, *J. Org. Chem.*, **11**, 484–498 (1946).

mum percentage deviation from the smoothed curve of the experimental points. For all the compounds except the 2-chlorocyclohexyl 2-chloroethyl sulfide the mean deviation is less than 2%. The mean and the maximum deviation are also included for the points calculated, using the least squares equation, from the smoothed curve values. The small percentage deviations of these points indicates that the equation describes the curve accurately over the temperature range studied.

TABLE II

PRECISION OF DATA

Alkyl group	Percentage deviation from the smoothed curve of Experimental points Mean	Maximum	Points calculated from least squares equation Mean	Maximum
Methyl	0.5	1.1	0.2	0.3
Ethyl	0.9	1.5	.02	.05
2-Chloroethyl	1.5	3.8	.3	.7
Allyl	0.6	0.9	.2	.4
Benzyl	1.8	2.2	.1	.3
2-Chlorocyclopentyl	1.9	2.9	.1	.2
2-Chlorocyclohexyl	3.5	6.1	1	.3
Bis-(2-chloroethyl) trisulfide	1.5	2.7	3	.8

A consideration of the known sources of error involved in these determinations would indicate a probable error of ±1 to 2%, depending upon the size of the sample collected in the weighing trap. However, since several of the systemic errors tend to cause low results, it is almost certain that the results herein reported will tend to be low, if in error.

The two samples of bis-(2-chloroethyl) sulfide, prepared by different methods, gave vapor pressure determinations which were in excellent agreement as shown by a percentage deviation from the mean of only 0.5% at both ends of the temperature range, and since the sign of the deviation was the same at both limits, the curves were parallel. This speaks well for the reproducibility of the method. Balson, Denbigh and Adams[12] have recently reported their study of the vapor pressure of bis-(2-chloroethyl) sulfide made concurrently with our study. Their results over the temperature range common to both studies are in quite good agreement with our own.

The equations reported are supposed to apply quite precisely between 0 and 60°, but they may be used over a much larger temperature range if somewhat larger errors can be permitted. It must also be borne in mind that these equations are for the liquid phase only.

Acknowledgment.—The authors gratefully acknowledge the kind assistance given by Professor H. E. Bent of the University of Missouri in permitting one of us (C. E. R.) to use his equipment and to become familiar with his technique prior to constructing our apparatus. Thanks are due Miss Drusilla Van Hoesen and Mr. Joseph Savit for their assistance in making some of the determinations.

Summary

1. The volatility of eight 2-chloroethyl alkyl (or cycloalkyl) sulfides has been measured between 0 and 60° by a transpiration method.

2. Vapor pressures have been calculated from the volatility measurements, and using these values logarithmic equations have been calculated for both the volatility and the vapor pressure of these compounds.

3. The mean molar latent heat of evaporation has been calculated from the derived vapor pressure equation for each compound.

4. The probable error of these determinations over the temperature range 0 to 60° is estimated to be ±1 to 2%. The equations may be used for extrapolating to temperatures outside these limits with somewhat larger errors.

CHICAGO, ILLINOIS RECEIVED APRIL 10, 1947

---

(12) Balson, Denbigh and Adams, *Trans. Farad. Soc.*, **43**, 42 (1947).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

The Vapor Pressure of "Mustard Gas" (β,β'-Dichloroethylsulfide), Diphenyl Ether and their Mixtures

BY H. E. BENT AND R. J. FRANCEL[1]

In 1940 when this work was begun, vapor pressure data on mustard gas showed poor agreement and data on solutions of mustard were almost lacking. Our object was to develop a physical method of measurement which would be suitable for not only mustard but also other compounds of similar characteristics. We attempted to keep each individual experimental error below 0.1%.[2]

The following corrections have not been applied. The true vapor pressure is less than that under one atmosphere pressure of air by about 0.5%. No correction has been applied for the solubility of air in mustard, which probably introduces an error of 0.1%. No correction has been made for deviations from the gas laws which may introduce an additional error of 0.1% to 0.2%.

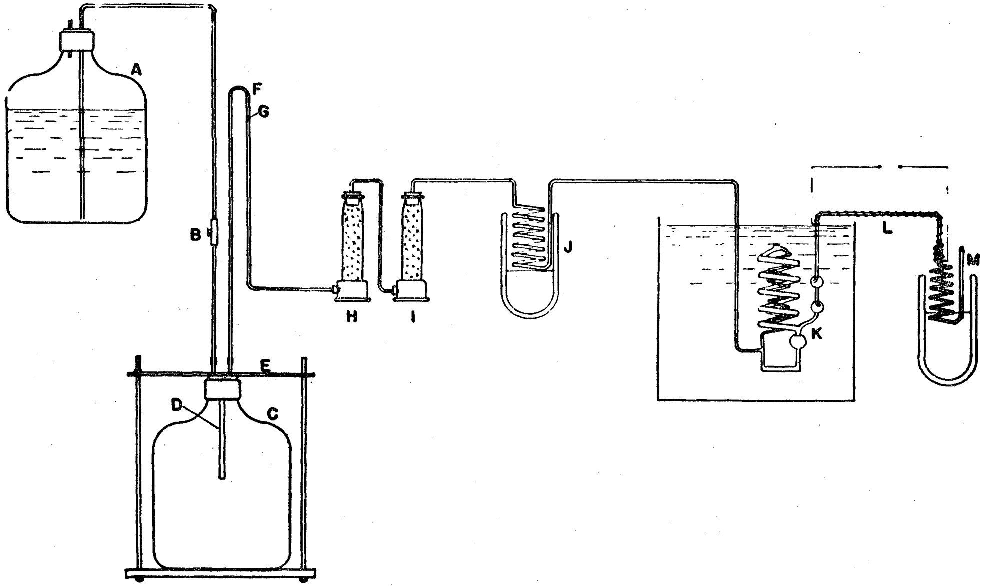


Fig. 1

The dynamic method is well known and perhaps needs little description aside from the information given in Fig. 1. Water in A displaces dry air in C which is in turn again dried by calcium chloride in H, phosphorus pentoxide in I and liquid air in J. The saturator at K is a spiral which exposes a continually fresh surface of liquid since the air stream circulates a small amount of liquid through the apparatus as shown in more detail in Fig. 2. Great care was taken to avoid the formation of spray in this saturator and to avoid fog in the collector at M. Each part of the apparatus was carefully checked and then the apparatus as a whole checked, first by carrying out runs with different rates of flow and second by measuring the vapor pressure of water. The accepted value at 30° is 31.842. We obtained as a result of ten runs 31.79 ± 0.05 mm.

Purity of Compounds.—Mustard was prepared by treating a 15-ml. portion of Union Carbide and Carbon "Kromfax" solvent (β,β'-dihydroxyethylsulfide) with excess of concentrated hydrochloric acid at 60° for thirty minutes. The mustard forms as a water insoluble layer thus

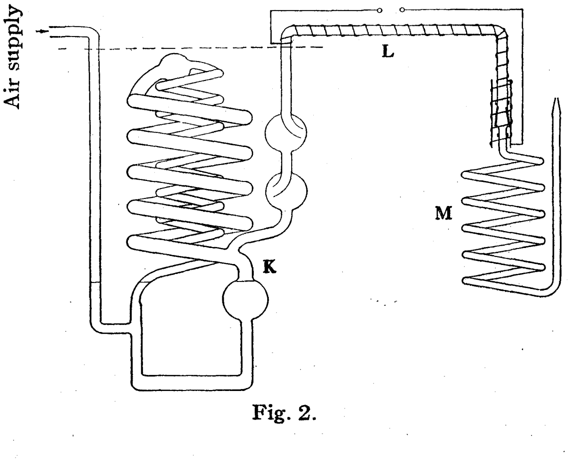


Fig. 2.

---

[1] This paper is condensed from a thesis submitted in partial fulfillment of the requirements for the Master's degree.

[2] For a detailed discussion of experimental errors the reader is referred to the original thesis of R. J. Francel, University of Missouri library.

separating it from water soluble impurities possibly present in the original material. No impurities insoluble in water were present in the "Kromfax" solvent. After allowing the reaction mixture to cool, the mustard was separated by decantation and then washed several times with small amounts of distilled water. Since the reaction is slow at 60° with hydrochloric acid, one may infer that at room temperature several rapid washings will not hydrolyze the mustard. The liquid was then distilled under reduced pressure at from 85 to 100° out of contact with rubber. Five fractions were collected, all of which agreed in refractive index to less than 0.0001, but only the middle three fractions were used. Substitution of nitrogen for air in the runs gave no indication of oxidation of mustard.

Diphenyl ether, Eastman Kodak Co. White Label, was distilled under reduced pressure at 95–110°. The two end fractions were discarded.

Solutions of diphenyl ether and mustard were prepared volumetrically and analyzed by determining the refractive index. A refractive index curve (unpublished) prepared by C. A. Krinbill was used. We are also indebted to C. A. Krinbill for assistance during the construction of the apparatus and testing of various designs.

The refractive index for the mustard we found to be 1.5227 at 30° which may be compared with the value calculated from the equation of Mumford, Phillips and Ball[3] of 1.5226. The error in the composition of the solution due to 0.0001 in the refractive index is 0.002 in the mole fraction.

Calculation of Results

Vapor Pressure.—The vapor pressure is obtained with the aid of the expression

$$p = \frac{RT_W}{M} \div \left[V \times \frac{T_2}{T_1} \times \frac{P_1}{P_2 - p}\right]$$

in which V is the volume of bottle C, the next term takes care of the difference in temperature between the bottle and the thermostat and the last takes care of the difference in pressure when the bottle was closed and during a run. "p" is a small correction factor, the vapor pressure of the liquid being studied, obtained by successive approximations.

Values of the vapor pressure are given in Table I and are represented graphically in Figs. 3 and 4. The equations for these curves are for mustard

$$\log_{10} p = 9.4819 - \frac{3117.2}{(t + 273.1)}$$

and for diphenyl ether

$$\log_{10} p = 9.5842 - \frac{3351.9}{(t + 273.1)}$$

which give with the aid of the Clapeyron equation 14,300 ± 50 calories for the heat of vaporization of mustard and 15,300 ± 500 calories for the heat of vaporization of diphenyl ether.

A comparison of our results, Table I, with previous investigators shows poor agreement with Mumford, *et al.*,[3] better agreement with Vedder[4] and still better agreement with the recently published work of Balson and co-workers.[5] The results of Holst and Melander[6] are approximately 100% higher than ours and are not included in the table.

TABLE I

THE VAPOR PRESSURE OF MUSTARD AND DIPHENYL ETHER

The observed values are averages of from three to eight determinations.

Mustard

Temp., °C.	Vedder	Mumford, *et al.*	Balson, *et al.*	This work Obs.	This work Calcd. from equation
15	0.0417	0.075			0.0459
20	.0650	.115	0.072		.0702
30	.1500	.225	.162	0.1575 ± 3	.1576
40		.45	.351	.3363 ± 3	.3358
50		.83	.716	.6822 ± 11	.6826
			Diphenyl Ether		
40				0.0751 ± 1	0.0756
50				.1647 ± 7	.1622
60				.3298 ± 3	.3322

Raoult's law may be expressed as

$$p_1 = p_1^0 N_1$$

Deviations from Raoult's law may be expressed by either of two expressions, one involving the mole fraction and the other involving the volume fraction. Hildebrand[7] has shown the latter is to be preferred when the molecular volumes of the two components differ appreciably. We may write this expression as

$$RT \ln p_1/p_1^0 N_1 = \beta v_1 V_2^2$$

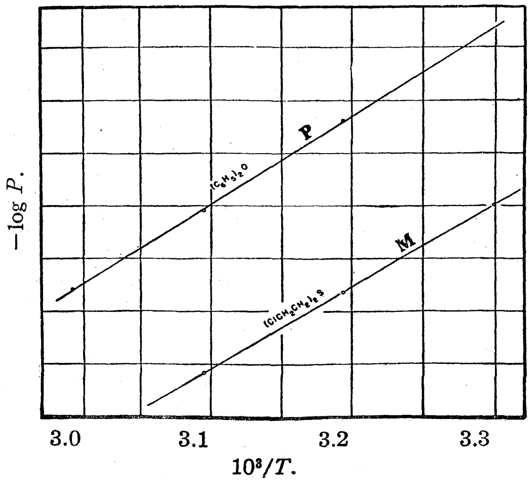


Fig. 3.—P, $(C_6H_5)_2O$; M, $(ClCH_2CH_2)_2S$.

---

[3] Mumford, Phillips and Ball, *J. Chem. Soc.*, 589 (1932).

[4] Vedder, "Medical Aspects of Chemical Warfare," Williams and Wilkins Co., Baltimore, Md., 1925, p. 127.

[5] Balson, Denbigh and Adam, *Trans. Farad. Soc.*, **43**, 42 (1947).

[6] Holst and Melander, *Chem. Abs.*, **40**, 2706 (1946).

[7] Hildebrand, "Solubility," Reinhold Publishing Corp., New York, N. Y.

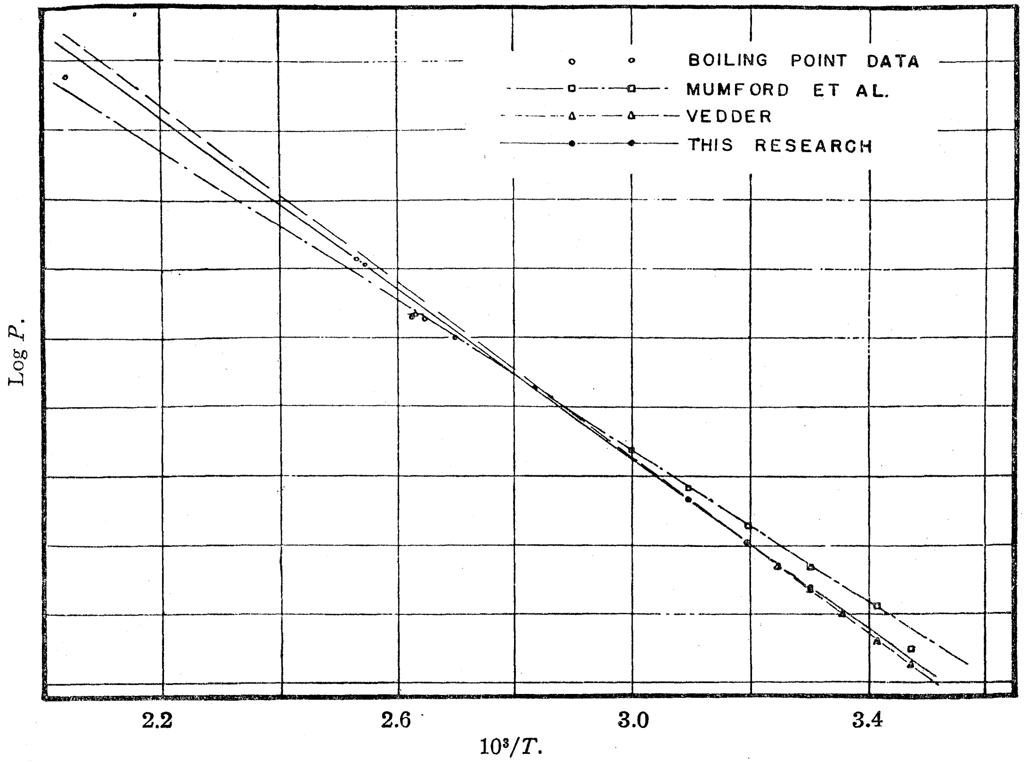


Fig. 4.

and the corresponding equation for the other component with subscripts interchanged. v_1 is the molar volume of the first component and V_2 the volume fraction of the second component. The molar volumes of the pure liquids were obtained using the equation of Wilkinson and Wernlund[8] for the density of mustard and that of Zhuravlev[9] for the density of diphenyl ether. For mustard gas $d = 1.2790 - 1.058 \times 10^{-3} (t - 15)$ and for diphenyl ether $d = 1.0880 - 8.6 \times 10^{-4}\, t$.

The values obtained for β at a mole fraction of 0.658 are 1.87 at 30°, 1.85 at 40°, 1.83 at 50° and, with a mole fraction of mustard of 0.330, 1.76 at 50°. This lack of constancy of β is not as significant as it might at first appear, as it determines the deviation from Raoult's law and not the part of the volatility to be expected from this law and is not much greater than our experimental error, as can be seen from Table II in which calculated volatilities are compared with the experimental values. In this table an average value of 1.83 is used.

Table II

Comparison of Calculated Values of the Volatility of Solutions of Mustard and Diphenyl Ether with Experimental Values. Volatility is Expressed as Mg./Liter

Temp., °C.	Mole fraction	Calcd. volatility with β = 1.83 Mustard	Ether	Total	Experimental
30	0.658	0.927	0.123	1.050	1.051 ± 2
40	.658	1.910	.268	2.178	2.179 ± 3
50	.658	3.756	.555	4.311	4.316 ± 8
50	.330	2.149	.952	3.101	5.083 ± 3

One objection to using volume fractions instead of mole fractions in calculating deviations from Raoult's law is the added labor in carrying out the calculations. This means having values for the densities of the liquids at various temperatures. In order to eliminate this labor for any one wishing to use our results we have given values for the activity coefficient in Table III.

Table III

Activity Coefficients of Mustard Gas[a]

Values of γ in the equation $p/p^0 = \gamma N$ in which N is the mole fraction.

Mole fraction of mustard gas	30°	40°	50°
0.0	1.466	1.453	1.441
.2	1.306	1.298	1.290
.4	1.179	1.174	1.170
.6	1.084	1.082	1.080
.8	1.022	1.022	1.021

[a] For a more complete table of activity coefficients, order Document 2484 from American Documentation Institute, 1719 N Street, N. W., Washington 6, D. C., remitting $0.50 for microfilms or $0.50 for photoprints.

We may use our average value of β to calculate the heat of vaporization from the relation given by Hildebrand

$$\beta = \left[\left(\frac{E_1}{v_1}\right)^{1/2} - \left(\frac{E_2}{v_2}\right)^{1/2}\right]^2$$

---

(8) Wilkinson and Wernlund, This Journal, **42**, 1382–1385 (1920).

(9) Zhuravlev, *J. Phys. Chem.* (*U. S. S. R.*), **9**, 875–882 (1937).

Since our data are better for mustard, we will use this equation to calculate the heat of vaporization of diphenyl ether, giving 13,800 which may be compared with 15,300 ± 500 by the slope of the vapor pressure curve. The discrepancy is somewhat more than might be expected. However, there is an uncertainty of 500 cal. in the heat of vaporization of diphenyl ether, perhaps 100 in the heat for mustard and another hundred in the value for β and of course departures in the behavior of these liquids from the assumptions of Hildebrand in deriving the above equation. Perhaps the most obvious such deviation would be that of association of the mustard. Considering all of these factors perhaps the agreement is as good as can be expected. Finally we may use the value of E/v to place these compounds in Hildebrand's series of internal pressure, the value for mustard being 114.0 and for diphenyl ether 95.9. This places mustard between bromoform and bromine and diphenyl ether with aniline.

As an independent check we have the composition of the vapor as determined by Krinbill[10] using a refractometer. The agreement between the calculated composition using the data from this paper and the observed composition determined with the aid of the refractometer is within the experimental error.

TABLE IV

MOLE FRACTION OF MUSTARD IN LIQUID AND VAPOR AT 50°

Liquid	Vapor Calculated	Vapor Observed
0.658	0.877	0.884
.330	.706	.708

We wish to acknowledge indebtedness to our colleagues, particularly to Professor L. B. Thomas, who tested an early form of the apparatus.

Summary

1. The vapor pressure of mustard (β,β-dichloroethylsulfide) is given by the expression

$$\log_{10} p = 9.4819 - 3117.2/(t + 273.1)$$

and for diphenyl ether by the expression

$$\log_{10} p = 9.5842 - 3351.9/(t + 273.1)$$

Results on mustard agree closely with those of Vedder and with Balson, *et al.*, but not with those of Mumford, Phillips and Ball.

2. Mixtures of these two liquids show small positive deviations from Raoult's law which can be expressed by the equation

$$RT \ln \frac{p_1}{p_1^0 N_1} = 1.83 v_1 V_2^2$$

in which v_1 is the molal volume and V_2 is the volume fraction. A table of activity coefficients is given in order to eliminate the labor involved in using the above equation.

COLUMBIA, MISSOURI RECEIVED MAY 19, 1947

---

[10] Unpublished research.

[CONTRIBUTION FROM THE UNIVERSITY OF CHICAGO TOXICITY LABORATORY]

The Volatility and Vapor Pressure of Nine Organic Arsines[1]

BY C. ERNST REDEMANN,[2] SAUL W. CHAIKIN, RALPH B. FEARING[3] AND DORA BENEDICT[4]

As part of a systematic study of the properties of certain toxic compounds the volatility and vapor pressure were determined between 0 and 60° for a series of nine organic arsines. The vapor pressure has been measured for some of these arsines previously; however, these measurements were made at temperatures above 60° in most instances and for lower temperatures values were obtained by extrapolation. To reduce the uncertainty of these values over the desired temperature interval the volatility[5] was measured directly by an air (or nitrogen) saturation method devised by Regnault.[6] The vapor pressure was in turn computed from the volatility by the method outlined in an earlier report.[7]

Gibson and Johnson[8] published data on the vapor pressure of methyldichloroarsine, ethyldichloroarsine and *n*-propyldichloroarsine obtained by measuring the boiling point under various pressures. Baxter and co-workers[9] reported equations for the vapor pressure of phenyldichloroarsine and methyldichloroarsine determined by a procedure very similar to that used by the present authors. Lewis and Perkins[10] cite unpublished data of Baxter on the vapor pressure of 2-chlorovinyldichloroarsine (Lewisite). Boiling point and density measurements as well as vapor pressure are given by Sartori[11] for methyldichloroarsine

---

[1] This work was carried out under contract with the National Defense Research Committee of the Office of Scientific Research and Development.

[2] Present address: 770 S. Arroyo Parkway, Pasadena 2, Calif.

[3] Present address: 622 N. East Ave., Oak Park, Ill.

[4] Present address: 959 Matadero Road, Palo Alto, Calif.

[5] Volatility is expressed in milligrams per liter of air or nitrogen in this report.

[6] Regnault, *Ann. chim. phys.*, [3] **15**, 129 (1845).

[7] Redemann, Chaikin and Fearing, THIS JOURNAL, **70**, 631 (1948).

[8] Gibson and Johnson, *J. Chem. Soc.*, 2518 (1931).

[9] Baxter, Bezzenberger and Wilson, THIS JOURNAL, **42**, 1386 (1920).

[10] Lewis and Perkins, *Ind. Eng. Chem.*, **15**, 290 (1923).

[11] Sartori, "The War Gases," 1st English Ed., J. and A. Churchill Ltd., London, 1939, Chapt. XV.

TABLE I

CONSTANTS OF THE SUBSTITUTED ARSINES USED

Arsine	Formula	Boiling point °C.	Mm.	Refractive Index n_D	°C.	Density g./cc.	°C.	Constants for equations A	A'	B
Dichloromethyl[a]	CH_3AsCl_2	131.5[b]	745	1.5588	29	1.8358[c]	20	8.1981[d]	11.6097	2142.6[d]
Dichloroethyl[e]	$C_2H_5AsCl_2$	44	14			1.6808[f]	25	8.4497	11.8997	2331.1
Dibromoethyl[a]	$C_2H_5AsBr_2$	81.5–82.5	15	1.6405	26	2.400	22	8.49558	12.12207	2608.7
Dichloro-5-*n*-propyl[a]	$n\text{-}C_3H_7AsCl_2$	99	75	1.5297	28	1.5380	20	8.8516	12.3332	2572.0
Dibromo-*n*-amyl[a]	$n\text{-}C_5H_{11}AsBr_2$	124–125	14	1.5760	31.5	1.939	21	9.06147	12.75225	3132.7
Dichlorophenyl[g]	$C_6H_5AsCl_2$	141.5	30			1.6444	27	8.76036[d]	12.31371	3048.3[d]
Dichloro-(2-chlorovinyl)[g,h]	$ClCH{=}CHAsCl_2$	72–73	10	1.6068	25	1.8799[i]	25	9.1000[i]	12.6281	2786.6[i]
Bis-(2-chlorovinyl)-methyl[a]	$(ClCH{=}CH)_2AsCH_3$	91	12	1.5654	28	1.473	28	9.0918	12.6252	2908.5
Cyanoethyl-*n*-propyl[a]	$CNAs(C_2H_5)(C_3H_7)$	90	13	1.4850	23	1.1587	24	8.9078	12.3511	2850.3

[a] Submitted by Dr. C. S. Hamilton. [b] Seide and Gorski, *Ber.*, **62**, 2190 (1929), give the boiling point as 132–133° at atmospheric pressure. Zappi, *Anales soc. quim. Argentina*, **3**, 447 (1915), gives b. p. 132° (760 mm.). [c] Fries and West, ("Chemical Warfare," 1921, McGraw–Hill Book Co., New York), give d^{20} 1.838. [d] Baxter, Bezzenberger and Wilson (ref. 9) give 8.6944 and 2281.7 for dichloromethylarsine and 9.150 and 3164 for dichlorophenylarsine. [e] Submitted by Dr. M. S. Kharasch. [f] Gibson and Johnson (ref. 8) report the density as 1.6595 at 20°. [g] Supplied by Edgewood Arsenal. [h] This is for isomer I. (The method of preparation used gives almost pure isomer I. Careful distillation failed to reveal the presence of any isomer II.) [i] Baxter (see Lewis and Perkins, ref. 10) gave 9.123 and 2789.69, respectively, for these constants. Lewis and Perkins give d^{20} 1.888.

ethyldichloroarsine, 2-chlorovinyldichloroarsine and phenyldichloroarsine. The work reported in the present paper confirms certain of these values but disagrees with others.

Experimental

The apparatus employed in these determinations has been described in earlier reports.[7,12] Dry nitrogen was used as the entrainment gas to avoid any possible oxidation of the arsines. Measurements were made at 20, 40 and 60° for all compounds except dichloromethylarsine, where 0, 20 and 40° were necessary, and for dichlorophenylarsine, where 40 and 60° were used because of the very small volatility at lower temperatures. From three to eight measurements were made at each temperature and the arithmetic mean value was computed for each temperature from these points. Values of known error were discarded, as were high values sometimes obtained in the first measurements after filling the saturator. When there was any definite trend in a series of determinations it was repeated to ascertain whether the trend resulted from a change in composition of the material in the saturator or if it was fortuitous. In some cases the refractive index and the density before and after the run were compared to see if any change in composition had taken place during the run.

The arsines were all prepared in laboratories other than our own (see Table I). In most cases the samples were carefully purified before they were submitted to our laboratory. However, the samples were all fractionally distilled under reduced pressure from all-glass equipment prior to use. Only fractions having essentially a constant boiling point were used.[13] When a new compound was placed in the saturator dry nitrogen was passed through the apparatus to remove traces of more volatile impurities before starting a run. The observed values for the boiling point, refractive index and density of the samples used in the volatility measurements are recorded in Table I.

Discussion

An arithmetic mean of the acceptable points at each given temperature was taken. Curves of the form

$$\log p = A - B/T \qquad (1)$$

and

$$\log WT = A' - B/T \qquad (2)$$

were fitted by the method of least squares to the mean points for the several temperatures studied. The values for A, A' and B thus derived are recorded in Table I. These constants apply when the pressure, p, is in millimeters of mercury, the temperature, T, is in ° K. and the volatility, W, is in milligrams per liter of nitrogen (or air).

The mean and the maximum percentage deviation from the smoothed curve of the experimental points and of the points calculated from the least squares equation are recorded in Table II. The mean deviation for each of these compounds is less than 2%. The small values for the deviations of the mean points from the points calculated from the least squares equations indicate that these equations satisfactorily reproduce the experimentally determined points. An examination of the probable sources of error indicates that if the experimental points are in error the values are apt to be small rather than large.

TABLE II

PRECISION OF DATA

Arsine	Percentage deviation from smoothed curve of Experimental points Maximum	Mean	Points calculated from Least squares equation Maximum	Mean
Dichloromethyl	0.15	0.1	Identical	
Dichloroethyl	1.3	0.9	0.7	0.3
Dibromoethyl	2.5	0.8	0.4	0.2
Dichloro-*n*-propyl	1.6	1.1	0.6	0.4
Dibromo-*n*-amyl	7.5	1.9	2.8	1.7
Dichlorophenyl	2.3	1.6	0.9	0.6
Dichloro(2-chlorovinyl)	1.5	0.9	0.2	0.06
Bis(2-chlorovinyl)methyl	0.6	0.3	Identical	
Cyanoethyl-*n*-propyl	6.0	1.9	0.5	0.3

A brief comparison of vapor pressures at different temperatures as calculated from the equations of Baxter and co-workers[9] and from the present equations for two of the arsines is given in Table III. This comparison appears justified since the measurements were made in a similar manner over

---

[12] Bent and Francel, THIS JOURNAL, **70**, 634 (1948).

[13] Actually, some variation in boiling point was observed in some cases, probably due to the slight variations in pressure during the course of the distillation. A variation of 1° was tolerated in three cases, see Table I.

part of the same temperature interval by both authors.

TABLE III

COMPARATIVE DATA ON TWO SUBSTITUTED ARSINES

°C.	Pressure in millimeters Dichloromethylarsine Baxter	This Work	Dichlorophenylarsine Baxter	This Work
0	2.20	2.26	0.0037	0.0040
60	70.2	58.6	0.451	0.409
133[a]	1188	832	....	......
250[b]	.....	....	1259	855

[a] This is the value most frequently given in the literature as the boiling point at 760 mm. pressure for dichloromethylarsine. [b] This is an average value for the values quoted for the boiling point at 760 mm. of dichlorophenylarsine.

If we assume the two normal boiling points to be correct,[14] we then see that an error of about 10% is present in values calculated for the vapor pressure at temperatures considerably above the experimental range.

Summary

1. The volatility of nine substituted arsines has been measured between 0 and 60° by a transpiration method.

2. Vapor pressures have been calculated from the volatility measurements, and from these data logarithmic equations have been developed for both the volatility and the vapor pressure as a function of the temperature.

3. The mean molar latent heat of evaporation over the temperature range 0 to 60° has been computed from the vapor pressure equation for each compound.

4. The average precision of these measurements is better than ±2% over the specified temperature range. However, the equations may be used to extrapolate to other temperatures with somewhat less precision.

CHICAGO, ILLINOIS

RECEIVED JULY 19, 1947

[14] This seems unlikely since normal boiling points are quoted for dichlorophenylarsine ranging from 247 to 257°, with the value 250° appearing most frequently.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

The Electrolyte Effects in the Hydration of Isobutene[1,2]

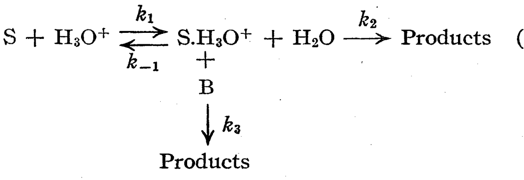
BY FRANK G. CIAPETTA[3] AND MARTIN KILPATRICK[4]

The problem of electrolyte effects of large magnitude in reactions involving an uncharged substrate and the hydrogen ion has been a subject of study in this Laboratory.[5,a,b,c,d] More recently Olson and Tong[6] have attempted to interpret these salt effects, and Sullivan and M. L. Kilpatrick,[7] and M. L. Kilpatrick[8] have advanced a different viewpoint which should be considered.

Whereas Leininger and Kilpatrick[5b] postulated the pre-equilibrium with k_2 the rate determining

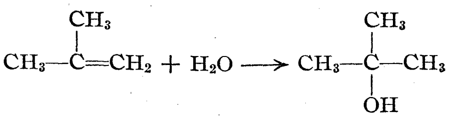
$$S + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \{S\cdot H_3O\}^+ \xrightarrow{k_2} \text{Products} \quad (1)$$

step, M. L. Kilpatrick[8] for the hydrolysis of cyanamide, where the cation is formed in appreciable concentration, found the rate determining step to be the reaction of the solvated cation with the base water (k_2), and if additional bases are present the rate is higher than that anticipated on the basis of a hydrogen ion catalysis. This is due to the concurrent reaction (k_3) of the base B with the solvated cation.



$$\begin{array}{c} S + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S.H_3O^+ + H_2O \xrightarrow{k_2} \text{Products} \\ + \\ B \\ \downarrow k_3 \\ \text{Products} \end{array} \quad (2)$$

The present investigation deals with the effect of electrolyte concentration on the rate of hydration of isobutene in aqueous solutions of strong acids and the weaker chloroacetic acids. The reaction in nitric acid solution has been shown to be



$$CH_3-\underset{}{\overset{\displaystyle CH_3}{\overset{|}{C}}}=CH_2 + H_2O \longrightarrow CH_3-\underset{\displaystyle OH}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_3 \quad (3)$$

first order with respect to isobutene and its rate proportional to the acid concentration at constant ionic strength,[9] and this conclusion has been verified by G. R. Lucas and Hammett.[10]

Lucas and Eberz followed the course of the reaction analytically but the dilatometric method

---

[1] Abstracted from the dissertation of Frank G. Ciapetta presented to the Faculty of the Graduate School of the University of Pennsylvania in partial fulfilment of the requirement for the degree of Doctor of Philosophy, April, 1947.

[2] Presented before the Division of Physical and Inorganic Chemistry at the 112th meeting of the American Chemical Society at New York, N. Y., September, 1947.

[3] E. I. du Pont de Nemours and Company Fellow, 1946–1947. Present address: The Atlantic Refining Company, Philadelphia, Pa.

[4] Present address: Department of Chemistry, Illinois Institute of Technology, Chicago 16, Illinois.

[5] (a) L. C. Riesch and M. Kilpatrick, *J. Phys. Chem.*, **39**, 561 (1935); (b) P. M. Leininger and M. Kilpatrick, THIS JOURNAL, **60**, 2891 (1938); (c) P. M. Leininger and M. Kilpatrick, *ibid.*, **60**, 2510 (1938); (d) M. Kilpatrick, "Handbuch der Katalyse," Vol. II, Julius Springer, Wien, 1940, p. 258.

[6] A. R. Olson and L. K. J. Tong, THIS JOURNAL, **66**, 1555 (1944).

[7] M. J. Sullivan and M. L. Kilpatrick, *ibid.*, **67**, 1815 (1945).

[8] M. L. Kilpatrick, *ibid.*, **69**, 40 (1947).

[9] H. J. Lucas and W. F. Eberz, *ibid.*, **56**, 460 (1934).

[10] G. R. Lucas and L. P. Hammett, *ibid.*, **64**, 1928 (1942).

was employed in the present investigation. The hydration of isobutene proceeds with a contraction in volume, but due to the low solubility of isobutene (*ca.* 0.005 mole per liter at 25°) the experimental volume change is so small that it was necessary to employ dilatometers of larger volume than usual to obtain the desired accuracy. In considering the design of the dilatometer, the problem of obtaining rapid thermal equilibrium with the constant temperature bath becomes important. It is also necessary to control the bath temperature within narrow limits.

Experimental Part

Apparatus.—One of the dilatometers is shown in Fig. 1 where F_1, F_2, F_3 and F_4 are four interconnecting cylinders each of approximately 80-ml. capacity giving a total reaction vessel volume of 465 ml. The reaction vessel is connected through stopcock A to the mixing chamber G with side arm C, and through stopcock B to a small mercury reservoir fitted with a steel plunger operating on a screw (not shown). A fritted glass disc H was sealed in the bottom of the reservoir through which the isobutene was introduced to saturate the water. The calibrated capillary of 2.28×10^{-3} sq. cm. cross section gave a maximum linear change during an experiment of 8–9 cm. corresponding to a volume change of 0.017–0.020 ml. The other dilatometer was of similar dimensions. The dilatometers were mounted on brass racks in well-stirred insulated water-baths whose temperature was controlled by large-capacity mercury–alcohol thermoregulators and F. G. 57 thyratron tubes.[11] Every effort was made to minimize temperature fluctuations in the bath by vigorous stirring, careful regulation of heating and cooling periods and clean mercury surfaces. The temperature was determined by means of a certified platinum resistance thermometer in conjunction with a Mueller bridge. Tests with the resistance thermometer showed only slight variations ($< \pm 0.001°$) with time and only negligible stratification throughout the bath when the room temperature was quite constant ($\pm 1°$) and not more than 2–3° below the bath temperature. The importance of temperature control is emphasized by the fact that a change of ± 0.001° corresponds to a difference in reading of 0.07–0.08 cm. on the capillary of the dilatometer. Investigation of the time necessary for the dilatometer to come to thermal equilibrium using water revealed that the half-time was 2.6 minutes.

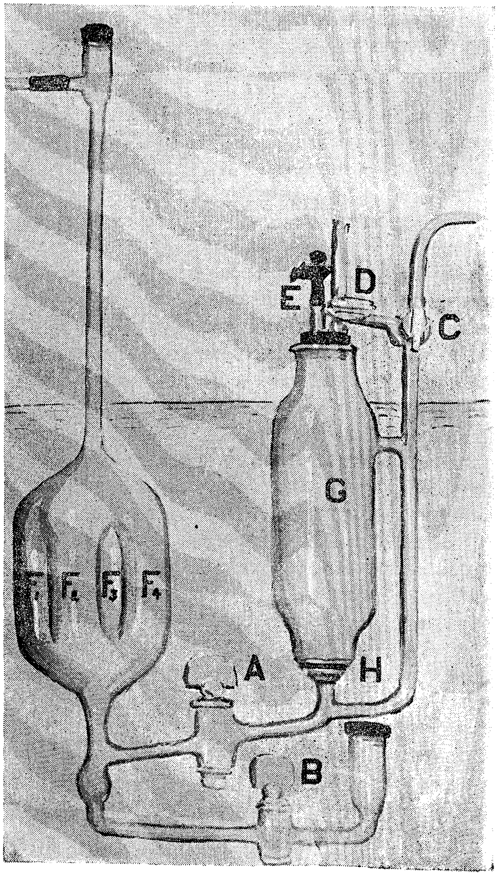


Fig. 1.—Dilatometer.

Determination of Rate.—The following procedure was adopted in the determination of the rate. With cocks D and B closed and tube E sealed off by means of a piece of rubber tubing with a screw clamp (Fig. 1), isobutene was introduced into the dilatometer through cocks C and A for fifteen minutes to purge the dilatometer of air. Cocks A and C were closed and 500 ml. of water placed in reservoir G. With cock D open, isobutene gas was introduced through cock C to the bottom of the reservoir where the gas was dispersed into small bubbles by the fritted disc before passing through the water. The isobutene was bubbled through the water for one and a half hours at a constant back pressure (*ca.* 5 cm.) of mercury. Cock C was closed and a 10-ml. pipet introduced below the surface of the solution through tube E and connected to it by a short piece of rubber tubing. By introducing isobutene gas through cock D a sample of the solution for the determination of the isobutene concentration could be obtained without loss of dissolved isobutene. The solution was stirred with a motor-driven glass stirrer for five minutes after which the required amount of acid was added and the stirring continued for five minutes longer. The solution was forced into the dilatometer by introducing isobutene through cock D (E closed) and opening cock A. Cock A was then sealed off with mercury using the procedure of Brönsted, Kilpatrick and Kilpatrick[12] and the readings started as soon as possible.

After the addition of the acid the time required to fill the dilatometer was approximately fifteen to twenty minutes. In experiments at temperatures of 30 and 35° the reaction mixture required ten to fifteen minutes after sealing in the dilatometer to come to thermal equilibrium. Hence no attempt was made to study reactions whose half-time was less than thirty to thirty-five minutes. No trouble was experienced from the formation of gas bubbles, except in the dichloroacetic acid–sodium dichloroacetate buffer experiment where the total electrolyte concentration was high. In this experiment small gas bubbles, probably isobutene, appeared during the filling of the dilatometer.

In all cases the progress of the reaction was followed by contraction of the solution as read from the graduated capillary of the dilatometer.

The observed velocity constants were evaluated by the method reported by Guggenheim.[13] In a few experiments the experimentally observed infinity reading was used for the second set of readings. In determining the best straight line through the experimental points observed values of ΔV which were less than one were not included since the errors due to temperature fluctuations were accentuated at these low values.

Isobutene.—Isobutene was prepared by the catalytic dehydration of tertiary butyl alcohol. Two different procedures were employed during the course of this investigation. In the first the alcohol was dehydrated over activated aluminum oxide pellets at a temperature of 370–

---

[11] A. W. Hull, *Gen. Elec. Rev.*, **32**, 213 (1929).

[12] J. N. Brönsted, M. L. Kilpatrick and M. Kilpatrick, This Journal, **51**, 428 (1929).

[13] E. A. Guggenheim, *Phil. Mag.*, 538 (1926).

380°.[14] The catalyst was supported in a vertical reaction tube (2.8 cm. i.d. and 86 cm. in length) heated in an automatically controlled aluminum-bronze block furnace.[15] The alcohol was delivered at a constant rate of 3 ml. per minute to the top of the reaction chamber by a Tropsch-Mattox bellows pump.[16] After leaving the reaction chamber the products were cooled by a water condenser and the isobutene bubbled through two wash bottles in series containing water to remove entrained alcohol vapors. The scrubbed gas then passed through a drying tube and condensed in a high-pressure cylinder (200-ml. capacity) cooled in a Dry Ice-acetone-bath. Two samples of isobutene prepared by this procedure were analyzed by a Consolidated Mass Spectrometer.[16a] Both samples were found to contain 99.9% isobutene and 0.1% isobutane. The second procedure employed was similar to that described by Spence and Hurd.[17] The alcohol was dehydrated by refluxing with oxalic acid and the isobutene purified and collected in the same manner as described above. Consistent results were obtained using isobutene prepared by either procedure.

Determination of Concentrations.—The isobutene concentration was determined by a modification of the method employed by Lucas and Eberz.[9] The acid concentration was determined at the completion of an experiment by titration with carbonate-free sodium hydroxide standardized against benzoic acid. No change was found in the acid concentration, within the experimental error (0.10%) in those runs where both the initial and final acid concentrations were determined.

Experimental Results

Order of the Reaction.—Since Lucas and Liu[18] found some falling off in the velocity constant in the hydration of trimethylethylene, careful experiments were carried out to demonstrate that the reaction is first order. As the data cannot be shown graphically on a small scale the data and calculations for a typical run at 25° are tabulated in Table I. Column 2 gives the first set of readings taken over a period approximately two and a half times the half-time. Readings taken two and four hours later are given in columns 3 and 4. When the logarithms of ΔV, the differences between the readings in columns 2 and 3 and 2 and 4, are plotted against the time given in column 1 the slope of the best straight lines through the points is $-0.4343\ k_{obs}$. In this particular experiment the lines were exactly parallel. Columns 5 and 6 give $\Delta V_{obs.} - \Delta V_{calcd.}$, the deviations of any point from the line.

TABLE I

HYDRATION OF ISOBUTENE IN PERCHLORIC ACID SOLUTION AT 25.00°

$HClO_4$, 0.3974*M*; Isobutene, 0.00483*M*; $k_{obs.} = 13.22 \times 10^{-3}$; $t_{1/2} = 52$ min.

1	2	3	4	5	6
	Dilatometer reading			$\Delta V_{obs.} - \Delta V_{calcd.}$ from columns	
Time, min.	at *t*	After 2 hr.	After 4 hr.	(2), (3)	(2), (4)
0	18.84	13.50	12.43	+0.11	+0.11
5	18.34	13.42	12.41	+ .03	+ .04
10	17.91	13.35	12.40	− .01	.00
15	17.53	13.27	12.38	− .02	.00
20	17.19	13.19	12.36	.00	.00
25	16.86	13.12	12.35	− .01	− .01
30	16.56	13.05	12.35	.00	− .02
35	16.27	13.00	12.33	− .01	− .01
40	16.00	12.94	12.31	− .02	− .02
45	15.77	12.89	12.30	.00	.00
50	15.53	12.84	12.29	.00	.00
55	15.33	12.80	12.28	.00	+ .01
60	15.13	12.75	12.27	+ .01	+ .01
65	14.93	12.71	12.26	.00	.00
70	14.76	12.69	12.25	.00	+ .01
75	14.59	12.65	12.25	.00	.00
80	14.44	12.62	12.24	.00	+ .01
85	14.28	12.58	12.24	.00	.00
90	14.14	12.56	12.23	− .01	.00
97	13.97	12.51	12.23	+ .01	− .01
100	13.89	12.48	12.22	+ .01	− .01
105	13.79	12.47	12.21	+ .01	+ .01
110	13.68	12.46	12.21	.00	.00
115	13.58	12.44	12.20	.00	.00
120	13.50	12.43	12.20	.00	+ .01

The data shown in Table I are for the same experiment, the only difference being the time interval between the two sets of readings. The second set of readings was taken immediately after the completion of the first set, while the third set of readings was taken after an additional interval of two hours. By this procedure the reaction was followed to 99% completion. In both cases the deviations of the observed values of ΔV from those calculated, with the exception of the first value, are well within the experimental error. Thus the reaction is strictly first order with respect to the isobutene concentration over the entire range.

Results with Strong Acids.—The hydration of isobutene was studied in the presence of perchloric, hydrochloric, and *p*-toluenesulfonic acid to determine the electrolyte effect of these acids. The results are summarized in Tables II, III and IV. Column 1 gives the molarity of the acid, column 2 the observed velocity constant (in minutes) and column 3 the second order constant, $k_{H_3O^+}$, obtained by dividing the observed velocity constant by the acid concentration.

It is to be noted that at 25° the second order constant consistently increases with increasing electrolyte concentration. The results at 30 and 35° are somewhat erratic but show the same general increase in the second-order constant with increasing electrolyte concentration. The erraticalness is due to the fact that the isobutene is less soluble at higher temperatures and the smaller volume change combined with the poorer constancy of temperature (±0.003° compared to ±0.001°) means less accurate experiments. The initial concentration of isobutene ranged from 0.0052 to 0.0047 molar at 25°, 0.0046 to 0.0039 at 30° and 0.0037 to 0.0032 at 35°.

---

(14) V. N. Ipatieff and B. B. Corson, *Ind. Eng. Chem.*, **27**, 1069 (1935).

(15) A. V. Grosse, J. C. Morrell and W. J. Mattox, *ibid.*, **32**, 530 (1940).

(16) H. Tropsch and W. J. Mattox, *ibid.*, **26**, 1338 (1934).

(16a) These analyses were obtained through the courtesy of The Atlantic Refining Company.

(17) L. U. Spence and C. D. Hurd, THIS JOURNAL, **51**, 3561 (1929).

(18) H. J. Lucas and Y. P. Liu, *ibid.*, **56**, 2138 (1934).

TABLE II

THE EFFECT OF PERCHLORIC ACID ON THE RATE OF HYDRATION OF ISOBUTENE

Molarity of $HClO_4$	$10^3\ k_{\text{obs.}}$	$10^2\ k_{\mathrm{H_3O^+}}$
	Temp., 25.00°	
0.0990	2.303	2.326
.1553	4.099	2.639
.2328	6.539[a]	2.809
.2784	8.566[b]	3.077
.3585	11.74	3.275
.3974	13.22	3.327
.4788	17.59	3.674
	Temp., 29.99°	
0.0563	2.671	4.748
.0757	3.730	4.927
.0771	3.638	4.717
.0969	4.513	4.657
.1221	5.802	4.752
.1283	6.631	5.168
.1520	7.552	4.968
.1739	8.658	4.977
.1810	9.671	5.343
.1987	9.855	4.960
.2019	10.22	5.062
.2174	10.87	5.000
.2390	13.17	5.511
.2420	13.17	5.442
.2799	15.93	5.691
	Temp., 35.00°	
0.0550	4.329	7.867
.0775	7.322	9.444
.0961	7.737	8.055
.1248	9.210[c]	7.380
.1463	13.54	9.255
.1957	19.02	9.719
.2009	23.07	11.48

[a] In presence of ultraviolet light. [b] Solution 0.1 *M* in *t*-butyl alcohol. [c] Solution 0.2 *M* in *t*-butyl alcohol.

Several experiments were carried out in perchloric acid solutions in the presence of *t*-butyl alcohol to determine the effect, if any, of the reaction product on the velocity constant. At 25° for a solution 0.1 molar in the alcohol the first and second order constants were consistent with those found in the absence of the alcohol. However, at 35° for a solution 0.2 molar in the alcohol, the values were lower than was expected for the acid concentration employed.

The effect of ultraviolet light on the reaction velocity was investigated at 25°; the results indicated that the radiation had no effect on the rate of the reaction.

TABLE III

THE EFFECT OF HYDROCHLORIC ACID ON THE RATE OF HYDRATION OF ISOBUTENE

Molarity of HCl	$10^3\ k_{\text{obs.}}$	$10^2\ k_{\mathrm{H_3O^+}}$
	Temp., 25.00°	
0.1044	2.556	2.450
.2078	5.664	2.726
.3090	9.394	3.041
.3505	11.01	3.141
.3932	13.17	3.349
.4895	17.59	3.593
	Temp., 29.99°	
0.0563	2.487	4.421
.0763	4.052	5.314
.1034	4.974	4.810
.1284	6.355	4.949
.1517	7.460	4.918
.1835	9.487	5.170
.2085	10.68	5.122
.2451	13.49	5.504
.2511	13.54	5.392
.2673	14.83	5.548
.2947	16.86	5.721
	Temp., 35.00°	
0.05416	4.651	8.588
.07622	6.401	8.399
.1002	9.118	9.100
.1284	11.61	9.042
.1538	14.41	9.372
.1886	18.70	9.915

TABLE IV

THE EFFECT OF *p*-TOLUENESULFONIC ACID ON THE RATE OF HYDRATION OF ISOBUTENE

Molarity of *p*-$CH_3C_6H_4SO_3H$	$10^3\ k_{\text{obs.}}$	$10^2\ k_{\mathrm{H_3O^+}}$
	Temp., 25.00°	
0.1062	2.533	2.385
.1857	4.743	2.554
.2517	6.631	2.635
.3193	8.842	2.769
3701	10.13	2.737
.4424	12.80	2.894
	Temp., 35.00°	
0.0544	4.743	8.727
.0794	6.401	8.058
.0959	8.289	8.640
.1127	9.993	8.867
.1593	14.18	8.901
.1907	17.41	9.130

In order to compare the magnitude of the electrolyte effects of the acids at 25° the second-order constants obtained at 30 and 35° were converted to 25° by means of the energy of activation for the reaction. The energy of activation was computed by the equation employing the average values of the second-order constants at zero electrolyte concentration, $k^0_{\mathrm{H_3O^+}}$, for 25 and 35°. The values of $k^0_{\mathrm{H_3O^+}}$ for perchloric, hydrochloric, *p*-toluenesulfonic and nitric[9] acids at 25°, hydrochloric, *p*-toluenesulfonic and nitric[9] acids at 35°, and the average values of $k^0_{\mathrm{H_3O^+}}$ at these temperatures are given in Table V.

$$E_{\mathrm{A}} = \frac{2.303RT_1T_2}{T_1 - T_2} \log \frac{k_{\mathrm{T_1}}}{k_{\mathrm{T_2}}} \qquad (4)$$

With the exception of the value for nitric acid at 35°, the values of $k^0_{\mathrm{H_3O^+}}$ were obtained by plot-

TABLE V

VALUES OF THE SECOND ORDER CONSTANT AT ZERO ELECTROLYTE CONCENTRATION

Acid	$10^2 k^0_{\mathrm{H_3O}}$ 25°C.	$10^2 k^0_{\mathrm{H_3O}}$ 35°C.
$HClO_4$	2.134	...
HCl	2.211	8.030
p-$CH_3C_6H_4SO_3H$	2.291	8.007
HNO_3	2.190	7.887
	Av. 2.207	7.975

ting the logarithm of the second order constant at a function of the acid concentration and taking the intercept at zero electrolyte concentration from the best straight line (as found by the method of averages) through the experimental points for each acid. The value of $k^0_{\mathrm{H_3O^+}}$ for nitric acid at 35° was calculated from the value of $k^0_{\mathrm{H_3O^+}}$ for this acid at 25° and the energy of activation found by Lucas and Eberz.[9] The energy of activation for the hydration of isobutene obtained from the data given in Table V is 23.46 kcal. per mole which is in agreement with the value 23.39 kcal. given by Lucas and Eberz.[9]

In Fig. 2 the logarithms of the second order constants obtained at 25° and those calculated to 25° by the above procedure for perchloric, hydrochloric and p-toluenesulfonic acids are shown plotted as a function of the acid concentration. Using the logarithm of the average value of $k^0_{\mathrm{H_3O^+}}$ at 25° given in Table V as the intercept at zero electrolyte concentration the best straight line was drawn through the data for each of the acids. Also shown in Fig. 2 are the data of Lucas and Eberz[9] for nitric acid at 25°. Figure 2 shows that the logarithm of the second order constant for the acids investigated increases linearly with acid concentration over the range of acid concentration investigated and thus obeys an equation of the type where C is the concentration of the acid in

$$\log k_{\mathrm{H_3O}} = \log k^0_{\mathrm{H_3O^+}} + BC \qquad (5)$$

moles per liter and B is a constant depending on the acid employed. The following equations express the electrolyte effect of the various acids studied.

$$\log k_{\mathrm{H_3O^+}} = \bar{2}.3433 + 0.47C_{\mathrm{HClO_4}} \qquad (6)$$

$$\log k_{\mathrm{H_3O^+}} = \bar{2}.3433 + 0.44C_{\mathrm{HCl}} \qquad (7)$$

$$\log k_{\mathrm{H_3O^+}} = \bar{2}.3433 + 0.30C_{p\text{-}\mathrm{CH_3C_6H_4SO_3H}} \qquad (8)$$

The electrolyte effect of nitric acid on the second order constant at 25° calculated from the data of Lucas and Eberz[9] is given by the equation

$$\log k_{\mathrm{H_3O^+}} = \bar{2}.3405 + 0.21C_{\mathrm{HNO_3}} \qquad (9)$$

The values of the B term show that these acids have a large electrolyte effect on the rate of the reaction. The effect decreases in the order $HClO_4$ > HCl > p-$CH_3C_6H_4SO_3H$ > HNO_3 which is different from that found by Lucas and Liu[18] for the hydration of trimethylethylene; their data indicate the order of decreasing electrolyte effect to be HCl > $HClO_4$ > HNO_3 > p-$CH_3C_6H_4SO_3H$. However, with the exception of nitric acid this order of electrolyte effect on the rate of hydration of trimethylethylene is based on one experiment for each of the acids at a concentration of 0.1 M.

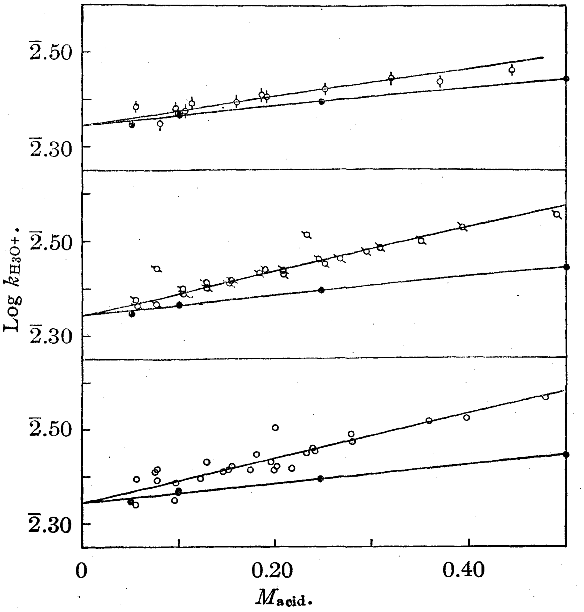


Fig. 2.—Hydration of isobutene: ○, $HClO_4$; ϕ, p-$CH_3C_6H_4SO_3H$; -○-, HCl; ●, HNO_3; temp. 25°.

Hantzsch and Weissberger[19] studied the effect of strong monobasic acids on the rate of inversion of sucrose at 25°. Their data for perchloric, hydrochloric, hydrobromic, benzenesulfonic and nitric acids are shown in Fig. 3, where the logarithms of the second-order velocity constants are plotted as a function of the acid concentration. Over the range of acid concentrations investigated the second-order constants increase linearly with acid concentration. The electrolyte effects of these acids on the second-order constants are given by the equations

$$\log k_{\mathrm{H_3O^+}} = \bar{3}.560 + 0.29C_{\mathrm{HClO_4}} \qquad (10)$$

$$\log k_{\mathrm{H_3O^+}} = \bar{3}.520 + 0.27C_{\mathrm{HBr}} \qquad (11)$$

$$\log k_{\mathrm{H_3O^+}} = \bar{3}.540 + 0.25C_{\mathrm{C_6H_5SO_3H}} \qquad (12)$$

$$\log k_{\mathrm{H_3O^+}} = \bar{3}.536 + 0.21C_{\mathrm{HCl}} \qquad (13)$$

$$\log k_{\mathrm{H_3O^+}} = \bar{3}.550 + 0.17C_{\mathrm{HNO_3}} \qquad (14)$$

The values of the B term for the various acids indicate that for the inversion of sucrose, as for the hydration of isobutene, perchloric acid has the largest electrolyte effect on the velocity constant and nitric acid the lowest. However, for perchloric and hydrochloric acids the magnitudes of the B term are much greater for the hydration of isobutene than for the inversion of sucrose.

Riesch and Kilpatrick[5a] also observed that the perchlorate ion had the largest electrolyte effect on the rate of hydrolysis of diethyl acetal at 0°. For this reaction the order of decreasing electrolyte effect for the anion of the sodium salts in-

---

[19] A. Hantzsch and A. Weissberger, *Z. physik. Chem.*, **125**, 251 (1927).

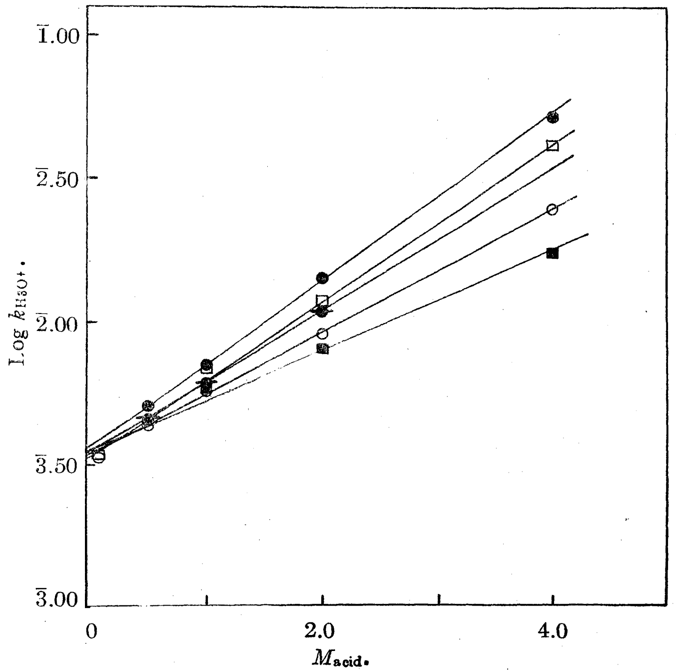


Fig. 3.—The inversion of sucrose at 25°: ●, $HClO_4$; -●-, $C_6H_5SO_3H$; ■, HNO_3; □, HBr; O, HCl.

vestigated was $ClO_4^- > Cl^- > NO_3^- > p\text{-}CH_3C_6H_4SO_3^- \eqsim C_6H_5SO_3^-$. The smaller electrolyte effect observed for the *p*-toluenesulfonate and benzenesulfonate ions than for the nitrate ion is not in agreement with the electrolyte effects of these ions on the rates of hydration of isobutene and the inversion of sucrose. The magnitudes of the *B* terms for sodium perchlorate and sodium chloride at a salt concentration of 0.5 *M* are similar to those found for perchloric and hydrochloric acids in the hydration of isobutene.

Results with chloro-substituted acetic acids.—In the hydrolysis of cyanamide[7] the observed velocity constant was in some cases found to be greater in solutions of trichloroacetic acid than in solutions of nitric acid of the same concentration. To compare the observed velocity constants for these two acids for the hydration of isobutene trichloroacetic acid was purified by recrystallization from benzene and hydration experiments carried out in the usual way. The reaction was first order and tests for chloride ion showed no decomposition of the acid during the reaction. The results are summarized in Table VI and the comparison of the observed velocity constants for the two acids presented graphically in Fig. 4. The data revealed that the observed velocity constants are higher for trichloroacetic acid below 0.4 *M* than for nitric acid, while the reverse is true at higher concentrations in spite of the fact that trichloroacetic acid is considered to be a weaker acid than nitric acid. The possibility that Scheme 2 is operative in the hydration of isobutene and we are not dealing with a specific hydrogen ion-catalyzed reaction was tested in the following way.

Dichloroacetic acid was purified by vacuum distillation and a middle fraction boiling from 95–96° (mainly at 95.5°) at 18 mm. mercury pressure was used to prepare a dichloroacetic acid–sodium dichloroacetate buffer solution with an acid to base ratio approximately unity. The observed velocity constant for the hydration was determined with a portion of this solution, and other portions of the original stock solution were diluted with water containing the required amount of sodium chloride to keep the ionic strength nearly constant and the velocity constant again determined. The last solution had approximately one fourth of the concentration of dichloroacetic acid and dichloroacetate of the first solution. The results are presented in Table VII.

The stoichiometric composition of the buffer solutions is given in columns 1 to 3, the observed velocity constant in column 4, the calculated hydrogen ion concentration based on a value of the dissociation constant of 7.05×10^{-2} calculated from the data of Harned and Hawkins[20] in column 5, and the value of the

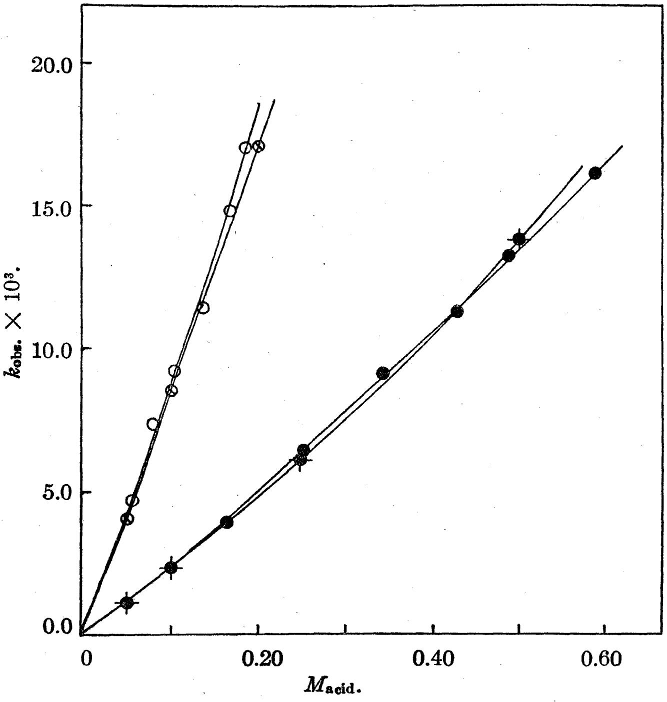


Fig. 4.—Hydration of isobutene at 25°: ●, CCl_3COOH: -●-, HNO_3 at 35°; O, CCl_3COOH; ⊘, HNO_3.

---

[20] H. S. Harned and J. E. Hawkins, This Journal, **50**, 85 (1928).

TABLE VI

EFFECT OF TRICHLOROACETIC ACID ON THE RATE OF HYDRATION OF ISOBUTENE

Molarity of CCl_3COOH	$10^3 k_{obs.}$	$10^2 k_{obs.}/M_{CCl_3COOH}$
	25.00°C.	
0.1637	3.914	2.391
.2523	6.447	2.555
.3432	9.118	2.657
.4275	11.28	2.639
.4881	13.22	2.709
5870	16.12	2.746
	35.00°C.	
0.0550	4.697	8.542
.07933	7.368	9.288
.1037	9.210	8.881
.1366	11.42	8.360
.1677	14.83	8.843
.1847	17.04	9.226

TABLE VII

HYDRATION OF ISOBUTENE IN DICHLOROACETATE BUFFER SOLUTIONS

Moles per liter Acid	Moles per liter Na salt	NaCl	$10^3 k_{obs.}$	$[H_3O^+]^a$	$10^2 k_{H_3O^+}$
0.5276	0.4623	....	2.533	0.0625	4.05
.3766	.3592	0.0862	2.349	.0547	4.30
.2506	.2395	.2114	2.187	.0491	4.45
.1285	.1126	.3732	1.681	.0405	4.15

[a] Calculated from $K_c = 7.05 \times 10^{-2}$.[20]

second order constant $k_{H_3O^+}$ obtained by dividing the observed velocity constant by the calculated hydrogen ion concentration in column 6. The first solution gave no test for chloride ion after the completion of the run so that there was no detectable decomposition of the acid or its anion. The constancy of $k_{H_3O^+}$ (last column) indicates there is no detectable effect of dichloroacetic acid or dichloroacetate on the velocity constant and one must conclude that the rate is proportional to the hydrogen ion concentration for these experiments.

A further test was carried out in monochloroacetic acid–monochloroacetate buffers at the same ionic strength and the results are reported in Table VIII. Here the hydrogen ion concentration remains constant as there is very little change in acid–base ratio on dilution. Unfortunately the chloroacetate ion loses chloride[21] and the contraction in volume is offset by an expansion due to this unavoidable side reaction. However, the half-times of the reaction in the two buffer solutions were approximately the same, indicating no difference in rate in spite of the fourfold difference in concentration of the buffer constituents, and scheme 2 does not appear to apply to this reaction.

TABLE VIII

HYDRATION OF ISOBUTENE IN MONOCHLOROACETATE BUFFER SOLUTIONS

Moles per liter Acid	Moles per liter Na salt	NaCl	$[H_3O^+]^a$	$(t_{1/2})_{obs.}$
0.5021	0.4979	....	0.00241	≅6 days
.1255	.1244	0.3750	.00250	≅6 days

[a] Calculated from $K_c = 2.51 \times 10^{-3}$.[22]

Discussion

If the reaction is an example of specific hydrogen ion catalysis with unusually large electrolyte effects it should be possible to calculate the dissociation constant of trichloroacetic and dichloroacetic acids and compare the results with values obtained by other methods. To make such a calculation a value for the electrolyte effect of the anion must be assumed. Since the observed velocity constants are in some cases lower for nitric acid the assumption that the primary kinetic electrolyte effect of trichloroacetate is equal to that of nitrate would lead to absurd answers. Hence, the assumption is made that the kinetic electrolyte effect of trichloroacetate is equal to that for perchlorate. If the electrolyte effect of the chloride ion were taken instead of perchlorate the calculated dissociation constant would be somewhat higher. The hydrogen ion concentration is determined by dividing the observed velocity constant for trichloroacetic acid by the second-order constant for the perchloric acid solution at the corresponding ionic strength, and the classical dissociation constant

$$K_c = [H_3O^+]^2/[CCl_3COOH] \qquad (15)$$

is computed and given in Table IX. Since these dissociation constants (column 5) are at different ionic strengths the activity coefficients are needed to obtain the thermodynamic dissociation constant, but as these are not known a fair approximation is to take those of acetic acid from the data of Harned and Hickey.[23] In other words, the K_c/K_a ratio for acetic acid is divided into the values of K_c in column 5 and the thermodynamic dissociation constant, K_a, obtained (column 6). The average value of K, 0.98, is in fair agreement with the value 1.2 reported by Ostwald[24] which was obtained from a value of the dissociation constant of dichloroacetic acid of 0.051 obtained from conductivity data and a determination of the ratio of the

TABLE IX

THE DISSOCIATION CONSTANT FOR TRICHLOROACETIC ACID AT 25°

Molarity CCl_3-COOH	$k_{obs.} \times 10^3$	$k_{H_3O^+} \times 10^2$	$[H_3O^+]$	Kc	Ka
0.1637	3.914	2.598	0.151	1.79	1.1
.2523	6.447	2.825	.228	2.15	1.2
.3432	9.118	3.048	.299	2.02	1.1
.4275	11.28	3.229	.349	1.55	0.8
.4881	13.22	3.369	.392	1.60	.9
.5870	16.12	3.577	.451	1.49	.8

---

[21] H. M. Dawson and E. R. Pycock, *J. Chem. Soc.*, 153 (1936).

[22] Saxton and Lange, THIS JOURNAL, **55**, 3638 (1933).

[23] H. S. Harned and F. C. Hickey, *ibid.*, **59**, 1284 (1937).

[24] W. Ostwald, *Z. physik. Chem.*, **3**, 369 (1889).

dissociation constant of tri- and di-chloroacetic acids by a comparison of the rates of inversion of sucrose for the two acids. A calculation neglecting the effect of ionic atmosphere on the mobilities of the ions using the conductance data of Ostwald[24] gives a value of the dissociation constant which is almost a power of ten lower after correction for activity coefficients. Hall[25] reports a value of 2×10^{-1} and Baughan[26] rightly claims there is no reliable value of the dissociation constant of trichloroacetic acid in water. The conductance data are not accurate enough to attempt a calculation using the procedure of Onsager.[27] A calculation of the dissociation constant from the data of Hantzsch and Weissberger[19] making the same assumptions as used in handling the kinetic data for the hydration of isobutene yields an average value of K_a, 0.478, which is not in agreement with the other kinetic data. A similar calculation using the data reported by Taylor[28] for the hydrolysis of ethyl acetate in trichloroacetic acid solutions with and without the addition of potassium trichloroacetate gives an average value 0.98 in agreement with that calculated from the kinetic data of the hydration of isobutene.

In Table X are given the calculated values of the dissociation constant for dichloroacetic acid based on the kinetic data of Table VII and calculated on the same assumptions used in obtaining the dissociation constant of trichloroacetic acid. The average value of $K_a = 0.043$ is higher than the value 0.0332 reported by Harned and Hawkins[20] from kinetic measurements on the rate of hydrolysis of ethyl acetate, but lower than the value 0.0514 reported by Ostwald[24] from conductance data. A recalculation of part of the conductance data taking into account the change in mobility and activity coefficients with ion concentration yields a value 0.046 for the thermodynamic dissociation constant at 25°, but too much reliance cannot be placed on this value as Ostwald himself pointed out that the experimental data in dilute solutions are not too reliable.

TABLE X

DISSOCIATION CONSTANT FOR DICHLOROACETIC ACID AT 25°

Moles per liter					
Acid	Na salt	NaCl	$[H_3O^+]$	K_c	K_a
0.1285	0.1126	0.3732	0.0429	0.078	0.0415
.2506	.2395	.2114	.0571	.088	.0468
.3766	.3592	.0862	.0613	.082	.0436
.5276	.4623		.0648	.074	.0394

With our present incomplete knowledge of the dissociation constant of trichloroacetic acid at infinite dilution and at any electrolyte concentration, no reliable calculation of the possibility of acid molecule catalysis can be made. The results with dichloroacetate and monochloroacetate buffer solutions do not indicate any detectable catalytic effect of the molecules of these acids. These experiments also indicate that the mechanism proposed in scheme 2 where the anion might have a catalytic effect is not applicable and one is forced to consider that the hydration of isobutene is another reaction catalyzed solely by hydrogen ion and exhibiting an unusually large electrolyte effect.

Summary

1. The rate of hydration of isobutene in aqueous solutions of perchloric, *p*-toluenesulfonic, hydrochloric and trichloroacetic acids has been investigated by the dilatometric method.
2. The electrolyte effects of the strong acids on the rate of the reaction are larger than predicted by the Brönsted theory of primary salt effects.
3. In trichloroacetic acid solutions the observed velocity constants appear to be larger than would be expected on the basis that the reaction is catalyzed solely by hydrogen ion. However, the results obtained in dichloroacetate and monochloroacetate buffer solutions do not indicate any basic catalysis of the cation of isobutene or catalysis by the molecular acid.
4. The dissociation constants of trichloro- and dichloroacetic acids have been calculated from the kinetic measurements.

PHILADELPHIA, PA. RECEIVED JULY 30, 1947

---

[25] N. F. Hall, *Chem. Rev.*, **8**, 191 (1931).

[26] E. C. Baughan, *Nature*, **146**, 461 (1940).

[27] L. Onsager, *Z. physik. Chem.*, **28**, 294 (1927).

[28] H. S. Taylor, *Meddel fran K. Vet-Akads Nobelinstitute*, **2**, no. 37 (1913).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MUTUAL CHEMICAL COMPANY OF AMERICA]

Some Properties of Lithium Dichromate

BY WINSLOW H. HARTFORD AND KEITH A. LANE

Lithium dichromate has been described[1,2] and the system Li_2O–CrO_3–H_2O has been investigated at 30°,[3] while Heydweiller[4] has investigated the density and equivalent conductance of dilute solutions at 18°. The black or brownish-black crystals of lithium dichromate dihydrate previously described were suspected of being impure in view of the characteristic red to orange color of the other alkali dichromates. The growing importance of lithium salts and of the dichromates has rendered the reevaluation of the properties of this salt desirable.

Experimental

Preparation of Lithium Dichromate Dihydrate.—Lithium carbonate of N. F. grade was employed as a source of lithium. This material assayed 99.60%, the principal impurities being other alkalies and sulfate.[5] Technical chromium trioxide, 99.7% pure, was used as the source of chromium, the principal impurities in this material being Cr(III), sulfate and moisture. The procedure for the preparation of a typical batch of lithium dichromate dihydrate was as follows:

Three and one-half kilograms of chromium trioxide was dissolved in water to give 7.5 liters of solution. Solid lithium carbonate was added, with agitation, until a *p*H of 3.5 was reached, about 1.3 kg. of lithium carbonate being employed. Cr (III) was converted to Cr (VI) by electrolysis of the solution at 4.5 volts, using lead electrodes. The oxidation of Cr (III) was judged complete when the solution became bright orange-red in color. The batch was filtered free of lead chromate, concentrated to a volume of 4.0 liters and allowed to cool with agitation, when a crop of crystals separated which were centrifuged and dried in a stream of warm air in a small rotating dryer. Additional yields may be obtained from reconcentration of the mother liquor. The crystals are bright red-orange in color, deliquescent, and consist of thin plates with crystal angles resembling those of sodium dichromate dihydrate. The black color reported by the original investigators[1,2] was evidently due to trivalent chromium present in the chromium trioxide used. Their identification of the salt as the dihydrate was confirmed by the following analyses: For $Li_2Cr_2O_7 \cdot 2H_2O$: calcd.: Li_2O, 11.24, CrO_3, 75.21; H_2O, 13.55. Found: Li_2O (as sulfate) 11.23, 11.31; CrO_3 (by electrometric titration with $FeSO_4$) 74.91, 74.91; H_2O (by weight loss), 13.54.

Existence of the Anhydrous Salt and Behavior on Heating.—The dihydrate is converted to the anhydrous salt on heating. All water is removed on heating four days at 110°; Schulerud[1] reports dehydration at 130°. On heating the crystalline dichromate slowly with saturated solution to the boiling point and then cooling with agitation, no evidence was obtained of any transition point on plotting a time–temperature curve. The anhydrous salt does not exist as a crystalline phase in contact with solution at temperatures below the boiling point of a saturated solution, 149°.

When the solid dihydrate is slowly heated with agitation in air, it melts with partial decomposition at 187°. Water and oxygen are evolved and the salt is partially decomposed to lithium chromate and chromic chromates.

Density of the Solid Dihydrate.—The density of the solid dihydrate was measured in a pycnometer at 30°, using light mineral oil as the immersion liquid, giving d^{30}_{4} 2.34.

Density of the Solution.—The salt dissolves congruently in water, and no difficulty was experienced in measuring the density of the solution in a pycnometer. The following values were obtained at 30°.

% $Li_2Cr_2O_7 \cdot 2H_2O$ by weight	d^{30}_{4}	% $Li_2Cr_2O_7 \cdot 2H_2O$ by weight	d^{30}_{4}
0.00	0.9957	36.64	1.2575
4.05	1.0195	38.79	1.2777
6.15	1.0320	41.48	1.3026
8.16	1.0455	44.64	1.3325
12.13	1.0705	46.10	1.3470
15.37	1.0930	50.72	1.3954
18.98	1.1178	52.67	1.4177
22.38	1.1427	56.44	1.4602
26.82	1.1767	61.96	1.5246
30.82	1.2082	65.11	1.567[a]

[a] Extrapolated to saturation concentration.

The data are plotted in Fig. 1, and may be shown to fit the empirical equation

$$d^{30}_{4} = 0.9957 + 0.00586C + 0.000233C^2 + 0.000000303C^3$$

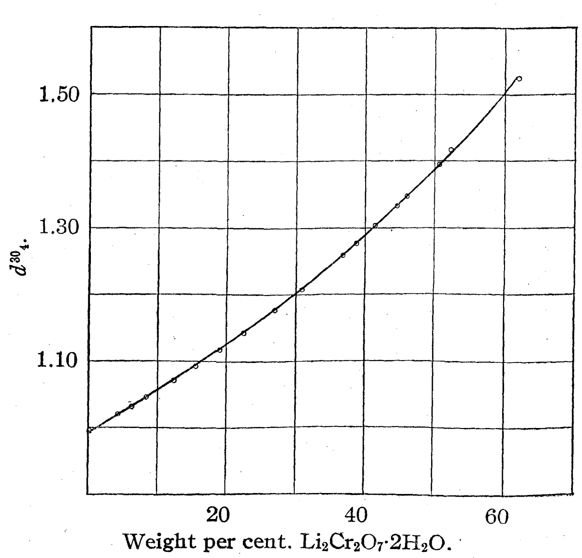


Fig. 1.—Density of lithium dichromate solutions at 30°.

---

[1] L. Schulerud, *J. prakt. Chem.*, [2] **19**, 36 (1879).
[2] C. Rammelsberg, *Pogg. Ann*, **128**, 324 (1866).
[3] F. A. H. Schreinemakers, *Z. physik. Chem.*, **55**, 77–81 (1906).
[4] A. Heydweiller, *Z. anorg. Chem.*, **116**, 42 (1921).
[5] Foote Mineral Co., Philadelphia, Pa., private communication.

where C is concentration in weight per cent. of $Li_2Cr_2O_7 \cdot 2H_2O$, with an average error of 0.0006 in the density. These data are in substantial agreement with those of Heydweiller,[4] which cover the range up to 23%, when the temperature difference is taken into consideration.

Solubility in Water.—This was determined by agitating about 2 liters of solution with an excess of the solid phase in a covered container at a constant temperature provided by an immersion heater and a vapor–mercury sensitive element. After reaching equilibrium (about six hours) a sample of the clear solution was removed by means of a sintered glass funnel and analyzed. The results given are the average of duplicate analyses for chromate on each of two samples, which checked with an average error of 0.04%. The value for 0.8° was obtained by surrounding the solution container with crushed ice, and represents an average of temperatures varying from 0.6 to 1.0°. The following data were obtained:

Temp., °C.	Soly., % by weight $Li_2Cr_2O_7 \cdot 2H_2O$	Temp., °C.	Soly., % by weight $Li_2Cr_2O_7 \cdot 2H_2O$
0.8	62.36	70.0	69.49
30.0	65.11[a]	80.0	70.76
40.0	66.08	90.0	72.26
50.0	67.28	100.0	73.55
60.0	68.39		

[a] Schreinemakers' data[3] at 30° give 65.4% $Li_2Cr_2O_7 \cdot 2H_2O$ for the solubility.

These data, when plotted, deviate an average of 0.06% from the empirical equation: $S = 62.18 + 0.0890t + 0.000243t^2$, where S is solubility in weight per cent. and t is temperature in degrees C. The maximum deviation is 0.12%.

Freezing Point of Solutions.—Five hundred milliliter portions of analyzed solutions were cooled in an insulated container by means of solid carbon dioxide and alcohol. Time–temperature heating and cooling curves were employed to determine the ice-point for each solution, and these data further checked by observation of the appearance and disappearance of ice-crystals. The following data were obtained:

% $Li_2Cr_2O_7 \cdot 2H_2O$ by weight	Ice point, °C.	% $Li\ Cr_2O_7 \cdot 2H_2O$ by weight	Ice point, °C.
0.0	0.0	41.10	−24.0
20.14	− 6.2	47.39	−35.4
29.97	−12.0	52.32	−49.8
34.82	−17.2	57.53	No crystallization at −60

A smooth curve may be drawn through these points with an average deviation of 0.4°.

Eutectic Point.—Facilities did not permit investigation of the system below −60°. Graphical analysis indicates the eutectic composition to be close to 56.5% $Li_2Cr_2O_7 \cdot 2H_2O$ and the eutectic temperature below −70°.

Solubility in Organic Liquids.—Lithium dichromate dihydrate is insoluble in ether, carbon tetrachloride and hydrocarbon solvents. It dissolves in ethyl alcohol to the extent of about 20 g. per 100 ml. of solvent at room temperature. No exact measurement is possible because of the rapid oxidation of the alcohol and reduction of the dichromate. In acetone solution occurs at first, then the dichromate decomposes with precipitation of yellow lithium chromate.

Summary

1. Lithium dichromate dihydrate has been prepared and shown to consist of red-orange crystalline plates when pure.

2. Its density, solubility and behavior on heating have been described.

3. Data have also been presented giving the density and freezing point of aqueous solutions, and the eutectic composition and temperature estimated.

4. The solubility in common organic liquids has been qualitatively examined.

BALTIMORE, MARYLAND RECEIVED SEPTEMBER 25, 1947

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Colorimetric Determination of Iron with 4-Hydroxybiphenyl-3-carboxylic Acid[1]

BY JOHN H. YOE AND AUBREY E. HARVEY, JR.[2]

As early as 1834,[3,4,5] the color reactions between ferric ions and phenolic derivatives were observed and used as a qualitative test for the aromatic hydroxyl group. Salicylic acid was the first phenol to be used for the detection of ferric ions,[6,7,8,9] and for its quantitative determination.[10–16] Derivatives of salicylic acid which have been used as quantitative colorimetric reagents for iron are: sulfosalicylic acid,[17,18,19] salicylaldoxime,[20] and β-resorcylic acid.[21]

This paper introduces 4-hydroxybiphenyl-3-carboxylic acid as a new colorimetric reagent for ferric iron. The reagent is very sensitive and is

---

(1) Abstracted from the Ph.D. thesis of Aubrey E. Harvey, Jr., University of Virginia, 1946.

(2) Present address: Department of Chemistry, University of Louisville.

(3) Runge, *Pogg. Ann.*, **31**, 65 (1834); *Z. prakt. Chem.*, **1**, 22 (1834).

(4) H. Schiff, *Ann.*, **159**, 164–168 (1871).

(5) O. Hesse, *ibid.*, **182**, 160–163 (1876).

(6) Griggi, *Z. anal. Chem.*, **34**, 450 (1895); *Bull. chim. pharm.*, **1895**, 484.

(7) Pagliani, *J. Chem. Soc.*, **36**, 748 (1879); *Gazz. chim. ital.*, **9**, 23 (1879).

(8) E. F. Smith, *Proc. Am. Phil. Soc.*, **18**, 214 (1880).

(9) A. Vogel, *N. Rept. Pharm.*, **25**, 178–180 (1876).

(10) W. J. Agnew, *Analyst*, **53**, 30 (1928).

(11) A. W. Gregory, *Proc. Chem. Soc.*, **23**, 263 (1907); *J. Chem. Soc. Trans.*, **93**, 93 (1908).

(12) J. P. Mehlig, *Ind. Eng. Chem., Anal. Ed.*, **9**, 162–163 (1937).

(13) J. P. Mehlig, *ibid.*, **10**, 136–138 (1938).

(14) A. Sagaidachnuii and M. Ravich, *J. Russ. Phys.-Chem. Soc.*, **58**, 1018–1022 (1926).

(15) F. D. and C. T. Snell, "Colorimetric Methods of Analysis," D. Van Nostrand Co., New York, 1936, p. 301.

(16) J. L. Steenkamp, *J. S. African Chem. Inst.*, **13**, 64 (1930).

(17) K. Dietrich and K. Schmitt, *Z. anal. Chem.*, **111**, 176–178 (1937).

(18) M. Kennard and C. R. Johnson, *Proc. Trans. Texas Acad. Sci.*, **27**, 45–51 (1944).

(19) A. Thiel and O. Peter, *Z. anal. Chem.*, **103**, 161–166 (1935).

(20) D. E. Howe and M. G. Mellon, *Ind. Eng. Chem., Anal. Ed.*, **12**, 448–50 (1940).

(21) A. R. Armstrong, Dissertation, University of Virginia, 1945.

practically specific, its only other color reaction being with the uranyl ion. The latter reaction will be studied in more detail. The colorless solution of the reagent in ethanol appears to be stable indefinitely. The iron complex is soluble in slightly acid 40% ethanol solution; its intense violet color is stable for at least fourteen hours. Iron may be determined without difficulty in the presence of titanium, and there is remarkably little interference from other cations. Anions such as phosphate, fluoride, oxalate, phthalate, and tartrate which form complexes with the ferric ion, either reduce the sensitivity of the reaction or prevent color formation altogether. The procedure for the determination of iron is simple and may be applied to a wide variety of materials with highly satisfactory results.

Apparatus and Solutions

Instruments.—Spectrophotometric measurements were made with a Beckman quartz spectrophotometer, Model D, using 10.0 mm. Corex glass transmission cells, at a spectral band width of 5 mμ.

Visual color matching was made in 50-ml. Nessler cylinders (220 mm.); also with a color comparator[22] using 100-ml. tubes (160 mm.).

Reagent Solution.—4-Hydroxybiphenyl-3-carboxylic acid, mol. wt. 214, was furnished by courtesy of E. I. du Pont de Nemours and Company. The compound is only slightly soluble in water, but is highly soluble in 70% ethanol. The melting point is 214–215° (cor.) as compared with 212–213° reported in the literature.[23] Solutions containing 0.1916 and 1.0000 g. of solute, respectively, in 100 ml. of 95% ethanol were used. One milliliter of the more dilute solution added to 50 ml. of a solution containing 10 p. p. m. iron furnished 1 mole of reagent to 1 gram-ion of ferric ions. Reagent solutions appear to be stable indefinitely.

Standard Iron Solution.—7.0224 g. of ferrous ammonium sulfate hexahydrate was dissolved in 100 ml. of distilled water, 5 ml. of concentrated sulfuric acid and 1 ml. of bromine were added, and the solution boiled to oxidize the iron and expel the excess bromine. The solution was diluted to 1 liter and the iron determined gravimetrically. The solution should contain 1.00 mg. of iron per ml. More dilute solutions may be prepared from this stock solution as needed.

Solutions of Diverse Ions.—Solutions of salts were prepared from reagent grade, iron-free chemicals, and contained 0.5 mg. of the desired ion per ml.

Spectrophotometric Study of the Color Reaction

Spectrophotometric measurements were made to determine the effect of reagent concentration on the color intensity in an effort to establish the empirical formula for the violet complex formed in 40% ethanol solution.[24] Two series of solutions were prepared in which the molar ratio of reagent to iron varied from 0.2:1 to 10:1. The *p*H of one series was adjusted to 2.8 and of the other to 3.0. All solutions contained 10 p. p. m. of iron and 40% ethanol. The absorbancy ($-\log T$) was measured for each solution at 575 mμ, the wave length of maximum absorption for the complex. The results are plotted in Fig. 1.

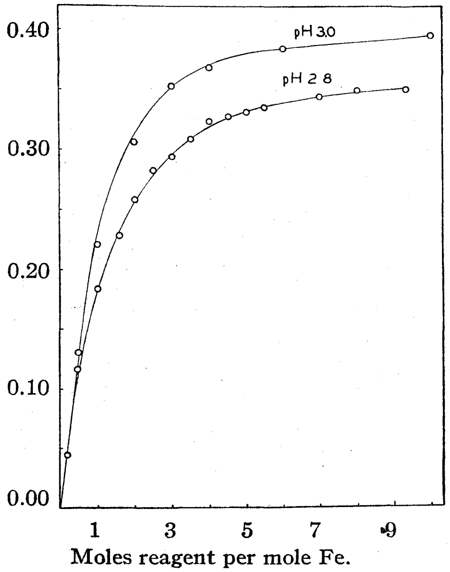


Fig. 1.—Effect of reagent concentration: 10 p. p. m. Fe; λ575 mμ.

These curves show no sharp break or leveling off to a constant maximum absorbancy. The absorbancy is still increasing slightly at a reagent–iron ratio of 10:1, indicating that the complex is appreciably dissociated in solution. The curves show, moreover, that a large excess of reagent (at least a 10:1 molar ratio) is necessary to insure full color development.

The method of "continuous variation" first proposed by Job[25] and extended by Vosburgh and co-workers[26,27] was applied to the determination of the ratio of reagent to iron in the complex studied in this investigation. A 1.79×10^{-4} M solution of ferric ions (10 p. p. m.) and a reagent solution of the same molarity were prepared in 40% ethanol. The *p*H of these solutions was adjusted to 3.0. Twelve solutions of the colored complex were obtained by mixing x ml. of the reagent solution and $(20 - x)$ ml. of the iron solution. The *p*H of each solution after mixing was checked with a glass electrode and found to be 3.0. The values of x were chosen so that the molar ratio varied from 0.25 to 9 moles of reagent for each mole of iron. In one experiment, ammonium sulfate was added to the reagent solution so that the concentration of sulfate ion remained constant in the whole series. This precaution did not affect the results in any way. The absorbancy was determined at 550, 575 and 600 mμ, respectively. In Fig. 2 the absorbancy values at 575 mμ are plotted against the volume of reagent solution [expressed x liters added to $(1-x)$ liters of iron solution].

---

(22) J. H. Yoe and T. B. Crumpler, *Ind. Eng. Chem., Anal. Ed.*, **7**, 78 (1935).

(23) L. F. Fieser and C. K. Bradsher, This Journal, **58**, 1738–1740 (1936).

(24) J. H. Yoe and A. L. Jones, *Ind. Eng. Chem., Anal. Ed.*, **16**, 111–115 (1944).

(25) P. Job, *Ann. chim.*, [10] **9**, 113–199 (1928).

(26) W. C. Vosburgh and G. R. Cooper, This Journal, **63**, 437–442 (1941).

(27) R. K. Gould and W. C. Vosburgh, *ibid.*, **64**, 1630–1634 (1942).

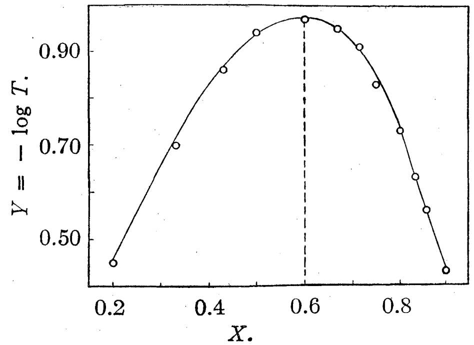


Fig. 2.—X liters of 1.79×10^{-4} M reagent solution added to $(1 - X)$ liters of 1.79×10^{-4} M Fe^{+++} solution: λ, 575 mμ, pH 3.0.

A Y function, first introduced by Job[25], may be defined as the difference between the observed absorbancy and the calculated absorbancy, assuming no reaction between the components of the colored complex.

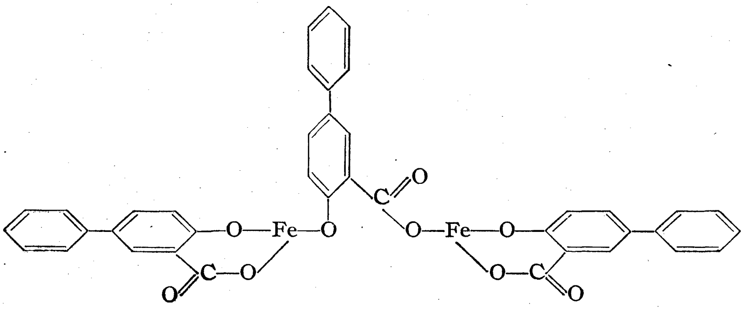
$$Y = E_{\text{obs.}} - d[\epsilon_1 M(1 - x) + \epsilon_2 Mx]$$

The symbols ϵ_1 and ϵ_2 represent, for a given wave length, the molecular extinction coefficients of ferric ion and the reagent, respectively; M the molarity of the solutions used; d the thickness of the ransmission cell; $(1 - x)$ and x the volumes in liters of the solutions mixed.

The new iron reagent is colorless and therefore ϵ_2 is zero at any wave length in the visible range. The term $\epsilon_1 M(1 - x)$ may be neglected because ferric ions show no appreciable absorption at the concentration used in this procedure. The Y function for this particular case is then simply the observed absorbancy (−log T). It has been shown[26] that if Y is plotted against x, the value of x for which the curve passes through a maximum or a minimum will give the value of n in the formula FeR_n by the relationship $n = x/(1 - x)$. The maximum in Fig. 2 indicates a formula of $FeR_{1.5}$ or Fe_2R_3 for the complex. The curve has a rather broad maximum which is to be expected when there is appreciable dissociation.

Vosburgh and Cooper[26] point out that for solutions in which only one complex is formed, the maximum or minimum in Y will occur at the same value of x for any wave length at which measurements are made. The absorbancy values at 10 mμ intervals from 520 to 620 mμ were determined for solutions containing 10 p. p. m. of iron with the following molar ratios of reagent to iron: 0.2:1, 0.5:1, 1:1, 2:1, 3:1 and 9:1. Plotting log E against wave length gave curves which were identical in shape and could be superimposed by adding a suitable constant to the ordinates of each curve. This shows that in the color system under consideration the reagent forms only one complex with ferric iron.

Various attempts have been made to establish the structures of complexes formed by the reaction between ferric ions and phenolic derivatives.[28,29,30,31,32,33,34] Wesp and Brode[35] found that the absorption curves for the water-soluble complexes of ferric ions with 44 phenols and 10 naphthols, as well as the curves for the ferric–salicylic acid color in 28 different solvents were identical in shape, though the wave length of maximum absorption depended on the particular phenolic derivative used and varied also with the solvent. The characteristic shape of these absorption curves is duplicated by that of the ferric thiocyanate complex. This similarity indicates that all the complexes have the same or very similar structures. Bent and French,[36] and also Edmonds and Birnbaum[37] independently, have reported that the color of the thiocyanate complex is due to the $Fe[CNS]^{+2}$ ion. Gould and Vosburgh[27] confirmed the presence of the $Fe[CNS]^{+2}$ ion using the method of continuous variation. Hence it would seem that the water-soluble iron complexes with phenolic derivatives have the formula FeR^{+2} in solution. Weinland and Binder[33] have assigned the formula $[Fe(OC_6H_4OCH_3)_4]H$ to the violet complex formed by ferric ions and guaicol in alcoholic solution. Wesp and Brode[35] point out that the structure of the guaicol compound may well differ from that of the other phenolic complexes of iron because the compound is insoluble in water. The same reasoning would apply in the present case since the complex under investigation is insoluble in water and the color is formed in ethanol solution. It is probable that a molecule rather than an ion is responsible for the color. Since the reagent has two replaceable hydrogens, it is reasonable to assume that the structure of the complex may be represented as



A Spectrophotometric Study of the Effect of pH on the Color Reaction.—Attempts to form the colored complex of ferric ions with 4-hydroxy-

---

(28) W. R. Brode, *J. Phys. Chem.*, **30**, 56–59 (1926).

(29) M. Claasz, *Arch. Pharm.*, **253**, 360–366 (1915).

(30) G. Illari, *Ann. chim. applicata*, **30**, 65–72 (1940).

(31) C. Morton, *Quart. J. Pharm. Pharmacol.*, **4**, 451–460 (1931).

(32) F. Raschig, *Z. angew. Chem.*, **20**, 2065–2071 (1907).

(33) R. F. Weinland and K. Binder, *Ber.*, **45**, 2498–2502 (1912).

(34) R. F. Weinland and K. Binder, *ibid.*, **46**, 874–885 (1913).

(35) E. F. Wesp and W. R. Brode, THIS JOURNAL, **56**, 1037–1042 (1934).

(36) H. E. Bent and C. L. French, *ibid.*, **63**, 568 (1941).

(37) S. M. Edmonds and N. Birnbaum, *ibid.*, **63**, 1471 (1941).

biphenyl-3-carboxylic acid in aqueous solution were unsuccessful. The reagent precipitates immediately from solutions as dilute as 0.15 mg. per ml. if the *p*H is 3.3 or below. In higher concentrations the reagent precipitates at any *p*H below 4.4. At this latter *p*H the precipitation of ferric hydroxide from aqueous solution interferes with the color reaction.

The intensity of the color in 40% ethanol is extremely sensitive to changes in hydrogen-ion concentration. Visual observations indicated that maximum absorption is reached at a *p*H of about 3. In more acid solutions, the absorption is markedly diminished. Decreasing the acidity not only causes a decrease in color intensity, but also a change in hue from violet to reddish-violet at *p*H 4. This change in hue is thought to be due to the formation of colloidal, hydrated ferric oxide. Solutions containing 10 p. p. m. iron in 40% ethanol developed a red color without addition of the reagent when the *p*H was adjusted to 4.0 or above. Ferric hydroxide precipitated from these solutions on standing overnight.

Spectrophotometric measurements were made on a series of solutions containing 10 p. p. m. iron and varying in *p*H from 2.1 to 3.6. All solutions contained 4 moles of reagent to each mole of iron. Absorbancy measurements were made at 10 mμ intervals from 400 to 700 mμ. The absorbancy *vs.* wave length curves are shown in Fig. 3. The solutions of *p*H 2.1, 2.4 and 2.8 are deep violet in color and have absorption maxima at 575 mμ, the absorbancy being greatest at *p*H 2.8. The curve at *p*H 3.6 shows a slight shift of the maximum toward the shorter wave lengths, and increased absorption from 400 to 500 mμ. These variations are increasingly pronounced from *p*H 3.8 to 4.3 and correspond with a change in hue to reddish-violet. The increased absorption between 400 and 500 mμ could be explained by the formation of colloidal ferric oxide, which absorbs in this range. On standing twenty-four hours, the reddish-violet solutions of *p*H 3.6 and above became turbid, the color faded and a reddish-brown precipitate gradually settled out.

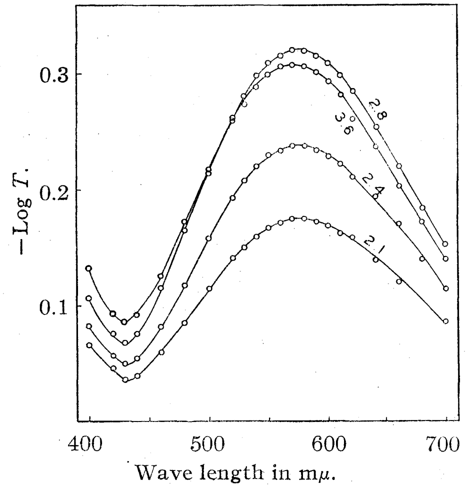


Fig. 3.—Effect of *p*H on extinction: moles reagent: moles Fe = 4:1; 10 p. p. m. Fe.

In order to determine more closely the optimum *p*H range, three solutions were used having *p*H values of 2.8, 3.0 and 3.2. These solutions differed from the first series in that each contained a 10:1 molar ratio of reagent to iron. Their extinction is plotted against wave length in Fig. 4. The upper curve of Fig. 3 is reproduced in Fig. 4. The curves for *p*H 3.0 and 3.2 coincide at all wave lengths. The difference in intensity of these solutions and of that at *p*H 2.8 cannot be detected visually. The optimum *p*H range may therefore be set at 2.8–3.2.

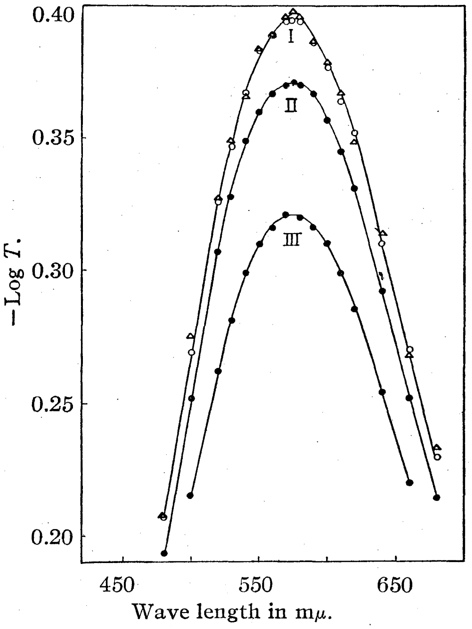


Fig. 4.—Effect of *p*H on extinction: moles reagent: moles Fe; I and II 10:1, III 4:1; △, *p*H 3.2, ○, *p*H 3.0, ●, *p*H 2.8.

It was found that the *p*H can be adjusted closely enough by adding 1 *N* sodium hydroxide until the solution is alkaline to congo red paper, and then 0.1 *N* hydrochloric acid until a drop of the solution turns the paper light blue. The use of a buffer was dispensed with in order not to decrease the sensitivity of the reaction.

Conformity to Beer's Law

The new iron complex was found to conform to Beer's law up to an iron concentration of 10 p. p. m. Solutions containing 15 and 20 p. p. m. iron showed increasing deviation from Beer's law, and on standing a short while gave a mixed blue-white precipitate of complex and reagent. Spectrophotometric measurements were made over a wave length range from 520 to 620 mμ.

Stability of the Colored Complex.—Solutions of the colored complex in the optimum *p*H range, containing a large enough excess of reagent for full color development, are stable from fourteen to sixteen hours in the diffuse light of the laboratory. A precipitate of reagent and complex separates from solutions containing 10 p. p. m. iron after thirty-six hours, and from solutions with 1 p. p. m. after a week. It is recommended that fresh standards be prepared daily.

Sensitivity of the Reaction.—The limit of sensitivity of the violet iron complex is 1 part of iron in 40 million parts of solution when observations are made either in 50-ml. tall-form Nessler cylinders or in a color comparator.[22] Solutions having a *p*H of 3.0 and containing 1 part of iron in 10, 20, 30, 40 and 50 million parts of solution, respectively, with 1 ml. of 1% reagent and 40 ml. of 95% ethanol per 100 ml. of solution were transferred to comparator tubes or Nessler cylinders. Three independent observers were able to arrange the four more concentrated solutions in the proper order and to distinguish from a reagent blank, the solution containing 1 part of iron in 40 million.

The optimum concentration range for comparison in the Nessler cylinders is 0.2 to 1 p. p. m. of iron. Over this range, increments of 1 part of iron in 30 million parts of solution may be detected. Solutions containing 5 p. p. m. of iron are too dark for comparison in Nessler cylinders, though solutions of this concentration differing by 1 part of iron in 20 million parts of solution may be distinguished in the color comparator.

The spot-plate sensitivity was determined by transferring 0.05 ml. (one drop) of iron solutions of varying concentrations to depressions of a white porcelain spot-plate and adding 0.05 ml. of a 1% reagent solution of *p*H 3. Two-tenths of a microgram of iron could thus be detected.

Effect of Diverse Ions

Reactions with Various Ions.—Spot-plate tests were made by adding a drop of 1% reagent solution to a drop of the solution containing 1 mg. per ml. of the respective ions. Tests were made in acid, neutral and alkaline media when the character of the ion permitted. No color or precipitate formation was observed with the following ions: Al^{+3}, Ag^{+1}, As^{+3}, AsO_4^{-3}, $AuCl_4^{-1}$, $B_4O_7^{-2}$, Ba^{+2}, Be^{+2}, Bi^{+3}, Br^{-1}, CO_3^{-2}, Ca^{+2}, CbO_4^{-3}, Cd^{+2}, Ce^{+3}, Cl^{-1}, Co^{+2}, Cr^{+3}, Cs^{+1}, Dy^{+3}, Er^{+3}, Eu^{+3}, F^{-1}, Fe^{+2}, Ga^{+3}, Gd^{+3}, Ge^{+4}, HfO^{+2}, Hg^{+1}, Hg^{+2}, I^{-1}, In^{+3}, Ir^{+4}, K^{+1}, La^{+3}, Li^{+1}, Mg^{+2}, Mn^{+2}, MoO_4^{-2}, NO_2^{-1}, NO_3^{-1}, Na^{+1}, Nd^{+3}, Ni^{+2}, OsO_5^{-2}, HPO_4^{-2}, Pb^{+2}, Pd^{+2}, Pr^{+3}, $PtCl_6^{-2}$, Rb^{+1}, ReO_4^{-1}, Rh^{+3}, Ru^{+3}, S^{-2}, SO_4^{-2}, Sb^{+3}, Sc^{+3}, SeO_3^{-2}, SiO_3^{-2}, Sm^{+3}, Sn^{+2}, Sn^{+4}, Sr^{+2}, TaO_4^{-3}, TeO_4^{-2}, Th^{+4}, Ti^{+4}, Tl^{+3}, Tm^{+3}, VO^{+2} WO_4^{-2}, Y^{+3}, Yb^{+3}, Zn^{+2}, ZrO^{+2}.

TABLE I

EFFECT OF DIVERSE IONS

Ion	Added as	Amount present p. p. m.	Results
Al^{+3}	$Al(NO_3)_3$	100	M
Ca^{+2}	$Ca(NO_3)_2$	100	M
Co^{+2}	$Co(NO_3)_2$	100	X (reddish)
		50	M
Cr^{+3}	$Cr(NO_3)_3$	25	NM
		10	M+
		5	M
$Cr_2O_7^{-2}$	$K_2Cr_2O_7$	5	X (gray)
		1	M+
Cu^{+2}	$Cu(NO_3)_2$	25	NM
		10	M+
		5	M+
		1	M
F^{-1}	KF	5	NM, D
		1	M
Fe^{+2}	$Fe(NH_4)_2(SO_4)_2$	1	NM (oxidizes)
K^{+1}	KCl	100	M
Mg^{+2}	$MgSO_4$	100	NM (slight reddish tint)
		50	M
Mn^{+2}	$MnCl_2$	100	M
Na^{+1}	NaCl	100	M
NH_4^{+1}	NH_4Cl	100	NM (reddish tint)
		50	M (slight reddish tint)
Ni^{+2}	$Ni(NO_3)_2$	25	NM
		10	M+
		5	M+
		1	M
PO_4^{-3}	Na_3PO_4	100	B
		1	NM
SiO_3^{-2}	Na_2SiO_3	100	NM (color develops slowly)
		50	M−
		25	M (after five minutes)
Sn^{+2}	$SnCl_2$	1	NM, D
Sn^{+4}	$SnCl_4$	5	NM, D
		1	M
Ti^{+4}	$TiCl_4$	1	NM (gray solution)
		Concn. in millimoles per liter	
Acetate	Acetic acid	500	NM
		350	M
Borate	Sodium tetraborate	20	NM
		10	M
Citrate	Citric acid	1	B
Malate	Malic acid	50	NM
		10	M
Oxalate	Oxalic acid	1	B
Phthalate	Potassium hydrogen phthalate	10	NM
		5	M
Succinate	Succinic acid	50	NM
		10	M
Tartrate	Tartaric acid	1	B

Key to symbols: M = matches 1 p. p. m., M+ = 1.05 p. p. m., M− = matches 0.95 p. p. m., NM = no match or matches 1.10 or 0.90 p. p. m., X = off-tint, D = intensity greatly decreased, B = color bleached.

Ferric ions produced a violet color and a blue precipitate; UO_2^{+2} an orange color. These are the only ions reacting with the reagent in acid solution; in ammoniacal solution, the cupric ion gives a green color.

Determination of Iron in the Presence of Other Ions.—In determining the interference of diverse ions, a measured volume of a standard solution of the diverse ion and 20 ml. of 95% ethanol were added to 5.0 ml. of standard iron solution (0.01 mg. per ml.) in a 50-ml. tall-form Nessler cylinder; the volume was made up to 45 ml. with distilled water and the *p*H adjusted to about 3 with congo red paper; 1 ml. of 1% reagent solution was added; the tube was filled to the mark and the solution mixed. These solutions containing 1 p. p. m. of iron with the diverse ion were compared with color standards containing 0.90, 0.95, 1.00, 1.05 and 1.10 p. p. m. of iron, respectively. The diverse ion was judged not to interfere if the solution was not off-tint, and the intensity could be matched with that of the 1 p. p. m. standard. If the solution matched the 0.95 or 1.05 p. p. m. standard, it is so indicated. If the color corresponded to the 1.10 or 0.90 p. p. m. standard, "no match" is reported. No concentration of diverse ions greater than 100 p. p. m. or less than 1 p. p. m. was used. The results of these tests are shown in Table I.

These data show that the most serious interference is encountered with anions such as fluoride, phosphate, and the anions of organic acids which are common constituents of buffer solutions. Fortunately, the acidity may be satisfactorily adjusted with the aid of congo red paper. Fluoride must be removed if its concentration is greater than that of the iron. Phosphate interferes at a concentration equal to that of the iron.

Of the metallic ions which interfere, only Cu^{+2} and Ti^{+4} are likely to exceed the limiting concentration in materials to which colorimetric methods for iron are commonly applied. Copper is easily separated from iron by precipitation as copper sulfide. An investigation showed that the interference of titanium is due to hydrolysis and that this can be avoided by decreasing the *p*H of the solution. A gray color results when the reagent is added to solutions containing 1 p. p. m. each of iron and titanium. These solutions give a brownish precipitate on standing a few hours. A similar precipitate was observed in 40% ethanol solution of *p*H 3.0 containing 1 p. p. m. of these metals without the reagent. If the *p*H of the solution and color standards is adjusted to 2.5, the solution containing titanium shows no off-tint, and a match may be made without difficulty.

Recommended Procedure

A procedure for the colorimetric determination of iron with 4-hydroxybiphenyl-3-carboxylic acid has been based on the foregoing study of the properties of the reagent. The color must be developed in 35–40% ethanol solution because of the small solubility of the reagent in water. A 10:1 molar ratio of reagent to iron is sufficient for full color development at the optimum *p*H of 3. If titanium is present adjust the *p*H to 2.5.

Weigh out a sample containing 1 mg. of iron or less. Dissolve the sample by alkali fusion, mineral acid treatment, or both as may be necessary. If interfering ions are present in excess of the limiting concentrations shown in Table I, remove them by standard methods. Dilute the solution in a volumetric flask to 100 ml. with distilled water. After thorough mixing, transfer 5 ml. (or an aliquot part that will give an iron concentration of 0.1 to 1 p. p. m. when diluted to 50 ml.) to a Nessler cylinder. Add 20 ml. of 95% ethanol and dilute to 40–45 ml. with distilled water. Add 1 *N* sodium hydroxide dropwise until a drop of the solution on a stirring rod does not change the color of congo red paper. Then add 0.1 *N* hydrochloric acid until the indicator paper just turns blue when tested with a drop of the solution. If the acid concentration in the aliquot is excessively high, the solution should be partially neutralized with a stronger solution of base before the 1 *N* sodium hydroxide is added. After the *p*H has been adjusted, add 1 ml. of 1% reagent solution, dilute to the mark with distilled water, mix thoroughly, and compare the color with a series of standard solutions similarly prepared.

If the sample contains titanium, the solution will develop a gray color on addition of the reagent. In this case, add 0. 1 *N* hydrochloric acid dropwise until the color becomes violet. Add the same amount of acid to the standards, before matching. The *p*H of standards and sample should be checked with the *p*H meter after matching and should agree within 0.1 of a *p*H unit. If the titanium is known to be present in high enough concentration to interfere, the *p*H may be adjusted to 2.5 before the reagent is added.

Determination of Iron in Various Materials.—The applicability of the reagent to the colorimetric determination of iron in various materials

TABLE II

DATA ON IRON DETERMINATIONS

Materials N. B. S.	Fe_2O_3 N. B. S. value, %	Fe_2O_3 found, %	Diff., %
Feldspar 70	0.03	0.05	+0.02
		.04	+ .01
Glass sand 81	.073[a]	.072	− .001
		.072	− .001
Dolomite 88	.084	.086	+ .002
		.086	+ .002
Silica brick 102	.66[b]	.67	+ .01
		.66	.00
Soda lime glass 128	.039	.039	.000
		.036	− .003
	%Fe	%Fe	
Sheet brass 37b	.21	.22[c]	+ .01
		.23[c]	+ .02

[a] Sample contained 0.095% TiO_2. Matched at *p*H 2.5.
[b] Sample contained 0.16% TiO_2. Matched at *p*H 2.5.
[c] Copper removed as CuS.

was established by analyzing a representative group of samples issued by the National Bureau of Standards. The results are recorded in Table II.

Discussion of Results

The data in Table II show that the reagent may be used successfully for the determination of small amounts of iron in various materials. All values determined with the new reagent are well within the range of values reported by the Bureau. The precision between individual analyses is excellent. Feldspar 70, dolomite 88, silica brick 102 and soda lime glass 128 contained, respectively, 0.012, 0.003, 0.025 and 0.01% of P_2O_5. No interference from phosphate was encountered with any of these samples. When no interfering ions are present, a sodium carbonate fusion of the sample may be taken up in dilute hydrochloric acid, filtered directly into a 100-ml. volumetric flask, diluted to the mark and mixed. An aliquot part of the solution is taken for analysis. Dehydration of the silica before filtration is not necessary.

Summary

A new, sensitive and practically specific reagent for the colorimetric determination of iron is presented. The nature of the reaction and the optimum conditions for color formation have been determined spectrophotometrically. The colored complex obeys Beer's law over the useful range of iron concentration.

The reagent is sensitive to 1 part of iron in 40 million parts of solution when observations are made in Nessler cylinders (50-ml. tall-form). An analytical procedure based on visual methods of color matching has been applied to a variety of materials with good accuracy. The number of interfering cations is small. Iron may be determined in the presence of titanium without interference.

CHARLOTTESVILLE, VA. RECEIVED JULY 31, 1947

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

The Effect of Fluorine Substitution on Chemotherapeutic Agents. I. Synthesis of Some Fluorine-Containing Medicinals[1]

BY H. LEON BRADLOW[2] AND CALVIN A. VANDERWERF

Because of the increasing interest in organic compounds containing fluorine we have undertaken a program involving the synthesis of a variety of fluorine substituted compounds, with the ultimate aim of determining the effect on the pharmacological properties of various medicinals produced by the substitution of fluorine atoms for other groups in the molecule. The present paper describes the synthesis of sample compounds of a number of types, the pharmacological and germicidal testing of which it is hoped will provide leads for future work. Previous investigations of this nature have been concerned mainly with the substitution of fluorine for other halogen atoms[3]; in view of the fact that a number of isosteres of important medicinal agents have proved to be as effective or better than the original drugs,[4] however, emphasis in the present work has been placed upon the substitution of fluorine atoms for the isosteric amino and hydroxy groups.[5] Representative fluorine-containing compounds related to medicinals of the following general types were prepared: (1) antimalarials, (2) arsenicals, (3) diphenylsulfones, (4) antiseptics derived from resorcinol and (5) sulfonanilides.

Experimental[6,7]

***p*-Nitrofluorobenzene.**—Direct nitration of fluorobenzene by dropwise addition, with vigorous stirring, of 3 moles to 600 cc. of a 2:1 (by volume) mixture of concentrated sulfuric acid and yellow fuming nitric acid (sp. g. 1.5) at −10°, followed by addition of ice, ether extraction and careful fractionation through a packed column of the residue after removal of the ether, gave 338 g. (80%) of *p*-nitrofluorobenzene, b. p. 109–109.5° at 36 mm., f. p. from cooling curve 26.0°, together with 40.0 g. (7.2%) of 2,4-dinitrofluorobenzene, b. p. 129–130° at 2.7 mm. In an alternate method *p*-nitrofluorobenzene was obtained from *p*-nitroaniline in 65% yield by diazotization followed by decomposition at 40° in anhydrous hydrogen fluoride.

***p*-Fluoroaniline.**—Reduction of *p*-nitrofluorobenzene in absolute alcohol using Raney nickel catalyst with a small amount of platinum tetrachloride as promoter repeatedly gave 92–95% yields of *p*-fluoroaniline, b. p. 98–99° at 33 mm. With Adams catalyst the reduction in either absolute alcohol or acetic acid gave only 65–70% yields of the amine together with 5% of *p*-fluoroacetanilide, m. p. 150.6–151.1°, when the latter solvent was used; this

---

[1] Presented before the Organic Division of the American Chemical Society at the Atlantic City meeting in April, 1947.

[2] H. P. Cady Fellow, 1946.

[3] See, for example: (a) Dunker and Starkey, THIS JOURNAL, **61,** 3005 (1939); (b) Suter and Weston, *ibid.*, **61,** 2317 (1939); (c) **62,** 604 (1940); (d) Suter, Lawson and Smith, *ibid.*, **61,** 161 (1939); (e) English, Mead and Niemann, *ibid.*, **62,** 350 (1940).

[4] Compare the bactericidal action of sulfathiazole and of sulfadiazine with that of sulfapyridine, the analeptic activity of the N,N-diethylamide of thiazole-5-carboxylic acid with that of the corresponding derivative of pyridine and the hypnotic properties of dialkyl derivatives of 2,4-dioxothiazolidine with those of the analogous barbiturates.

[5] Relatively few studies of this type have been made; see: (a) Schiemann and Winkelmüller, *Ber.*, **65B** 1435 (1932); (b) Hansen, THIS JOURNAL, **59,** 280 (1937); (c) Fosdick and Campaigne, *ibid.*, **63,** 974 (1941).

[6] All melting points corrected; boiling points uncorrected.

[7] All analyses by Oakwood Laboratories, Alexandria, Virginia.

last-named product was obtained in 77% yield when the reduction was carried out in acetic anhydride.

The low yields (30–35%) of *p*-fluoroaniline consistently obtained from *p*-aminoacetanilide by the Schiemann reaction, followed by hydrolysis of the resulting *p*-fluoroacetanilide, were not improved by the use of the modification[8] in which the borofluoride is added gradually to xylene at 140°.

2-Carboxy-5-chloro-4′-fluorodiphenylamine.—In a modification of the general method of Magidson[9] a mixture consisting of 16.7 g. (0.15 mole) of *p*-fluoraniline, 26.1 g. (0.13 mole) of 2,4-dichlorobenzoic acid, 24 g. of potassium carbonate, 10.1 g. of potassium acetate, 0.15 g. of copper powder and 180 ml. of *n*-butyl alcohol was refluxed for four hours, then steam distilled. The product was isolated in the usual manner[10] and 24–25 g. (90–94%) of reprecipitated material, m. p. 204–209°, was obtained. It crystallized from glacial acetic acid as long yellow needles, m. p. 212.0–213.1°.[11]

Anal. Calcd. for $C_{13}H_9O_2NClF$: N, 5.3; Cl, 13.4. Found: N, 5.4, 5.4; Cl, 13.8, 13.8.

The procedure of Price and Roberts[11] gave the desired product in very poor yield and that of Bachman[10] in 70–75% yields.

2-Fluoro-6,9-dichloroacridine.—Exactly 5.0 g. of 2-carboxy-5-chloro-4′-fluorodiphenylamine was refluxed for four hours with 35.0 g. of phosphorus oxychloride. The latter compound was then partially removed at the water pump and the residue poured into water and chloroform. The chloroform layer was washed with cold water, dried over drierite, and the solvent removed at the pump. After trituration of the black residue with acetone to remove the dark color 2.5 g. (50%) of the desired product was obtained. Because of its obvious instability it was not further characterized.

2-Fluoro-6-chloro-9-(1-methyl-4-diethylaminobutyl)-aminoacridine.—The total product obtained as described above was dissolved in 10 cc. of phenol and 1.5 g. of 1-diethylamino-4-aminopentane was added. After the mixture had been heated on the steam-bath for two hours with stirring the product was isolated in the usual manner as the dihydrochloride. One recrystallization from alcohol–ether gave 2.75 g. (63%) of fine yellow crystals, m. p. 225.0–226.5°, with darkening at 219°.

Anal. Calcd. for $C_{22}H_{29}N_3Cl_3F$: N, 9.1; Cl, 23.0. Found: N, 8.9, 8.9; Cl, 22.7, 22.6.

4-Fluoro-3-nitroaniline.—The procedure of Holleman[12] was modified as follows: 13.8 cc. of yellow fuming nitric acid (sp. g. 1.5) in 72 cc. of concentrated sulfuric acid was added dropwise with stirring at −5° (internal cooling with Dry Ice) to a solution of 33.3 g. (0.3 mole) of *p*-fluoroaniline in 175 cc. of concentrated sulfuric acid. After being stirred at −5° for one hour the mixture was allowed to come to 0° over the course of an additional hour, then poured onto ice, neutralized with sodium carbonate and filtered. Washed with water and dried, the product (36 g., 77%) was obtained as red plates, m. p., after one recrystallization from water, 97.0–98.2°.

4-Fluoro-3-nitrophenylarsonic Acid.—This product, obtained as yellow plates in 49% yield from 4-fluoro-3-nitroaniline by the general method of Doak,[13] darkened at 260° and melted at 279.2–281.3° after recrystallization from hot water.

An alternate sequence *via* the nitration of *p*-fluorophenylarsonic acid was abandoned because of our failure to obtain the acid by any of three plausible methods.[13,14]

3,3′-Diamino-4,4′-difluoroarsenobenzene.—Prepared by the general procedure of Ehrlich and Bertheim,[15] this compound was obtained in 73% yield. It was purified as the dihydrochloride, m. p. 195.2–196.4°, from methyl alcohol–ether. Both compounds are extremely sensitive to oxygen, and satisfactory analyses were not obtained.

3-Amino-4-fluorophenylarsonic Acid.—This compound was obtained in 53% yield by the general method of Stevinson and Hamilton.[16] The procedure of Jacobs[17] gave less satisfactory results.

Because of the extreme air-sensitiveness of the free amine, it was converted directly to the acetyl derivative by treatment of the water solution with acetic anhydride under the Schotten–Baumann conditions. The 3-acetylamino-4-fluorophenylarsonic acid was isolated as brown needles melting at 217.1–218.2° after recrystallization from ethyl alcohol–water.

Anal. Calcd. for $C_8H_9O_4NFAs$: N, 5.1. Found: N, 5.2, 5.0.

***p*-Amino-*p*′-fluorodiphenylsulfone.**[18]—To a solution of 13.8 g. of *p*-amino-*p*′-nitrodiphenylsulfone[19] in 35 cc. of concentrated hydrochloric acid and 60 cc. of water, 3.5 g. of sodium nitrite dissolved in 25 cc. of water was added rapidly. After the mixture had been stirred for twenty minutes 17.0 g. of sodium fluoborate in a minimum of water was added and stirring was continued for an additional forty-five minutes. A quantitative amount (18.4 g.) of the borofluoride was isolated in the usual manner.

In a typical decomposition, a small flask containing 8.1 g. of the borofluoride was immersed in an oil-bath heated to 145° until evolution of boron trifluoride ceased. The black product was extracted with benzene, the combined extracts filtered and the filtrate concentrated to give 4.1 g. (63%) of fine crystals. These were reduced[20] directly to yield 2.6 g. (70%) of *p*-amino-*p*′-fluorodiphenylsulfone, m. p., after recrystallization from alcohol–water, 200.4–201.6°.

Anal. Calcd. for $C_{12}H_{10}O_2NSF$: S, 12.8; N, 5.6. Found: S, 12.6, 12.7; N, 5.8, 5.9.

***p*-Fluorobenzenesulfonyl Chloride.**—The procedure of Huntress[21] was found to be satisfactory on a large scale if the reaction was conducted at −5 to 0° with vigorous stirring and the reaction mixture was then allowed to stand overnight. The product, purified by distillation at 105–110° at 5 mm., was isolated in 83% yield. The amount of sulfone formed was negligible.

***p*-Chloro-*p*′-fluorodiphenylsulfone.**—This compound was prepared in 69% yield by the procedure of Beckurts,[22] modified in that the reaction mixture after hydrolysis was steam distilled to remove excess chlorobenzene. Recrystallized from alcohol–water, it formed large prisms melting at 113.2–113.6°.

Anal. Calcd. for $C_{12}H_8O_2SClF$: S, 11.9. Found: S, 12.1, 12.1.

***p*-Fluoro-*p*′-hydroxydiphenylsulfone.**—The methoxy derivative was prepared in 90% yield by the method of Beckurts[22] with the modification described above. It melted at 88.5–90.1° after recrystallization from alcohol–water.

---

(8) Zenitz and Hartung, *J. Org. Chem.*, **11**, 444 (1946).

(9) Magidson, Grigorovskii and Gal'perin, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 56 (1938).

(10) Bachman and Wetzel, *J. Org. Chem.*, **11**, 454 (1946).

(11) Price and Roberts, *ibid.*, **11**, 463 (1946).

(12) Holleman, *Rec. trav. chim.*, **23**, 225 (1904).

(13) Doak, THIS JOURNAL, **62**, 167 (1940).

(14) (a) Ruddy, Starkey and Hartung, *ibid.*, **64**, 828 (1942); (b) Palmer with Adams, *ibid.*, **44**, 1356 (1922).

(15) Ehrlich and Bertheim, *Ber.*, **45**, 756 (1912).

(16) Stevinson and Hamilton, THIS JOURNAL, **57**, 1298 (1935).

(17) Jacobs, Heidelberger and Rolf, *ibid.*, **40**, 1580 (1918).

(18) The obvious method for the preparation of this compound by way of *p*-amino-*p*′-nitrodiphenyl sulfide was attempted but abandoned because of our failure, despite repeated attempts, to obtain the latter compound by the procedure of Raiziss, *et al.*, *ibid.*, **61**, 2763 (1939).

(19) Obtained by the hydrolysis of *p*-nitro-*p*′-acetylaminodiphenylsulfone ["Organic Syntheses," Vol. 22, 31 (1942)] with hydrochloric acid in alcohol solution.

(20) According to method of Ferry, Buck and Baltzly, ref. cited under (19).

(21) Huntress and Carten, THIS JOURNAL, **62**, 511 (1940).

(22) Beckurts and Otto, *Ber.*, **11**, 2066 (1878).

Anal. Calcd. for $C_{13}H_{11}O_3SF$: S, 12.1. Found: S, 12.2, 12.4.

The desired hydroxy compound was prepared by refluxing 10.0 g. of the methoxy derivative in a mixture of 100 cc. of acetic acid and 125 cc. of concentrated hydrobromic acid for sixty hours. The reaction mixture was diluted with water, made almost neutral with sodium hydroxide, and the product extracted with benzene which was then back-extracted with 20% sodium hydroxide solution. The latter solution was re-acidified and extracted with benzene. After washing with water and drying the solvent was evaporated leaving 7.0 g. (74%) of *p*-fluoro-*p*′-hydroxydiphenylsulfone, m. p. 111.8–113.1°, following recrystallization from alcohol–water.

Anal. Calcd. for $C_{12}H_9O_3SF$: S, 12.7. Found: S, 12.9, 12.9.

***p*,*p*′-Difluorodiphenylsulfone.**—Because of the facts that the application of the generalized Schiemann procedure in the case of *p*,*p*′-diaminodiphenylsulfone led only to the formation of tarry material and that the results of Huntress[21] could not be duplicated[23] the conventional method of Beckurts[22] was employed. The compound, m. p. 97.5–98.1°,[24] even after repeated recrystallization from alcohol, was obtained in 95% yield.

Anal. Calcd. for $C_{12}H_8O_2SF_2$: S, 12.6. Found: S, 12.5, 12.5.

m-Fluorophenol.—Approximately 580 g. (29 moles) of anhydrous hydrogen fluoride was added to 163 g. (1.5 moles) of *m*-aminophenol contained in a 1-liter copper beaker cooled in ice. To the stirred mixture 104 g. (1.5 moles) of sodium nitrite was added over the course of one hour; stirring was continued for two more hours. The reaction mixture was then allowed to stand for two days in an iron flask provided with an efficient hydrogen fluoride condenser, after which it was steam distilled and the distillate extracted with ether. After the ether extract had been washed with ammonium hydroxide and dried, the solvent was removed and the residue distilled to yield 58.2 g. (35%)[25] of *m*-fluorophenol, b. p. 97–103° at 46 mm.

An alternate method of synthesis using the Schiemann reaction was attempted unsuccessfully. Preparation of *m*-nitroanisole by the procedure of Vermeulen[26] was effected in quantitative yields provided that carefully purified *m*-nitrophenol was used. The *m*-nitroanisole was reduced to *m*-anisidine in 82% yield with Raney nickel catalyst in absolute alcohol. The borofluoride of the latter compound, however, decomposed spontaneously at room temperature.

2-Acetoxymercuri-5-fluorophenol.[27]—To a solution of 3.9 g. of *m*-fluorophenol in 60 cc. of water was added 10.8 g. of mercuric acetate in 30 cc. of water acidulated with acetic acid. After four days of standing the mixture was filtered and the precipitate washed with water, dried and recrystallized from acetic acid. The product (10.4 g., 80%) crystallized as colorless plates, decomposing over a wide range starting at 250°.

The *s*-Amyl-5-fluorophenols.—Application of the method of Klarman, *et al.*,[28] to *m*-fluorophenol gave two isomers, the first boiling at 88–91° at 1.5 mm., and the second at 93–95° at 0.4 mm. No attempt was made to determine the exact structure of these compounds, which are probably 2-*s*-amyl-5-fluorophenol and 4-*s*-amyl-5-fluorophenol.

Anal. Calcd. for $C_{11}H_{15}OF$: C, 72.5; H, 8.2. Found for first isomer: C, 72.3, 72.7; H, 8.0, 8.1. Found for second isomer: C, 72.1, 72.4; H, 8.1, 8.1.

3,3-bis-(4-Fluorophenyl)-phthalide.—To a mixture of 8.0 g. of phthaloyl chloride and 40 cc. of fluorobenzene kept at 60–70° anhydrous aluminum chloride (7.6 g.) was added in small portions with shaking. The mixture was warmed on a steam-bath for three hours and then allowed to stand at room temperature overnight. Following removal of the fluorobenzene at the water pump the residue was stirred with dilute sodium hydroxide solution for several hours and the mixture was then acidified to yield 12.0 g. (92%) of the phthalide, m. p., after recrystallization from alcohol–water, 125.1–126.2°.

Anal. Calcd. for $C_{20}H_{12}O_2F_2$: C, 74.5; H, 3.7. Found: C, 74.4, 74.4; H, 3.9, 3.8.

Attempted condensation of fluorobenzene and phthalic anhydride in the presence of sulfuric acid or anhydrous hydrogen fluoride under a variety of conditions was unsuccessful.

N^4-Acetyl-*p*′-fluorosulfanilanilide.—Exactly 13.0 g. of acetylsulfanilyl chloride was added gradually to a solution of 5.6 g. of *p*-fluoroaniline in 34 cc. of acetone and 5 cc. of pyridine. After standing overnight the mixture was filtered, the filtrate concentrated, 50 cc. of water added with stirring and the mixture filtered to yield 9.8 g. (63%) of colorless needles, m. p. 189.9–190.1°, after recrystallization from alcohol–water.

Anal. Calcd. for $C_{14}H_{13}O_3N_2SF$: N, 9.1; S, 10.4. Found: N, 9.1, 9.1; S, 10.6, 10.7.

Hydrolysis of the acetyl compound gave a 94% yield of *p*′-fluorosulfanilanilide, m. p. 163.2–164.1°[29] after recrystallization from alcohol–water.

N^4-Succinyl-*p*′-fluorosulfanilanilide.—Prepared in 92% yield by the general procedure of Miller, *et al.*,[30] this product melted at 141.3–142.9° after recrystallization from alcohol–water.

Anal. Calcd. for $C_{16}H_{15}O_5N_2SF$: S, 8.8; N, 7.7. Found: S, 8.3, 8.4; N, 7.9, 8.0.

4′-Fluoro-4-succinimido-benzenesulfonanilide.—This compound was prepared in 61% yield by the general method of Miller, *et al.*[30] It formed micro-crystals from hot water, m. p. 156.1–157.5°.

Anal. Calcd. for $C_{16}H_{13}O_4N_2SF$: S, 9.2; N, 8.1. Found: S, 9.2, 8.9; N, 8.0, 8.0.

Acknowledgment.—We wish to acknowledge the kindness of Dr. C. M. Suter of the Winthrop Research Institute for supplying the noval diamine and to Parke, Davis and Company for supplying the *p*,*p*′-diaminodiphenylsulfone used in this investigation.

Summary

As the preliminary step in a study designed to determine the effect of fluorine substitution on chemotherapeutic and germicidal agents a number of new fluorine-containing compounds related to medicinals of the following general types have been prepared and described: (1) antimalarials, (2) arsenicals, (3) diphenylsulfones, (4) antiseptics derived from resorcinol and (5) sulfonanilides. Specifically, synthesis of the following compounds has been described: 2-fluoro-6-chloro-9-(1-methyl-4-diethylaminobutyl)-aminoacridine as an

---

(23) Despite repeated attempts, the only product obtained by the direct action of chlorosulfonic acid on fluorobenzene, even when more drastic conditions were employed, was *p*-fluorobenzenesulfonyl chloride. The reported formation of *p*,*p*′-difluorodiphenylsulfone may, perhaps, be due to the unsuspected presence in the reaction mixture of small amounts of some catalytic agent.

(24) Huntress and Carten, ref. 21, reported 100°.

(25) Although the yield is low, this procedure has the advantages of simplicity and ready availability of the starting material, *m*-aminophenol.

(26) Vermeulen, *Rec. trav. chim.*, **25**, 12 (1906).

(27) Although the exact structure of the compound has not been proved, the assigned structure appears likely on the basis of the strong *para*-orienting effect of the fluorine atom.

(28) Klarman, Shternov and Gates, This Journal, **55**, 2576 (1933).

(29) In agreement with value reported by Suter and Weston, ref. 3c.

(30) Miller, Rock and Moore, This Journal, **61**, 1198 (1939).

analog of atebrin; 3,3′-diamino-4,4′-difluoroarsenobenzene, 3-amino-4-fluorophenylarsonic acid and 3-acetylamino-4-fluorophenylarsonic acid as analogs of the trypanocidal 3-amino-4-hydroxy-compounds; *p*-amino-*p*′-fluorodiphenylsulfone, *p*-chloro-*p*′-fluorodiphenylsulfone, *p*-fluoro-*p*′-hydroxydiphenylsulfone and *p*,*p*′-difluorodiphenylsulfone as analogs of diphenylsulfones of current interest; 2-acetoxymercuri-5-fluorophenol and two isomeric *s*-amyl-5-fluorophenols as analogs of the germicidal resorcinol derivatives; 3,3-bis-(4-fluorophenyl)-phthalide as an analog of phenolphthalein; and *p*-fluoro- derivatives of N^4-succinylsulfanilanilide and 4-succinimido-benzenesulfonanilide.]

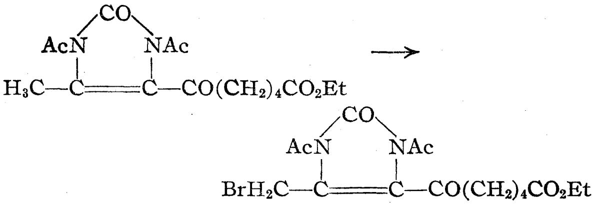
LAWRENCE, KANSAS RECEIVED AUGUST 23, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

Synthesis of Imidazolones Structurally Related to Biotin by Means of N-Bromosuccinimide[1]

BY ROBERT DUSCHINSKY AND L. ALLEN DOLAN

The preparation of 1,3-diacetyl-4-bromomethyl-5-(δ-carbethoxyvaleryl)-2-imidazolone as illustrated



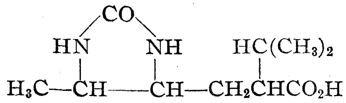
by application of Ziegler's[2] bromination method and the replacement of the bromine by oxygen-containing groups were essential steps in a recently reported synthesis of O-heterobiotin.[3]

The present paper demonstrates the versatility of the bromination and replacement reactions in the synthesis of a number of imidazolone derivatives. Some of them are structurally related to biotin since they possess its C,N skeleton and carry in the α-position of the side chains heteroatom-containing groups. The bromo compounds and substitution products are listed in Table I. Starting materials are the corresponding bromine-free compounds.

With the exception of 4-methyl-5-carbethoxy-2-imidazolone, which directly reacted with bromine to give I, diacylated imidazolones were used for the bromination by Ziegler's method.[4] The bromination was achieved by refluxing a carbon tetrachloride solution of such an imidazolone with one or, for the preparation of the dibromo compound IV, with two moles N-bromosuccinimide until the latter was completely converted into succinimide. The bromo compounds obtained in good yields are crystalline, not lachrymatory solids, which are sometimes inclined to undergo decomposition with release of hydrobromic and acetic acid. It is, therefore, advantageous to proceed at once with the desired replacement reaction. Depending on the reagent and reaction conditions, the replacement of the bromine may be accompanied by total or partial loss of the acetyl groups. Formation of mixtures of unacetylated, mono- and diacetylated products explains some of the low yields encountered in the substitution reactions.

Proof of the introduction of bromine into the methyl group has been established for the keto ester VI.[3] The same is true for compound I, because it was found to be identical with the product obtained from ethyl δ-ethoxy-β-ketobutyrate via 4 - ethoxymethyl - 5 - carbethoxy - 2 - imidazolone (IA).[5]

The structure of III was established by conversion into an acetyl-free substitution and hydrogenation product. Thus, application of a method described for the preparation of 5-allyl-5-isopropylbarbituric acid[6] gave the barbiturate IIIA in fair yield. Due to its "de-aromatization" by acetyl groups,[3] the compound could be hydrogenated with palladium charcoal catalyst at room temperature, whereby only one of the two possible diastereomers, undoubtedly the *cis* form, was obtained in excellent yield.[7] It was readily deacetylated by cold sodium hydroxide. The obtained 4-methyl-5-(5′-isopropyl-5′-barbiturylmethyl)-2-imidazolidone was microbiologically inactive. Attempts to cleave the barbiturylimidazolone and imidazolidone for the purpose of obtaining the desthiobiotin isomer VIII correspond-



VIII

---

[1] Presented before the Division of Organic Chemistry, 109th Meeting of the American Chemical Society, Atlantic City, New Jersey, April 10, 1946.

[2] Ziegler, Späth, Schaaf, Schumann and Winkelmann, *Ann.*, **551**, 80 (1942).

[3] Duschinsky and Dolan, "Jubilee Vol. Emil Barell," Basle, 146 (1946).

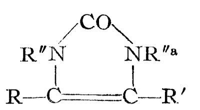
[4] 1,3-Diacetyl-4,5-dimethyl-2-imidazolone reacted also with bromine to give the dibromo derivative IV, but the yield was very low.

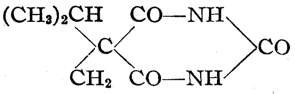
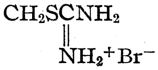
[5] Duschinsky and Dolan, THIS JOURNAL, **68**, 2350 (1946).

[6] Hoffmann–La Roche and Co., German Patent 526,854 (1930); *C. A.*, **25**, 4893 (1931).

[7] The barbiturate IIIA and its hydrogenation product were found devoid of hypnotic properties by Dr. G. Lehmann of the Pharmacological Laboratories of Hoffmann–La Roche Inc.

TABLE I



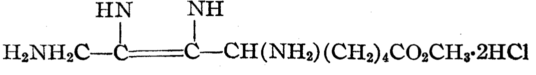
Bromo cpd. (R = CH_2Br) No.	R′	R″	Reactant	Substitution product isolated No.	R	R′	R″
I	CO_2Et	H	NaOEt	IA	CH_2OEt	CO_2Et	H
	CO_2Et	H	Ag acetate	IB	CH_2OAc	CO_2Et	H
II	H	Ac	Ethyl calcio malonate	IIA	$CH_2CH(CO_2H)_2$	H	H
	H	Ac	Dibenzylamine	IIB	$CH_2N(CH_2C_6H_5)_2$	H	Ac[b]
III	CH_3	Ac	Na isopropylbarbiturate	IIIA		H	Ac
IV	CH_2Br	Ac	Na acetate	IVA	CH_2OAc	CH_2OAc	Ac
V	$CO(CH_2)_4CO_2Me$	Ac[c]	Ag benzoate	VA	$CH_2O_2CC_6H_5$	$CO(CH_2)_4CO_2Me$	Ac
	$CO(CH_2)_4CO_2Me$	Ac	Thiourea	VB	 $CH_2S\underset{\overset{\Vert}{NH_2^+Br^-}}{C}NH_2$	$CO(CH_2)_4CO_2Me$	Ac
	$CO(CH_2)_4CO_2Me$	Ac	Dibenzylamine	VC	$CH_2N(CH_2C_6H_5)_2$	$CO(CH_2)_4CO_2Me$	H
VI	$CO(CH_2)_4CO_2Et$	Ac	Dibenzylamine[d]	VIA	$CH_2N(CH_2C_6H_5)_2$	$CO(CH_2)_4CO_2Et$	Ac[b]
	$CO(CH_2)_4CO_2Et$	Ac	Dibenzylamine[e]	VIB	$CH_2N(CH_2C_6H_5)_2$	$CO(CH_2)_4CO_2Et$	H
	$CO(CH_2)_4CO_2Et$	Ac	Na_2SO_3	VIC	CH_2SO_3Na	$CO(CH_2)_4CO_2Et$	H
VII	COC_6H_5	Ac	Dibenzylamine	VIIA	$CH_2N(CH_2C_6H_5)_2$	COC_6H_5	Ac[b]
	COC_6H_5	Ac	$AgNO_2$	VIIB	CH_2NO_2	COC_6H_5	Ac

[a] The diacyl compounds are written as N,N-derivatives, although the possibility of N,O-acylation cannot be excluded. [b] One acetyl group only. [c] The dipropionyl derivative was also prepared. [d] Four moles at room temperature. [e] Five and one-half moles, refluxed in benzene.

ing in structure to Kögl's "α-biotin"[8] were abandoned when the accomplished synthesis of such desthiobiotin isomers by Brown and Ferger[9] became known to us.

Structures II, V and VII are assigned by analogy without direct proof. For the dibromo compound IV a symmetrical structure is assumed.

Treatment of the diacetyl bromo compounds with dibenzylamine, depending on the temperature and the excess of amine present, causes more or less stepwise removal of one acetyl group, replacement of the bromine and finally removal of the second acetyl group. 4-Dibenzylaminomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone (VC), obtained from V in 70% yield, gave an oxime (84% yield) which upon palladium–charcoal catalyzed hydrogenation in presence of hydrochloric acid afforded 4-aminomethyl-5-(α-amino-ε-carbomethoxyamyl)-2-imidazolone dihydrochloride (IX) in 46% yield.


IX

The same sequence of reactions was performed with the ethyl ester VI.

Sulfur-containing substituents were introduced by treating bromoesters V and VI with thiourea and sodium sulfite, respectively. The isothiouronium bromide VB and the sodium sulfonate VIC resulted in fair to good yields.

It was previously reported that the keto group located in the α-position of *unacetylated* imidazolones undergoes easily hydrogenolysis and is converted into methylene.[5,10] In an analogous manner the keto esters VC and VIC lost the keto groups upon catalytic hydrogenation under mild conditions. Compound VC was also debenzylated. The ring double bond as well as the α-amino and α-sulfo groups remained intact, however. 4-Aminomethyl-5-(ε-carbomethoxyamyl)-2-imidazolone hydrochloride and the sodium salt of 4-sulfomethyl-5-(ε-carbethoxyamyl)-2-imidazolone were isolated in good yields.

1,3 - Diacetyl - 4 - methyl - 5 - (ε - carbethoxyamyl)-2-imidazolone[10] and 1,3-diacetyl-4,5-dipropyl-2-imidazolone reacted with two moles of bromosuccinimide whereby an amount of succinimide was recovered which indicated bromination in the α-methylene groups. However, no crystalline dibromo derivatives could be isolated.

Experimental[11]

4-Bromomethyl-5-carbethoxy-2-imidazolone (I).—To a stirred boiling suspension of 51 g. of 4-methyl-5-carbethoxy-2-imidazolone[5] in one liter of carbon tetrachloride 48 g. of bromine was added within one hour. Boiling and stirring were continued for five more hours. After cooling the bromo ester was filtered and washed with carbon tetrachloride; yield 73.5 g. (98.5%). The substance decomposed *in vacuo* at *ca.* 220°. No depression was observed in admixtures with material obtained by a previously described method.[5]

---

[8] Kögl and Borg, *Z. physiol. Chem.*, **281**, 65 (1944).

[9] Brown and Ferger, THIS JOURNAL, **68**, 1507 (1946). We are indebted to Dr. Vincent du Vigneaud for communicating to us the contents of this paper prior to its publication.

[10] Duschinsky and Dolan, *ibid.*, **67**, 2079 (1945).

[11] Melting points were determined with an uncalibrated set of Anschütz thermometers. For the microanalyses we are indebted to Dr. Al Steyermark and his staff, for the microbiological assays to Dr. S. H. Rubin and his staff.

4-Ethoxymethyl-5-carbethoxy-2-imidazolone (IA).—To a solution of 11.1 g. of the foregoing bromo ester in 220 cc. of ethanol (obtained by short boiling and subsequent cooling) 43.2 cc. of *N* sodium ethoxide solution was added until the mixture was slightly alkaline to methyl orange. Evaporation *in vacuo* and crystallization of the residue from 5 cc. of water yielded 6.2 g. (65%) of needles, melting at 178–180° and showing no depression in admixtures with material obtained previously.[5]

4-Acetoxymethyl-5-carbethoxy-2-imidazolone (IB).—To a solution of 4.98 g. of bromo ester I in 90 cc. of hot acetic acid 3.34 g. of silver acetate was added with stirring. After ten minutes the silver bromide was filtered and the solution evaporated *in vacuo*. The residue was crystallized from 10 cc. of ether; yield 2.75 g. (60%). The substance was recrystallized by dissolving in 100 cc. of boiling ethyl acetate and adding 100 cc. of petroleum ether; m. p. 154–155°.

Anal. Calcd. for $C_9H_{12}O_5N_2$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.51; H, 5.36; N, 12.33.

1,3-Diacetyl-4-bromomethyl-2-imidazolone (II).—A solution of 9.1 g. of 1,3-diacetyl-4-methyl-2-imidazolone[10] in 30 cc. of carbon tetrachloride was refluxed with 8.55 g. of bromosuccinimide for twenty minutes until the potassium iodide reaction was negative and the succinimide was visible as a layer covering the top of the liquid. After cooling, the imide was filtered off, the filtrate evaporated *in vacuo* and the residue crystallized from ether; yield, 9.14 g. (70%). It crystallized in needles, melting at 80–81°, which were inclined to turn pink. For the analysis a sample was sublimed at 0.3 mm. and 90° (bath).

Anal. Calcd. for $C_8H_9O_3N_2Br$: C, 36.80; H, 3.47; N, 10.73. Found: C, 36.52; H, 3.34; N, 10.40.

4-(β,β-Dicarboxyethyl)-2-imidazolone (IIA).—The carbon tetrachloride solution obtained in the above described manner by reaction of 3.64 g. of 1,3-diacetyl-4-methyl-2-imidazolone and 3.54 g. of bromosuccinimide and filtering the succinimide was added slowly to 20 cc. of a 1.1 *N* calcio diethyl malonate[12] solution in carbon tetrachloride. The mixture was refluxed with stirring for four and one-half hours, then washed in a separatory funnel with water until the washings were bromine-free. The carbon tetrachloride layer was dried over sodium sulfate and evaporated to a yellow oil. After removing excess malonic ester by heating *in vacuo* in a bath at 140°, a solution of 8 g. of sodium hydroxide in 55 cc. of water was mixed with the residue and let stand overnight. Some tar was filtered off, the solution was concentrated on a water-bath to 20 cc., neutralized with hydrochloric acid and evaporated to dryness. The residue was extracted three times with 25 cc. of boiling dioxane. The dioxane extract was evaporated to dryness and extracted three times with 10 cc. of ether. The ether insoluble residue was crystallized from 6 cc. of water; yield 610 mg. (15%) as needles which after recrystallization from 10 cc. of water melted in an evacuated capillary tube at 253–255°.

Anal. Calcd. for $C_7H_8O_2N$: C, 42.00; H, 4.03; N, 14.00. Found: C, 41.80; H, 3.89; N, 13.76.

Acetyl-4-dibenzylaminomethyl-2-imidazolone (IIB).—A solution of 1.64 g. of II in 25 cc. of benzene was mixed with a solution of 6.3 g. (5 moles) of dibenzylamine in 25 cc. of benzene. The mixture was refluxed with stirring for three hours. The crystallized dibenzylamine hydrobromide (1.62 g.) was sucked off, the filtrate evaporated and finally dried *in vacuo* at 100°. The resulting honey-like mass was twice extracted with 50 cc. of petroleum ether whereupon it became almost solid. Crystallization from 10 cc. of methanol and recrystallization from ethanol gave 190 mg. (9%) of needles melting at 174–176°. The analysis indicated the presence of some diacetyl compound.

Anal. Calcd. for $C_{20}H_{21}O_2N_3$: C, 71.62; H, 6.31; N, 12.53; CH_3CO, 12.83. Found: C, 71.47; H, 6.17; N, 11.77; CH_3CO, 14.30.

1,3-Diacetyl-4-bromomethyl-5-methyl-2-imidazolone (III).—A solution of 19.6 g. of 1,3-diacetyl-4,5-dimethyl-2-imidazolone[13] in 200 cc. of carbon tetrachloride was refluxed for fifteen minutes with 17.5 g. (1 mole) of bromosuccinimide and worked up as described above. Crystallization from 30 cc. of ether yielded 22.3 g. (81.5%) of colorless needles melting at 84–89°.

Anal. Calcd. for $C_9H_{11}O_3N_2Br$: C, 39.29; H, 4.03. Found: C, 39.41; H, 4.45.

1,3-Diacetyl-4-methyl-5-(5′-isopropyl-5′-barbiturylmethyl)-2-imidazolone (IIIA).—A solution of 21.96 g. of the foregoing freshly prepared bromo compound in 80 cc. of dioxane was added gradually to a cooled solution of 13.89 g. of 5-isopropyl-barbituric acid in 81 cc. of *N* sodium hydroxide which held 0.2 g. of copper–bronze powder in suspension. After shaking the mixture consisting of two layers for fourteen hours it was evaporated to a heavy oil which was dissolved in 70 cc. of methanol. Gradual addition of 70 cc. of water yielded crystals which were washed with 90 cc. of 50% methanol until they were bromine free; yield 13.93 g., m. p. 164–172°. Extraction with 100 cc. of dry ether left undissolved 10.89 g. material melting at 183–186° (37.4%). The product can be recrystallized from aqueous 40% ethanol. It melts then at 189–191°.

Anal. Calcd. for $C_{16}H_{20}O_6N_4$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.61; H, 5.37; N, 15.51.

1,3-Diacetyl-4-methyl-5-(5′-isopropyl-5′-barbiturylmethyl)-2-imidazolidone.—The foregoing ether-washed imidazolone (IIIA) (2.44 g.) was hydrogenated for three hours with 750 mg. of 10% palladium-charcoal catalyst in 25 cc. of acetic acid at room temperature and atmospheric pressure until 1 mole hydrogen was taken up and the reaction stopped. The filtered solution was evaporated and the well-dried residue became crystalline upon addition of 20 cc. of ether; yield 1.97 g. (83%), melting at 237–241°, and after recrystallization from 30 volumes of 50% ethanol at 243–244°.

Anal. Calcd. for $C_{16}H_{22}O_6N_2$: C, 52.45; H, 6.05. Found: C, 52.61; H, 6.39.

4-Methyl-5-(5′-isopropyl-5′-barbiturylmethyl)-2-imidazolidone.—The above diacetyl compound (760 mg.) was dissolved in 7.2 cc. of *N* sodium hydroxide. After five hours the solution was neutralized with 7.2 cc. of *N* hydrochloric acid. The separated crystals were filtered and washed with water; yield 490 mg. (84%), melting at 261–263°, and after recrystallization from water at 269–271° (*in vacuo*). The compound revealed neither biotin nor antibiotin activity for *Saccharomyces cerevisiae* No. 139 and *Lactobacillus casei*.

Anal. Calcd. for $C_{12}H_{18}O_4N_2$: C, 51.05; H, 6.43; N, 19.85. Found: C, 51.17; H, 6.50; N, 19.70.

1,3-Diacetyl-4,5-bis-(bromomethyl)-2-imidazolone (IV).—A solution of 3.92 g. of 1,3-diacetyl-4,5-dimethyl-2-imidazolone in 40 cc. of carbon tetrachloride was refluxed for thirty minutes under stirring with 7.08 g. (2 moles) of bromosuccinimide. The solution filtered from the succinimide was concentrated to a sirup which became crystalline upon addition of 10 cc. of dry ether. The crystals were washed with ether; yield 3.51 g. (49.6%), m. p. 108–110°. The product can be recrystallized from ether containing 4% dioxane.

Anal. Calcd. for $C_9H_{10}O_3N_2Br_2$: C, 30.53; H, 2.85; N, 7.91. Found: C, 30.97; H, 3.07; N, 7.97.

1,3-Diacetyl-4,5-bis-(acetoxymethyl)-2-imidazolone (IVA).—A mixture of 380 mg. of IV, 10 cc. of dry acetone and 1 g. of anhydrous potassium acetate was shaken for forty-eight hours. Addition of ether to the filtered solution produced 135 mg. (43%) of crystals melting at *ca.* 133°, which after sublimation at 0.4 mm. and 160° (bath) melted at 143–145°.

Anal. Calcd. for $C_{13}H_{16}O_7N_2$: C, 50.00; H, 5.16; N, 8.97. Found: C, 49.95; H, 5.18; N, 8.98.

---

(12) Prepared by modifying a method described by Lund, *Ber.*, **67**, 935 (1934).

(13) Biltz, *ibid.*, **40**, 4801 (1907).

1,3-Diacetyl-4-methyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone.—A mixture of 37.9 g. of 4-methyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone[5] and 165 cc. of acetic anhydride was refluxed for twenty minutes. The resulting solution was concentrated to a small volume first at atmospheric pressure, then *in vacuo*. The residue was taken up with 165 cc. of acetic anhydride. The refluxing and evaporating were repeated. The final residue was dried for one hour at 100° *in vacuo* and crystallized by addition of 40 cc. of methanol and cooling in an acetone–Dry Ice-bath; yield 44.2 g. (87%), melting at 68–69°, and after recrystallization from methanol at 69–70°.

Anal. Calcd. for $C_{15}H_{20}O_6N_2$: C, 55.55; H, 6.22. Found: C, 55.59; H, 6.16.

The **dipropionyl derivative** was obtained as described above in a yield of 84% by substituting propionic anhydride for acetic anhydride. It melted at 65–66°.

Anal. Calcd. for $C_{17}H_{24}O_6N_2$: C, 57.94; H, 6.86. Found: C, 57.74; H, 6.76.

1,3-Diacetyl-4-bromomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone (V).—A solution of 16.2 g. of 1,3-diacetyl-4-methyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone in 95 cc. of carbon tetrachloride was refluxed for one hour with 8.55 g. of bromosuccinimide. The solution filtered from the succinimide (4.44 g.) was evaporated and the residue crystallized from 50 cc. of cold ether; yield 18.5 g. (92%) colorless needles melting at 58–60°, and after recrystallization from 4 volumes of methanol at 59–61°.

Anal. Calcd. for $C_{15}H_{19}O_6N_2Br$: C, 44.68; H, 4.75. Found: C, 44.74; H, 4.54.

1,3-Dipropionyl-4-bromomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone.—It was obtained in an analogous manner with a yield of 53%, m. p. 59–61°.

Anal. Calcd. for $C_{17}H_{23}O_6N_2Br$: C, 47.34; H, 5.37. Found: C, 47.38; H, 5.40.

1,3-Diacetyl-4-benzoxymethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone (VA).—A solution of 4.03 g. of crude bromo ester V in 50 cc. of dioxane was shaken for two days with 5 g. of silver benzoate. The filtered bromine-free solution was evaporated. The residue was extracted with ether which left some silver-containing material undissolved. The ether extract was evaporated to an oil which became crystalline upon addition of methanol; yield 2.34 g. (53%). The material melting at *ca.* 90° was recrystallized by dissolving in 40 cc. of ether, adding methanol and evaporating the ether *in vacuo;* yield 1.8 g. of crystals melting at 90–93°.

Anal. Calcd. for $C_{22}H_{24}O_8N_2$: C, 59.45; H, 5.44; N, 6.30. Found: C, 59.70; H, 4.90; N, 6.12.

1,3-Diacetyl-4-guanylthiomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone Hydrobromide (VB).—To a solution of 0.76 g. of thiourea in 50 cc. of anhydrous dioxane 4.03 g. of bromo ester V was added. The mixture was refluxed for ten minutes, then cooled, whereupon the hydrobromide crystallized in fine leaflets. It was filtered and washed with dioxane and ether; yield 3.23 g. (68%). The substance melted at 161–162° and after recrystallization from 12 volumes of dioxane at 164–165°.

Anal. Calcd. for $C_{16}H_{23}O_6N_4SBr$: C, 40.09; H, 4.84; N, 11.69; S, 6.69. Found: C, 40.13; H, 4.90; N, 11.62; S, 6.24.

Acetyl-4-bromomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone.—When a carbon tetrachloride solution of diacetyl bromo ester V was treated for fifteen minutes at room temperature with one mole of dibenzylamine a substantial amount (*ca.* 20%) of monoacetyl bromo ester crystallized out. It was recrystallized from benzene, m. p. 129–130°.

Anal. Calcd. for $C_{13}H_{17}O_5N_2Br$: C, 43.22; H, 4.75; N, 7.76; Br, 22.13. Found: C, 43.53; H, 4.73; N, 7.85; Br, 22.15.

4-Dibenzylaminomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone (VC).—Solutions of 44 g. of crude bromo ester V in 700 cc. of benzene and of 120 g. (5.6 moles) of dibenzylamine in 100 cc. of benzene were mixed and refluxed with stirring for six and one-half hours. After cooling the crystallized 28.5 g. (94%) of dibenzylamine hydrobromide was filtered off. The filtrate was evaporated to a yellowish sirup which was washed by four extractions with a total of 1.5 liters of petroleum ether. The petroleum ether insoluble oil became crystalline when mixed with 250 cc. of ether. The still pasty crystals were filtered off and recrystallized from 200 cc. of methanol; yield 33.2 g. (70%), m. p. 134–135°. After a second recrystallization the substance melted at 135–136°.

Anal. Calcd. for $C_{25}H_{29}O_4N_3$: C, 68.49; H, 6.71; N, 9.65. Found: C, 68.92; H, 6.51; N, 9.66.

The **free acid** was prepared from the foregoing ester by heating on a water-bath for one hour with a mixture of 10 volumes of *N* sodium hydroxide and 5 volumes of methanol and neutralizing with hydrochloric acid. It was recrystallized from aqueous ethanol, m. p. 207–208°.

Anal. Calcd. for $C_{24}H_{27}O_4N_3$: C, 68.39; H, 6.46. Found: C, 68.26; H, 6.17.

Acetyl-4-dibenzylaminomethyl-5-(δ-carbethoxyvaleryl)-2-imidazolone (VIA).—To a solution of 835 mg. of bromo ethyl ester VI in 20 cc. of benzene 790 mg. of dibenzylamine (2 moles) in 20 cc. of benzene was added dropwise with stirring. Dibenzylamine hydrobromide was filtered off after letting the mixture stand for twenty hours. Since only 300 mg. of hydrobromide (59%) was recovered another 790 mg. of dibenzylamine was added. An additional crop of dibenzylamine hydrobromide (total 90%) was filtered off after letting the mixture stand overnight. The filtrate was concentrated to a sirup which was mixed with ethanol to produce 430 mg. (45%) of crystals melting at 98–100°, and after recrystallization from 5 cc. of ethanol at 101–102°.

Anal. Calcd. for $C_{28}H_{33}O_5N_3$: C, 68.41; H, 6.77; CH_3CO, 8.76. Found: C, 68.31; H, 7.27; CH_3CO, 9.18.

4-Dibenzylaminomethyl-5-(δ-carbethoxyvaleryl)-2-imidazolone (VIB).—The bromo ethyl ester VI (8.34 g.) after reaction with 21.5 g. (5.5 moles) of dibenzylamine in the manner described for the methyl ester V gave 6.93 g. (74%) of dibenzylamino compound melting at 103–106°. Several recrystallizations from 95% ethanol raised the melting point to 107–109°. The product was acetyl free and contained one molecule water of crystallization.

Anal. Calcd. for $C_{26}H_{31}O_4N_3 \cdot H_2O$: C, 66.79; H, 6.68; N, 8.99. Found: C, 67.16, 67.23; H, 6.67, 6.85; N, 9.01.

Upon drying *in vacuo* at 100° the substance melted to a yellowish resin and became anhydrous.

Anal. Calcd. for $C_{26}H_{31}O_4N_3$: C, 69.46; H, 6.94. Found: C, 69.43; H, 7.01.

4-Dibenzylaminomethyl-5-(α-oximino-ε-carbomethoxyamyl)-2-imidazolone.—A solution of 8.7 g. of crude methyl ester (VA) in 14 cc. of pyridine was mixed with 2.8 g. (2 moles) of finely powdered hydroxylamine hydrochloride and heated with occasional shaking for thirty-eight hours at 39°. After initial dissolution crystallization started. The reaction mixture was diluted with 120 cc. of water, the crystals were filtered and washed chlorine free with water, then with methanol and ether; yield 7.55 g. (84%), m. p. 188–190°. For the analysis the oxime was recrystallized from 12 volumes methanol. It melted at 191–192°.

Anal. Calcd. for $C_{25}H_{30}O_4N_4$: C, 66.64; H, 6.71; N, 12.44. Found: C, 66.40; H, 6.80; N, 12.76.

4-Dibenzylaminomethyl-5-(α-oximino-ε-carbethoxyamyl)-2-imidazolone was obtained in 65% yield from the crude ethyl ester (VIB) in the above described manner. It was recrystallized from 100 volumes of ethanol and melted at 184–185°.

Anal. Calcd. for $C_{26}H_{32}O_4N_4$: C, 67.22; H, 6.94. Found: C, 67.14; H, 6.84.

4-Aminomethyl-5-(α-amino-ε-carbomethoxyamyl)-2-imidazolone Dihydrochloride (IX).—A mixture of 13.16 g. of crude 4-dibenzylaminomethyl-5-(α-oximino-ε-carbomethoxyamyl)-2-imidazolone, 135 cc. of methanol, 5 cc. of concentrated hydrochloric acid and 7 g. of prehydrogenated palladium oxide catalyst (Baker and Co.) was hydrogenated for one hour at room temperature and four hours at 50° at a pressure of 900–1000 lb. The filtered solution was evaporated *in vacuo* below 40° to a sirup, which was mixed with 35 cc. of methanol and 60 cc. of ether. On standing in the cold 4.38 g. (46%) of thin plates was obtained which melted and decomposed at 173–175°, and after dissolving in 20 volumes of hot methanol and adding 5 volumes of ether at 176–178°. The product gave an intense red ferric chloride reaction indicating the presence of the imidazolone double bond.

Anal. Calcd. for $C_{11}H_{20}O_3N_4 \cdot 2HCl$: C, 40.13; H, 6.74; N, 17.02; Amino N, 8.51. Found: C, 39.82; H, 6.53; N, 17.03; Amino N, 8.78, 8.31.

4-Aminomethyl-5-(α-amino-ε-carbethoxyamyl)-2-imidazolone dihydrochloride was obtained in 56% yield by an analogous hydrogenation in ethanol of 1.75 g. of corresponding oximino ethyl ester. The substance was recrystallized from 85% ethanol and ether. It melted at 164–166° and gave an intense ferric chloride reaction.

Anal. Calcd. for $C_{12}H_{22}O_3N_4 \cdot 2HCl$: C, 41.99; H, 7.05; N, 16.32; Amino N, 8.16. Found: C, 41.97; H, 6.90; N, 16.26; Amino N, 8.41.

4-Aminomethyl-5-(ε-carbomethoxyamyl)-2-imidazolone Hydrochloride.—A suspension of 970 mg. of keto ester (VC) and of 1 g. of prehydrogenated palladium oxide catalyst in 20 cc. of methanol and 0.2 cc. of concentrated hydrochloric acid was hydrogenated at room temperature and atmospheric pressure. Two moles of hydrogen was absorbed in twenty minutes, two additional moles in three hours. The filtered solution was evaporated to a small volume until crystals separated, the amount of which was increased by addition of acetone; yield 410 mg. (70%), m. p. 181–182°. Two recrystallizations from a little methanol raised the melting point to 186–188°. The substance gives an intense red ferric chloride reaction.

Anal. Calcd. for $C_{11}H_{19}O_3N_3 \cdot HCl$: C, 47.56; H, 7.26; N, 15.13; Amino N, 5.04. Found: C, 47.70; H, 7.11; N, 14.92; Amino N, 5.34.

Sodium Salt of 4-Sulfomethyl-5-(δ-carbethoxyvaleryl)-2-imidazolone (VIC).—A mixture of 1.53 g. of bromo ester VIA, 0.93 g. of sodium sulfite (2 moles) and 5 cc. of water was refluxed until after fifteen minutes a clear solution was obtained. Considerable sulfur dioxide evolution was observed. The resulting slightly acidic solution gave upon evaporation *in vacuo* a crystalline cake. In order to decompose any remaining sulfite the product was dissolved in 5 cc. of hot 10% acetic acid and the resulting solution evaporated. The final residue was dissolved in 2 cc. of hot water. Upon addition of 8 cc. of ethanol and cooling, fine needles separated which were washed bromine free by 80% ethanol; yield 0.59 g. (45%). The substance melted under decomposition in an evacuated capillary tube at about 272° and after recrystallization by dissolving in 2 cc. of 10% warm acetic acid and adding 10 cc. of ethanol, whereby 0.52 g. was recovered, at 280–282°.

Anal. Calcd. for $C_{12}H_{17}O_7N_2SNa$: S, 9.00; Na, 6.45; C_2H_5O, 12.65. Found: S, 8.91; Na, 6.57; C_2H_5O, 12.10.

Sodium Salt of 4-Sulfomethyl-5-(ε-carboxyamyl)-2-imidazolone.—The foregoing keto compound (320 mg.) was hydrogenated at room temperature and atmospheric pressure with 300 mg. of prehydrogenated platinum oxide catalyst (Baker and Co.) in 10 cc. of acetic acid. Although in twenty minutes the hydrogen uptake (2 moles) had practically stopped, shaking was continued for fifty minutes. The filtered solution was evaporated *in vacuo* and the obtained residue dissolved in 5 cc. of methanol. Addition of 10 cc. of ether and scratching produced crystallization in microscopic rhombs; yield 230 mg. (76%). The substance was recrystallized with little loss by dissolving in 5 cc. of hot 90% methanol and adding 12 cc. of ether. It melted and decomposed *in vacuo* at about 252° and gave an intense red ferric chloride reaction indicating the presence of the imidazolone double bond.

Anal. Calcd. for $C_{12}H_{19}O_6N_2SNa$: C, 42.10; H, 5.59; S, 9.36; Na, 6.72. Found: C, 42.59; H, 6.11; S, 9.11; Na, 6.80.

1,3-Diacetyl-4-bromomethyl-5-benzoyl-2-imidazolone (VII).—A solution of 2.86 g. of 1,3-diacetyl-4-methyl-5-benzoyl-2-imidazolone[10] in 25 cc. of carbon tetrachloride was refluxed for twenty-five minutes with 1.77 g. of bromosuccinimide. The filtrate from the recovered succinimide (94%) was evaporated to a sirup which became crystalline upon addition of 25 cc. of ether; yield 3.25 g. (89%), m. p. 131–132°. Recrystallization from 20 volumes of ethanol did not change the melting point.

Anal. Calcd. for $C_{15}H_{13}O_4N_2Br$: C, 49.33; H, 3.59. Found: C, 49.44; H, 3.64.

Acetyl-4-dibenzylaminomethyl-5-benzoyl-2-imidazolone (VIIA).—Solutions of 3.13 g. of VII in 40 cc. of benzene and 3.38 g. (2 moles) of dibenzylamine in 20 cc. of benzene were mixed and stirred for two hours, then allowed to stand overnight. The filtrate from the dibenzylamine hydrobromide was evaporated to a volume of *ca.* 10 cc. and mixed with 10 cc. of petroleum ether. The formed crystals were filtered and washed with methanol. The mother liquor gave a second crop on evaporation and addition of 20 cc. of methanol: total yield 1.58 g. (42%) melting at about 195°. Recrystallization from 10 volumes of ethanol raised the melting point to 204–205°, without causing much loss of material.

Anal. Calcd. for $C_{27}H_{25}O_3N_3$: C, 73.78; H, 5.73; N, 9.56; CH_3CO, 9.80. Found: C, 74.32; H, 5.59; N, 9.75; CH_3CO, 10.14.

1,3-Diacetyl-4-nitromethyl-5-benzoyl-2-imidazolone[14] **(VIIB).**—A solution of 1.5 g. of VII in 25 cc. of anhydrous dioxane was shaken for fifteen hours with 2 g. of dry silver nitrite. The solution was rendered bromine free by addition of 1 g. more of silver nitrite and stirring for one hour at 50°. A small amount of sodium chloride was added to the filtrate in order to eliminate silver ions. Evaporation to a sirup and addition of 20 cc. of 50% ethanol yielded 440 mg. (30%) of crystals melting at 137–138° and after recrystallization from 20 cc. of ethanol at 139–140°. The substance contains apparently one molecule of water of crystallization which is not eliminated by drying *in vacuo* at 60°.

Anal. Calcd. for $C_{15}H_{13}O_6N_3 \cdot H_2O$: C, 51.58; H, 4.33; N, 12.03. Found: C, 52.02; H, 4.09; N, 11.80.

1,3-Diacetyl-4,5-dipropyl-2-imidazolone.—4,5-Dipropyl-2-imidazolone[15] (16.8 g.) was acetylated by twice refluxing and evaporating with 90 cc. of acetic anhydride. It was crystallized from ethanol at −30°; yield 18.88 g. (74%), m. p. 57–59°.

Anal. Calcd. for $C_{13}H_{20}O_3N_2$: C, 61.88; H, 7.99. Found: C, 62.19; H, 7.81.

Acknowledgment.—The authors are indebted to Mrs. Donna Ressetar and Mr. Sigfried Muller for technical assistance in a portion of this work.

Summary

A number of 4- and 5-substituted 2-imidazolones were brominated in the α-position of the side chains by applying with one exception Ziegler's N-bromosuccinimide method to the diacyl derivatives. The bromo compounds were submitted to various replacement reactions (Table I).

Imidazolones were prepared which possess the C,N-skeleton of biotin and carry in the α-positions oxygen, nitrogen and sulfur-containing groups (VA, VB, VC, VIA, VIB, VIC, and IX).

Catalytic hydrogenation of the double bond in the diacetyl compound IIIA was possible under

---

(14) The alternative formulation as nitrous acid ester is less likely in view of the stability of the compound toward water and alcohol.

(15) Basse and Klinger, *Ber.*, **31**, 1221 (1898).

mild conditions. Catalytic hydrogenation of the unacetylated compounds VC and VIC caused reduction of the α-keto group to methylene whereas the double bond and the α-amino and α-sulfo group remained intact.

NUTLEY, NEW JERSEY RECEIVED JULY 2, 1947

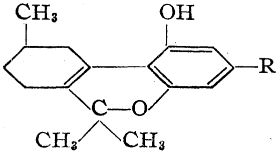
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE SCHOOL OF MEDICINE, UNIVERSITY OF UTAH]

Tetrahydrocannabinol Homologs. XVII.[1]

BY ROGER ADAMS, BEN F. AYCOCK, JR., AND S. LOEWE

Modification of the 3-alkyl substituent of the synthetic tetrahydrocannabinol molecule (I) has resulted in the production of compounds of varying marihuana activity. Such compounds containing a 1′-methylalkyl side-chain have been shown to possess greatly enhanced activity compared to their *n*-alkyl analogs, and the most potent compound previously synthesized, the homolog with a 1′-methylheptyl group, has an activity greater than that of natural tetrahydrocannabinol.[1] Two additional members of the series, the 1′-methyloctyl and the 1′-methylnonyl, have now been synthesized.

The effect of distance from the aromatic ring of a substituent methyl in the 3-alkyl group has been investigated by the synthesis and testing of compounds with the 2′-, 3′- and 4′-methylpentyl groups in the 3-position. In Table I are included for comparison the pharmacological activities of these compounds, the 1′-methyloctyl and 1′-methylnonyl homologs and certain closely related compounds.



I

Inspection of Table I leads to several interesting conclusions. The 1′-methyloctyl homolog (no. 5) has an activity double that of the next lower member (no. 4) and over four times that of natural tetrahydrocannabinol (no. 14); thus it becomes the most potent substance ever tested. As a result of the unusual duration of action of the next higher homolog (no. 6) it is impossible to say where the peak of activity in this series occurs. The 1′-methylnonyl compound is only slightly soluble in propylene glycol and therefore was injected as an emulsion. This fact may account for the prolonged action exhibited by this substance.

It is also apparent that substitution of the alkyl group in the position in the side-chain next to the ring has a much greater effect than in a more distant position, the activity falling from 3.7 in the 1′-methylpentyl to 1.14 in the 4′-methylpentyl. Furthermore, the order of activity of the various isomeric hexyl side chains studied shows that all except the 1′-methylpentyl have a lower potency than the *n*-hexyl, the activities falling in the order: 1′-methylpentyl > *n*-hexyl > 1′-ethylbutyl > 2′-methylpentyl > 3′-methylpentyl > 4′-methylpentyl (isohexyl). It is significant that although the isohexyl homolog was reported to have negligible activity[7] by the Gayer test,[8] its potency, according to the dog ataxia test, is even greater than that of the standard.

The methods of preparation of these homologs are essentially those of Adams and Baker,[9] and

TABLE I

PHARMACOLOGICAL ACTIVITY OF TETRAHYDROCANNABINOL HOMOLOGS

	3-Substituent	No. of expts.	Potency
1	$-C_5H_{11}$-*n*	20	1.00 standard
2	$-C_6H_{13}$-*n*[2]	7	1.82 ± 0.18 (max. in *n*-series)
3	$-C_8H_{17}$-*n*[2]	7	0.66 ± 0.12
4	$-CH(CH_3)C_6H_{13}$[1]	10	16.4 ± 3.67
5	$-CH(CH_3)C_7H_{15}$	19	32.6 ± 3.02[3]
6	$-CH(CH_3)C_8H_{17}$	7	2.08 ± 1.49[3,4]
7	$-CH(CH_3)C_4H_9$[1]	8	3.17 ± 0.33
8	$-CH_2CH(CH_3)C_3H_7$	7	1.58 ± 0.41[3]
9	$-CH_2CH_2CH(CH_3)C_2H_5$	10	1.26 ± 0.18[3]
10	$-CH_2CH_2CH_2CH(CH_3)_2$	4	1.14 ± 0.10[3]
11	$-CH(C_2H_5)C_3H_7$[1]	11	1.67 ± 0.33
12	Natural tetrahydrocannabinol acetate (from charas)[5]	5	14.6 ± 1.05
13	Natural tetrahydrocannabinol by hydrolysis of 12[5]	15	7.8 ± 0.47
14	Tetrahydrocannabinol from cannabidiol[6]	20	7.3 ± 0.89

---

[1] For previous paper see Adams, Chen and Loewe, THIS JOURNAL, **67**, 1534 (1945).

(2) Adams, Loewe, Jelinek and Wolff, *ibid.*, **63**, 1971 (1941).

(3) The values for these compounds were calculated in the basis of standard error values. Miller and Tainter, *Proc. Soc. Exper. Biol. and Med.*, **57**, 261 (1944); Loewe, in press.

(4) Values for No. 6 are incommensurable, since this substance has at least five times the duration of action of its congeners in doses of equal intensity of peak effect.

(5) Wollner, Matchett, Levine and Loewe, THIS JOURNAL, **64**, 26 (1942).

(6) Adams, Loewe, Smith and McPhee, *ibid.*, **64**, 694 (1942).

(7) Russell, Todd, Wilkinson, MacDonald and Woolf, *J. Chem. Soc.*, 826 (1941).

(8) For a discussion of the Gayer test and the dog ataxia test used in these studies, see S. Loewe, *J. Pharm. Exper. Therap.*, **84**, 78 (1945), and "The Marihuana Problem in the City of New York," The Jacques Cattell Press, Lancaster, Pa., 1944, p. 175.

(9) Adams and Baker, THIS JOURNAL, **62**, 2405 (1940).

TABLE II

3,5-DIMETHOXYPHENYL ALKYL KETONES

Alkyl group	Yield, %	B. p.		Empirical formula	Analyses, %			
		°C.	Mm.		Calcd.		Found	
					C	H	C	H
—C_7H_{15}-*n*[2]	60	155	0.5					
—C_8H_{17}-*n*	77	180	1.0	$C_{17}H_{26}O_3$	73.36	9.42	73.32	9.47
—$CH(CH_3)CH_2CH_2CH_3$	61	150	1.0	$C_{14}H_{20}O_3$	71.16	8.96	71.26	8.89
—$CH_2CH(CH_3)CH_2CH_3$	60	150	1.0	$C_{14}H_{20}O_3$	71.16	8.96	71.42	8.75
—$CH_2CH_2CH(CH_3)_2$	81	135	0.5	$C_{14}H_{20}O_3$	71.16	8.96	71.24	8.60

TABLE III

3,5-DIMETHOXYPHENYL OLEFINS

R = 3,5-Dimethoxyphenyl	Yield, %	B. p.		n^{20}_D	Empirical formula	Analyses, %			
		°C.	Mm.			Calcd.		Found	
						C	H	C	H
R—$C(CH_3){=}CH(CH_2)_5CH_3$	87	148	1.0	1.5201	$C_{17}H_{26}O_2$	77.81	9.99	77.87	10.22
R—$C(CH_3){=}CH(CH_2)_6CH_3$	80	175	1.5	1.5143	$C_{18}H_{28}O_2$	78.21	10.21	78.44	10.49

TABLE IV

3,5-DIMETHOXYPHENYL ALKANES

R = 3,5-Dimethoxyphenyl	Yield, %	B. p.		n^{20}_D	Empirical formula	Analyses, %			
		°C.	Mm.			Calcd.		Found	
						C	H	C	H
R—$CH(CH_3)(CH_2)_6CH_3$	73	137	0.5	1.4970	$C_{17}H_{28}O_2$	77.22	10.67	77.17	10.83
R—$CH(CH_3)(CH_2)_7CH_3$	85	160	1.0	1.4898	$C_{18}H_{30}O_2$	77.64	10.86	78.13	11.25
R—$CH_2CH(CH_3)CH_2CH_2CH_3$	72	126	1.0	1.5034	$C_{14}H_{22}O_2$	75.63	9.98	75.68	10.19
R—$CH_2CH_2CH(CH_3)CH_2CH_3$	78	132	1.0	1.5043	$C_{14}H_{22}O_2$	75.63	9.98	75.72	10.12
R—$CH_2CH_2CH_2CH(CH_3)_2$	78	106	0.5	1.4993	$C_{14}H_{22}O_2$	75.63	9.98	75.98	10.10

TABLE V

3,5-DIHYDROXYPHENYL ALKANES (5-ALKYLRESORCINOLS)

R = 3,5-Dihydroxyphenyl	Yield, %	B. p.		Empirical formula	Analyses, %			
		°C.	Mm.		Calcd.		Found	
					C	H	C	H
R—$CH(CH_3)(CH_2)_6CH_3$	78	160	0.5	$C_{15}H_{24}O_2$	76.22	10.24	76.04	10.31
R—$CH(CH_3)(CH_2)_7CH_3$	74	188	1.0	$C_{16}H_{26}O_2$	76.75	10.47	76.62	10.64
R—$CH_2CH(CH_3)CH_2CH_2CH_3$	84	159	1.0	$C_{12}H_{18}O_2$	74.19	9.34	74.19	9.43
R—$CH_2C_2CH(CH_3)CH_2CH_3$	72	159	1.0	$C_{12}H_{18}O_2$	74.19	9.34	74.43	9.55
R—$CH_2CH_2CH_2CH(CH_3)_2$	74	125	0.5	$C_{12}H_{18}O_2$	74.19	9.34	74.05	9.52

TABLE VI

1-HYDROXY-3-ALKYL-9-METHYL-7,8,9,10-TETRAHYDRO-6-DIBENZOPYRONES

Alkyl group	Yield, %	M. p. (cor.), °C.	Solvent for recrystallizing	Empirical formula	Analyses, %			
					Calcd.		Found	
					C	H	C	H
—$CH(CH_3)(CH_2)_6CH_3$	38[10]	138	Ethanol–water	$C_{23}H_{32}O_3$	77.49	9.05	77.18	9.24
—$CH(CH_3)(CH_2)_7CH_3$	41[10]	125	Ethanol–water	$C_{24}H_{34}O_3$	77.80	9.25	77.53	9.29
—$CH_2CH(CH_3)CH_2CH_2CH_3$	60	194	Ethanol–water	$C_{20}H_{26}O_3$	76.40	8.34	76.28	8.55
—$CH_2CH_2CH(CH_3)CH_2CH_3$	72	157	Ethanol–water	$C_{20}H_{26}O_3$	76.40	8.34	76.24	8.44
—$CH_2CH_2CH_2CH(CH_3)_2$	73[11]	176.5	Ethanol–water	$C_{20}H_{26}O_3$	76.40	8.34	76.55	8.43

TABLE VII

1-HYDROXY-3-ALKYL-6,6,9-TRIMETHYL-7,8,9,10-TETRAHYDRO-6-DIBENZOPYRANS

Alkyl groups	Yield, %	B. p.		Empirical formula	Analyses, %			
		°C.	Mm.		Calcd.		Found	
					C	H	C	H
—$CH(CH_3)(CH_2)_6CH_3$	59	220	1.0	$C_{25}H_{38}O_2$	81.03	10.34	80.84	10.35
—$CH(CH_3)(CH_2)_7CH_3$	66	183	0.001	$C_{26}H_{40}O_2$	81.19	10.48	80.98	10.37
—$CH_2CH(CH_3)CH_2CH_2CH_3$	72	165	.01	$C_{22}H_{32}O_2$	80.43	9.82	80.37	9.99
—$CH_2CH_2CH(CH_3)CH_2CH_3$	61	180	.1	$C_{22}H_{32}O_2$	80.43	9.82	80.49	10.02
—$CH_2CH_2CH_2CH(CH_3)_2$	72[11]	165	.02	$C_{22}H_{32}O_2$	80.43	9.82	80.44	9.94

Adams, Chen and Loewe.[1] The method of reducing the 3,5-dimethoxyphenyl alkyl ketones to the corresponding methylene compounds by hydrogenation over copper chromite catalyst at 250° and 5000 pounds pressure was found prefer-

---

[10] These pyrones were prepared by the method of Adams and Baker.[8] The yield would unquestionably have been better if the procedure of Adams, Chen and Loewe had been followed as in the synthesis of the other pyrones.

[11] This pyrone was previously prepared[7] and reported to have a melting point of 177–180°, and the corresponding pyran b. p. 203° (1 mm.) (bath temperature).

able in many respects to the Wolff–Kishner procedure.

Experimental

All compounds prepared are described in Tables II–VII.

3,5-Dimethoxyphenyl Alkyl Ketones.—These ketones were prepared in the usual way[12] in ethyl ether without the addition of dibutyl ether.

3,5-Dimethoxyphenyl Olefins.—The olefins were prepared by the procedure of Adams, Chen and Loewe.[1]

3,5-Dimethoxyphenyl Alkanes.—The two 1′-methylalkyl derivatives were obtained by catalytic reduction of the ketones at high temperature and pressure in the presence of copper chromite as a catalyst. A typical conversion of a ketone to the correponding methylene compound is the preparation of $RCH_2CH_2CH(CH_3)CH_2CH_3$, where R = 3,5-dimethoxyphenyl. A mixture of 18.5 g. of $RCOCH_2CH(CH_3)CH_2CH_3$ and 3 g. of copper chromite catalyst was heated at 260° under an initial pressure of hydrogen (before heating was begun) of 3100 pounds. The hydrogen uptake reached the theoretical in seven hours. After cooling the bomb was opened, and the product rinsed out with ethanol, filtered and distilled. The yield of product was 13.5 g. (78%).

5-Alkylresorcinols.—The cleavage of the ethers was carried out as previously described.[1]

1-Hydroxy-3-alkyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrones.—The condensation of the resorcinols with 5-methyl-2-carbethoxycyclohexanone was effected according to the method of Adams, Chen and Loewe.[1]

1-Hydroxy-3-alkyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans.—The conversion of the pyrones to pyrans utilized the conventional treatment with 12 moles of methylmagnesium iodide.[9]

Summary

1. Two new tetrahydrocannabinol homologs with the groups $—CH(CH_3)(CH_2)_6CH_3$ and $—CH(CH_3)(CH_2)_7CH_3$ in the 3- position have been synthesized.

2. The activity of the 1′-methyloctyl homolog is 32. This is the most potent substance ever tested, having an activity over four times that of natural tetrahydrocannabinol. The 1′-methylnonyl, presumably because of decreased solubility, has a potency of only 2.08 but the duration of peak effect is five times that of its congeners.

3. Three isomeric methylpentyl groups have also been introduced into the 3- position, namely, $—CH_2CH(CH_3)CH_2CH_2CH_3$, $—CH_2CH_2CH(CH_3)CH_2CH_3$ and $—CH_2CH_2CH_2CH(CH_3)_2$.

4. The activities of these isomers varies inversely as the distance of the methyl group from the ring.

URBANA, ILLINOIS RECEIVED JUNE 7, 1947

---

[12] Suter and Weston, THIS JOURNAL, 61, 232 (1939).

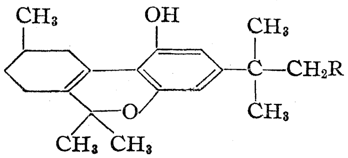
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE SCHOOL OF MEDICINE UNIVERSITY OF UTAH]

Tetrahydrocannabinol Homologs with Doubly Branched Alkyl Groups in the 3-Position. XVIII[1]

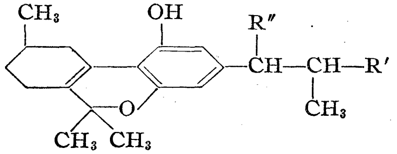
BY ROGER ADAMS, SCOTT MACKENZIE, JR., AND S. LOEWE

In synthetic tetrahydrocannabinols with *n*-alkyl groups or alkyl groups with a methyl substituent next to the ring in the 3-position the marihuana potency reaches a maximum of peak activity as the chain is lengthened. The significant increase in activity resulting from the introduction of a methyl group in the 1′-position of the 3-alkyl group stimulated a study of the activity of homologs having more highly branched side-chains in the 3-position.

Five pyrans have now been prepared, two of which, (I) and (II), have two methyl groups on the 1′-carbon of the side-chains in the 3-position. The other three, (III), (IV) and (V), have two alkyl groups, one on the 1′-carbon and the other on the 2′-carbon of the side-chain.



I R = C_2H_5
II R = C_5H_{11}



III R′ = C_2H_5; R″ = CH_3
IV R′ = CH_3; R″ = C_2H_5
V R′ = C_5H_{11}; R″ = CH_3

All products were tested by a procedure described previously. Activities of these compounds and certain isomers are listed for comparison in Table I.

Examination of Table I reveals the extreme variation in potency induced by changes in the structure of the 3-alkyl substituent. Branching of the side-chains not only increases activity but also requires larger groups to attain the maximum of peak effect (compare nos. 3 and 8). It is not surprising that the compound having the 1′,1′-dimethylbutyl side-chain in the 3-position is the most potent of the hexyl series of compounds. The substances with the 1′,1-dimethylalkyl substitution have activities comparable to the corresponding monomethyl derivatives, and the activity is much higher in the compound with a straight chain of seven carbon atoms than with

---

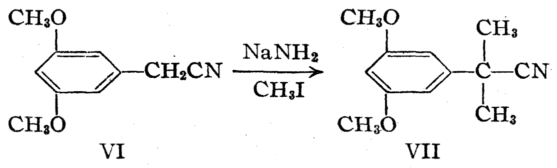
[1] For previous paper see Adams, Aycock and Loewe, THIS JOURNAL, 70, 662 (1948).

TABLE I
PHARMACOLOGICAL ACTIVITY OF TETRAHYDROCANNABINOL HOMOLOGS

	3-Substituent	No. of expts.	Potency
1	$-C_5H_{11}$-*n*[2]	20	1.00 Standard
2	Natural tetrahydrocannabinol from cannabidiol[3]	20	7.3 ± 0.89
Hexyl Isomers			
3	$-C_6H_{13}$-*n*[2]	7	1.82 ± 0.18 (max. in *n*-series)
4	$-CH(CH_3)C_4H_9$[4]	8	3.17 ± 0.33
5	$-CH(C_2H_5)CH(CH_3)CH_3$	6	3.40 ± 1.10
6	$-CH(CH_3)CH(CH_3)C_2H_5$	4	3.80 ± 0.32
7	$-C(CH_3)_2C_3H_7$	5	4.18 ± 0.34
Nonyl Isomers			
8	$-CH(CH_3)C_7H_{15}$[1]	19	32.6 ± 3.02 (max. in *s*-series)
9	$-CH(CH_3)CH(CH_3)C_5H_{11}$	18	512 ± 72.6
10	$-C(CH_3)_2C_6H_{13}$	5	21.8 ± 1.91

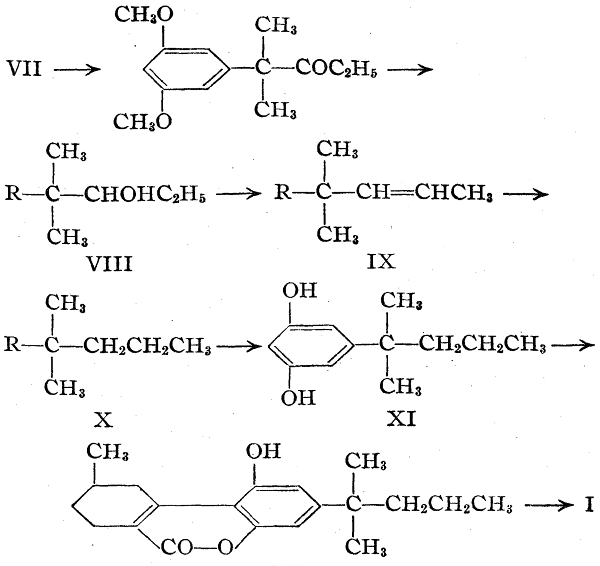
one of four carbon atoms. Although the 1′,2′-dimethylalkyl derivative with a total of six carbon atoms present in the side-chain is about equal in potency to the 1′,1′-dimethylalkyl derivative, the isomeric 1′,2′-dimethylalkyl analog with seven carbon atoms in the straight chain exceeds in activity the corresponding 1′,1′-isomer, and indeed has a value of 512. This is about sixteen times as potent as the most active homolog previously synthesized and seventy times the potency of natural tetrahydrocannabinol. The new order of the marihuana activity of the compound having the 1′,2′-dimethylheptyl side-chain makes generalization difficult at this time.

The 1′,1′-dimethylalkylpyrans were synthesized from 3,5-dimethoxybenzaldehyde. The aldehyde, first prepared by Mauthner[5] by the Rosenmund reduction, was obtained from the acid by the method described by McFadyen and Stevens[6] through 3,5-dimethoxybenzoyl-*p*-toluenesulfonylhydrazide. The aldehyde was hydrogenated in the presence of platinum oxide catalyst and the resulting benzyl alcohol was converted through the corresponding chloride and nitrile (VI) to 2-(3,5-dimethoxyphenyl)-2-methylpropionitrile (VII).



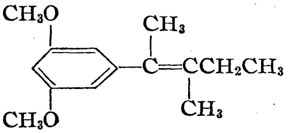
VI VII

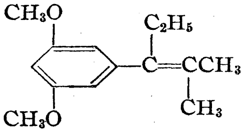
Both pyrans with two carbons on the 1′-carbon atom in the side-chains were prepared from this nitrile (VII) by the scheme shown below for the hexyl compound (VII–XII).


VIII IX X XI XII

The nitrile (VII) was converted by the action of ethylmagnesium bromide to the corresponding ketone which with hydrogen and copper chromite catalyst was reduced to the carbinol (VIII). Attempted dehydration of VIII by acidic reagents always resulted in rearrangement; the olefins thus formed were isolated, reduced and condensed to the pyrones, the structures of which were demonstrated by synthesis using unequivocal methods. The xanthate method of dehydration described by Tschugaeff[7] produced the unrearranged olefin (IX). This was reduced, demethylated, converted to the pyrone (XII), then to the pyran by the procedure previously described.[4,8]

Although Tschugaeff's assertion that no rearrangement occurs when alcohols are dehydrated by the xanthate method was further substantiated by Whitmore,[9] the structure of the tertiary olefin was more conclusively established. Dehydration of the pentanol (VIII) with acidic reagents would lead to the formation of either of two rearrangement products, (XIII) or (XIV). Both of these


XIII


XIV

olefins were synthesized from 3,5-dimethoxybenzamide[10] by conversion first to the ketone with the appropriate Grignard reagent, followed by the action of methyl- or ethyl-magnesium halide to form the carbinol. These were dehydrated, reduced and demethylated to the resorcinols which were converted to the pyrones.

---

[2] Adams, Loewe, Jelinek and Wolff, THIS JOURNAL, **63**, 1971 (1941).

[3] Adams, Pease, Cain and Clark, *ibid.*, **64**, 694 (1942).

[4] Adams, Chen and Loewe, *ibid.*, **67**, 1534 (1945).

[5] Mauthner, *J. prakt. Chem.*, **100**, 176 (1920).

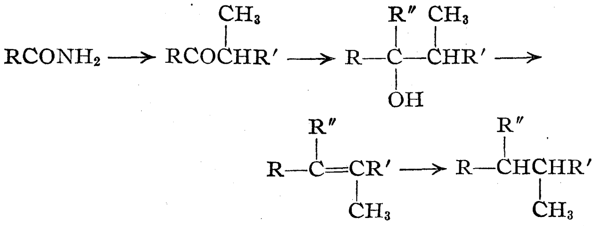
[6] McFadyen and Stevens, *J. Chem. Soc.*, 584 (1936).

[7] Tschugaeff, *Ber.*, **32**, 3332 (1889).

[8] Adams and Baker, THIS JOURNAL, **62**, 2405 (1940).

[9] Whitmore and Simpson, *ibid.*, **55**, 3809 (1933).

[10] Suter and Weston, *ibid.*, **61**, 232 (1939).



R = 3,5-dimethoxyphenyl; R′ = C_2H_5, R″ = CH_3; R′ = CH_3, R″ = C_2H_5

Neither of the pyrones was identical with the pyrone (XII) prepared from the neopentyl type carbinol by the Tschugaeff method. The tertiary structure of the olefin (IX) obtained by the xanthate method is thus confirmed. The pyrones were converted to pyrans in the usual way.

Experimental

The procedures used for the conversion of a 5-alkylresorcinol dimethyl ether to the corresponding pyran have been described previously.[8]

Ethyl 3,5-Dimethoxybenzoate.—A mixture of 100 g. of 3,5-dimethoxybenzoic acid, 350 ml. of anhydrous benzene, 2 ml. of pyridine and 300 g. of purified thionyl chloride was refluxed for three hours. After removal of the solvent and excess thionyl chloride by distillation, 300 ml. of cold absolute ethanol was added to the cooled residue. The resulting solution was refluxed for four hours. The ethanol was removed by distillation and an ethereal solution of the residue was extracted with aqueous sodium bicarbonate. After removal of the ether the residue was distilled under reduced pressure. The product, collected at 120–125° (3 mm.), was a colorless liquid, n^{20}_D 1.5214. The yield was 100 g. (87%).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 63.05; H, 6.79.

3,5-Dimethoxybenzhydrazide.—A mixture of 100 g. of ethyl 3,5-dimethoxybenzoate, 100 g. of 85% hydrazine hydrate and 110 ml. of absolute ethanol was refluxed for eight hours. The yield of brilliant white plates obtained by cooling the solution was 97 g. (83.5%). The product was purified from ethanol, m. p. 168–169° (cor.)

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.10; H, 6.12. Found: C, 55.17; H, 6.15.

3,5-Dimethoxybenzoyl-*p*-toluenesulfonylhydrazide.—A mixture of 100 g. of 3,5-dimethoxybenzhydrazide, 100 g. of *p*-toluenesulfonyl chloride and 100 ml. of pyridine was heated for one hour on a steam cone and then allowed to stand overnight. The solution was poured into 750 ml. of water and stirred until a granular, light brown solid was produced. The product was purified by recrystallization from aqueous ethanol. The total yield of large brilliant plates, m. p. 165–166°, was 117.5 g. (79%).

Anal. Calcd. for $C_{16}H_{18}N_2O_5S$: C, 54.86; H, 5.14. Found: C, 54.90; H, 5.34.

3,5-Dimethoxybenzaldehyde.—Into a one-liter Erlenmeyer flask heated by an oil-bath were placed 100 ml. of glycerol and 25 g. of 3,5-dimethoxybenzoyl-*p*-toluenesulfonylhydrazide. The mixture was stirred manually and heated to 125°. A hot (100°) solution of 20 g. of potassium carbonate in 100 ml. of glycerol was added all at once. The solution was heated rapidly to 135–140° and maintained at this temperature for about thirty seconds. After the evolution of gases partially subsided the solution was poured onto 300 g. of ice. The aqueous suspension was extracted three times with ether and the ether portions were combined and dried over anhydrous magnesium sulfate. After removal of the ether the liquid residue was distilled under reduced pressure. The fraction collected at 125–130° (1–2 mm.) was crude aldehyde and was purified by recrystallization from petroleum ether (b. p. 90–110°). The yield of fine lusterless needles, m. p. 45–46°, was 8 g. (68%). Mauthner[5] reported m.p. 45–46°.

3,5-Dimethoxybenzyl Alcohol.—The aldehyde was hydrogenated at room temperature and at 2–3 atm. pressure in the presence of platinum oxide catalyst. Ethanol was used as the solvent. The yield of fine white needles, m. p. 47–48°, from 16.6 g. of aldehyde was 16.0 g. (95%). The reported m. p. is 47–48°.[5]

3,5-Dimethoxybenzyl Chloride.—A solution of 22.5 g. of purified thionyl chloride in 100 ml. of anhydrous ether was added in 20-ml. portions with occasional shaking to a solution of 15 g. of 3,5-dimethoxybenzyl alcohol and 1 ml. of pyridine in 200 ml. of anhydrous ether. The mixture was allowed to stand for fifteen minutes and then was extracted twice with 100-ml. portions of cold water. The ether was allowed to evaporate *in vacuo* at low temperature. The crude chloride was purified by recrystallization from petroleum ether (b. p. 90–110°). The yield of fine needles, m. p. 46°, was 16.0 g. (96%).

Anal. Calcd. for $C_9H_{11}O_2Cl$: C, 57.91; H, 5.90. Found: C, 57.94; H, 6.09.

3,5-Dimethoxybenzyl Cyanide.—A mixture of 16 g. of 3,5-dimethoxybenzyl chloride, 300 ml. of ethanol, 30 g. of sodium cyanide and 75 ml. of water was refluxed for three hours. The solution was poured onto 400 g. of ice. The solid was collected on a filter and purified by recrystallization from petroleum ether (b. p. 90–110°). The yield of fine lusterless needles, m. p. 53°, was 14.5 g. (95%).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.80; H, 6.21. Found: C, 67.81; H, 6.42.

2-(3,5-Dimethoxyphenyl)-2-methylpropionitrile.—3,5-Dimethoxybenzyl cyanide was methylated using a slight modification of the procedure described by Smith and Spillane[11] for the preparation of 2-(3,5-dimethylphenyl)-2-methylpropionitrile. The sodamide solution obtained from 3.5 g. of sodium, 200 ml. of liquid ammonia and a few crystals of ferric nitrate was allowed to evaporate to a volume of about 75 ml. The remaining ammonia was displaced by 200 ml. of anhydrous ether and a solution of 25 g. of 3,5-dimethoxybenzyl cyanide in 100 ml. of anhydrous ether was added all at once and the mixture refluxed for eighteen hours. Then 25 g. of methyl iodide was added to the cooled solution as rapidly as possible with stirring. The solution was refluxed for two hours, heating was discontinued and 50 ml. of ethanol was added with stirring. After washing and drying the reaction mixture was again subjected to methylation.

When reaction was complete the solvent was removed and the crude product obtained by distillation under reduced pressure was heated for one hour with 0.25 tablespoonful of Raney nickel and 200 ml. of absolute ethanol to remove any amide. Upon fractionation, a yield of 21.5 g. (72.5%) was obtained. The colorless product, b. p. 147–150°, n^{20}_D 1.5201, d^{20}_4 1.0813, became slightly yellow on standing.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.24, H, 7.32. Found: C, 70.03; H, 7.53.

2-(3,5-Dimethoxyphenyl)-2-methylpropanoic Acid.—A mixture of 50 ml. of ethylene glycol, 1 g. of the propionitrile, 1 g. of potassium hydroxide and 1 ml. of water was refluxed for four hours. The solution was diluted with water, extracted with ether, acidified and extracted four times with ether. After removal of the solvent the crude acid was recrystallized from petroleum ether (b. p. 90–110°). The yield of colorless crystals, m. p. 99°, was 0.5 g. (46%).

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.29; H, 7.14. Found: C, 64.45; H, 7.29.

2-Methyl-2-(3,5-dimethoxyphenyl)-3-pentanone.—A solution of 26 g. of 2-methyl-2-(3,5-dimethoxyphenyl)-propionitrile in 100 ml. of anhydrous ether was added to the Grignard reagent prepared from 41.2 g. of ethyl bromide, 5.9 g. of magnesium and 200 ml. of dry ether. The ether was replaced by 300 ml. of dry benzene and the solu-

---

[11] Smith and Spillane, THIS JOURNAL, **65**, 202 (1943).

TABLE II

KETONES

R = 3,5-Dimethoxy-phenyl	Yield, %	B. p., °C.	Mm.	$n^{20}D$	d^{20}_4	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$RC(CH_3)_2COC_2H_5$	70	104	0.3	1.5165	1.0476	$C_{14}H_{20}O_3$	71.19	8.47	71.02	8.45
$RCOCH(CH_3)C_2H_5$[a]	76	124–128	0.5	1.5266	....	$C_{13}H_{18}O_3$	70.27	8.11	70.03	8.18
$RCOCH(CH_3)CH_3$[a]	71	117–119	1.0	1.5290	1.0928	$C_{12}H_{16}O_3$	69.23	7.69	69.28	7.82
$RC(CH_3)_2COC_5H_{11}$	78	140–145	0.5	1.5088	1.0131	$C_{17}H_{26}O_3$	73.38	9.35	73.33	9.51
$RCOCH(CH_3)C_5H_{11}$[a]	82	147	1.0	1.5136	....	$C_{16}H_{24}O_3$	72.72	10.00	72.58	9.31

[a] Ketones prepared from 3,5-dimethoxybenzamide contained traces of the amide which were not removed on redistillation. Refluxing an alcoholic solution with Raney nickel was helpful.

TABLE III

3,5-DIMETHOXYPHENYL OLEFINS

R = 3,5-Dimethoxyphenyl	Yield	B. p. °C.	Mm.	$n^{20}D$	d^{20}_4	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$RC(CH_3)_2CH{=}CHCH_3$	75	103–106	0.5	1.5179	0.9858	$C_{14}H_{20}O_2$	76.32	9.15	76.43	9.34
$RC(CH_3){=}C(CH_3)C_2H_5$	91	110	1.0	1.5277	1.0126	$C_{14}H_{20}O_2$	76.32	9.15	76.46	9.27
$RC(C_2H_5){=}C(CH_3)CH_3$[b]	75	102–106	0.5	....	....	$C_{14}H_{20}O_2$	76.32	9.15	...	...
$RC(CH_3)_2CH{=}CHC_4H_9$	90	127–130	0.5	1.5080	0.9862	$C_{17}H_{26}O_2$	77.86	9.92	77.90	10.10
$RC(CH_3){=}C(CH_3)C_5H_{11}$	85	132–134	1.0	1.5131	0.9616	$C_{17}H_{26}O_2$	77.86	9.92	77.83	9.94

[b] The sample of this compound, made to check the identity of the corresponding pyrone, was too small for adequate purification.

TABLE IV

3,5-DIMETHOXYPHENYL ALKANES

R = 3,5-Dimethoxyphenyl	Yield, %	B. p. °C.	Mm.	$n^{20}D$	d^{20}_4	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$R—C(CH_3)_2C_3H_7$[a]	92	115–117	1.5–2	1.5071	0.9834	$C_{14}H_{22}O_2$	75.68	9.91	75.69	10.08
$R—CH(CH_3)CH(CH_3)C_2H_5$[b]	91	98–100	0.5	1.5012	0.9787	$C_{14}H_{22}O_2$	75.68	9.91	75.85	10.01
$R—CH(C_2H_5)CH(CH_3)CH_3$[b,d]	73	104	.5	....	....	$C_{14}H_{22}O_2$	75.68	9.91	...	...
$R—C(CH_3)_2C_6H_{13}$[c]	93	122	.5	1.5006	0.9558	$C_{17}H_{28}O_2$	77.27	10.61	77.64	10.80
$R—CH(CH_3)CH(CH_3)C_5H_{11}$[a]	79	120	.5	1.5036	0.9523	$C_{17}H_{28}O_2$	77.27	10.61	77.51	10.73

[c] Olefin hydrogenated at roo re using Raney nickel. [d] Olefin subjected to two successive hydrogenations at 175° using copper chromite.

TABLE V

3,5-DIHYDROXYPHENYL ALKANES

R = 3,5-Dihydroxyphenyl	Yield, %	B. p. °C.	Mm.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$R—C(CH_3)_2C_3H_7$	75	151–154	1.0	$C_{12}H_{18}O_2$	74.19	9.34	74.37	9.29
$R—CH(CH_3)CH(CH_3)C_2H_5$	84	145–146	1.0	$C_{12}H_{18}O_2$	74.19	9.34	74.03	9.34
$R—CH(C_2H_5)CH(CH_3)CH_3$[b]	50	145	0.5	$C_{12}H_{18}O_2$	74.19	9.34	...	...
$R—C(CH_3)_2C_6H_{13}$	80	161–163	0.5	$C_{15}H_{18}O_2$	76.27	10.17	76.42	10.12
$R—CH(CH_3)CH(CH_3)C_5H_{11}$	80	167–169	1.0	$C_{15}H_{18}O_2$	76.27	10.17	76.27	10.12

tion was refluxed for forty-eight hours. The reaction mixture was decomposed with dilute sulfuric acid and the benzene was removed by distillation. The resulting mixture of acid and crude ketone was heated for an additional two hours on the steam cone. After cooling the mixture was extracted with ether, and the ether was removed. The crude product was distilled twice under reduced pressure to give a yield of 21 g. (70%) of colorless liquid (Table II).

2-Methyl-2-(3,5-dimethoxyphenyl)-3-pentanol.—The ketone was hydrogenated at a temperature of 150–170° under a pressure of hydrogen of 3000 pounds in the presence of copper chromite. The product was fractionated under reduced pressure, those fractions having $n^{20}D$ 1.5249 ± 0.0001 being combined.. The yield of colorless, viscous liquid, b. p. 129–130°(0.5 mm.), d^{20}_4 1.0980, was 15.2 g. (72.5%).

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.59; H, 9.24. Found: C, 70.52; H, 9.44.

2-Methyl-2-(3,5-dimethoxyphenyl)-3-pentene.—A solution of 15.2 g. of the pentanol in 100 ml. of dry ether was allowed to react over a six-hour period with a suspension of 2.5 g. of metallic potassium (previously powdered in Stanolind) in 200 ml. of ether. An equimolar quantity of carbon disulfide was added and the mixture was stirred for one-half hour. To the thick white mass was added 9.0 g. of methyl iodide. The suspension was refluxed for six hours and allowed to stand overnight. The potassium iodide was removed by filtration. After removal of the ether the yellow residue was placed in a 50-ml. modified Claisen flask and distilled under reduced pressure. About one-half hour of careful heating was necessary before the actual distillation of light yellow product began. An alcoholic solution of the distillate was refluxed with Raney nickel and redistilled. The final product was a colorless liquid (Table III).

2-Methyl-2-(3,5-dimethoxyphenyl)-3-octanone.—A solution of 18.6 g. of 2-methyl-2-(3,5-dimethoxyphenyl)-propionitrile in 100 ml. of anhydrous ether was added to the Grignard reagent prepared from 42.1 g. of *n*-amyl bromide, 6.63 g. of magnesium and 150 ml. of anhydrous ether. After replacement of the ether with dry benzene the mixture was refluxed for forty-eight hours. The decomposition with dilute sulfuric acid and the purification of the product were carried out as described for the pentanone (Table II).

TABLE VI

1-HYDROXY-3-ALKYL-9-METHYL-7,8,9,10-TETRAHYDRO-6-DIBENZOPYRONES

3-Substituent	Yield,[e] %	M. p. (cor.) °C.	Solvent for recryst.	Empirical formula	Analyses, % Calcd. C	H	Found C	H
$—C(CH_3)_2C_3H_7$	73	218–220	Ethanol–water	$C_{20}H_{26}O_3$	76.50	8.28	76.33	8.31
$—CH(CH_3)CH(CH_3)C_2H_5$	30	177–178	Ethanol–water	$C_{20}H_{26}O_3$	76.50	8.28	76.63	8.30
$—CH(C_2H_5)CH(CH_3)CH_3$	28	181–182	Ethanol–water	$C_{20}H_{26}O_3$	76.50	8.28	76.47	8.45
$—C(CH_3)_2C_6H_{13}$	36.5	156–157	(1) Nitromethane (2) Ethanol–water	$C_{23}H_{32}O_3$	77.53	8.99	77.52	9.17
$—CH(CH_3)CH(CH_3)C_5H_{11}$	24	134–136	(1) Nitromethane (2) Ethanol–water	$C_{23}H_{32}O_3$	77.53	8.99	76.73	9.14

[e] The yield depended considerably on sample size.

TABLE VII

1-HYDROXY-3-ALKYL-6,6,9-TRIMETHYL-7,8,9,10-TETRAHYDRO-6-DIBENZOPYRANS

3-Substituent	Yield, %	B. p. °C.	Mm.	Empirical formula	Analyses, % Calcd. C	H	Found C	H
$—C(CH_3)_2C_3H_7$	65	158	0.02	$C_{22}H_{32}O_2$	80.43	9.82	80.18	9.75
$—CH(CH_3)CH(CH_3)C_2H_5$	72	160–162	.02	$C_{22}H_{32}O_2$	80.43	9.82	80.64	9.76
$—CH(C_2H_5)CH(CH_3)CH_3$[f]	40	176	.1	$C_{22}H_{32}O_2$	80.43	9.82	...	...
$—C(CH_3)_2C_6H_{13}$	65	176–176	.04	$C_{25}H_{38}O_2$	81.08	10.27	80.98	10.43
$—CH(CH_3)CH(CH_3)C_5H_{11}$	80	170–173	.04	$C_{25}H_{38}O_2$	81.08	10.27	80.81	10.48

[f] The sample of this compound, made primarily to check the identity of the corresponding pyrone, was too small for adequate purification. The pyrone, was purified to constant melting point.

2-Methyl-2-(3,5-dimethoxyphenyl)-3-octanol.—The ketone was hydrogenated in the presence of copper chromite under conditions identical with those described above. After fractionation under reduced pressure, the yield of colorless liquid, b. p. 162° (0.5 mm.), n^{20}_D 1.5138, d^{20}_4 1.0262, was 15.5 g. (79%).

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.86; H, 10.00. Found: C, 72.72; H, 10.19.

2-Methyl-2-(3,5-dimethoxyphenyl)-3-octene.—The preparation of the xanthate was carried out as described above. Gentle heating for three hours was necessary before the decomposition was complete (Table III).

Summary

1. Tetrahydrocannabinols have been prepared with the following alkyl groups in the 3-positions: $—C(CH_3)_2CH_2CH_2CH_3$, $—C(CH_3)_2CH_2(CH_2)_4CH_3$, $—CH(CH_3)CH(CH_3)CH_2CH_3$, $—CH(CH_3)CH(CH_3)CH_2(CH_2)_3CH_3$, $—CH(C_2H_5)CH(CH_3)_2$.

2. The resorcinols required for the first two were synthesized from 3,5-dimethoxybenzoic acid. This was converted to the resorcinol dimethyl ether derivatives by the following steps: $—COOH, \rightarrow —CHO \rightarrow —CH_2OH \rightarrow —CH_2Cl \rightarrow —CH_2CN \rightarrow —C(CH_3)_2CN \rightarrow —C(CH_3)_2COCH_2R \rightarrow —C(CH_3)_2CHOHCH_2R \rightarrow —C(CH_3)_2CH{=}CHR \rightarrow —C(CH_3)_2CH_2CH_2R$. Finally, demethylation yielded the resorcinols which were converted by previously described methods to the corresponding pyrans.

3. The resorcinols for the last three substances mentioned in (1) were made from 3,5-dimethoxybenzamide. This was converted as follows to the resorcinol dimethyl ether derivatives: $—CONH_2 \rightarrow —COCH(CH_3)R \rightarrow —C(R')(OH)CH(CH_3)R \rightarrow —C(R'){=}C(CH_3)R \rightarrow —CH(R')CH(CH_3)R$.

4. The substances with the 1',1-dimethylalkyl substitution have activities comparable to the corresponding monomethyl derivatives, and the activity is much higher in the compound with a straight chain of seven carbon atoms than with one of four carbon atoms. Although the 1',2'-dimethylalkyl derivative with a total of six carbon atoms present in the side-chain is about equal in potency to the 1',1'-dimethylalkyl derivative, the isomeric 1',2'-dimethylalkyl analog with seven carbon atoms in the straight chain exceeds in activity the corresponding 1',1'-isomer and indeed has a value of 512. This is about sixteen times as potent as the most active homolog previously synthesized and seventy times the potency of natural tetrahydrocannabinol.

URBANA, ILLINOIS RECEIVED JUNE 7, 1947

[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE]

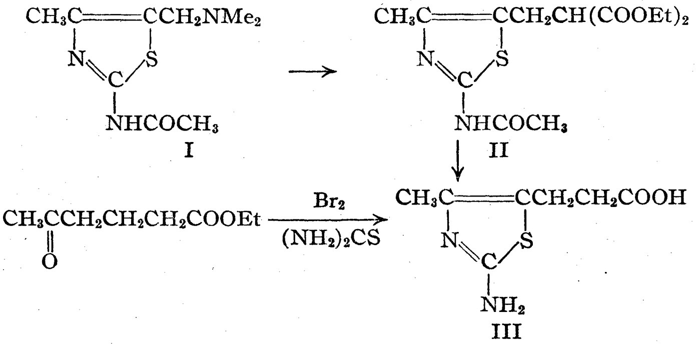
Alkylation with Non-ketonic Mannich Bases. Aminothiazoles and Pyrrole

BY NOEL F. ALBERTSON

Several years ago it was observed independently, both in this Laboratory and elsewhere, that gramine, 3-(dimethylaminomethyl)-indole, or one of its quaternary salts could be employed to alkylate malonic ester,[1,2] and this fact was used to develop a synthesis of tryptophan.[2,3] At that time the dialkylaminomethylindoles were the only reported examples of non-ketonic Mannich bases which can serve as alkylating agents for reactive methylene compounds. In fact, gramine was unique not only in its reaction but also in its preparation as compared with all of the other examples of Mannich bases compiled by Blicke.[4] The synthesis of gramine involves the introduction of a dialkylaminomethyl group directly onto a carbon atom in a ring which does not contain a ketonic or phenolic group.

It appeared unlikely that gramine should be so unique. On the contrary, it seemed probable that heterocyclic compounds of a phenolic nature, which contain a suitably activated hydrogen atom, would undergo the Mannich reaction to form "allylic" amines which could, in turn, serve as alkylating agents.

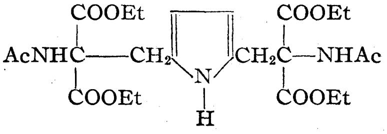
To test this supposition 2-acetamido-4-methylthiazole was treated with dimethylamine and formalin in acetic acid. From the reaction mixture a compound was obtained which, based on analysis, was the Mannich amine I. Sodioacetamidomalonic ester was readily alkylated by this base, in the form of its methyl sulfate, to give diethyl 5-(2-acetamido-4-methylthiazylmethyl)-acetamidomalonate. Since it has been pointed out by Bodendorf and Koralewski[5] that amides react with formalin and amines, an alternative structure for the Mannich base must be considered wherein the dimethylaminomethyl group is on the amide nitrogen. The fact that acetamide failed to react under the conditions under which 2-acetamido-4-methylthiazole reacted militated against this structure. Direct proof that the substitution actually took place on the ring rather than on the amide nitrogen was obtained by using the Mannich base (I) to alkylate malonic ester. The product obtained (II) was hydrolyzed and partially decarboxylated to yield III, a propionic acid which proved to be identical with that synthesized by interaction of ethyl γ-acetobutyrate, bromine and thiourea, and subsequent hydrolysis. The establishment of structure III for the propionic acid is indirect proof of the structure of the Mannich base (I).



When 2-acetamidothiazole was substituted for 2-acetamido-4-methylthiazole it also gave a Mannich base which served as an alkylating agent.

As one would expect, elimination of the 2-acetamido group greatly diminished the reactivity of the thiazole nucleus toward this type of reaction. 2,4-Dimethylthiazole gave a very minute yield of an unidentified product in the Mannich reaction. 2-Methyl-4-phenyloxazole gave only the acetate when treated with dimethylamine and formalin in acetic acid. A single attempt to use 2-(dimethylaminomethyl)-thiophene as an alkylating agent was unsuccessful.

The alkylation of acetamidomalonic ester with 2-(dimethylaminomethyl)-pyrrole has been reported recently.[6] Before the appearance of this work we had found that it is possible to replace not only the amino group of a monosubstituted pyrrole, but that both amino groups of a 2,5-bis-(aminomethyl)-pyrrole may be eliminated in an alkylation reaction. Thus, 2,5-bis-(piperidinomethyl)-pyrrole[7] reacted with acetamidomalonic ester to give ethyl pyrrole-2,5-bis-(2-acetamido-2-carbethoxypropionate), IV.



IV

---

[1] Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944).

[2] Albertson, Archer and Suter, *ibid.*, **66**, 500 (1944).

[3] (a) Snyder and Smith, *ibid.*, **66**, 350 (1944); (b) Albertson, Archer and Suter, *ibid.*, **67**, 36 (1945); (c) Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945); (d) Albertson and Tullar, *ibid.*, **67**, 502 (1945).

[4] Blicke, "The Mannich Reaction" in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942.

[5] Bodendorf and Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

[6] Herz, Dittmer and Cristol, "Preparation of Some Monosubstituted Derivatives of Pyrrole by the Mannich Reaction," presented before the 111th meeting of the A. C. S. at Atlantic City N. J. THIS JOURNAL, **70**,504 (1948).

[7] Bachman and Heisey, THIS JOURNAL, **68**, 2948 (1946).

Experimental

2-Acetamido-4-methyl-5-(dimethylaminomethyl)-thiazole (I).[8]—A mixture of 15.6 g. of 2-acetamido-4-methylthiazole, 8 ml. of 37% formalin solution and 25 ml. of a solution of dimethylamine in glacial acetic acid (equivalent to 0.11 mole of amine) was warmed for seven hours on a steam-bath. Then 50 ml. of water was added, the solution made basic with potassium carbonate and extracted with five 50 ml. portions of chloroform. Removal of the solvent *in vacuo* left 25.9 g. of viscous residue. This was dissolved in alcohol and acidified with alcoholic hydrogen chloride. The crude hydrochloride was filtered and washed with alcohol; yield 23.0 g. (92%), m. p. 208–210°. This material was used for alkylation. A sample, recrystallized from aqueous acetone, melted at 223°.

Anal. Calcd. for $C_9H_{15}N_3OS \cdot HCl$: S, 12.84. Found: S, 12.64.

The free base, m. p. 138–139.5°, may be obtained by treating the hydrochloride with aqueous sodium carbonate. However, the hydrochloride is just as satisfactory for alkylation reactions as is the free base provided sufficient sodium ethylate is employed.

2-Acetamido-5-(dimethylaminomethyl)-thiazole.—This compound was prepared in the same manner as the analogous 4-methylthiazole; m. p. 248–249°.

Anal. Calcd. for $C_7H_{11}N_3OS \cdot HCl$: Cl, 15.04; S, 13.60. Found: Cl, 15.10; S, 13.51.

2-Acetamido-5-(piperidinomethyl)-thiazole.—This compound was prepared in the manner described above; m. p. 159–161.5° (free base).

Anal. Calcd. for $C_{11}H_{17}N_3OS$: C, 55.21; H, 7.16; N, 17.56. Found: C, 55.43; H, 7.13; N_k, 17.25.

Diethyl 5-(2-acetamido-4-methyl) thiazylmethylacetamidomalonate.—To a solution of 0.93 g. of sodium in 75 ml. of absolute alcohol was added 8.80 g. of acetamidomalonic ester, 7.2 g. of crude 2-acetamido-5-(dimethylaminomethyl)-4-methylthiazole (free base) and 6.3 ml. of dimethyl sulfate. It was necessary to cool the reaction flask in ice water occasionally. After four hours the reaction mixture was poured onto 200 g. of water–ice mixture containing 2.4 ml. of acetic acid. The white crystals (6.5 g.) were filtered, washed and dried; m. p. 183°. A sample for analysis, recrystallized from aqueous alcohol, melted at 183.5°.

Anal. Calcd. for $C_{16}H_{23}O_6N_3S$: C, 49.86; H, 6.01; N, 10.90. Found: C, 49.70; H, 6.09; N, 10.56.

Diethyl 5-(2-Acetamidothiazylmethyl)-acetamidomalonate.—This product was prepared in the same manner as the analogous 4-methylthiazole except that the hydrochloride rather than the free Mannich base was used. An additional amount of sodium ethylate (equivalent to the hydrochloride) was used in the reaction; m. p. 224–225°.

Anal. Calcd. for $C_{15}H_{21}N_3O_6S$: N, 11.31; S, 8.63. Found: N, 11.30; S, 8.80.

Diethyl 5-(2-Acetamidothiazylmethyl)-malonate.—This was prepared in the same manner as the above two compounds by substituting malonic ester for acetamidomalonic ester, m. p. 150.5–152°.

Anal. Calcd. for $C_{13}H_{18}N_2O_5S$: S, 10.20. Found: S, 10.29.

β-[5-(2-Amino-4-methylthiazyl)]-propionic Acid (A) from Mannich Base.—To 1.45 g. of sodium in 100 ml. of dry alcohol was added 15 ml. of malonic ester, 6.6 g. of 2-acetamido-5-dimethylaminomethyl-4-methylthiazole hydrochloride and 4.9 ml. of dimethyl sulfate. The reaction mixture was cooled by swirling in ice water. After four hours the reaction mixture was poured onto ice and water containing 3 ml. of acetic acid. The product was extracted with chloroform. The solvent and excess malonic ester were removed on a steam-bath under 2 mm. pressure and the residual 4.2 g. of oil hydrolyzed by refluxing for two hours with 20 ml. of hydrochloric acid (1:1). The solution was charcoaled, filtered and concentrated *in vacuo*. The viscous yellow residue was dissolved in 10 ml. of water and the *p*H brought to 7 with ammonium hydroxide. The solution slowly deposited crystals of the acid, m. p. 253–257° dec.

Anal. Calcd. for $C_7H_{10}N_2O_2S$: S, 17.22; N, 7.52. Found: S, 17.52; N, 7.30.

(B) **From Ethyl γ-Acetobutyrate.**—Ethyl γ-acetobutyrate was prepared as described below. To a suspension of 15.8 g. of ethyl γ-acetobutyrate and 15.2 g. of thiourea was added 15.9 g. of bromine with shaking.[9] After all of the bromine had been added the mixture was warmed for two and one-half hours on the steam-bath whereupon it became brown. A small amount of water was added, the mixture warmed and the clear solution treated with charcoal. Addition of ammonium hydroxide to a sample of the filtrate gave a black unpromising solution from which an oil slowly separated. Consequently, the main filtrate was warmed for forty minutes on the steam-bath to effect hydrolysis. The solution was filtered from sulfur and neutralized with ammonium hydroxide. The acid which precipitated was filtered, washed with water, alcohol and ether; yield 9.1 g. The product can be purified by reprecipitation from sodium hydroxide solution with acetic acid or from hydrochloric acid solution with ammonium hydroxide. The product melted at 254–256° and when mixed with the acid prepared by method A also melted at 254–256°.

γ-Acetobutyric Acid.—Condensation of methyl acrylate with a two-fold excess of acetoacetic ester in the presence of sodium ethylate gave a 73% yield of β-(carbomethoxyethyl)-acetoacetic ester as a pale yellow oil, b. p. 109–110° at 2 mm., $n^{25}D$ 1.4385.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.24; H, 7.46.

Hydrolysis of β-(carbomethoxyethyl)-acetoacetic ester was effected by refluxing with concentrated hydrochloric acid (3 ml. per g.) until evolution of carbon dioxide ceased. Most of the water was then removed *in vacuo* until the monohydrate started to crystallize. Water of crystallization was removed by addition of benzene and azeotropic distillation. The γ-acetobutyric acid boiled at 107.5–109° (5 mm.); yield, 85%.[10]

Esterification[11] yielded the ethyl ester (67%), b. p. 52–59° (1 mm.), which was used without further purification.

Ethyl 2,5-Pyrrole-bis-(2-acetamido-2-carbethoxypropionate).—Sodium (3.3 g.) was dissolved in 200 ml. of dry ethanol. There was then added 31 g. of acetamidomalonic ester,[12] 7.8 g. of 2,5-bis-(N-piperidinomethyl)-pyrrole[7] and 11.0 ml. of dimethyl sulfate. After twelve hours the mixture was diluted with water and extracted with chloroform. Evaporation of the chloroform gave a crystalline residue in practically quantitative yield. Several recrystallizations from aqueous alcohol gave a product melting at 160–160.8° (cor.).

Anal. Calcd. for $C_{24}H_{35}N_3O_{10}$: C, 54.85; H, 6.71; N, 7.99. Found: C, 54.75; H, 6.60; N, 7.90.

Summary

2-Acetamidothiazoles, unsubstituted at position five, were found to react with formalin and dimethylamine to introduce a dimethylaminomethyl group directly onto the ring. These Mannich bases were used to alkylate malonic esters.

2,5-bis-(Piperidinomethyl)-pyrrole reacted with two moles of acetamidomalonic ester to give the symmetrically substituted pyrroledipropionate.

RENSSELAER, N. Y. RECEIVED JULY 23, 1947

---

[8] Bock, Johnson and Armstrong in U. S. Patent 2,409,829 (which issued after the completion of this work) describe the preparation of some Mannich bases of 2-acylaminothiazoles. No mention was made of any attempt to use these Mannich bases as alkylating agents.

[9] *Cf.* Dodson, THIS JOURNAL, **67**, 2242 (1945).

[10] Bentley and Perkin, *J. Chem. Soc.*, **69**, 1511 (1900).

[11] Vorländer, *Ann.*, **294**, 270 (1897).

[12] See ref. 3; this chemical is now commercially available.

[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

A Novel Synthesis of Substituted Phenylglyoxylic Acids[1]

BY I. MOYER HUNSBERGER[2] AND E. D. AMSTUTZ

Up to the present time there has not been available a general and convenient method for the synthesis of hydroxy-substituted phenylglyoxylic acids. Of the methods which have been used for the preparation of phenylglyoxylic acids only one[3] appears to be suited to the use of mono- and polyhydroxybenzenes. This procedure uses cyanogen and yields by-products formed by reaction of both nitrile groups.

In this paper is reported the synthesis of a series of new 2,4-dihydroxy-5-*n*-alkylphenylglyoxylic acids (I) and of 2,4-dihydroxy-3-ethyl-5-methylphenylglyoxylic acid (II) by condensation of alkylresorcinols with ethyl cyanoformate in the presence of anhydrous hydrogen chloride. These glyoxylic acids were desired in order to compare their antibacterial activity with that of the alkylresorcinols from which they are derived. Especial interest was taken in compound II because of the striking structural similarity of one of its quinonoidal forms (such as IIa and b) with that deduced[4] for the antibiotic citrinin (III). Further, it was felt that the cyanoformate condensation might have some value in synthetical work on citrinin.

The ethyl cyanoformate condensation first was applied to resorcinol and orcinol, 2,4-dihydroxyphenylglyoxylic acid and 2,4-dihydroxy-6-methylphenylglyoxylic acid lactone (IV), respectively, being obtained in agreement with Karrer and Ferla's[3] results using cyanogen. The general procedure then was extended to 4-ethyl-, 4-*n*-butyl-, 4-*n*-hexyl-, 4-*n*-octyl-, 4-*n*-nonyl-, 4-*n*-dodecyl- and 2-ethyl-4-methyl-resorcinol, the results of which are recorded in Table I. In all cases dry hydrogen chloride was introduced into a dry ethereal solution of ethyl cyanoformate and alkylresorcinol. After a length of time depending on the individual reaction the ketimine ethyl ester hydrochloride precipitated as highly-colored crystals which were hydrolyzed by hot water to the glyoxylic acid ethyl ester and thence by water or dilute alkali to the free glyoxylic acid (I).[5] In no case did the esters crystallize well so that purification was effected after saponification. Purification of the acids increased in difficulty with increase in weight of the 5-*n*-alkyl group.

TABLE I

PREPARATION OF HYDROXYPHENYLGLYOXYLIC ACIDS

Substituted 2,4-dihydroxyphenylglyoxylic acids	Crystallization solvent	Yield, %	M. p., °C.	Color	Analyses, % Calcd. C	H	Found C	H
Lactone of 6-methyl-(IV)[a]	None	53	213.1–215[b]	Yellow				
5-Ethyl-	Water	60	148.5–149.4	Golden yellow	57.14	4.80	57.22	5.66
5-*n*-Butyl-	Water	70	152–154	Light yellow	60.50	5.92	60.75	6.09
5-*n*-Hexyl-	5% ethanol	50	151–153.2	Bright	63.23	6.77	62.84	7.03
5-*n*-Octyl-[c]	20% ethanol	..	144.2–145	yellow	65.29	7.54	65.01	7.82
5-*n*-Nonyl-[d]	40% ethanol	30	143.5–146[e]	Bright	66.21	7.84	66.58	8.18
5-*n*-Dodecyl-	65% ethanol	62	150.5–152[e]	yellow	68.55	8.62	68.74	8.70
3-Ethyl-5-methyl-(II)[f]	Bz. pet. ether (b. p. 35–60°)	15	128–129.5	Light orange	58.92	5.39	58.70	5.46

[a] The insoluble reaction product was removed by filtration, washed with fresh ether and hydrolyzed directly to produce the lactone by thirty minutes heating in water near the boiling point. Extraction of the aqueous filtrate with ether followed by removal of the acid with sodium bicarbonate yielded additional (IV). [b] Karrer and Ferla (ref. 3) listed 212°. [c] Anhydrous zinc chloride was added. A suck-back of the concentrated sulfuric acid traps necessitated pouring contents of reaction flask and acid traps separately into ice. The solidified material thus obtained was saponified under nitrogen to the crude acid. [d] Since no crystallization had occurred, water and ice were added to the reaction mixture. After removing the ether the ethyl ester separated as a red oil which was extracted with ether and the ether with sodium bicarbonate. Upon heating the latter a cream-colored precipitate settled out and was filtered off. Its solubility in water indicated it to be the sodium salt, and acidification produced the crude acid. Evaporation of the ether produced the ethyl ester as a red oil, from which more crude acid was obtained as above. Fractionation was effected by successive dilutions with water. [e] Uncorrected. [f] The ethyl ester was obtained as brown-orange crystals, m. p. 74–77°, saponification of which produced crude II.

Although the position of the entering ketocarboxyl (COCOOH) group as *ortho* to one and *para* to the other phenolic hydroxyl group of the resorcinol nucleus was not proved rigorously in this investigation,[6] the general behavior of resor-

---

(1) Taken in part from a thesis submitted by I. Moyer Hunsberger in partial fulfillment of the requirements for the M.S. degree.

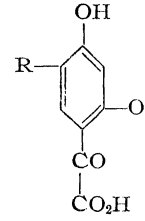
(2) The Wm. S. Merrell Co. Fellow, 1945–1946; American Chemical Society Predoctoral Fellow, 1946–.

(3) Karrer and Ferla, *Helv. Chim. Acta*, **4**, 203 (1921).

(4) Coyne, Raistrick and Robinson, *Phil. Trans. Roy. Soc.*, **220**, 297 (1931); Hetherington and Raistrick, *ibid.*, **220**, 269 (1931). Very recent evidence [*cf.* Sprenger and Ruoff, *J. Org. Chem.*, **11**, 189 (1946); Gore, Panse and Venkataraman, *Nature*, **157**, 333 (1946)] has cast doubt on the correctness of structure III.

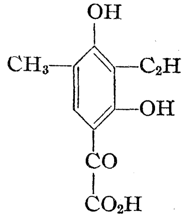
(5) Only in the case of compounds derived from 4-*n*-octyl- and 4-*n*-nonyl-resorcinol did the ketimine salt fail to crystallize, a circumstance very probably the result of failure to introduce hydrogen chloride for a sufficient period. However, slight modification of the general procedure used in handling the reaction product permitted isolation of the corresponding glyoxylic acids in a pure state.

(6) Bulow and Wagner [*Ber.*, **36**, 1941 (1903)] established the position of the COCOOH group in 2,4-dihydroxylphenylglyoxylic acid by their preparation of this compound from 2-phenyl-7-hydroxy-1,4-benzopyranol-4-carboxylic acid.

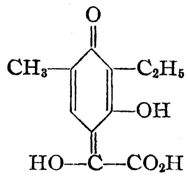


R = *n*-alkyl or H

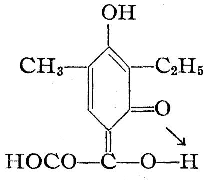
I



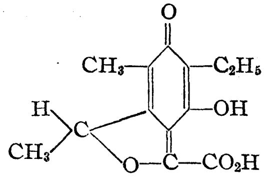
II



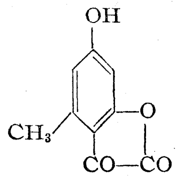
IIa



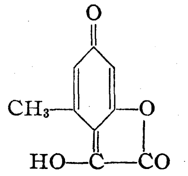
IIb



III



IVa



IVb

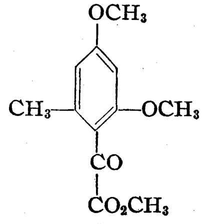
cinol lends strength to the proposed formulation. That the initial insoluble reaction products are ketimine hydrochlorides is indicated by their solubility in water and insolubility in ether. The condensation therefore is related closely to the familiar Gattermann and Houben–Hoesch syntheses.

Since neither the ketocarboxyl nor resorcyl fragment of the 2,4-dihydroxyphenylglyoxylic acid molecule is strongly chromophoric, the bright yellow color exhibited by such compounds is considered to be the result of a contribution of the *ortho* (such as IIb) or possibly the *para* (such as IIa) methylenequinone structure.[7] By supposing chelation to exert a color-deepening effect (resonance stabilization of the *ortho*-quinonoid form[8]), a rather satisfactory correlation between structure and the color of numerous hydroxy-substituted acetophenones, benzophenones, benzoquinones, naphthoquinones, anthraquinones and phenylglyoxylic acids, as compared to the respective unsubstituted compounds, can be drawn.

All 2,4-dihydroxy-5-alkylphenylglyoxylic acids prepared in this investigation gave dark red-brown colorations with ferric chloride and colors ranging from light yellow-brown to dark bluish-green with a mixture of thiophene–benzene and concentrated sulfuric acid.

An attempt to form a 2,4-dinitrophenylhydrazone of the hexyl acid failed. This result is in accord with Karrer and Ferla's[3] inability to form either an oxime or phenylhydrazone from 2,4-dihydroxyphenylglyoxylic acid and also bespeaks an interaction of the carbonyl and the ortho hydroxyl group. The many earlier reports of facile oxime, hydrazone, phenylhydrazone and bisulfite addition product formation[9] can be understood more readily when it is recalled that none of the early acids contained both *ortho* and *para* hydroxyl groups.

We have not been able to isolate any pure crystalline materials from the diazomethane methylation of the acids of series I. Whereas the relationship between IIa and b well may involve the phenomenon of resonance, we felt that with IVa and b the equilibrium should be rather of the tautomeric type; hence, the isomer IVb conceivably might have real and independent existence. Thus, methylation with diazomethane under essentially anhydrous conditions (avoiding lactone hydrolysis) could yield both colorless (from IVa) and colored (from IVb) methyl ethers. We were successful in isolating only the latter and in small yields. The material possessed a deep yellow color with analytical data corresponding to that calculated for a monomethyl ether of IV. Moist diazomethane yielded an orange–red crude product from which was isolated the colorless trimethylated derivative V, which corresponded in every detail to the product obtained by Karrer[3] with dimethyl sulfate and alkali. Both methylation and hydrolysis undoubtedly proceeded simultaneously during this wet methylation. We believe the orange–red color of the crude product was due to the presence of materials which first were methylated and then perhaps hydrolyzed and further methylated. However, we were unable to isolate any such products in a pure state.



V

Work along the general lines outlined in this paper is being continued.

All the compounds prepared were tested for antibacterial activity against *S. aureus*, *E. coli* and *B. subtilis* by both the broth serial dilution (BSD) and agar streak plate (ASP) techniques. The so-

---

[7] Chromophoric character is an attribute of such a structure not without precedent, for almost twenty years ago Robertson and Robinson [*J. Chem. Soc.*, 2196 (1927)] used a similar assumption to explain the bright yellow color of 2,6-dihydroxy-3,5-dimethylbenzaldehyde. Furthermore, it is expected that the two *ortho-para* orienting ring substituents would combine their influence with that of the carboxyl group on the methylene carbon atom to stabilize the methylenequinone structure [*cf.* Gomberg and West, This Journal, **34**, 1529 (1912)] in the case of 2,4-dihydroxyalkylphenylglyoxylic acids.

[8] *Cf.* J. R. Johnson, "Modern Electronic Concepts of Valence," Vol. II, chapter 25, of "Organic Chemistry," H. Gilman, editor-in-chief, second edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 1870; Geissman, Schlatter, Webb and Roberts, *J. Org. Chem.*, **11**, 741 (1946).

[9] Schad, *Ber.*, **26**, 216 (1893); Tiemann, *ibid.*, **24**, 2877 (1891); Vorländer, *ibid.*, **44**, 2463 (1911); Bouveault, *Bull. soc. chim.*, [3] **15**, 1014 (1896).

dium salt of the 5-*n*-octyl-2,4-dihydroxyphenylglyoxylic acid was the most active, completely inhibiting the growth of *S. aureus* at 1:12,500 dilution (BSD) and *B. subtilis* at 1:25,000 dilution (ASP). None of the compounds had significant action against *E. coli*. The octyl compound was also active at 1:8,000 dilution against the fungi *Epidermophyton floccosum*, *Microsporon canis* and *Trichophyton rubrum*.

Acknowledgments.—The authors wish to express their appreciation to the Wm. S. Merrell Company for financial assistance and to Drs. M. G. Van Campen, Jr., and Milton Foter for arranging the antibacterial and antifungal tests. We also appreciate the assistance rendered by Sharp and Dohme who generously supplied us with hexylresorcinol, and Mr. V. Warren Fox, who prepared some of the glyoxylic acid from hexylresorcinol.

Experimental[10]

4-Alkylresorcinols.—All 4-alkylresorcinols used in this work were prepared by Clemmensen reduction of the ketone formed by condensation of resorcinol with the proper carboxylic acid in the presence of zinc chloride. Only in the purification of 4-n-dodecylylresorcinol was modification of the standard procedure[11] necessary.

2-Ethyl-4-methylresorcinol.—2,6-Dihydroxyacetophenone was prepared by alkaline cleavage of 4-methyl-7-hydroxy-8-acetylcoumarin[12] and reduced to 2-ethylresorcinol by a slight modification[13] of Clemmensen's method. The latter compound was transformed to 2,4-dihydroxy-3-ethylbenzaldehyde by a modification[14] of the Gattermann aldehyde synthesis. Another Clemmensen reduction then produced the desired 2-ethyl-4-methylresorcinol, which was purified according to Robinson and Shah.[15]

2,4-Dihydroxyphenylglyoxylic Acid.—The preparation of this acid illustrates the general procedure for all hydroxyphenylglyoxylic acids.

In a flask equipped with reflux condenser, stirrer and gas inlet tube were placed 11.0 g. (0.100 mole) of vacuum dried resorcinol, 10.8 g. (0.109 mole) of ethyl cyanoformate[16] and 100 ml. of absolute ether (dried over sodium). A rapid stream of dry hydrogen chloride was introduced for two hours, cold water being used at intervals to dissipate the heat generated. Hot water hydrolyzed the precipitated ketimine salt directly to a mixture of the crude keto acid (2.2 g.) and its ethyl ester (14.6 g.), the two being separated by extraction of an ethereal solution with sodium bicarbonate. The ester formed yellow–orange crystals, m. p. 65–68°, after recrystallization from water; it is soluble in benzene, ethanol, ether and chloroform, but insoluble in low-boiling petroleum ether.

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.1; H, 4.80. Found. C, 57.6; H, 5.12.

Saponification of this ester with 10% potassium hydroxide produced more of the desired acid as mustard–yellow crystals, m. p. 161.5–163°,[17] after recrystallization from water.[18]

Anal. Calcd. for $C_8H_6O_5$: C, 52.8; H, 3.32. Found: C, 52.7; H, 3.32.

On standing six days the ethereal mother liquor from the original insoluble ketimine salt deposited a small quantity of light yellow crystals. The ether was decanted and the crystals covered with fresh ether which was neutralized with sodium bicarbonate. Evaporation of the ether produced orange crystals, presumably the ketimine ethyl ester, which did not melt below 330°. This product was slightly soluble in ether but quite insoluble in water; it gave no halogen test with silver nitrate but evolved ammonia when treated with 50% potassium hydroxide.

We found that satisfactory neutral equivalents of the acids prepared in this investigation could be determined by visual titration in water or aqueous alcohol using phenolphthalein as indicator (two acid hydrogens titrated per mole) when the end-point was not obscured by fluorescence.[19]

2,4-Dimethoxy-6-methylphenylglyoxylic Acid Methyl Ester (V).—An ethereal solution, not previously dried, containing about 2.8 g. (0.065 mole) of diazomethane was added gradually to a solution of 2.3 g. (0.013 mole) of pure 2,4-dihydroxy-6-methylphenylglyoxylic acid lactone (IV) in 60 ml. of ordinary ether at 0°. Evaporation of the ether produced an orange–red solid from which 0.4 g. (14%) of pure ester (V) was obtained as snow-white crystals, m. p. 73–74°, by repeated fractional crystallization from aqueous acetic acid. Saponification of the ester yielded the colorless free acid, m. p. 138.8–139.2°.[20]

Anal. Calcd. for $C_{11}H_{12}O_5$ (acid): C, 58.93; H, 5.40. Found: C, 59.12; H, 5.66.

Monomethyl Ether of 2,4-Dihydroxy-6-methylphenylglyoxylic Acid Lactone.—An ethereal solution containing *ca.* 2.1 g. (0.050 mole) of diazomethane (previously dried for three hours over potassium hydroxide and thirty minutes over sodium wire) gradually was added to 3.0 g. (0.017 mole) of 2,4-dihydroxy-6-methylphenylglyoxylic acid lactone (IV) dissolved in 70 ml. of absolute ether which had been dried over sodium. After six hours, the ether was evaporated to an oil which crystallized on standing overnight in a refrigerator. This solid was refluxed thirty minutes (nitrogen atmosphere) with excess 3% sodium hydroxide. The cold alkaline solution was filtered and acidified, whereupon 1.1 g. of crude product, m. p. 143–153°, separated.[21] This material was extracted twice with boiling water and the insoluble residue dissolved in hot 10% sodium bicarbonate solution and reprecipitated with acid. The yellow product thus obtained was extracted fractionally and crystallized with carbon tetrachloride to yield four fairly pure fractions (melting between the extremes of 163° and 171°), which after combination and retreatment with sodium bicarbonate and acid, as before, produced a small amount of pure monomethyl ether of IV as a bright yellow precipitate, m. p. 168–170.5°. There was no color with ferric chloride.

---

[10] All melting points are corrected for stem emergence unless specified otherwise.

[11] Dohme, Cox and Miller, THIS JOURNAL, **48**, 1688 (1926).

[12] Russell and Frye, "Organic Syntheses," **21**, 22 (1941).

[13] Russell, Frye and Mauldin, THIS JOURNAL, **62**, 1441 (1940).

[14] Adams and Levine, *ibid.*, **45**, 2373 (1923).

[15] Robinson and Shah, *J. Chem. Soc.*, 1491 (1934). They found that the intermediate 2,4-dihydroxy-3-ethylbenzaldehyde melted at 115–118°; we found 119.5–121°. The higher value probably can be attributed to the superiority of water to benzene as recrystallization solvent.

[16] Gluud, Nussler and Keller, German Patent 592,539; *Chem. Zentr.*, **105**, II, 3437 (1934).

[17] Karrer and Ferla (ref. 3) listed 168° and stated that the value of 194° (ref. 6) was probably a typographical error.

[18] A few drops of concentrated hydrochloric acid added to an almost saturated solution hastened crystallization.

[19] Titrations performed with a Beckmann *p*H meter produced curves having well defined equivalence points corresponding to titration of one acid hydrogen ion. These equivalence points fell in a *p*H range of 5.12 to 5.80, indicating the strongly acidic nature of the compounds. However, the neutral equivalents calculated from such points were almost invariably 18 to 70 units too high. These results may be due to the presence of a phenolic group ortho to the ketocarboxyl side chain, since Anschütz [*Ann.*, **368**, 80 (1909)] found *o*-acetoxyphenylglyoxylic acid to behave normally on visual titration.

[20] Karrer and Ferla (ref. 3) reported 73–74° and 138–139° for the ester and acid, respectively.

[21] A considerable quantity of unreacted starting material (m. p. 206–209°) was recovered by ether extraction of the filtrate from the crude product. More starting material was recovered during later fractionations.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.49; H, 4.20. Found: C, 62.69; H, 4.64.

Summary

1. The condensation of ethyl cyanoformate with alkyl derivatives of resorcinol has been used to prepare a number of new 2,4-dihydroxyalkylphenylglyoxylic acids.

2. The use of ethyl cyanoformate is proposed as a general method for introducing the ketocarboxyl (COCOOH) group into activated positions on aromatic nuclei.

3. All hydroxyphenylglyoxylic acids prepared in this work have been subjected to antibacterial and antifungal testing but none showed exceptional activity.

BETHLEHEM, PENNSYLVANIA RECEIVED JUNE 9, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE GEORGIA SCHOOL OF TECHNOLOGY]

Alkoxyaryloxyketones and their Condensation with Isatins

BY R. L. SUBLETT AND PAUL K. CALAWAY

To continue our work[1,2] on the preparation of keto ethers and their conversion into substituted quinoline acids we have prepared a series of ketones from alkoxyphenols by the procedure of Hurd and Perletz.[3] The resulting alkoxyaryloxyketones have been condensed with both isatin and 5-methylisatin, by the method of Pfitzinger,[4] to produce 3-alkoxyaryloxy-4-quinaldinecarboxylic acids.

The yields of the ketones prepared ranged from 47.6%, in the case of the 2-methoxy-4-methylphenoxyacetone, to 73% for the 4-propoxyphenoxyacetone. All of the ketones were obtained, after purification, as light yellow, low-melting solids, which darkened on standing.

The potassium salts of the quinaldinecarboxylic acids were salted out by high concentrations of potassium hydroxide. In every instance, decarboxylation of these acids was observed to start well below the melting point, hence melting point values changed with the rate of heating and are of little significance.

Experimental

Preparation of Alkoxyaryloxyacetones.—The procedure for the condensation of chloroacetone with the alkoxyphenols was based on the method of Hurd and Perletz.[3]

To a vigorously stirred and refluxing suspension of 0.4 mole of the alkoxyphenol and 57 g. (0.41 mole) of anhydrous potassium carbonate in 150 ml. of dry acetone was added over a period of thirty minutes a solution of 50 g. (0.54 mole) of chloroacetone and 3 g. of potassium iodide in 50 ml. of dry acetone. The chloroacetone mixture had been allowed to stand for twenty hours prior to addition. After refluxing for seven hours, stirring was continued for an additional twenty hours at room temperature. The mixture was filtered and the salt washed well with dry acetone. To obtain the ketone from the filtrate it was diluted with water and cooled with ice. The precipitate was recrystallized twice from methanol and water, and again from cyclohexane. The essential data on the ketones and derivatives are tabulated in Table I.

TABLE I

ALKOXYARYLOXYACETONES, $CH_3COCH_2OC_6H_3R'OR''$

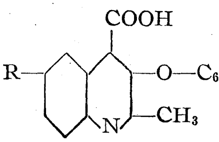
R′	R″	Yield, %	M. p., °C.	2,4-Dinitrophenylhydrazone	Semicarbazone
H	4-CH_3	64	48.5	149	192.3
H	4-C_2H_5	62	35.5	105.5	192
H	4-C_3H_7	73	39	91.5	188.8
H	4-C_4H_9	69	37	153	187.8
4-CH_3	2-CH_3	48	28.5	136	153

Preparation of 3-(4-Methoxyphenoxy)-4-quinaldinecarboxylic Acid.—Fourteen and seven-tenths grams (0.1 mole) of isatin was dissolved in 200 ml. of 33% aqueous potassium hydroxide solution and 17 g. (0.1 mole) of 4-methoxyphenoxyacetone was added. The resulting mixture was heated under reflux on the steam-bath for four hours, and upon cooling a solid cake of potassium 3-(4-methoxyphenoxy)-4-quinaldinecarboxylate separated in the reaction flask. The latter was disintegrated and dissolved in 800 ml. of hot water. The resulting solution was boiled with Nuchar, filtered, cooled in ice, and the quinoline acid precipitated by the addition of acetic acid (1:1). The product was separated by filtration, suspended in 600 ml. of hot water, and converted into the soluble potassium salt by the addition of 33% potassium hydroxide. The treatment with Nuchar was repeated, and 23 g. (74% yield) of the purified acid was obtained. The product was dried over phosphorus pentoxide in a vacuum desiccator.

The remaining 3-alkoxyaryloxy-4-quinaldinecarboxylic acids were formed in essential accordance with this general procedure. In each case a small sample was recrystallized from a large quantity of water and this material used for

TABLE II

3-ALKOXYARYLOXY-4-QUINALDINECARBOXYLIC ACIDS



R	R′	R″	Yield, %	M. p. °C. (dec.)	Nitrogen, % Calcd.	Nitrogen, % Found
H	H	4-CH_3	74	215	4.56	4.20
H	H	4-C_2H_5	56	214	4.33	4.19
H	H	4-C_3H_7	70	208	4.15	4.14
H	H	4-C_4H_9	77	150	3.99	3.70
H	4-CH_3	2-CH_3	75	232	4.33	4.14
CH_3	H	4-CH_3	67	234	4.33	4.25
CH_3	H	4-C_2H_5	64	198	4.15	4.30
CH_3	H	4-C_3H_7	62	204	3.99	4.01
CH_3	H	4-C_4H_9	60	193	3.83	3.85
CH_2	4-CH_3	2-CH_3	54	242	4.15	4.19

---

[1] Knight, Porter and Calaway, THIS JOURNAL, **66**, 1893 (1944).

[2] Newell and Calaway, *ibid.*, **69**, 116 (1947).

[3] Hurd and Perletz, *ibid.*, **68**, 38 (1946).

[4] (a) Pfitzinger, *J. prakt. Chem.*, **33**, 100 (1886); (b) **38**, 582 (1888): (c) **56**, 283 (1897).

the nitrogen analysis. Table II contains the data on these preparations.

Summary

Pfitzinger's method has been extended to include the utilization of alkoxyaryloxyacetones in the synthesis of ten substituted quinoline acids from isatin and 5-methylisatin, respectively.

ATLANTA, GEORGIA RECEIVED SEPTEMBER 5, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE]

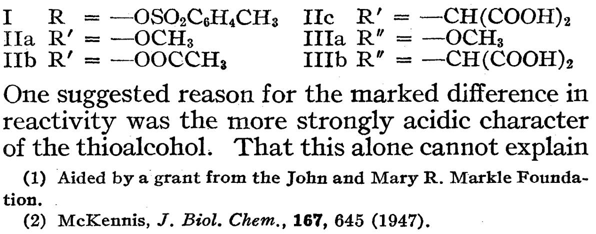
Some Reactions of Cholesteryl *p*-Toluenesulfonate[1]

BY HERBERT MCKENNIS, JR.

In a continuation of studies[2] on the relationship of the structure of cholesterol to its ability to promote growth of *Attagenus* larvae, a number of cholestene derivatives were desired. Cholesteryl *p* toluenesulfonate has been employed successfully in the preparation of 3-alkoxycholestenes,[3] 3-iodocholestene,[4] and a number of other derivatives.

The facile preparation of cholesteryl ethers by refluxing solutions of the *p*-toluenesulfonyl ester of cholesterol in an excess of various alcohols suggested the study of the possible reaction with corresponding mercaptans. This was of interest as a possible synthetic route to thioethers of cholesterol. Additional knowledge of the reactivity of cholesteryl *p*-toluenesulfonate was also desirable since we had planned to study the effect of this compound upon the growth of larvae.

Since *n*-propyl mercaptan has a boiling point quite close to that of methyl alcohol the former was selected for a preliminary study. Attempts to bring about the reaction of cholesteryl *p*-toluenesulfonate (I) with an excess of the mercaptan at reflux temperature for short periods were unsuccessful. After a three-hour period the ester was recovered in quantitative yield. Under similar conditions methanol reacts readily and cholesteryl methyl ether (IIIa) is easily obtained.



I II III

I R = —$OSO_2C_6H_4CH_3$ IIc R' = —$CH(COOH)_2$
IIa R' = —OCH_3 IIIa R'' = —OCH_3
IIb R' = —$OOCCH_3$ IIIb R'' = —$CH(COOH)_2$

One suggested reason for the marked difference in reactivity was the more strongly acidic character of the thioalcohol. That this alone cannot explain the results is clearly shown in experiments in which thiophenol and benzyl mercaptan were the alcohols employed. Thiophenol, kindly supplied by Dr. E. Emmett Reid, reacted readily with the tosyl ester to yield a bis-(phenylthio)-compound which is tentatively assigned the structure of 3,5-bis-(phenylthio)-cholestane. Benzyl mercaptan also reacted. The product in this instance was not, however, obtained in pure condition.

In view of the marked differences in reactivity observed it became desirable to know whether or not *n*-propyl alcohol itself would react under conditions drastic enough for the seemingly quantitative reaction with methanol, but not sufficiently drastic or prolonged for significant reaction with *n*-propyl mercaptan. The reaction with *n*-propanol under comparable conditions proceeded readily, and cholesteryl *n*-propyl ether was obtained in good yield.

In contrast to the marked reactivity of cholesteryl *p*-toluenesulfonate with methanol, propanol, thiophenol, and benzyl mercaptan at temperatures below 70°, the ester appeared not to react at all when heated with an excess of benzylamine at 70° for two hours. At reflux temperature (185°) reaction took place with the formation of an N-benzylamino compound which is assigned the quasi-committal name, N-benzylcholesterylamine, in accordance with the precedential designation, N-phenylcholesterylamine, for the product obtained by the analogous reaction of aniline and cholesteryl *p*-toluenesulfonate.[5] Under alkaline conditions cholesteryl *p*-toluenesulfonate reacts with methanol[3a] and other alcohols[3b] to give ethers, isomeric with the compounds obtained in the absence of alkali, for which structure IIa has been proposed.[6] Wagner-Jauregg and Werner[7] have found that a comparable situation obtains when cholesteryl chloride or bromide is heated with methanol. When the reaction was carried out in the presence of potassium acetate, *i*-cho-

---

[1] Aided by a grant from the John and Mary R. Markle Foundation.

[2] McKennis, *J. Biol. Chem.*, **167**, 645 (1947).

[3] (a) Stoll, *Z. physiol. Chem.*, **207**, 147 (1932); (b) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 907 (1936).

[4] Helferich and Gunther, *Ber.*, **72**, 338 (1939).

[5] (a) Bátyka, *Magyar Biol. Kutató Inézet Munkái*, **13**, 334 (1941); *C. A.*, **36**, 484 (1942); (b) Müller and Bátyka, *Ber.*, **74**, 705 (1941).

[6] Wallis, Fernholz and Gephart, THIS JOURNAL, **59**, 137 (1937); see also, Ford and Wallis, *ibid.*, **59**, 1415 (1937); Ford, Chakravorty and Wallis, *ibid.*, **60**, 413 (1938); and Butenandt and Suranyi, *Ber.*, **75**, 591 and 597 (1942), for additional evidence in support of this structure.

[7] Wagner-Jauregg and Werner, *Z. physiol. Chem.*, **213**, 119 (1932).

lesteryl methyl ether (IIa) was obtained, the normal ether being formed when no potassium acetate was present. The further observation that the iso compound was transformed slowly when heated with methanol and one equivalent of hydrogen chloride at 130° to the normal ether (IIIa) led to the suggestion by them that the iso compound is first formed and then, if no base is present, it is converted under the influence of liberated acid to the normal ether.

We have found that *i*-cholesteryl methyl ether in methanol containing *p*-toluenesulfonic acid is converted to IIIa in good yield at reflux temperature within three hours. Since the conditions used here were similar to those ordinarily employed for the direct preparation of the normal compound from the tosyl ester, the comparatively rapid conversion in this instance affords additional support to the conception of Wagner-Jauregg and Werner. In view of this corroboration it would be interesting to study the possible catalytic action of acids on reactions of the tosyl ester with amino and sulfhydryl compounds.

It is interesting that under certain conditions derivatives of both cholesterol and *i*-cholesterol can be obtained from cholesteryl *p*-toluenesulfonate. Beynon, Heilbron and Spring[3a] isolated cholesteryl benzyl ether and *i*-cholesteryl benzyl ether from the mixture obtained by reaction of cholesteryl *p*-toluenesulfonate with benzyl alcohol in the presence of potassium acetate. Kaiser and Svarz[8] noted that the mixture from the reaction of cholesteryl *p*-toluenesulfonate with sodiomalonic ester contained a number of cholesterol derivatives. Two compounds obtained from the saponified reaction mixture were assigned tentatively structures IIIb, 3-cholesterylmalonic acid, and IIc, *i*-cholesterylmalonic acid.[9] The latter and its methyl ester were found to give a negative Liebermann–Burchard test while the former responded positively.[9]

Wallis, Fernholz and Gephart[6] have reported the conversion of *i*-cholesteryl acetate (IIb) to cholesteryl acetate by treatment with acid, and also have described the conversion of *i*-cholesterol, which gives a positive Liebermann–Burchard reaction,[10] to a normal cholesterol derivative. *i*-Cholesteryl methyl ether which in methanolic solution can be converted to the normal ether in the presence of acid catalyst, was found in our study to give a positive Liebermann–Burchard reaction.

The positive Liebermann–Burchard reactions of *i*-cholesterol and *i*-cholesteryl methyl ether can, in view of the demonstrated conversions of iso to normal compounds, be tentatively ascribed to formation of Δ^5-3-cholestenyl derivatives which take place under the acidic conditions of the Liebermann–Burchard test and precede the development of color. In contrast, since 3-cholesterylmalonic acid gives a positive test and *i*-cholesterylmalonic acid gives a negative test, it can be assumed that the latter yields no Δ^5-3-cholestenyl derivative under the test conditions. These interpretations appear to be consistent with the known limited specificity of the Liebermann–Burchard reaction.

Experimental[11]

3,5-bis-(Phenylthio)-cholestane.—A mixture of 4.50 g. of cholesteryl *p*-toluenesulfonate and 24 cc. of thiophenol was heated at 50° for two hours. The ester went into solution quickly and, in time, white crystals formed. These, presumably *p*-toluenesulfonic acid, were hygroscopic and insoluble in benzene. Excess thiophenol was removed by shaking the mixture or its ethereal solution exhaustively with 2 *N* potassium hydroxide. The oily product was dissolved in 40 cc. of hot alcohol containing enough chloroform to completely solubilize the product. The solution, on cooling to room temperature, deposited white prisms, m. p. 180–184°. A solution of the product in a minimal amount of hot chloroform was diluted to a volume of 125 cc. with 95% ethanol. The yield of glistening white product, m. p. 186–186.5°, was 2.34 g.

Anal. Calcd. for $C_{39}H_{56}S_2$: C, 79.51; H, 9.59; S, 10.89. Found: C, 79.58; H, 9.65; S, 11.30; $[\alpha]^{25}D$ $-127°$, *c* 1.71, carbon tetrachloride.

Benzyl mercaptan reacted with the ester under the above conditions. Crystals of alleged *p*-toluenesulfonic acid were formed. After removal of acid and excess benzyl mercaptan an oil remained. This gave strong qualitative tests for sulfur, but failed to crystallize from the usual solvents.

N-Propyl Cholesteryl Ether.—A solution of 0.500 g. of cholesteryl *p*-toluenesulfonate in 30 cc. of *n*-propyl alcohol was heated at 62–63° for three hours. The solution was cooled and 8 cc. of water was added. The crude ether, m. p. 99°, weighed 346 mg. (87% of the calculated amount). A small additional amount of ether was obtained by further dilution of the mother liquor. N-Propyl cholesteryl ether prepared by other methods has been reported to melt at 99.5–100°[12], 100°[13], and at 100–100.5°[14].

When the above components were heated at 50° for two hours, a product was obtained which melted over a wide range and contained unreacted ester.

N-Benzylcholesterylamine.—A solution of 1.00 g. of cholesteryl *p*-toluenesulfonate in 6 cc. of benzylamine, protected by a sodalime tube, was heated under reflux for three hours. The mixture was diluted with 100 cc. of ether and washed with water until no more benzylamine could be extracted. The ethereal solution was dried over anhydrous sodium sulfate and then concentrated to an oil. The oily residue was dissolved in a minimal amount of acetone and diluted with 95% ethanol until a faint turbidity was produced. The solution was cooled. The yield of crude product, m. p. 110–118°, was 0.500 g. After one recrystallization from acetone the compound melted at 118–119°. *Anal.* Calcd. for $C_{34}H_{53}N$: C, 85.82; H, 11.23; N, 2.94. Found: C, 86.06; H, 10.61; N, 3.12; $[\alpha]^{28}D$ $-25.1°$, *c* 2.15, chloroform.

N-Acetyl-N-benzylcholesterylamine.—A mixture of 1.00 g. of N-benzylcholesterylamine, 34 cc. of ether, and 1 cc. of acetic anhydride was heated under reflux for thirty minutes and then concentrated to a volume of 15 cc. The product, m. p. 152–153°, was obtained as clusters of needles. The yield was 0.91 g. (84% of calculated amount). An additional crop was obtained by concentrating the mother liquor. For analysis the derivative was recrystallized several times from ethyl acetate. The melting point was unchanged. *Anal.* Calcd. for $C_{36}H_{55}NO$: C, 83.50;

---

(8) Kaiser and Svarz, THIS JOURNAL, **67**, 1309 (1945).

(9) Svarz and Kaiser, *ibid.*, **69**, 847 (1947).

(10) Eck and Thomas, *J. Biol. Chem.*, **128**, 267 (1939).

(11) Microanalyses by the Oakwold Laboratories, Alexandria, Virginia.

(12) Diels and Blumberg, *Ber.*, **44**, 2847 (1911).

(13) Bills and McDonald, *J. Biol. Chem.*, **72**, 1 (1927).

(14) Muller and Page, *ibid.*, **101**, 127 (1933).

H, 10.71. Found: C, 83.63; H, 10.72; $[\alpha]^{25}_{D}$ −8.6°, *c* 0.934, carbon tetrachloride.

N-Benzylcholesterylamine Hydrochloride.—Dry hydrogen chloride was passed into a solution of 70 mg. of N-benzylcholesterylamine in 20 cc. of absolute ether until no more gelatinous precipitate formed. The salt was obtained in granular form by recrystallization from methanol containing a little hydrochloric acid. The hydrochloride melted with decomposition above 300°. *Anal.* Calcd. for $C_{34}H_{53}N \cdot HCl$: Cl, 6.92. Found: Cl, 6.59.

Cholesteryl Methyl Ether from *i*-Cholesteryl Methyl Ether.—To a solution of 100 mg. of *p*-toluenesulfonic acid monohydrate in 36 cc. of methanol was added 300 mg. of *i*-cholesteryl methyl ether. The mixture was heated under reflux for two hours and then concentrated under diminished pressure to a volume of approximately 25 cc. When the solution was chilled the product separated. It was collected and washed with a small volume of cold methanol. The yield was 279 mg. (93% of the calculated amount). The melting point, 84°, which is in agreement with reported values, was not depressed by admixture of authentic cholesteryl methyl ether.

Summary

1. The comparative reactivity of several mercaptans, alcohols, and benzylamine with cholesteryl *p*-toluenesulfonate has been studied in a qualitative manner. Under conditions favorable for the reaction of methanol and propanol with the formation of the corresponding cholesteryl ethers, *n*-propyl mercaptan, and benzylamine fail to react appreciably. Thiophenol and benzyl mercaptan react readily with cholesteryl *p*-toluenesulfonate.

2. The positive Liebermann–Burchard reaction of *i*-cholesterol and of *i*-cholesteryl methyl ether has been interpreted in the light of the known reactions of these compounds under acidic conditions, while the negative reaction of the analogous *i*-cholesterylmalonic acid has been tentatively ascribed to the inability of the latter to yield appreciable amounts of Δ^5-3-cholestenyl derivative under the Liebermann–Burchard test conditions.

3. The preparation of bis-(phenylthio)-cholestane, and of N-benzylcholesterylamine and derivatives have been described.

BALTIMORE, MD. RECEIVED AUGUST 21, 1947

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MARYLAND]

N,N-Dialkyl-β-hydroxyamides via the Reformatsky Reaction[1,2]

BY NATHAN L. DRAKE, CHARLES M. EAKER[3] AND WILBUR SHENK[4]

When it seemed desirable to prepare certain N,N-dialkyl-β-hydroxyamides for testing as potential insect repellents, the use of the Reformatsky reaction[9] involving N,N-dialkyl-α-haloamides suggested itself as a direct approach to the desired compounds. The present paper records the results of a study which demonstrated that N,N-dialkyl-α-haloamides can be substituted for α-bromoesters in the Reformatsky reaction with little loss in yield.

TABLE I

N,N-DISUBSTITUTED-α-HALO AMIDES

Compound	Yield, %	Formula	B. p. °C.	Mm.	Analyses,[a] % Calculated C	H	Br	Found C	H	Br
N,N-Diethylbromoacetamide[5]	74	$C_6H_{12}BrNO$	89–90	1.0						
N,N-Dipropylbromoacetamide	48	$C_8H_{16}BrNO$	98–100	2.0						
N,N-Diisopropylbromoacetamide	45	$C_8H_{16}BrNO$	70–71 (m. p. 65.3–66.5)	0.3	43.24	7.21		43.40	7.32	
N,N-(Mixed)-diamylbromoacetamide	71	$C_{12}H_{24}BrNO$	128–129	0.7	51.80	8.63		51.57	8.42	
N,N-Diethyl-α-bromopropionamide	77	$C_7H_{14}BrNO$	74	0.2			38.46			38.83
N,N-Diethyl-α-bromocaproamide	56	$C_{10}H_{20}BrNO$	77–78	0.1	48.00	8.00		47.93	7.97	
N-Methyl-α-bromoacetanilide[6]	75	$C_9H_{10}BrNO$	M. p. 46.8–47.3		47.37	4.39	35.07	47.40	4.67	34.98
N-Ethyl-α-bromoacetanilide	73	$C_{10}H_{12}BrNO$	125–127	0.2	49.59	4.97		49.49	5.09	
N,N-Diethylchloroacetamide[7]	80	$C_6H_{12}ClNO$	117–118	17						
N-Methyl-α-chloroacetanilide[8]	80	$C_9H_{10}ClNO$	M. p. 69–70							

[a] Microanalyses by Miss E. Werble.

Miller and Johnson[5] have reported the preparation of N,N-diethylbromoacetamide (20% yield) by allowing diethylamine to react with bromoacetyl bromide in aqueous alkali. However, it is

---

[1] The initial phases of this research were conducted under a contract recommended by the National Defense Research Committee between the University of Maryland and the office of Scientific Research and Development. The greater part of the work was done after the expiration of the contract.

[2] From a thesis presented by C. M. E. in partial fulfillment of the requirements for the Ph.D. degree, June 1946.

[3] Present address: Monsanto Chemical Co., St. Louis, Mo.

[4] Present address: Harshaw Chemical Co., Cleveland, Ohio.

[5] Miller and Johnson, *J. Org. Chem.*, **1**, 139 (1930

[6] Bischoff, *Ber.*, **34**, 2125 (1901), reported a preparation of N-methyl-α-bromoacetanilide for which a melting point of 69° is given.

[7] Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 149 (1915).

[8] Jacobs and Heidelberger, *ibid.*, **21**, 105 (1915).

[9] Roger Adams, ed., "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 1.

TABLE II

N,N-DIALKYL-α-HYDROXYAMIDES

Formula	Name	Solvent halogen[a]	Yield, %	B. p./mm. and/or m. p. °C.	Mm.
$C_{11}H_{21}O_2N$	N,N-Diethyl-1-hydroxycyclopentaneacetamide	B, Br	13.5	94–95	0.1
$C_{11}H_{23}O_2N$	N,N-Diethyl-3,4-dimethyl-3-hydroxyvaleramide	B, Br	55	74–75	.1
$C_{11}H_{23}O_2N$	N,N-Diethyl-3-hydroxy-3-methylcaproamide	T, Br	52	94–95	.2
$C_{12}H_{23}O_2N$	N,N-Diethyl-1-hydroxycyclohexaneacetamide	B, T; Br	60	94–95	.2
$C_{12}H_{25}O_2N$	N,N-Dipropyl-3-hydroxy-3-methylvaleramide	B, T; Br	48	95–96	.3
$C_{12}H_{26}O_2N$	N,N-Diethyl-3-hydroxy-3,4,4-trimethylvaleramide	B, Br	69	97	.6
$C_{13}H_{19}O_2N$	N,N-Diethyl-3-hydroxy-3-phenylpropionamide	B, E; Br	58	137–138	.1
$C_{13}H_{25}O_2N$	N,N-Diethyl-1-hydroxycyclohexane-α-methylacetamide	T, Br	30	108–109	.1
$C_{13}H_{25}O_2N$	N,N-Diethyl-1-hydroxy-4-methylcyclohexaneacetamide	B, T; Br	59	104–105	.3
$C_{13}H_{25}O_2N$	N,N-Diethyl-1-hydroxy-4-methylcyclohexaneacetamide	B, T; Cl	32	.....	..
$C_{13}H_{27}O_2N$	N,N-Diethyl-3-hydroxy-4-methyl-3-isopropylvaleramide	B, Br	39	108–109	.6
$C_{13}H_{27}O_2N$	N,N-Diisopropyl-1-hydroxycyclohexaneacetamide	B, T; Br	42	106	.4
$C_{14}H_{19}O_2N$	N,N-Diethyl-β-anisylacrylamide[c]	B, E; Br	55	167–170	.4
$C_{16}H_{23}O_2N$	N,N-Diisopropyl-β-anisylacrylamide[c]	B, E; Br	30	163–165	.4
				M. p. 68.7–69.9	
$C_{16}H_{33}O_2N$	N,N-Diethyl-2-n-butyl-4-ethyl-3-hydroxycaproamide	B, E; Br	43	124–125	.3
$C_{17}H_{27}O_2N$	N-Methyl-N-phenyl-4-ethyl-3-hydroxycaprylamide	B, E; Br	76	135–136	.3
$C_{17}H_{27}O_2N$	N-Methyl-N-phenyl-4-ethyl-3-hydroxycaprylamide	B, T; Cl	24	144–146	.6
$C_{18}H_{37}O_2N$	N,N-(Mixed)-diamyl-4-ethyl-3-hydroxycaproamide	B, E; Br	65	144–146	.3
$C_{19}H_{21}O_2N$	N-Ethyl-N-phenyl-3-hydroxy-5-phenylvaleramide	B, Br	38	M. p. 109–109.5	
$C_{19}H_{23}O_2N$	N,N-Diethyl-3,3-diphenyl-3-hydroxypropionamide	B, T; Br	53	M. p. 92.6–93.6	

possible to obtain consistently yields above 65% of the calculated amount by adding an ether solution of the desired dialkylamine (2 moles) slowly to an ether solution of the desired bromoacyl halide (1 mole) cooled to −15°. The N,N-disubstituted-α-haloamides prepared in this way are listed in Table I; all of the bromoamides are strongly lachrymatory and sternutatory.

All of the amides listed in Table I were used successfully. It was noted, however, in the only two cases studied in which the disubstituted amides were related to high homologs of acetic acid, that yields obtained were considerably lower than those obtainable from corresponding acetamides. Thus, N,N-diethyl-α-bromocaproamide gave only a 43% yield of hydroxyamide when it reacted with 2-ethylbutyraldehyde; on the other hand, N,N-diamylbromoacetamide reacted with the same aldehyde and yielded 65% of the calculated amount of the expected hydroxyamide. A similar comparison can be made between yields obtained in the reaction of cyclohexanone with N,N-diethyl-α-bromopropionamide and N,N-diethyl-α-bromoacetamide, respectively. Branching of the alkyl groups attached to nitrogen appeared, from the very limited evidence available, to cause lower yields.

The reaction appears to be applicable to aliphatic or aromatic aldehydes and to most ketones. Worthy of note is the fact that we were unable to use furfural successfully as the carbonyl-bearing component. This finding is difficult to explain inasmuch as furfural participates normally in the usual form of the Reformatsky reaction. Nine ketones were investigated and all were converted to the expected hydroxyamide. Five aldehydes were studied; with the exception noted above, all participated in the reaction, but in the case of anisaldehyde the hydroxyamide underwent spontaneous dehydration.

The behavior of three alicyclic ketones, cyclohexanone, 4-methylcyclohexanone and cyclopentanone, was studied. The reaction proceeded satisfactorily with the first two but only poorly with the third. In four different attempts to bring about reaction between cyclopentanone and N,N-diethylbromoacetamide, the yield of desired product was never above 14%. Cyclic ketones in general appeared to form more insoluble zinc complexes than was the case with other carbonyl compounds investigated and vigorous stirring was necessary to prevent the separated zinc complex from coating the zinc alloy and stopping the reaction. It was found expedient to employ larger quantities of solvent in such cases to minimize this difficulty. In order to study steric effects in this reaction, methyl isopropyl ketone, diisopropyl ketone and pinacolone were used with N,N-diethylbromoacetamide in a series of similar reactions. All of the reactions occurred satisfactorily; the yields obtained were, respectively, 39, 69 and 55% of the calculated amounts. It is noteworthy that diisopropyl ketone, a substance which Conant and Blatt[10] found would react additively only with methylmagnesium iodide among various Grignard reagents studied, participates additively in the modified Reformatsky reaction to a considerable extent.

Several experiments in which attempts were made to substitute α-chloroamides for the corresponding α-bromoamides indicated that yields

---

(10) Conant and Blatt, THIS JOURNAL, 51, 1227 (1929).

TABLE II (*Continued*)

Sp. gr. 25°/25°	n^{25}D	MR Obs.	MR Calcd.	Analyses,[b] % Calculated C	H	N	Found C	H	N
1.005	1.4743	55.7	56.3	66.33	10.56		65.95 65.89	10.80 10.57	
0.9477	1.4548	57.5	58.5	65.67	11.54		65.30 65.13	11.68 11.51	
0.9402	1.4530	57.7	58.5	65.67	11.54		65.47 65.17	11.57 11.65	
1.005	1.4787	60.1	60.9	67.70	10.80	6.63	66.84 66.94	10.40 10.55	6.60 6.53
0.9327	1.4524	62.2	63.1	66.98	11.63		66.54 66.82	11.73 11.60	
0.9442	1.4577	62.4	64.2	66.66	12.04		66.54 66.29	11.78 11.71	
1.060	1.5265	64.1	63.1	70.59	8.60		70.04 70.25	8.68 8.59	
0.9978	1.4795	64.7	65.5	68.72	11.02		68.64 68.40	11.21 10.60	
0.9872	1.4760	64.9	65.5	68.72	11.02		68.23 68.43	10.83 11.11	
....	1.4770	..	..	...	...		... ...	... ...	
0.9520	1.4641	66.4	67.7	68.12	11.79		67.51 67.50	11.90 11.70	
....	1.4774	..	..	69.71	11.22		69.48 69.43	10.84 10.86	
1.068	1.5902	73.6	68.4	72.10	8.15		71.40 71.65	8.09 8.30	
....	....	..	..	73.56	8.81		73.66	9.18	
0.9303	1.4635	80.4	81.6	70.85	12.18		70.06 70.29	12.24 12.38	
0.9959	1.5079	82.9	81.6	73.65	9.75		74.29 74.01	9.80 10.08	
....	1.5078								
0.9105	1.4594	89.8	90.8	72.24	12.37		71.81 71.88	12.23 12.44	
....	....	..	..	77.29	7.13		76.80 76.54	7.14 7.13	
....	....	..	..	76.77	7.75		77.00 76.96	8.01 8.12	

[a] B = benzene; E = ether; T = toluene. Cl and Br refer to the halogen in the haloamide used. [b] Microanalyses by Miss E. Werble. [c] The hydroxyamide suffered dehydration during preparation.

obtainable from chloro compounds were considerably smaller than those from the corresponding bromoamides.

The dehydration of N,N-diethyl-β,β-diphenylhydracrylamide proceeds smoothly in the presence of 99% formic acid; it is probable that the other hydroxyamides described could be similarly converted to the corresponding unsaturated compounds.

Experimental

The aldehydes and ketones used were purified by usual methods.

Preparation of α-Haloamides.—An ether solution of the appropriate α-haloacyl halide was cooled to −15°, and an ether solution of 2 equivalents of the desired amine was added to the well-stirred solution at such a rate that the temperature of the mixture did not exceed −10°. After the reaction was complete, enough cold water was added to dissolve the precipitated amine hydrochloride. The organic layer was separated and washed successively with dilute phosphoric acid, dilute potassium carbonate and finally with saturated brine until neutral. After removal of the ether by distillation, the product was purified by distillation under diminished pressure, or by recrystallization.

The compounds prepared are found in Table I,

Preparation of N,N-Disubstituted-α-hydroxyamides.—The calculated quantity of turnings of zinc–copper alloy (8% copper) and a crystal of iodine were added to a 500 ml., three-necked flask for experiments in which 0.2 to 0.25 mole of reactants were employed. The flask was fitted with a reflux condenser, stirrer and dropping funnel and was protected from atmospheric moisture by drying tubes; before use the apparatus was flamed until dry while a stream of dry air was drawn through it. A small quantity (*ca.* 15 ml.) of a solution of the α-haloamide and the aldehyde or ketone in 100–150 ml. of the solvent listed in Table II was added, stirring was begun and the mixture was heated under reflux until the reaction started (usually within 15 min.). After the initial reaction had subsided, the remainder of the solution of reactants was added at such a rate that gentle refluxing occurred (*ca.* one hour). The mixture was then heated under reflux for one hour, cooled and poured onto 200 ml. of cold 10% sulfuric acid. Copper and unused zinc were removed by filtration, whereupon the organic layer was washed in turn with 5% solutions of sulfuric acid and potassium carbonate and finally with saturated brine until neutral. After the solution had been dried, the solvent was removed by distillation, and the product was purified by distillation or crystallization.

The compounds prepared and certain pertinent data are listed in Table II.

Dehydration of N,N-Diethyl-β,β-diphenylhydracrylamide.—The method used was similar to one already described.[11] The amide (3 g.) in 20 ml. of 99% formic acid was heated on a steam-bath for fifteen minutes. The cooled reaction mixture was poured into water, the product was extracted with benzene and the benzene solution was washed with 5% potassium carbonate and then with water until neutral. Evaporation of the benzene yielded a solid which was purified by recrystallization from petroleum ether (60–80°). Purified for analysis the compound melted at 83.6–84.3°. *Anal.* Calcd. for $C_{19}H_{21}NO$: C, 81.72; H, 7.53. Found: C, 81.87, 81.99.; H, 7.46, 7.47.

α,β-Dibromo-N,N-diethyl-β-anisylacrylamide.—Prepared from a solution of N,N-diethyl-β-anisylacrylamide in carbon tetrachloride by the addition of a 5% solution of bromine in the same solvent, and recrystallized from benzene–petroleum ether (1:1), the analytical sample melted at 122–122.8°. To obtain reproducible melting points, it was found necessary to heat the melting-point bath to 115° before inserting the capillary. *Anal.* Calcd. for $C_{14}H_{19}Br_2NO_2$: C, 42.75; H, 4.84. Found: C, 43.16, 42.86; H, 5.03, 5.23.

α,β-Dibromo-N,N-diisopropyl-β-anisylacrylamide.—Prepared as above, the analytical sample melted at 139–140°. *Anal.* Calcd. for $C_{16}H_{23}Br_2NO_2$: Br, 38.01. Found: Br, 37.70, 38.05.

---

[11] Bachmann and Edgerton, THIS JOURNAL, **62**, 2971 (1940).

Summary

1. The substitution of N,N-disubstituted-α-halomides for α-haloesters in the Reformatsky reaction has been studied and shown to be practical.

2. Sixteen different hydroxyamides prepared by this method are described.

3. Anisaldehyde reacted with two α-haloamides to yield the unsaturated relative of the expected hydroxyamide.

4. It was found impossible to isolate the expected product when furfural was one of the reactants.

College Park, Maryland

Received September 15, 1947

[Contribution from the Division of Physiology, National Institute of Health, U. S. Public Health Service]

Certain N-Alkyl, N-Carboxyalkyl and N-Hydroxyalkyl Derivatives of 4,4′-Diaminodiphenyl Sulfone

By Ernest L. Jackson

Numerous derivatives of 4,4′-diaminodiphenyl sulfone (I) have been reported[1] since the observation of the antibacterial activity of this sulfone by Buttle, *et al.*,[2] and by Fourneau, *et al.*[3] Among the amino substituted derivatives the results of biological studies[4] indicate the desirability of the presence of one free amino group and suggest the superiority of the alkyl type of substituent. The present paper reports the synthesis of a number of derivatives having an alkyl, carboxyalkyl or hydroxyethyl group substituted in one of the amino groups. Several similar derivatives of 4-amino-4′-nitrodiphenyl sulfone (II) were prepared both for use as intermediates in the synthesis of some of the derivatives of I and also for tests of their antibacterial activity, since compound II is known to show considerable bacteriostatic activity.

Two methods were employed in the preparation of the crystalline derivatives of I shown in the table: (1) direct alkylation or carboxyalkylation of I, an excess of I being used to minimize substitution in the second amino group of the molecule; (2) alkylation or hydroxyethylation of II and subsequent reduction of the nitro group of the product by iron and 1.5% hydrochloric acid in ethanol solution. The first method, the success of which depends on efficient separability of the product from I, was applied to the preparation of compounds IV and X–XIV. As alkylation and carboxyalkylation agents, ethyl iodide was used for the preparation of IV, the appropriate *n*-alkyl bromide for XII–XIV, bromoacetic acid for X and β-bromopropionic acid for XI. In the case of the glycine and β-alanine derivatives, separation from excess I was effected by removal of the carboxyl compounds as the water-soluble sodium salts. The acids required further purification, which was accomplished readily through the crystalline pyridine salts. The ethyl derivative crystallized from the ethylation solution at the end of the reaction. The difference in solubility of the *n*-butyl, *n*-amyl and *n*-tetradecyl derivatives in 2.5–5% hydrochloric acid as compared with I provides a convenient method of separation. Compounds IV and XIV were prepared also by the second method, which was the way the β-hydroxyethyl (VII) and benzyl (XVII) derivatives were obtained. The yields of amino derivatives in the reduction of the nitro compounds were excellent, 90% in one case.

The hydroxyethylation of II by reaction with 2-bromoethanol proceeds at a slow rate in boiling cellosolve solution to produce compound VI in a yield of 30–35%. Prolonged duration of the reaction results in a secondary reaction involving the hydroxyethyl group of the initial product (VI), as shown by the formation of both the β-hydroxyethyl (VII) and ethyl (IV) derivatives in the reduction of the mixture resulting from the hydroxyethylation reaction under certain conditions. Although the mechanism of the formation of IV in the two-step process has not been established, it seems possible that the compound might result from the reduction of 4-nitro-4′-β-bromoethylaminodiphenyl sulfone, which could be produced by the reaction of VI with the hydrobromic acid accumulated in the hot hydroxyethylation reaction solution. The direct hydroxyethylation of I by the reaction of 2-bromoethanol and I in equimolecular proportions at 100° produced a mixture from which only crystalline 4,4′-bis-(β-hydroxyethylamino)-diphenyl sulfone (VIII) was isolated. During the progress of this investigation Heymann and Heidelberger[1] reported the preparation of VIII, in low yield, through a pressure reaction of ethylene oxide with I followed by isolation of the product as the crystalline N,N′-dinitroso derivative. 2-Bromoethanol possesses advantages over ethylene oxide for the preparation of VIII, since

---

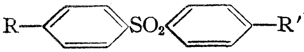
(1) For references see: Roblin, Williams and Anderson, This Journal, **63**, 1930 (1941); Heymann and Fieser, *ibid.*, **67**, 1979 (1945); Heymann and Heidelberger, *ibid.*, **67**, 1986 (1945); Jackson, *ibid.*, **68**, 1438 (1946).

(2) Buttle, Stephenson, Smith, Dewing and Foster, *Lancet*, **232**, 1331 (1937).

(3) Fourneau, Tréfouël, Nitti, Bovet and Tréfouël, *Compt. rend.*, **204**, 1763 (1937); **205**, 299 (1937).

(4) (a) Smith, Jackson and McClosky, *Am. Rev. Tuberc.*, **53**, 589 (1946); **55**, 366 (1947); (b) Youmans and Doub, *ibid.*, **54**, 287 (1946); Youmans, Feldman and Doub, *ibid.*, **54**, 295 (1946); (c) Smith, McClosky, Jackson and Bauer, *Proc. Soc. Exptl. Biol. Med.*, **64**, 261 (1947); see also Heymann and Fieser, ref. 1.

TABLE I

DERIVATIVES OF DIPHENYL SULFONE R——R′

No.	R	R′	M. p., °C.	Activity[a]	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found[b] C	Found[b] H	Found[b] N	Found[b] S
I	—NH_2	—NH_2	.....	++	....	...	..	...	...	...	..	...	...
II	—NO_2	—NH_2	.....	−	....	...	..	...	...	...	..	...	...
III	—NO_2	—$NHCH_2CH_3$	223–224	−	$C_{14}H_{14}N_2O_4S$	...	..	...	10.47	...	..	...	10.29
IV	—NH_2	—$NHCH_2CH_3$	199–200	++	$C_{14}H_{16}N_2O_2S$	60.84	5.84	10.14	11.60	60.93	5.92	10.28	11.59
V	—$NHCOC_6H_5$	—$NHCH_2CH_3$	226–227	−	$C_{21}H_{20}N_2O_3S$	66.30	5.30	7.37	...	66.29	5.44	7.53	...
VI	—NO_2	—$NHCH_2CH_2OH$	210–211	−	$C_{14}H_{14}N_2O_5S$	...	..	...	9.95	...	..	...	9.63
VII	—NH_2	—$NHCH_2CH_2OH$	143.5–144.5[c]	++	$C_{14}H_{16}N_2O_3S$	57.51	5.52	9.58	10.97	57.80	5.70	9.37	11.12
VIII	—$NHCH_2CH_2OH$	—$NHCH_2CH_2OH$	187–188	0	$C_{16}H_{20}N_2O_4S$	57.12	5.99	8.33	9.53	56.81	5.92	8.13	9.57
IX	—NO_2	—$NHCH_2COOH$	231–232	−	$C_{14}H_{12}N_2O_6S$	49.99	3.60	8.33	9.53	49.98	3.66	8.25	9.62
X[d]	—NH_2	—$NHCH_2COOH$	202–203	++	$C_{14}H_{14}N_2O_4S$	54.89	4.61	9.15	10.47	54.54	4.80	8.87	10.59
XI[e]	—NH_2	—$NH(CH_2)_2COOH$	127–128[c]	++	$C_{15}H_{16}N_2O_4S$	56.23	5.03	8.75	10.01	56.38	5.28	8.79	9.83
XII	—NH_2	—$NH(CH_2)_3CH_3$	192–193	+	$C_{16}H_{20}N_2O_2S$	63.13	6.62	9.21	10.53	63.08	6.55	9.07	10.39
XIII	—NH_2	—$NH(CH_2)_4CH_3$	148–149	+	$C_{17}H_{22}N_2O_2S$	64.12	6.97	8.80	10.07	64.29	7.08	8.51	10.06
XIV	—NH_2	—$NH(CH_2)_{13}CH_3$	174–174.5[c]	0	$C_{26}H_{40}N_2O_2S$	70.22	9.07	6.30	7.21	70.38	9.02	6.20	7.29
XV	—NO_2	—$NH(CH_2)_{13}CH_3$	98–99	−	$C_{26}H_{38}N_2O_4S$	...	..	...	6.75	...	..	...	6.83
XVI	—NO_2	—$NHCH_2C_6H_5$	149–150	+	$C_{19}H_{16}N_2O_4S$	...	..	...	8.70	...	...	...	8.79
XVII	—NH_2	—$NHCH_2C_6H_5$	188.5–189[c]	++	$C_{19}H_{18}N_2O_2S$	67.43	5.36	8.28	9.47	67.43	5.26	8.29	9.62
XVIII	—NH_2	—$N(CH_2C_6H_5)_2$	223–224	−	$C_{26}H_{24}N_2O_2S$	72.87	5.65	6.54	7.48	73.11	5.74	6.36	7.78
XIX	—$N(CH_2C_6H_5)_2$	—$N(CH_2C_6H_5)_2$	199–200	0	$C_{40}H_{36}N_2O_2S$	...	..	...	5.27	...	..	...	5.54

[a] Data supplied by Dr. M. I. Smith and Dr. J. M. Junge on qualitative tests against Type I pneumococcal infections in white mice. The slight activity or inactivity of several of the compounds may be due to poor absorption. Mice tolerate much larger doses of the derivatives than of diaminodiphenyl sulfone. For tests on compounds X and XI in experimental tuberculosis see ref. 4a and Smith, *N. Y. State J. Med.*, 45, 1665 (1945). In tests by Dr. E. W. Emmart marked inhibition of the growth of tubercle bacilli (human strain A27) was shown by compound VII in Kirchner's medium at a concentration of 4 mg.% and by compound IX in horse meat bouillon at a concentration of 25 mg. %. [b] Microcombustions and nitrogen analyses by Mr. C. A. Kinser, Mrs. Betty Mount and Mrs. Margaret M. Ledyard. [c] Corrected. Compound XI contained combined solvent. [d] Neut. equiv. calcd., 306; found, 305. [e] Neut. equiv. calcd., 320; found, 325.

the reaction of the former with I is carried out at atmospheric pressure and apparently the product is isolated more readily in crystalline condition.

The reaction of benzyl chloride and II in approximately equimolecular proportions afforded principally the monobenzyl (XVI) derivative and a smaller amount of 4-nitro-4′-dibenzylaminodiphenyl sulfone. The latter compound was not isolated, but its formation is evident since reduction of the benzylation mixture yielded both XVII and XVIII. Mingoia and Berti[5] obtained 4-nitro-4′-dibenzylaminodiphenyl sulfone through reaction of benzyl chloride with II; the monobenzyl derivative apparently was formed also, but the compound was not isolated in pure condition. Benzyl chloride and I in the molecular proportions of 3.5 to 1.0 yielded the tetrabenzyl (XIX) derivative, which has been described by Buttle, *et al.*[6]

Experimental

4-Nitro-4′-ethylaminodiphenyl Sulfone (III).—A solution of 20 g. of II and 12.3 g. of ethyl iodide in 150 cc. of 95% ethanol was refluxed for twenty-two hours and then cooled to room temperature. After the addition of 25 cc. of water and 7 g. of sodium bicarbonate, which produced crystallization, the refluxing was continued for an additional twenty-nine hours. The yellow crystals were separated from the hot mixture by filtration, washed first with cold 80% ethanol and finally with cold water. The nearly pure III weighed 5.8 g. and melted at 219–220°. The filtrate deposited at room temperature 11.3 g. of crystals melting at 155–160°, and upon concentration yielded more crystals showing a similar melting point. Additional III was obtained by recrystallization of the lower-melting material from ethanol. The compound is difficultly soluble in absolute ethanol, from which it crystallizes as elongated plates.

4-Amino-4′-ethylaminodiphenyl Sulfone (IV).—To a solution of 4 g. of pure III in 600 cc. of hot 95% ethanol was added 25 cc. of 38% hydrochloric acid. After the addition of 12 g. of 40-mesh, degreased iron filings in several portions to the hot solution, the mixture was refluxed for three hours, then filtered hot to remove excess iron, which was washed with hot ethanol. The hot filtrate was made slightly alkaline by the addition of concentrated aqueous sodium hydroxide solution, the precipitate filtered off and washed thoroughly with hot ethanol. The colorless filtrate, neutralized by hydrochloric acid, was concentrated *in vacuo* to dryness. The residue was extracted with 40 cc. of cold water in two portions to remove sodium chloride. The undissolved crystals were taken up in 70 cc. of hot absolute ethanol, from which a first crop of 2.7 g. of virtually pure IV crystallized. Additional crystals, isolated from the mother liquor, increased the yield to 3.3 g. or 91%. The compound usually crystallized from ethanol as slightly yellow, rod-shaped prisms, but sometimes was observed to crystallize as blades or thick plates. It showed diazotization and coupling according to the Bratton and Marshall[7] technique.

Compound IV was prepared also by direct ethylation of I. A mixture of 100 g. of I (2.0 molecular equivalents), 31.4 g. of ethyl iodide (1.0 molecular equivalent), 17 g. of sodium bicarbonate, 500 cc. of 95% ethanol and 100 cc. of water was refluxed for forty-eight hours. The solution deposited at room temperature 16.1 g. of slightly impure IV, which was collected, washed first with 80% ethanol and finally with water. These crystals were purified readily by recrystallization from absolute ethanol. The mother liquor from the crude IV yielded about 80 g. of crystals from which was separated by fractional recrystallization from ethanol about 1 g. of IV. The remainder of the material consisted principally of I.

---

(5) Mingoia and Berti, *Arquiv. biol.* (*São Paulo*), **28**, 84 (1944); *C. A.*, **39**, 2057 (1945).

(6) Buttle, Dewing, Foster, Gray, Smith and Stephenson, *Biochem. J.*, **32**, 1101 (1938).

(7) Bratton and Marshall, *J. Biol. Chem.*, **128**, 537 (1939); *cf.* Roblin and Winnek, THIS JOURNAL, **62**, 1999 (1940).

Benzoylation of IV.—To a solution of 0.4 g. of pure IV in 12 cc. of anhydrous pyridine at 0° was added 0.4 g. of benzoyl chloride. After being kept at room temperature for twenty-two hours, the solution was mixed with ice water which precipitated a sirup that soon crystallized. The crystals were collected and washed with cold water. In order to remove benzoic acid, the substance was extracted with 75 cc. of cold absolute diethyl ether. The undissolved crystals of crude monobenzoyl derivative (V) weighed 0.5 g. It was purified by recrystallization from acetone, from which it crystallized as colorless, rod-shaped prisms melting at 226–227° (uncor.). The compound possesses no free primary amino group, as indicated by its failure to show diazotization and coupling in aqueous acetone solution by the Bratton and Marshall[7] method.

4-Nitro-4′-(β-hydroxyethylamino)-diphenyl Sulfone (VI).—A solution of 50 g. of II and 23 g. of 2-bromoethanol in a mixture of 250 cc. of 2-ethoxyethanol and 30 cc. of water was refluxed for fifty-eight hours. The filtered solution was neutralized by sodium hydroxide solution and then concentrated *in vacuo*, with the bath at 65–75°, virtually to dryness. The solid residue was mixed thoroughly with 250 cc. of water, then filtered and washed with cold water. It was taken up in hot absolute ethanol, in which it is difficultly soluble, some Norit added and filtered off. The solution deposited yellow, boat-shaped prisms of VI. The mother liquor upon concentration yielded several crops of impure crystals, from which was isolated more VI by fractional recrystallization from ethanol; yield, 17.5 g. or 30%. The analytical sample was obtained by further recrystallization from ethanol.

In a modified experiment evidence was obtained to show that a secondary reaction, involving the hydroxyethyl group, occurs during prolonged refluxing of the reaction solution. A solution similar in composition to that described was refluxed for eighty hours, cooled and stirred with a glass rod to induce crystallization. After twenty-four hours a crop of impure crystalline product was separated. The filtrate, neutralized with sodium hydroxide solution and concentrated *in vacuo* to about one-half the original volume, deposited additional product which was filtered off. The solvent was then removed by distillation *in vacuo*, the residual sirup mixed with water, finally separated and extracted with 70 cc. of hot ethanol. After filtration of the undissolved crystalline product, more material was isolated from the filtrate to make the yield of crystals melting at 200–206° about 46%, calculated as VI. These crystals proved to be a mixture. In an extraction with three parts of hot acetone, about 80% of the crystals melting at 206–209° was undissolved. This material upon reduction by iron and 1.5% hydrochloric acid in hot ethanol solution yielded a mixture consisting principally of VII and about 10% of IV. The two compounds were separated by fractional recrystallization from absolute ethanol. The crystals of IV were identified by the melting point of 199–200° (uncor.) alone or mixed with authentic IV; also by benzoylation according to the previously described procedure to yield the crystalline monobenzoyl derivative melting at 226–227° (uncor.), not depressed by crystals of the authentic compound.

4-Amino-4′-(β-hydroxyethylamino)-diphenyl Sulfone (VII).—Recrystallized VI (8.9 g.), melting at 207–210°, was reduced by iron (27 g.) and 1.5% hydrochloric acid in hot ethanol solution (555 cc.) according to the procedure described for the preparation of IV. The crude product (VII), after being washed with cold water, was recrystallized from absolute ethanol as thick, virtually colorless plates; yield, 6.1 g. or 76%. It is readily soluble in acetone, soluble in ethanol and dioxane, also soluble in cold 1% hydrochloric acid, somewhat soluble in hot water, and only slightly soluble in cold water. The presence of a primary amino group in the molecule was demonstrated by diazotization.[7]

4,4′-bis-(β-Hydroxyethylamino)-diphenyl Sulfone (VIII).—Seventy-five grams of I (1.0 molecular equivalent) and 37.8 g. of 2-bromoethanol (1.0 molecular equivalent) were mixed thoroughly while being heated on the steam-bath. The mixture was kept at 100° under a reflux condenser for thirteen hours and then dissolved, apparently as the hydrobromides, in 200 cc. of warm water. The addition of 30 g. of sodium bicarbonate precipitated a sirup, which changed to a gum upon being cooled in ice water. The gum, after separation from the aqueous layer by decantation, was taken up in 50 cc. of methanol. The solution, upon being left for several days in an open flask at room temperature with occasional stirring, deposited 9.4 g. of somewhat impure crystals of VIII. The mother liquor, kept in an open beaker with occasional addition of methanol and stirring, yielded 7.7 g. of crystalline VIII. The remainder of the material was a sirup, which probably consisted of a mixture of I, VII and VIII. The crude VIII was purified by recrystallization from methanol as virtually colorless, rod-shaped prisms.

N-[p-(p-Nitrophenylsulfonyl)-phenyl]-glycine (IX).—A mixture of 50 g. of II, 23.9 g. of monobromoacetic acid, 16.7 g. of sodium bicarbonate and 280 cc. of water was shaken until effervescence ceased. After the addition of 420 cc. of 2-ethoxyethanol, the mixture was kept at 100° under a reflux condenser for thirty hours. The red solution was neutralized by sodium bicarbonate, the solvent removed by distillation *in vacuo* with the bath at 50°, some water added and evaporated *in vacuo*. The sodium salt of IX was separated from water-insoluble material by extraction of the residue with 900 cc. of cold water in several portions, the final portion showing no precipitate upon addition of hydrochloric acid. The undissolved solid weighed 39.1 g. and melted at 148–151°. The addition of hydrochloric acid to the sodium salt solution precipitated IX as a sirup which crystallized overnight. To an efficiently stirred suspension of the crude acid in water was added sodium hydroxide solution until the mixture was neutral to phenolphthalein. After filtration to remove some undissolved solid, the acid was precipitated by the addition of hydrochloric acid; air-dried; yield of virtually pure IX, 11.8 g. The analytical sample was obtained by recrystallization of the compound as yellow, spear-shaped prisms from a mixture of acetone and water.

N-[p-(p-Aminophenylsulfonyl)-phenyl]-glycine (X).—A solution of 100 g. of I (2.0 molecular equivalents), 28 g. of monobromoacetic acid (1.0 molecular equivalent) and 19 g. of sodium bicarbonate in a mixture of 500 cc. of water and 250 cc. of 2-ethoxyethanol was kept at 100° under a reflux condenser for thirty-two hours. The crude solid was isolated and preliminary purification accomplished by a procedure similar to that described for IX; air-dried; yield, 39 g. melting at 185–193°. About 62 g. of impure I was recovered. Although the acid could be recrystallized from methanol, its purification is facilitated by the preparation of the pyridine salt.

A solution of 37 g. of the acid in about 175 cc. of hot pyridine, upon being filtered and kept overnight at room temperature, deposited elongated, well-formed prisms of the pyridine salt which were filtered, washed first with cold pyridine and finally with methanol. Crystals obtained from the mother liquor, after concentration *in vacuo*, increased the yield to 38 g., most of which was nearly pure. After being recrystallized to constant melting point from pyridine and dried in an evacuated desiccator over calcium chloride, the pure salt melted at 167–168° (uncor.).

To a suspension of 10 g. of pure pyridine salt in 100 cc. of water was added 27.3 cc. of *N* sodium hydroxide solution. In order to remove pyridine, the filtered solution was concentrated to dryness *in vacuo* with the bath at 55–60°, the residual sirup taken up in water and the concentration repeated. After some absolute ethanol had been added and distilled off *in vacuo*, the sodium salt was dissolved in 35 cc. of water, the solution filtered and the acid precipitated by the addition of 27.3 cc. of *N* hydrochloric acid. The virtually colorless pure X was filtered off, washed with cold water and dried in the air at room temperature; yield, 7.5 g. The presence of a primary amino group in the molecule was demonstrated by a test with p-dimethylaminobenzaldehyde, also by diazotization and coupling.[7]

N-[*p*-(*p*-Aminophenylsulfonyl)-phenyl]-β-alanine (XI).—A mixture of 163 g. of I, 50 g. of β-bromopropionic acid, 30 g. of sodium bicarbonate, 500 cc. of water and 250 cc. of 2-ethoxyethanol was kept at 100° under a reflux condenser for forty-six hours. The solution, after being neutralized by sodium bicarbonate, deposited at room temperature 102 g. of I melting at 168–172°. Crude XI was isolated as a sirup in a similar way as described for IX. A solution of the sirup in a mixture of 65 cc. of methanol and 85 cc. of pyridine deposited at 5° crystals of the pyridine salt of XI. After the crystals had been filtered and washed with diethyl ether, the filtrate was concentrated *in vacuo* to a thin sirup which, upon being mixed with 15 cc. of pyridine, gave at 5° a second crop of crystals to make the yield 63 g. The pyridine salt is readily soluble in cold pyridine and in cold methanol, soluble in ethanol and only slightly soluble in diethyl ether. It crystallizes from a mixture of pyridine and absolute ethanol as colorless needles or elongated plates. After being dried in an evacuated desiccator over calcium chloride, the pure salt melts at 134–135° (cor.).

The acid was prepared as a nearly colorless sirup from 33 g. of the pyridine salt as described for X, 84 cc. of *N* sodium hydroxide solution and 84 cc. of *N* hydrochloric acid being used in the operation. The sirupy acid was separated from the aqueous layer at 0–5° by decantation and washed with a little water. The acid crystallized from a solution of the sirup in 23 cc. of methanol saturated with benzene; air-dried; weight, 24 g.; m. p. 119–120°. After being recrystallized further as spear-shaped prisms from a mixture of methanol and benzene and dried in an evacuated desiccator over calcium chloride, the virtually colorless pure XI melted at 127–128° (cor.). These crystals lost no weight at 65° *in vacuo*. Calcd. for $C_{15}H_{16}N_2O_4S + 0.5\ C_6H_6$: C, 60.1; H, 5.3. Found: C, 60.1; H, 5.5. The solvent-free analytical sample was obtained by evaporation of a solution of the crystals in acetone followed by drying the residual sirup at 100° *in vacuo*. The compound reacts with *p*-dimethylaminobenzaldehyde and shows diazotization and coupling,[7] results which demonstrate the presence of a primary amino group in the molecule.

4-Amino-4′-*n*-butylaminodiphenyl Sulfone (XII).—A solution of 85 g. of I (2.5 molecular equivalents) and 18.7 g. of *n*-butyl bromide (1.0 molecular equivalent) in a mixture of 495 cc. of 95% ethanol and 26 cc. of water was refluxed for twenty-five hours. The solution deposited at room temperature 19.3 g. of somewhat impure XII. The mother liquor was neutralized by sodium hydroxide solution, then treated hot with Norit and freed from solvent. The solid residue was extracted thoroughly with cold 2.5% hydrochloric acid. Neutralization of the hydrochloric acid solution by sodium hydroxide precipitated 50 g. of nearly pure I melting at 172–173°. The solid, which was undissolved by the hydrochloric acid, was washed with water and recrystallized from ethanol, yielding colorless plates of XII. The total yield was 27.5 g. or 66%. The compound showed diazotization and coupling.[7]

4-Amino-4′-*n*-amylaminodiphenyl Sulfone (XIII).—A yield of 72 g. or 70% of XIII was obtained from 200 g. of I and 49 g. of *n*-amyl bromide by a procedure similar to that described under XII. The compound crystallized from ethanol as almost colorless, spear-shaped prisms, which are readily soluble in acetone and virtually insoluble in water. It showed diazotization and coupling.[7]

4-Amino-4′-*n*-tetradecylaminodiphenyl Sulfone (XIV).—A solution of 10 g. of I and 4.5 g. of myristyl bromide in a mixture of 55 cc. of ethanol and 6 cc. of water was refluxed for thirty hours. The product was isolated and purified in a similar way as described for XII. It crystallized from absolute ethanol as colorless, thin blades; m. p. 174–174.5° (cor.).

Compound XIV was prepared also by the reaction of I and myristyl bromide in the molecular proportions of 1.25 to 1.00.

Reduction of 1.2 g. of the pure nitro derivative (XV) by iron filings (4 g.) and 1.5% hydrochloric acid in ethanol solution (84 cc.) yielded crystals of XIV. Identity with the crystals prepared from I was established by the melting point of 174–174.5° (cor.), not depressed by crystals prepared from I; also by resemblance in crystal form and solubility. Samples prepared by both methods showed diazotization and coupling.[7]

4-Nitro-4′-*n*-tetradecylaminodiphenyl Sulfone (XV).—A solution of 20 g. of II and 19.9 g. of myristyl bromide in a mixture of 100 cc. of 2-ethoxyethanol and 12 cc. of water was kept at 100° under a reflux condenser for fifty-four hours. The solid material was recovered and neutralized in aqueous suspension. Fractional recrystallization from absolute ethanol afforded a partial separation of XV from unreacted II. Crystals of pure XV were obtained by recrystallization of selected fractions of the mixture from acetone, from which the compound crystallized as yellow blades. The analytical sample was dried at 65° *in vacuo*.

4-Nitro-4′-benzylaminodiphenyl Sulfone (XVI).—A mixture of 200 g. of II, 96 g. of benzyl chloride, 480 cc. of 95% ethanol and 720 cc. of water was refluxed for fifty hours. After the reaction mixture had been kept overnight at 25°, the supernatant liquid was decanted from a sirup, which was washed thrice with cold water and then dissolved in 200 cc. of hot dioxane. The filtered solution deposited at room temperature 168 g. of crystals, the yield of crude product being increased to about 225 g. by the isolation of more crystals from the mother liquor. Purification was completed by recrystallization from dioxane as thick, yellow plates which, in the air-dried condition, retained combined solvent. The analytical sample was dried to constant weight at 100° *in vacuo;* it then melted at 149–150° (uncor.).

Some 4-nitro-4′-dibenzylaminodiphenyl sulfone is formed in the benzylation reaction, as shown below by the isolation of crystals of XVIII from the products of the reduction of some impure XVI.

4-Amino-4′-benzylaminodiphenyl Sulfone (XVII) and 4-Amino-4′-dibenzylaminodiphenyl Sulfone (XVIII).—A solution of 15 g. of XVI, which had been dried at 100° *in vacuo*, in 460 cc. of hot 95% ethanol was treated with 18 cc. of 38% hydrochloric acid and 45 g. of iron filings by the procedure described for the preparation of IV, with the exception that methanol was substituted for ethanol in washing the excess iron and iron compounds. The solution, neutralized by hydrochloric acid, deposited at room temperature 6.7 g. of crystals, melting at 178–180°, which proved to be a mixture of XVII and XVIII. The mother liquor was decolorized with carbon and concentrated virtually to dryness. The residue was stirred with 100 cc. of water, the undissolved crystals collected and washed with water. Extraction of the 6.7 g. of crystals with 100 cc. of hot methanol left undissolved 1.7 g. which, upon recrystallization from a mixture of acetone and methanol, yielded about 1 g. of difficultly soluble, rod-shaped prisms of XVIII. Fractional recrystallization of the remainder of the material from methanol, with the use of decolorizing carbon when necessary, afforded 7.6 g. or 55% of virtually pure, colorless blades of XVII. The crystals of XVII showed diazotization and coupling.[7] Crystals of pure XVIII in aqueous acetone solution gave a diazotization[7] value of 28% as compared with I; calculated, 29%.

4,4′-*bis*-(Dibenzylamino)-diphenyl Sulfone (XIX).—A mixture of 10 g. of I (1.0 molecular equivalent), 17.8 g. of benzyl chloride (3.5 molecular equivalents), 36 cc. of water and 24 cc. of 95% ethanol was refluxed for forty-seven hours. The crude product was isolated as a sirup, which crystallized from a mixture of acetone and ethanol. Purified by recrystallization first from a mixture of acetone and ethanol and finally from acetone, the colorless rod-shaped prisms melted at 199–200° (uncor.). Buttle, *et al.*,[6] reported a melting point of 200° (cor.).

Summary

A number of new derivatives of 4,4′-diaminodiphenyl sulfone having an alkyl, carboxyalkyl or

hydroxyethyl group substituted in one of the amino groups have been synthesized. Several similar derivatives of 4-amino-4′-nitrodiphenyl sulfone were prepared. The preparation and the properties of the compounds are described.

The antipneumococcal and antitubercular activities of certain of the compounds are recorded.

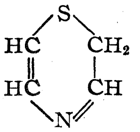
BETHESDA, MARYLAND RECEIVED SEPTEMBER 15, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KENTUCKY]

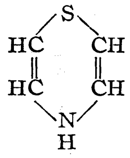
The Preparation of 1,4-Thiazine

BY CHARLES BARKENBUS AND PHILLIP S. LANDIS[1]

Compounds containing the uncondensed heterocyclic 1,4-thiazine ring have never been thoroughly investigated although, condensed with the benzene ring, this heterocyclic structure occurs in the important thiazine dyes. 1,4-Thiazine, which can theoretically exist in two forms (I) and (II), has never been described in the literature.



I



II

It has been found possible to synthesize 1,4-thiazine by making the imide of thiodiglycolic acid and reducing this imide with aluminum powder at an elevated temperature.

Thioglycolic acid, the starting point in the synthesis of 1,4-thiazine can be made easily by the usual method of the reaction of monochloroacetic acid with sodium sulfide. By extracting the acid from the reaction mixture with ether yields of 90% can be obtained.

The imide of thiodiglycolic acid was mentioned by Schulze in 1865 but no further reference to this interesting imide could be found. It was found that thiodiglycolimide could be made in excellent yields by heating the dry ammonium salt of thiodiglycolic acid in a partial vacuum.

The reduction of thiodiglycolimide to 1,4-thiazine is comparable to the preparation of pyrrole from succinimide. A literature search easily reveals that the reduction of succinimide, in spite of the large amount of space devoted to it by standard texts, is of very little preparative value and no one recommends this reduction as a means of making pyrrole or pyrrolidine. The most encouraging reduction method appeared to be that of Ray and Dutt,[2] who heated succinimide at an elevated temperature with aluminum powder instead of the customary zinc dust and obtained a 15% yield of pyrrole. The high temperature recommended, namely, dull red heat, placed some doubt as to whether the sulfur of the ring would survive such treatment. After many modifications of the original method, however, yields of 13% of 1,4-thiazine were finally obtained.

1,4-Thiazine, the mother substance of this interesting type of ring structure, is a colorless liquid boiling at 76.5–77°, miscible with water in all proportions, and is a weak base, $K = 4.0 \times 10^{-9}$. It has an ammoniacal odor combined with a faint but detectable odor of sauerkraut. It does not form a sulfonamide by the Hinsberg method and appears to be a tertiary amine having the structure corresponding to formula (I).

In investigating the many methods of reduction that have been tried on imides the reduction of chloro substituted imides appeared to offer some possibilities. Succinimide when treated with phosphorus pentachloride can be chlorinated to dichlorosuccinimide[3] which on further treatment gives tetrachloropyrrole. Prolonged treatment of thiodiglycolimide with phosphorus pentachloride completely destroyed the imide but careful heating of the imide with small amounts of phosphorus pentachloride gave a white crystalline compound having only one chlorine in the molecule. At first it was thought that this compound, because of the ease of hydrolysis of the chlorine, was an iminochloride. Mild treatment with alkali, however, did not regenerate the imide but produced instead thioglycolic acid, glyoxalic acid and ammonia. This would indicate that the chlorine had entered the α-position and that on hydrolysis a cyclic hemithioacetal was produced which on further hydrolysis gave the above products.

Experimental

Thiodiglycolic Acid.—Nine hundred and forty-five grams (10 moles) of monochloroacetic acid was placed in a 5 liter round-bottomed flask and dissolved in 1500 ml. of water. To this solution was added slowly with stirring 840 g. (10 moles) of solid sodium bicarbonate until the solution was neutral to litmus. The flask was placed in an ice-bath and 1320 g. (5.1 moles) of hydrated sodium sulfide dissolved in 1850 ml. of water was added slowly with stirring keeping the temperature between 25–30°. The solution was allowed to stand in the ice-bath for one hour and then 750 ml. of concentrated sulfuric acid was added with stirring, keeping the temperature between 25–30°.

The resulting solution was placed in a continuous extractor and ether passed through the solution at the rate of about 6 ml. per minute for twelve hours. At the end of each twelve-hour period fresh ether was placed in the extractor and the extraction continued for a total of thirty-

---

[1] Taken in part from a thesis presented in partial fulfillment of the requirements for the degree of Master of Science, University of Kentucky, August, 1947.

[2] A. C. Ray and S. B. Dutt, *J. Ind. Chem. Soc.*, **5**, 103 (1928).

[3] R. Anschutz, *Ann.*, **295**, 27 (1897).

six hours. Since thiodiglycolic acid is as soluble in water as it is in ether, an efficient extractor had to be designed which would also be capable of accommodating the large volume of solution to be extracted. The extractor was made by connecting two 2-liter round-bottom flasks and one 1-liter round-bottom flask to a 40-mm. diameter glass tube so that the over-all height was 2200 mm. The ether was conducted to the bottom of the apparatus by a 5 mm. tube to which was sealed a sintered glass filter stick. The combined ether extracts were evaporated to dryness and the crude acid dissolved in 2 liters of hot water, decolorized with charcoal and, after filtering, concentrated to a volume of 750 ml. After cooling with ice the crystals were filtered off and washed with three small portions of ice water. In order to remove such a small amount of liquid from the large mass of crystals a high vacuum was necessary. The acid on air-drying weighed 580 g., had a m. p. 129° and neut. equiv., 75.5. The filtrate was concentrated to 250 ml. and the acid obtained was recrystallized from 150 ml. of water. Seventy-two grams of acid of the same purity was obtained. The combined filtrates were concentrated to 100 ml. and this crop of acid recrystallized from 20 ml. of water. Eleven grams more of the same purity was obtained; total yield, 663 g. (88% yield).

Thiodiglycolimide.—One hundred and fifty grams of pure thiodiglycolic acid was placed in a 500-ml. three-necked round-bottom flask fitted with ground glass joints. A capillary tube was fitted into one of the openings and a short wide adapter connected the flask by a ground joint to a liter three-necked round-bottom flask. This was cooled with water and connected to a water pump. To the acid was added 150 ml. of concentrated ammonium hydroxide and the contents heated first to 100° in an oil-bath using a slight vacuum and then to 190° for one hour. Toward the end a vacuum was used to remove last traces of water. After substituting a clean flask for the receiver, the oil-bath was raised to 215–220° and a vacuum of about 10 mm. applied. The imide was slowly formed and distilled into the flask. It was necessary to heat the connecting tube to prevent the imide from blocking the opening. A total of two hours was necessary to complete the distillation.

The crude imide was dissolved in 400 ml. of 95% alcohol and, after decolorizing with charcoal, the solution was concentrated to 150 ml. On cooling and filtering 100 g. of the imide was obtained melting at 128°. On concentrating the filtrate 5.7 g. of imide of like purity was obtained; total yield 105.5 g. (82%).

The yields in this preparation are dependent on the purity of the acid. A quantity of acid from one run gave an excellent yield of the imide while that from another identical preparation gave practically no yield. This was rather remarkable since both samples of the acid had the same melting point and neutralization equivalent. One crystallization of this impure acid gave a product that produced an excellent yield of the imide. The nature of this interfering impurity was not determined but apparently only traces are necessary to interfere with the synthesis.

1,4-Thiazine.—Ten grams of thiodiglycolimide was placed in a six-inch test-tube fitted with a sealed inlet tube which extended to the bottom of the test-tube and an outlet tube fitted with a ground joint. The test-tube was connected to a glass tube 100 cm. long and 2 cm. in diameter packed to three-fourths of its length with pumice which had been coated with aluminum powder. A 500-ml. flask surrounded with ice was attached to this tube and the latter attached to a glass spiral cooled with ice and salt. The end of the spiral was allowed to dip into 300 ml. of 10% potassium hydroxide solution. The long glass tube was heated for three-fourths of its length to 450° in an electric furnace and a rapid stream of carbon dioxide was passed through the test-tube containing the imide which had been melted and heated to 180–190° by an oil-bath. In this manner the imide was slowly volatilized through the long tube. After the imide had been volatilized the receiving apparatus was washed well with water and the washings combined with the potassium hydroxide solution.

The water solution from five such runs was combined and saturated with potassium carbonate. One-half of this solution was distilled and the distillate treated in the same manner. This was continued until a volume of 20–25 ml. was obtained. On saturating this solution with potassium carbonate the upper layer was separated, allowed to stand over powdered potassium hydroxide and then distilled. On redistillation the 1,4-thiazine boiled at 76–76.5°; yield 5.5 g. (13.4%), n^{25}_{D} 1.5975, d^{25}_{4} 0.8465. *Anal.* Calcd for C_4H_5NS: S, 32.30. Found: S, 32.40.

This base gave no derivative when boiled with benzenesulfonyl chloride in pyridine for one hour. A water solution on warming reduced potassium permanganate and only oily products were obtained when the base was allowed to react with methyl iodide or methyl *p*-toluenesulfonate. A picrate formed readily which had m. p. 158–159°. It also formed a very insoluble chloroplatinate which, after washing well with alcohol and drying, melted at 236–238°. *Anal.* Calcd. for $(C_4H_5NS)_2 \cdot H_2PtCl_6$: Pt, 32.1. Found: Pt, 31.9. On passing dry hydrochloric acid gas through an anhydrous ether solution of the base a white precipitate of 1,4-thiazine hydrochloride was formed. This salt is very hygroscopic but after drying in a vacuum desiccator over phosphorus pentoxide melted at 74–75°.

α-Monochlorothiodiglycolimide.—In a 200-ml. round-bottom flask was placed 5 g. of thiodiglycolimide, 8 g. of phosphorus pentachloride and 10 ml. of toluene. On heating in a water-bath the solids dissolved and after one-half hour a yellowish white solid separated from the black solution. The reaction mixture was cooled and the black liquid decanted from the solid. The solid was dissolved in 200 ml. of boiling toluene, decolorized with charcoal and concentrated to 100 ml. On cooling, light yellow crystals separated which were filtered off and dried in a vacuum desiccator. The crystals had a m. p. of 135°. Repeated crystallization raised the m. p. to 135.5°. *Anal.* Calcd. for $C_4H_4O_2NSCl$: Cl, 21.4; S, 19.4. Found: Cl, 21.5; S, 19.8.

The α-monochlorothiodiglycolimide when treated in the cold with dilute sodium hydroxide solution readily lost the chlorine but on acidification the original imide was not obtained and the odor of thioglycolic acid was detected. On warming the alkaline solution, ammonia was evolved showing that a profound decomposition of the compound had taken place.

Summary

1,4-Thiazine, the mother substance of the 1,4-thiazine series, has been prepared for the first time by the reduction of thiodiglycolimide and some of its properties have been described.

Methods of preparation of thiodiglycolic acid and thiodiglycolimide have been investigated and a satisfactory method giving excellent yields has been worked out for each. Thiodiglycolimide has been chlorinated to α-monochlorothiodiglycolimide by means of phosphorus pentachloride.

LEXINGTON, KENTUCKY RECEIVED SEPTEMBER 2, 1947

[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

Studies in the Anthracene Series. III. Amino Ketones Derived from 9-Acetylanthracene

BY EVERETTE L. MAY AND ERICH MOSETTIG

This investigation was undertaken with the purpose of preparing anthracene-9-alkamines of the types —$CHOHCH_2NR_2$ and —$CHOHCH_2CH_2NR_2$ which could be expected to show antimalarial activity in view of the marked action of analogous 9-derivatives in the phenanthrene series.[1]

By the bromination of 9-acetylanthracene (V), 9-ω-bromoacetylanthracene (III), the desired intermediate for the preparation of the ethanolamine derivatives, was obtained in a yield of 50%. The bromo ketone III, however, failed under a variety of conditions to react normally with secondary amines.[2] The inertness of the bromine atom made its location in the side-chain appear somewhat doubtful, but eventually III could be obtained also by the Friedel–Crafts reaction of anthracene with bromoacetyl bromide, although only in yields of 2–3%. Aluminum isopropoxide reduction of III did not give the expected bromohydrin. In one instance, a 25% yield of a bromine-free compound, tentatively designated 9-(β-hydroxyethyl)-anthracene (IV),[3,4] was isolated, but usually only amorphous products were obtained. The product IV was shown by direct comparison to be different from 9-(α-hydroxyethyl)-anthracene.[5] Hydrogenation of the bromo ketone III with palladium–charcoal catalyst yielded readily 9-acetylanthracene.

By condensing, according to Mannich, 9-acetylanthracene, paraformaldehyde, and morpholine, 9-(3-morpholino-1-oxopropyl)-anthracene (VI) was obtained in a yield of 50%. The amino ketone VI, as hydrochloride, absorbed approximately two moles of hydrogen (platinum oxide), and 9-(3-morpholino-1-oxopropyl)-1,2,3,4-tetrahydroanthracene (VIII)[6] was obtained as the main product. As a by-product was isolated a small quantity of 9-propionyl-1,2,3,4-tetrahydroanthracene (IX) which increased in amount as the hydrogen absorption was allowed to proceed beyond two moles. When VI was reduced as base, three moles of hydrogen was absorbed and IX was isolated in a yield of 74%. Finally, amino ketone VIII slowly absorbed one mole of hydrogen, yielding ketone IX.

In the hydrogenation of 9-propionylanthracene, two moles of hydrogen was absorbed, and the resulting product was found to be identical with the ketone IX obtained in the reductive fission of the amino ketones VI and VIII. Moreover, we were able to prepare VIII by subjecting 9-acetyl-1,2,3,-4-tetrahydroanthracene (VII) (formed by catalytic reduction of V) to the Mannich condensation with paraformaldehyde and morpholine. Chromic acid oxidation of the ketones VII and IX gave 1,2,3,4-tetrahydro-9,10-anthraquinone (X).

The outlined series of reactions establishes the structure of the amino ketone VIII and the alkyl ketones VII and IX.[7] Obviously, owing to steric hindrance, the carbonyl group attached to the *meso* position of anthracene is resistant to catalytic hydrogenation, and one of the terminal benzene rings is attacked. This observation corroborates the failure of V and II to form, under standard conditions, semicarbazones, the failure of the bromo ketone III to react with secondary amines, and the resistance of 9-anthramide to hydrolysis.[8]

Recently Horeau and Jacques[9] found that the hydrogenation (Raney Nickel) of 9-benzoylanthracene yields in a ratio of about 1:5, 9,10-dihydroanthryl-9-phenylcarbinol and a product to which they assign the structure of 9-benzoyl-1,2,-3,4-tetrahydroanthracene. Our study appears to support the conclusions of these authors.

Acknowledgment.—We are indebted to H. George Latham, Jr., of this Laboratory for the preparation of 9-acetyl- and 9-propionylanthracenes. The microanalyses were carried out by C. A. Kinser and Betty Mount of this Institute.

Experimental[10]

9-Acetylanthracene (V) was prepared by the method of Lüttringhaus and Kačer[11] who quote the melting point *ca.* 80°. Our material melted at 74–76°.

9-Propionylanthracene (II).—It was found necessary to modify slightly[12] the directions of Lüttringhaus and Kačer[11] in the preparation of II. To a mixture of 50 g. of anthracene, 132 g. of propionyl chloride and 320 cc. of benzene, cooled to −5°, was added, with stirring, 75 g. of aluminum chloride at such a rate that the temperature did not rise above 0°. The temperature was maintained

---

(1) May and Mosettig, *J. Org. Chem.*, **11**, 10, 105 (1946).

(2) See Eisleb, *Med. u. Chemie Abhandl. Med.-Chem. Forschungsstätten I. G. Farbenind*, **3**, 48 (1936), for an analogous instance in the acridine series.

(3) *Cf.* Winstein, Jacobs, Henderson and Florsheim, *J. Org. Chem.*, **11**, 150 (1946).

(4) *Cf.* "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 193.

(5) Fieser and Hartwell, THIS JOURNAL, **60**, 2555 (1938).

(6) Compound VIII was originally believed to be 9-(3-morpholino-1-hydroxypropyl)-9,10-dihydroanthracene, and was entered as such (SN 1820) in Wiselogle, "Survey of Antimalarial Drugs, 1941–1945," Vol. II, J. W. Edwards, Ann Arbor, 1946, p. 358.

(7) Ketone VII has also been synthesized from 9-cyanotetrahydroanthracene. See a later paper of this series.

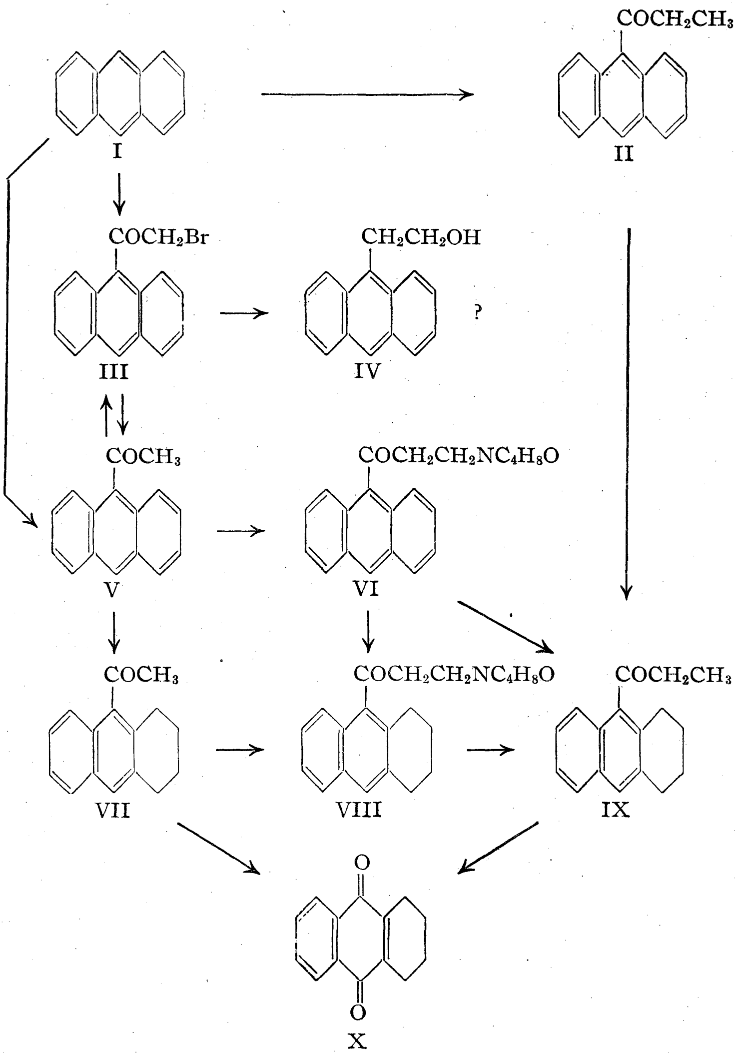
(8) See Karrer and Zeller, *Helv. Chim. Acta*, **2**, 485 (1919); see also a later paper of this series.

(9) Horeau and Jacques, *Bull. soc. chim.*, 71 (1946).

(10) All melting points given are uncorrected.

(11) Lüttringhaus and Kačer, German Patent 493,688; *C. A.*, **24**, 2257 (1930).

(12) The modified procedure was developed by H. George Latham, Jr., of this Laboratory.



at 0° for one and one-half hours, and allowed to rise to 10° during an additional hour (stirring). The complex was filtered, washed with cold benzene and decomposed in ice–hydrochloric acid. The resulting solid was extracted with ether, the ether was washed with 2 *N* sodium carbonate, dried over sodium sulfate and evaporated to give an oil which was digested with methanol. Insoluble material was filtered, the filtrate was evaporated to dryness, and the residue distilled in a high vacuum. The distillate was recrystallized from methanol to give 7.0 g. of II, m. p. 71–75°. A second crop weighed 8.3 g. and melted at 69–73°.

9-ω-Bromoacetylanthracene (III). (a) By Bromination of V.—To an ice-cooled solution of 5 g. of V in 50 cc. of dry ether was added 1.1 cc. of bromine during one hour. After stirring for an additional hour, 2.5 g. of solid was collected. The ethereal filtrate was concentrated and diluted with ligroin (b. p. 30–60°) to give a second fraction of 1.5 g. The two fractions were combined and recrystallized from benzene–ligroin; yield 3.2 g. (50%), m. p. 104.5–107°. The analytical sample melted at 107–108.5°; pale yellow prisms.

Anal. Calcd. for $C_{16}H_{11}BrO$: C, 64.2; H, 3.7. Found: C, 63.8; H, 3.8.

(b) By the Friedel–Crafts Reaction.—A mixture of 10 g. of anthracene, 65 cc. of benzene and 27 cc. of bromoacetyl bromide, stirred and cooled to −25°, was treated with 15 g. of aluminum chloride during ten minutes. The mixture was allowed to warm to 0° during one hour and decomposed in ice–hydrochloric acid. The benzene layer was diluted with ether and washed with dilute potassium hydroxide. It was dried over sodium sulfate and concentrated to a small volume to give, after cooling, 4.5–6.5 g. of anthracene. The filtrate was diluted to 200 cc. with ligroin (b. p. 30–60°), kept in the ice-box overnight, and decanted from some oil and crystals. On further dilution of the decantate to 300 cc., seeding, and cooling in the ice-box for forty hours, 0.2–0.4 g. (3–4% based on used anthracene) of prisms, m. p. 104.5–107°, separated. Mixed with the III from (a), they melted at 105–107.5°.

Debromohydrogenation of III.—A mixture of 1.0 g. of III, from either (a) or (b), 0.4 g. of palladium charcoal (5% Pd), and 50 cc. of absolute ethanol absorbed one mole of hydrogen in about one hour. After removal of catalyst, the filtrate was concentrated to 10 cc. to give, after ice-cooling, 0.5 g. (65%) of V, m. p. 74–76°.

Aluminum Isopropoxide Reduction of III.—One gram of III was reduced for four hours with 5 cc. of 1 *M* aluminum isopropoxide. The mixture was evaporated to dryness and the residue partitioned between benzene and dilute hydrochloric acid. The benzene layer was dried and concentrated to 4–6 cc. After addition of ligroin (b. p. 30–60°), 0.2 g. (25%) of leaflets (IV?), m. p. 105–107°, separated.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.5; H, 6.4. Found: C, 86.5; H, 6.3.

In subsequent experiments, attempts to isolate this compound failed.

9-(3-Morpholino-1-oxopropyl)-anthracene (VI).—A mixture of 25 g. of V, 15 g. of morpholine hydrochloride, 10 g. of paraformaldehyde and 125 cc. of absolute ethanol was refluxed for about twenty hours. After evaporation of solvent *in vacuo*, the residue was triturated with acetone to give 6 g. of morpholine hydrochloride. From the filtrate 12.5 g. of the hydrochloride of VI, m. p. 140–143°, was obtained. Upon recrystallization from absolute ethanol–ether it was converted to another crystalline form of m. p. 167–168.5°. Either form gave, with dilute ammonium hydroxide, VI which crystallized from methanol in prisms, m. p. 116–117.5°. Ten grams of V was recovered.

Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 79.0; H, 6.6. Found: C, 78.9; H, 6.6.

9-(3-Morpholino-1-oxopropyl)-1,2,3,4-tetrahydroanthracene (VIII).—A mixture of 3.0 g. of VI hydrochloride (m. p. 167–168.5°), 0.1 g. of platinum oxide, and 40 cc. of methanol absorbed two moles of hydrogen during 6.5 hours. Absorption was then constant at about 20 cc. per hour. The mixture was warmed to solution, filtered, concentrated *in vacuo*, and diluted with ether to give 1.9 g. (62%) of hydrochloride. Dilute ammonium hydroxide–alcohol converted it to the base which crystallized from alcohol–water in cubes, m. p. 103–104°.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 78.0; H, 7.8. Found: C, 77.8; H, 7.6.

The hydrochloride crystallized from 95% ethanol in prisms of m. p. 202.5–203°.

Anal. Calcd. for $C_{21}H_{26}ClNO_2$: C, 70.1; H, 7.3. Found: C, 70.1; H, 7.6.

9-Propionyl-1,2,3,4-tetrahydroanthracene (IX). (a). From the Reduction of VI Hydrochloride.—The filtrate from the 1.9 g. of VIII hydrochloride above was evaporated to dryness and the residue partitioned between water and ether. The ether-soluble material was dried and evaporatively distilled in a high vacuum to give a small amount of oil which crystallized from methanol in plates of m. p. 58.5–59.5°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.6. Found: C, 85.4; H, 7.6.

(b) **From VI (base).**—A mixture of 1.1 g. of VI (m. p. 115–117°), 0.05 g. of platinum oxide, and 25 cc. of methanol absorbed three moles of hydrogen in twenty-five hours. After filtration of catalyst and evaporation of solvent, the residue was recrystallized from methanol to give 0.6 g. (74%) of IX, m. p. 56–58°.

(c) **From VIII.**—The base VIII (0.2 g.) absorbed one mole of hydrogen (platinum oxide) to give 0.1 g. of IX, m. p. 56.5–58°.

(d) **By Hydrogenation of 9-Propionylanthracene.**—A mixture of 1.0 g. of II (m. p. 72–75°), 0.04 g. of platinum oxide, and 20 cc. of methanol absorbed two moles of hydrogen during fifteen to twenty-five hours. After filtration, concentration of the filtrate and ice-cooling, 0.6 g. (60%) of IX, m. p. 57.5–59° was obtained. It gave no depression when mixed with any of the samples of IX obtained as described above.

The semicarbazone of IX could not be obtained (boiling ethanol). Ketone IX was recovered.

9-Acetyl-1,2,3,4-tetrahydroanthracene (VII).—As described under (d) above, VII was obtained in a yield of 74%. It crystallized from methanol in prisms, m. p. 74.5–75.5°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.2. Found: C, 85.2; H, 7.2.

In an attempt to prepare the semicarbazone (four hours in refluxing ethanol) VII was recovered quantitatively.

Preparation of VIII from VII.—The Mannich reaction using 0.7 g. of VII, 0.5 g. of morpholine hydrochloride, 0.3 g. of paraformaldehyde, and 7 cc. of absolute ethanol yielded as described for the preparation of VI, 0.2 g. (21%) of VIII, m. p. 102.5–103°. The m. p. was not depressed by mixture with VIII described above. Two-tenths gram of VII was recovered.

1,2,3,4-Tetrahydro-9,10-anthraquinone (X). (a) **From VII.**—To a stirred mixture of 1.0 g. of VII and 10 cc. of acetic acid was added during one-half hour, 2.0 g. of chromic acid in 1 cc. of water and 5 cc. of acetic acid. After three and one-half hours stirring, water was added and the mixture was cooled in ice; yield of X, 0.25 g. (27%), m. p. 145–153°. After one recrystallization from alcohol it melted at 152–154°, m. p. not depressed by authentic material.

(b) **From IX.**—One gram of IX in 20 cc. of acetic acid gave, as above, 0.2 g. (22%) of X.

Summary

Attempts failed to prepare, by standard methods, the alkamines —$CHOHCH_2NR_2$ and —$CHOHCH_2CH_2NR_2$ derived from anthracene and carrying the side chain in position 9. 9-ω-Bromoacetylanthracene does not react with secondary amines. In the catalytic reduction of 9-(3-morpholino-1-oxopropyl), 9-acetyl and 9-propionyl-anthracenes the carbonyl group is not attacked while one of the terminal benzene rings adds two moles of hydrogen.

BETHESDA 14, MARYLAND RECEIVED SEPTEMBER 11, 1947

[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

Studies in the Anthracene Series. IV. *Meso*-Substituted 9,10-Dihydroanthracene Derivatives

BY EVERETTE L. MAY AND ERICH MOSETTIG

In the foregoing communication[1] we have shown that the catalytic hydrogenation of 9-(3-morpholino-1-oxopropyl)-anthracene hydrochloride (VIII), with the absorption of two moles of hydrogen, yields chiefly 9-(3-morpholino-1-oxopropyl)-1,2,3,4-tetrahydroanthracene. Originally, we had assumed this reduction product to be 9-(3-morpholino-1-hydroxypropyl)-9,10-dihydroanthracene (XIII). Analogously, alkyl 9-anthryl ketones gave the corresponding alkyl 9-tetrahydroanthryl ketones and not the expected alkyldihydroanthrylcarbinols. In order to study the chemistry and some biological aspects of the 9-substituted 9,10-dihydroanthracene derivatives, we elaborated their synthesis together with structural proofs.

9-Acetyl-9,10-dihydroanthracene (VI) was first prepared by Nenitzescu and co-workers[2] through the Friedel–Crafts reaction on 9,10-dihydroanthracene with acetyl chloride. On repeating this remarkable reaction,[3] we obtained, in modifying the isolation procedure, the oily ketone VI and small but varying amounts of 2-acetylanthracene. In a similar manner we prepared 9-propionyl-9,10-dihydroanthracene (II). The dihydro ketones could also be obtained in satisfactory yields in the hydriodic acid–phosphorus reduction[4] of 9-acetyl- and 9-propionylanthracenes. Moreover, VI was synthesized from 9,10-dihydro-9-anthroic acid (IX) via the diazo and bromo ketones. Acid IX was obtained in a yield of 27% in the Beckmann rearrangement of the stereochemically heterogeneous oxime of 9-benzoyl-9,10-dihydroanthracene, along with anthracene (26%) and a nitrogen-containing compound (17%) to which we assign tentatively formula XII. Anthracene has been formed, very likely, from the intermediate 9-amino-9,10-dihydroanthracene, unstable under the conditions of hydrolysis following rearrangement.[5]

The Mannich condensation on ketone VI, employing morpholine as the base, gave the morpholino ketone X which was readily hydrogenated (platinum oxide) to 9-(3-morpholino-1-hydroxypropyl)-9,10-dihydroanthracene (XIII). The

---

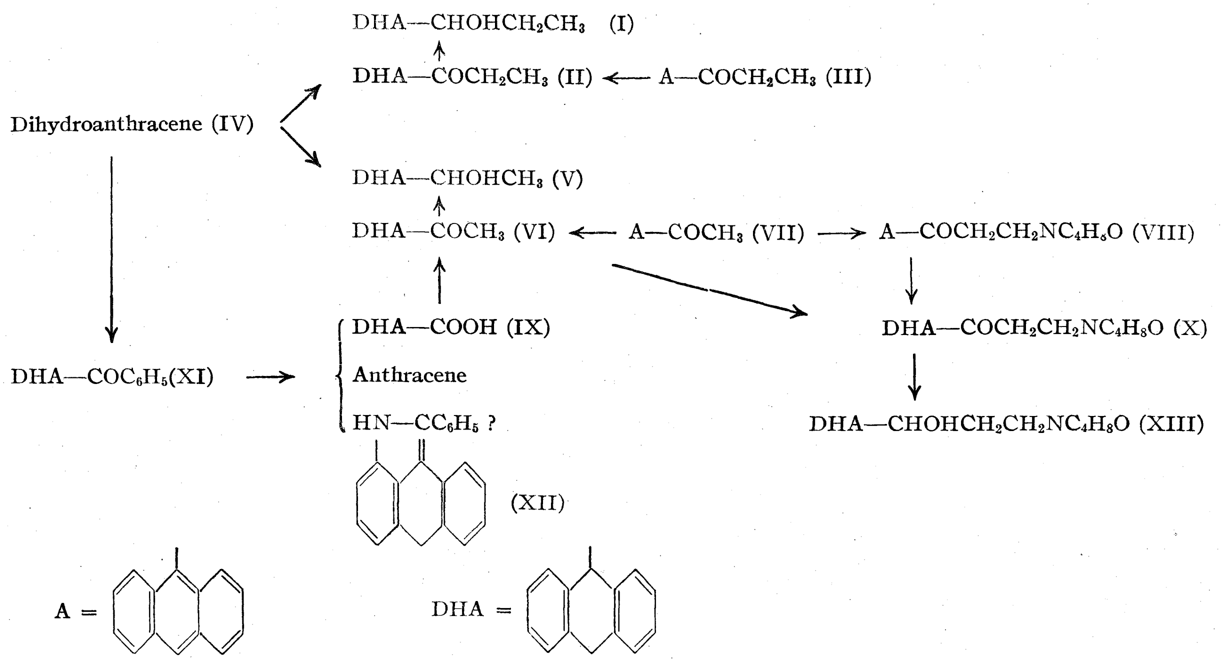
(1) May and Mosettig, THIS JOURNAL, **70**, 686 (1948).

(2) Nenitzescu, Gavăt and Cocora, *Ber.*, **72**, 819 (1939).

(3) See also Cook, Robinson and Roe, *J. Chem. Soc.*, 266 (1939).

(4) This reductive method was employed by Cook, *J. Chem. Soc.*, 1677 (1926), in the preparation of 9-benzoyldihydroanthracene.

(5) Goldmann, *Ber.*, **23**, 2522 (1890).



structure of compound X was ascertained through its formation in the hydriodic acid–phosphorus reduction of amino ketone VIII.[1] Finally, the dihydroanthrylcarbinols V and I were prepared by aluminum isopropoxide reduction of ketones VI and II respectively, in order to show their non-identity with the corresponding, isomeric 9-acetyl- and 9-propionyltetrahydroanthracenes.[1]

Most of the 9-substituted-9,10-dihydroanthracene derivatives are rather unstable, and gradually become colored on standing. This was especially true of the oily ketone VI which, after a few days, yielded anthracene and occasionally some higher-melting material.[6]

Acknowledgment.—The microanalyses were carried out by C. A. Kinser and Betty Mount of this Institute. We are indebted to H. George Latham, Jr., for technical assistance.

Experimental[7]

Beckmann Rearrangement of the Oxime of XI.—A mixture of 6 g. of XI[2], 4.5 g. of hydroxylamine hydrochloride, 25 cc. of absolute alcohol and 8 cc. of pyridine was refluxed for four hours, concentrated *in vacuo* and diluted with water to give a rapidly-crystallizing oil. It crystallized from aqueous ethanol in a yield of 5.5 g., m. p. *ca.* 160–170°.[4] It was dissolved in 23 cc. of acetic acid and 16 cc. of acetic anhydride. Dry hydrogen chloride was bubbled into the solution until crystallization began (thirty to forty-five minutes). After standing for five hours at room temperature followed by ice-cooling, the amide mixture (3.3 g.), 25 cc. of acetic acid and 12 cc. of concentrated hydrochloric acid were refluxed together for thirty hours. The mixture was cooled in ice, filtered and the precipitate digested with hot, dilute sodium carbonate to give 1 g. of undissolved anthracene and 1.3 g. of IX,[8] m. p. 200–202°, on acidification of the filtrate.

The filtrate from the 3.3 g. of the amide mixture above was evaporated to dryness and the residue was refluxed with acetic acid–hydrochloric acid. Cooling and filtration gave a small amount of anthracene. The filtrate was evaporated to dryness, the residue treated with dilute sodium carbonate, and the insoluble material collected and sublimed. Recrystallization of the sublimate from aqueous ethanol gave 1.0 g. of light, yellow prisms of m. p. 145–150° (XII). The analytical sample melted at 152–153°.

Anal. Calcd. for $C_{21}H_{15}N$: C, 89.7; H, 5.4. Found: C, 89.7; H, 5.5.

The hydrochloride of XII crystallized from absolute ethanol–ether in orange prisms of m. p. 287–292° (dec.).

Anal. Calcd. for $C_{21}H_{16}ClN$: C, 79.4; H, 5.1. Found: C, 79.5; H, 5.3.

The acetyl derivative of XII, prepared in acetic anhydride–pyridine, crystallized from ethanol in long prisms, m. p. 183–183.5°.

Anal. Calcd. for $C_{23}H_{17}NO$: C, 85.4; H, 5.3. Found: C, 85.5; H, 5.5.

9,10-Dihydro-9-anthroyl Chloride.—A mixture of 3.8 g. of IX, 5 cc. of dry benzene and 4 cc. of thionyl chloride was refluxed for one hour and evaporated to dryness *in vacuo*. The residue crystallized from ligroin (b. p. 30–60°) in prisms; yield 3.7 g. (90%), m. p. 57–58°. The analytical sample melted at 57–58.5°.

Anal. Calcd. for $C_{15}H_{11}ClO$: C, 74.2; H, 4.6. Found: C, 74.2; H, 4.8.

9-(2-Bromo-1-oxoethyl)-9,10-dihydroanthracene.—The foregoing chloride (3.5 g.) in 25 cc. of dry ether was added during thirty minutes to 70 cc. of a stirred ether solution of diazomethane (from 7 g. of nitrosomethylurea) maintained at 3 to 5°. After one-half hour of stirring at 3 to 5° and one hour at room temperature, most of the ether was evaporated to remove excess diazomethane, 50 cc. of ether was added, and the stirred solution treated dropwise with 3.5 cc. of 48% hydrobromic acid in 3.5 cc. of ether (temperature 15–20°). After fifteen minutes at room temperature, the mixture was shaken with dilute sodium carbonate, dried, and evaporated to 10–15 cc. Addition of an equal volume of ligroin (b. p. 30–60°) gave, after cooling, 3.1 g. (73%) of bromo ketone, m. p. 104–105°; needles from ether–ligroin or methanol, m. p. 107–108° (strong gas evolution).

---

(6) Ocampo, *Quimica* (Mex.), **4,** 70 (1946); *C. A.*, **40,** 6458 (1946).

(7) All melting points given are uncorrected.

(8) Meerwein and Migge, *Ber.*, **62,** 1046 (1929); Gilman and Bebb, THIS JOURNAL, **61,** 109 (1939); Burtner and Cusic, *ibid.*, **65,** 1582 (1943).

Anal. Calcd. for $C_{16}H_{13}BrO$: Br, 26.5. Found: Br, 26.8.

Analyses for carbon–hydrogen gave consistently high values.

9-Acetyl-9,10-dihydroanthracene (VI) Semicarbazone. (a) From 9-(2-Bromo-1-oxoethyl)-9,10-dihydroanthracene.—A mixture of 1.0 g. of the above bromo ketone, 0.2 g.of palladium–charcoal (10% Pd) and 25 cc. of absolute ethanol absorbed one mole of hydrogen in one hour. After removal of catalyst, the filtrate was treated with a slight excess of alcoholic ammonia and concentrated *in vacuo*. Semicarbazide hydrochloride (0.9 g.), 1.3 g. of sodium acetate and some water were added. The mixture was refluxed for one hour. The prisms (0.7 g. (77%), m. p. 223–225°) which separated overnight were recrystallized from dioxane–water and then from alcohol; m. p. 224–226° (gas evolution).

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.1; H, 6.1. Found: C, 73.0; H, 6.4.

(b) By the Friedel–Crafts Reaction.—To an ice-cooled, stirred mixture of 10 g. of dihydroanthracene,[9] 6 cc. of acetyl chloride and 100 cc. of carbon disulfide was added during ten minutes, 8 g. of aluminum chloride. After stirring for six hours without cooling, the solvent was decanted and the residue was partitioned between ice–hydrochloric acid and ether. The ether was washed with dilute sodium carbonate, dried and evaporated *in vacuo* to give 7.8 g. of a light-colored oil. Instead of purifying this oil by distillation (Nenitzescu and co-workers[2]), it was dissolved in 30–40 cc. of 95% ethanol to give, on cooling in the ice-box overnight, 0.2–0.5 g. of 2-acetylanthracene. The filtrate was refluxed for one hour with 5 g. of semicarbazide hydrochloride, 3.5 g. of fused sodium acetate, an additional 25 cc. of ethanol and 15–20 cc. of water. After cooling, the precipitate was recrystallized from dioxane–water. The yield of semicarbazone, identical with that described above, was 4.5–6 g. (30–40%), m. p. 224–226°.

(c) From 9-Acetylanthracene.[4]—A mixture of 10 g. of VII,[10] 2.8 g. of red phosphorus, 5 cc. of 55% hydriodic acid, and 100 cc. of acetic acid was refluxed for two and one-half hours, filtered and the filtrate evaporated *in vacuo*. The residue was partitioned between ether and an excess of 5–10% sodium hydroxide. The ether was washed with water, dried and evaporated. The semisolid residue was triturated with 20–25 cc. of 95% ethanol and cooled in ice to give 3.1 g. of IV, m. p. 103–107°. The filtrate, refluxed with 5 g. of semicarbazide hydrochloride, 3 g. of sodium acetate and some water, yielded 5.5 g. (43%) of the semicarbazone of VI, m. p. 220–224°.

Oxime of VI.—The semicarbazone of VI (0.5 g.), and 5 cc. of 10% hydrochloric acid were refluxed together for two hours. The resulting oil (0.4 g. after drying in ether), 0.3 g. of hydroxylamine hydrochloride, 3 cc. of absolute ethanol and 1 cc. of pyridine, refluxed for one hour yielded, on dilution with water and cooling, an oxime which crystallized from 95% ethanol in a yield of 0.25 g., m. p. 165–166°; prisms.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 81.0; H, 6.4. Found: C, 80.8; H, 6.4.

Nenitzescu and co-workers,[2] who prepared the oxime in alcohol, quote the melting point 148–149°.

9-Propionyl-9,10-dihydroanthracene (II). (a) By the Friedel–Crafts Reaction.—To a stirred mixture of 10 g. of IV, 7 g. of propionyl chloride and 100 cc. of carbon disulfide, cooled in ice, was added 8 g. of aluminum chloride during ten minutes. The mixture was stirred for six hours without cooling, ice–hydrochloric acid was added, and the carbon disulfide washed with dilute sodium carbonate, dried and evaporated. The residual oil was dissolved in 90 cc. of 95% ethanol, 10 g. of semicarbazide hydrochloride, 7.5 g. of fused sodium acetate and about 30 cc. of water were added and the whole refluxed for two and one-half hours. Addition of water and cooling gave a crude solid which was fractionally crystallized from dioxane–water to yield 4.4 g. (28%) of prisms, m. p. 200–202°. A mixture of 2.5 g. of this semicarbazone and 20 cc. of 10% hydrochloric acid was refluxed for one hour. The resulting oily II was dried in ether and crystallized from methanol; white crusts, m. p. 62.5–63°.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.4; H, 6.8. Found: C, 86.4; H, 7.1.

The semicarbazone crystallized from 95% ethanol in prisms, m. p. 198–200° (bubbling).

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.7; H, 6.5. Found: C, 73.7; H, 6.6.

(b) From 9-Propionylanthracene.—As described for VI under method (c), 10 g. of III[1,10] yielded 4.1 g. of IV and 3.4 g. of II semicarbazone, m. p. 192–197°.

9-(1-Hydroxyethyl)-9,10-dihydroanthracene (V).—The semicarbazone of VI (1 g.) and 10 cc. of 10% hydrochloric acid were refluxed together for two hours. The resulting oil, dried in ether, was reduced with 6 cc. of 1 *M* aluminum isopropoxide for one-half hour. The solvent was distilled *in vacuo* and the residue partitioned between ether and dilute hydrochloric acid. Drying and evaporation of the ether left an oil which crystallized from methanol–water; yield 0.5 g. (63%), m. p. 88–89.5°. Recrystallized from ethanol–water and finally from 95% ethanol, it melted at 89.5–90.5°; prisms.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.2. Found: C, 85.7; H, 7.4.

9-(1-Hydroxypropyl)-9,10-dihydroanthracene (I).—As described in the previous experiment, 1.0 g. of II (m. p. 62–63°) (reaction time one to two hours) yielded, from ligroin (b. p. 30–60°), 0.6 g. of I, m. p. 68–72°. After two recrystallizations from ligroin, the melting point was constant at 75.5–76.5°; prisms.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.7; H, 7.6. Found: C, 86.0; H, 7.9.

9-(3-Morpholino-1-oxopropyl)-9,10-dihydroanthracene Hydrochloride (X). (a) From VIII.—A mixture of 2.0 g. of VIII,[1] 2 cc. of 55% hydriodic acid, 0.5 g. of red phosphorus and 20 cc. of acetic acid was refluxed for two and one-half hours, cooled and filtered. The filtrate was evaporated to dryness *in vacuo* and the residue partitioned between ether and 5% sodium hydroxide. The ether was dried and acidified with ethereal hydrogen chloride to give an oil which crystallized from acetone–ether in a yield of 0.6 g., m. p. 168–170°. The analytical sample melted at 169–171°; long needles.

Anal. Calcd. for $C_{21}H_{24}ClNO_2$: C, 70.5; H, 6.8. Found: C, 70.1; H, 6.9.

(b) From VI.—The semicarbazone of VI (1.3 g.) was hydrolyzed as described above. The resulting oily VI, 0.6 g. of morpholine hydrochloride, 0.2 g. of paraformaldehyde and 5 cc. of absolute ethanol were refluxed for four hours. An additional 0.2 g. of paraformaldehyde was added and the refluxing continued overnight. Evaporation of the alcohol *in vacuo* and trituration of the residue with acetone gave a small amount of morpholine hydrochloride. Ether dilution of the filtrate yielded an oil which crystallized on cooling in ice. It crystallized from absolute ethanol–ether in a yield of 0.5 g. (30%), m. p. 169–171°, and did not depress the m. p. of X prepared as described by procedure (a).

9-(3-Morpholino-1-hydroxypropyl)-9,10-dihydroanthracene Hydrochloride (XIII).—The hydrochloride of X (0.8 g.) was converted to the base (dilute aqueous ammonia) which was dried in ether, dissolved in 10 cc. of methanol, and the solution hydrogenated with 0.05 g. of platinum oxide. One mole of hydrogen was absorbed during two to three hours. The catalyst was removed and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in acetone and acidified with ethereal hydrogen chloride to give 0.5 g. of the hydrochloride of XIII, m. p. 200–202°. It crystallized from absolute ethanol–ether in plates of m. p. 202–203° (dec.).

---

(9) Garlock and Mosettig, THIS JOURNAL, **67**, 2255 (1945).

(10) Lüttringhaus and Kačer, German Patent 493,688; *C. A.*, **24**, 2757 (1930).

Anal. Calcd. for $C_{21}H_{26}ClNO_2$: C, 70.1; H, 7.3. Found: C, 69.7; H, 7.5.

The hydrobromide of XIII crystallized from absolute ethanol–ether in plates, m. p. 184–186° (dec.).

Anal. Calcd. for $C_{21}H_{26}BrNO_2$: C, 62.4; H, 6.5. Found: C, 62.3; H, 6.7.

The hydrochloride of X could also be hydrogenated to XIII.

Summary

The preparation of 9-acetyl- and 9-propionyl-9,10-dihydroanthracenes is described.

9-Acetyl-9,10-dihydroanthracene was subjected to the Mannich condensation (morpholine as base), and the resulting amino ketone was hydrogenated to the corresponding amino carbinol.

Phosphorus–hydriodic acid reduction provides an excellent means of converting 9-acyl and 9-aminoacyl derivatives of anthracene to the corresponding 9,10-dihydroanthracene derivatives.

BETHESDA, MARYLAND RECEIVED SEPTEMBER 11, 1947

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL AND L'INSTITUT DE CHIMIE, UNIVERSITY OF MONTREAL]

The Papilionaceous Alkaloids. II. *Baptisia australis* (L.) R. Br.[1]

BY LÉO MARION AND JACQUES OUELLET

Few of the species belonging to the genus *Baptisia* have been investigated for alkaloids and none of these investigations has been at all thorough. Cytisine is the only alkaloid reported so far in these plants. It has been isolated from *Baptisia tinctoria* R.Br.[2] and detected by means of a microchemical test in *Baptisia australis* (L.) R.Br., *B. exaltata*, Sweet and *B. leucantha*, T. & G.[3] It seemed improbable that these plants should contain only one alkaloid, and, indeed, a thorough investigation of *Baptisia australis* has now revealed the presence in it of several other alkaloids.

B. australis (L.) R.Br. used in this investigation was grown at the Experimental Farm, Dominion Department of Agriculture, Ottawa, through the kindness of Dr. H. A. Senn, to whom the authors acknowledge their indebtedness. The aerial part of the plant and the root were examined separately, but were found to contain the same alkaloids. Four alkaloids have been isolated. The two main bases are N-methylcytisine and *d*-sparteine. The third in importance is cytisine while the fourth, alkaloid P_2, was present in such small quantity that it could not fully be characterized. With the possible exception of alkaloid P_2, all the alkaloids found in the plant are known and have been isolated previously from other sources. It is of interest to note that the four alkaloids reported in *Anagyris foetida*[4] differ from those of *B. australis* only in that anagyrine is substituted for alkaloid P_2 of the latter.

B. australis also contains a non-nitrogenous substance A which can be hydrolyzed by acids to a new substance B. Both substances A and B are soluble in aqueous sodium hydroxide.

Experimental

The dried and ground aerial part of *B. australis* (2620 g.) was extracted in Soxhlet extractors with methanol and the solvent, largely distilled from the combined extract which was then diluted with water, made acid to congo red by the addition of hydrochloric acid and kept on the steam-bath for nine hours. The mixture was cooled, filtered and the insoluble cake warmed again with dilute acid, cooled and filtered. The combined aqueous acid filtrate was repeatedly extracted with ether and the extract distilled to dryness. It left a residue consisting of a mixture of crystals and a thick oil which were separated by filtration through a fritted glass funnel. The crystalline substance A was purified by repeated crystallization from boiling methanol from which it separated as colorless needles, m. p. 261°.[5]

Anal. Found: C, 71.91, 72.14; H, 4.90, 4.82. Calcd. for $(C_{25}H_{20}O_6)_n$: C, 72.11; H, 4.81.

Substance A dissolved in aqueous sodium hydroxide to give an intensely yellow solution from which it was recovered by acidification. Refluxing for two hours with 10% sulfuric acid converted substance A into a new substance, B, which after repeated crystallization from boiling methanol was obtained as clusters of small crystals which in bulk had a slightly brownish-yellow color. It softened at 331° and melted at 334°.

Anal. Found: C, 61.28, 61.15; H, 3.89, 3.92. Calcd. for $(C_{14}H_{10}O_6)_n$: C, 61.31; H, 3.57.

The aqueous acid solution which had been extracted with ether was alkalized with strong potassium hydroxide and extracted repeatedly with chloroform. The combined extract was distilled to dryness and the residual amorphous base (6 g.) dissolved in warm dilute hydrochloric acid, the cooled solution filtered through charcoal and extracted with ether (discarded). The aqueous solution was alkalized with ammonia and repeatedly extracted first with ether (extract A) and then with chloroform (extract B). Extract A was evaporated to dryness and the residual oily base distilled *in vacuo*. It yielded the following: fraction I, b. p. 95–115° (0.4 mm.), a colorless oil, wt. 0.182 g.; fraction II, b. p. 130–155° (0.4 mm.), a yellowish oil, part of which crystallized on standing, wt. 0.163 g.; fraction III, b. p. 175–195° (0.4 mm.), a yellowish oil which crystallized on standing, wt. 0.61 g.; fraction IV, b. p. 200–215° (0.4 mm.), a thick, brownish oil, wt. 0.324 g.; fraction V, b. p. 215–220° (0.4 mm.), a thick brown oil, wt. 0.107 g., and an appreciable residue.

Isolation of *d*-Sparteine.—The colorless fraction I was dissolved in methanol and the solution added to a methanolic solution of picric acid. On cooling, a picrate sepa-

---

[1] (a) Published as National Research Council Bull. No. 1530. (b) Previous paper in this series: L. Marion, THIS JOURNAL, **68**, 759 (1946).

[2] K. Gorter, *Arch. Pharm.*, **235**, 321 (1897).

[3] G. Klein and Elisabeth Farkass, *Österr. botan. Z.*, **79**, 107 (1930); *Chem. Centr.*, **101**, II, 1257 (1930).

[4] H. R. Ing, *J. Chem. Soc.*, 1053 (1935).

[5] All melting points are corrected.

rated which after two recrystallizations from boiling methanol was obtained as lemon-yellow prismatic needles, m.p. 208°.

Anal. Found: C, 46.68; H, 4.71; N, 16.19. Calcd. for $C_{15}H_{26}N_2 \cdot 2C_6H_3O_7N_3$: C, 46.81; H, 4.62; N, 16.18.

The melting point and analytical figures are in good agreement with those of *l*-sparteine dipicrate but the melting point was depressed by admixture with an authentic sample. The base was therefore recovered from some of the pure picrate, redistilled twice (b.p. 95–105° (0.3 mm.)) and used for the determination of the optical activity: $[\alpha]^{24}D$ +17.1° (c = 2.16 in absolute ethanol). The value $[\alpha]_D$ +16.3° (alcohol) is recorded in the literature.[6] The base recovered from the ethanol solution was divided into two portions. One portion was dissolved in methanol, the solution neutralized to congo red with 65% perchloric acid and diluted with ether to the point of incipient turbidity. On standing, the perchlorate separated in colorless needles forming feathery aggregates, m. p. 173°, which is almost identical with the melting point (171–172°) recorded for *d*-sparteine monoperchlorate. Furthermore, the salt can be extracted with chloroform from an ammoniacal aqueous solution, a property characteristic of sparteine monoperchlorate.[4]

Anal. Found: C, 53.70, 53.75; H, 8.32, 8.31; N, 8.58, 8.64. Calcd. for $C_{15}H_{26}N_2 \cdot HClO_4$: C, 53.83; H, 8.07, N, 8.37.

The second portion of the base employed for determining the optical rotation was dissolved in a little 10% hydrochloric acid and a slight excess of a 5% aqueous platinic chloride solution added. After concentration, the chloroplatinate separated as clusters of small flat orange needles which darkened at 253° and melted at 261° (dec.). This is in agreement with the behavior of *l*-sparteine chloroplatinate. In admixture with *l*-sparteine chloroplatinate the melting point was depressed.

Anal. Found: Pt, 29.08. Calcd. for $C_{15}H_{26}N_2 \cdot H_2PtCl_6 \cdot 2H_2O$: Pt, 28.69.

Isolation of N-Methylcytisine.—Fraction II was dissolved in methanol and converted to picrate. It yielded mostly *d*-sparteine dipicrate. Fraction III was also converted to picrate in methanol and added to the mother-liquor obtained from fraction II. The resulting solution when concentrated yielded a picrate which after two recrystallizations from boiling methanol was obtained as pale yellow needles melting at 192–193°, but after three more recrystallizations from the same solvent it melted at 234°. A sample of N-methylcytisine picrate reported by Manske and Marion[7] as melting at 193° was recrystallized several times from boiling methanol and found also to melt at 234° either alone or in admixture with the above picrate. The highest melting point recorded[8] so far for N-methylcytisine picrate is 229–230° (uncor.).

Anal. Found: N, 16.22, 16.27. Calcd. for $C_{12}H_{16}ON_2 \cdot C_6H_3O_7N_3$: N, 16.16.

The base recovered from the picrate was redistilled. It consisted of a thick straw-colored oil, b.p. 160–168° (0.6 mm.), which crystallized on standing. Recrystallized from ether–petroleum ether, it separated as colorless prismatic needles, m. p. 138°, either alone or in admixture with N-methylcytisine.

Anal. Found: C, 70.65; H, 7.95; N, 13.51. Calcd. for $C_{12}H_{16}ON_2$: C, 70.59; H, 7.84; N, 13.41.

A small quantity of the base was dissolved in methanol and the solution made just acid to congo red by the cautious addition of 65% perchloric acid. A perchlorate separated on standing which after recrystallization from methanol consisted of brilliant, colorless needles, m. p. 282°, either alone or in admixture with N-methylcytisine perchlorate.

Anal. Found: C, 47.15; H, 5.69. Calcd. for $C_{12}H_{16}ON_2 \cdot HClO_4$: C, 47.30; H, 5.58.

Isolation of Cytisine.—Fraction IV was combined with fraction V, dissolved in methanol and added to a methanolic solution of picric acid. A very small quantity of a picrate first separated which was filtered and, after several recrystallizations from methanol, consisted of small yellow platelets, m. p. 238°. This is further dealt with under alkaloid P_2. The mother-liquor from the above picrate deposited after some time a second crop of crystals. This second picrate was difficult to purify and after repeated recrystallization still consisted of a mixture. It was decomposed and the recovered base when distilled *in vacuo* yielded first a thick, colorless oil, b.p. 175–190° (0.35 mm.) which crystallized on cooling and then a crystalline fraction subliming at 190–200° (0.35 mm.). The first crystalline base melted at 154° and in admixture with cytisine at 155°.

Anal. Found: C, 69.52, 69.65; H, 7.24, 7.30. Calcd. for $C_{11}H_{14}ON_2$: C, 69.47; H, 7.37.

A small quantity of this base was converted to picrate in methanolic solution. After several recrystallizations the picrate was obtained as small, pale-yellow needles, m. p. 289.5°, either alone or after admixture with cytisine picrate.

Anal. Found: C, 48.64, 48.48; H, 4.30, 4.15; N, 16.71, 16.88. Calcd. for $C_{11}H_{14}ON_2 \cdot C_6H_3O_7N_3$: C, 48.68; H, 4.06, N, 16.70.

A small quantity of the base was converted to perchlorate. After recrystallization from boiling methanol, the salt melted at 298° either alone or after admixture with cytisine perchlorate.

Isolation of Alkaloid P_2.—The crystalline sublimate obtained in the course of the purification of cytisine melted at 293° and after two recrystallizations from methanol–ether melted at 300°. The quantity of base was so small that it was converted to perchlorate in order to increase the weight of product. The base perchlorate, after recrystallization from methanol, consisted of colorless needles, m. p. 198°.

Anal. Found: C, 46.05; H, 6.55; N, 9.67. Calcd. for $C_{11}H_{18}ON_2 \cdot HClO_4$: C, 44.83; H, 6.45; N, 9.51.

Insufficient material was available for a better characterization of alkaloid P_2. The picrate, m. p. 238°, isolated in the course of the purification of cytisine picrate could not be characterized fully owing to the small quantity of material on hand and a complete analysis was not possible. The incomplete analytical figures indicate that the picrate might be that of alkaloid P_2.

Anal. Found: C, 50.35, 50.20; H, 5.18, 5.12. Calcd. for $C_{11}H_{18}ON_2 \cdot C_6H_3O_7N_3$: C, 48.22; H, 4.96.

The chloroform extract B of the crude base was distilled to dryness, the residue distilled *in vacuo* and the various fractions (total wt. 1.0 g.) treated exactly as the similar fractions obtained from the ether extract A. It yielded further quantities of the bases already described.

Acknowledgment.—The authors wish to express their grateful indebtedness to the National Research Council of Canada for a Studentship awarded to one of them (J. O.) and to Professor Lionel Lemay, University of Montreal, who rendered the collaboration possible.

Summary

1. *Baptisia australis* (L.) R.Br. has been shown to contain four alkaloids, *i. e.*, N-methylcytisine, *d*-sparteine, cytisine and alkaloid P_2.

2. The first three of these alkaloids are already known. Alkaloid P_2, which could not fully be characterized, may be new.

OTTAWA, CANADA RECEIVED AUGUST 1. 1947

---

[6] A. Orechov, M. Rabinowitch and R. Konowalowa, *Ber.*, **66**, 621 (1933).

[7] R. H. F. Manske and L. Marion, *Can. J. Research*, **21B**, 144 (1933).

[8] S. S. Norkina, T. Narkuziev and A. Orechov, *J. Gen. Chem., U. S. S. R.*, **7**, 906 (1937).

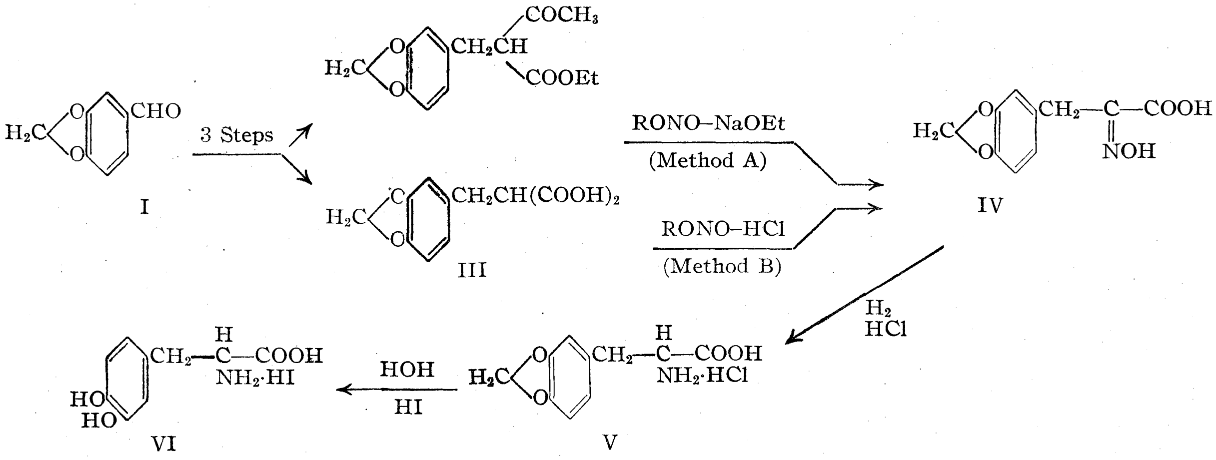
[FROM THE RESEARCH LABORATORY, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

A New Synthesis of 3,4-Dihydroxyphenylalanine (Dopa)[1a]

BY RICHARD H. BARRY,[1b] ALBERT M. MATTOCKS[1c] AND WALTER H. HARTUNG

3,4-Dihydroxyphenylalanine (dopa) has been postulated as an intermediate in the biological synthesis of melanin[2] and epinephrine.[3,4] The *levo*-isomer may be isolated from the velvet bean[5] or prepared synthetically from *l*-tyrosine.[6] Many of the syntheses of *dl*-dopa and its derivatives[3,7a–c] are tedious and often give an impure product. Improvements in the azlactone synthesis from vanillin have been made by Harington and McCartney[7c] but the method is not entirely suitable for large scale preparations.

Previous work in this Laboratory has shown that α-amino acids can be conveniently prepared by the reduction of α-oximino acids.[8] The preparation of α-oximino acids from substituted acetoacetic and malonic esters and from substituted malonic acids[9] offered methods for preparing intermediates leading to the synthesis of dopa. It has been shown[9] that 3,4-substituted benzylacetoacetic esters, *e. g.*, 3,4-methylenedioxybenzylacetoacetic ester, are sensitive to a high concentration of acids and therefore cannot be nitrosated by the usual acid-catalyzed procedure.[8] When the nitrosation of 3,4-methylenedioxybenzylacetoacetic ester II was carried out in ethanolic sodium ethoxide with alkyl nitrite, a 60% yield of α-oximino β-(3,4-methylenedioxyphenyl)-propionic acid IV was obtained (Method A). A more satisfactory method for the preparation of IV is the nitrosation of 3,4-methylenedioxybenzylmalonic acid III with alkyl nitrite in the presence of hydrogen chloride (Method B). Yields from 85 to 90% were obtained consistently. Catalytic reduction of IV produced 3,4-methylenedioxyphenylalanine V, which was hydrolyzed with hydriodic acid to dopa-HI, VI. Slight discoloration of the dopa salt was noted after five or six days. 3,4-Methylenedioxyphenylalanine V, on the other hand, is quite stable over long periods and it is suggested that this intermediate amino acid be kept and converted into dopa as needed. Equations for the synthesis of dopa-HI, starting with piperonal[10] are shown



Experimental

3,4-Methylenedioxybenzylacetoacetic Ester (II).—This ester, b. p. 160–161 (4 mm.), was prepared in 61% yield in the usual manner from sodioacetoacetic ester and piperonyl chloride.[11]

3,4-Methylenedioxybenzylidenmalonic Ester.—Prepared according to the directions of Knoevenagel,[12] the ester distilled at 215–225 (8–10 mm.). The yield was 50%; if allowance was made for recovered piperonal, the yield was 87%.

3,4-Methylenedioxybenzylmalonic Acid (III).—A solution of 73 g. (0.25 mole) of 3,4-methylenedioxybenzylidenmalonic ester in 250 ml. of ethanol was shaken with 3 g. of 10% palladium–charcoal catalyst[13] in an atmosphere of hydrogen for three hours, when the theoretical quantity of hydrogen was taken up. The catalyst was removed by filtration, the 3,4-methylenedioxybenzylmalonic ester was not isolated but was converted into the acid by adding to the clear alcoholic filtrate 56 g. (1 mole) of potassium

---

[1] (a) Paper no. 8 on amino acids; for no. 7 see Waters and Hartung, *J. Org. Chem.*, **12**, 469 (1947). (b) Present address: The Maltbie Chemical Company, Newark, N. J. (c) Present address: School of Pharmacy, Western Reserve University, Cleveland, Ohio.

[2] H. S. Raper, *Biochem. J.*, **20**, 735 (1926).

[3] C. Funk, *J. Chem. Soc.*, **99**, 55 (1911).

[4] A. Vinet, *Bull. soc. chim. biol.*, **22**, 559 (1940); *Compt. rend.*, **210**, 552 (1940).

[5] T. Torquati, *Arch. farmacol. sper.*, **15**, 213, 308 (1913).

[6] E. Waser and N. Lewandowski, *Helv. Chim. Acta*, **4**, 657 (1921).

[7] (a) H. Stephen and C. Weizmann, *J. Chem. Soc.*, **105**, 1152 (1914); (b) C. Granacher, *Helv. Chim. Acta*, **6**, 458 (1923); (c) C. R. Harington and W. McCartney, *Biochem. J.*, **21**, 852 (1927)

[8] K. E. Hamlin, Jr., and W. H. Hartung, *J. Biol. Chem.*, **145**, 349 (1942).

[9] R. H. Barry and W. H. Hartung, *J. Org. Chem.*, **12**, 460 (1947).

[10] Veratraldehyde or other 3,4-dialkoxybenzaldehydes may be employed with equally good results.

[11] H. Decker and O. Koch, *Ber.*, **38**, 1741 (1905).

[12] E. Knoevenagel, *Ber.*, **31**, 2594 (1898).

[13] W. H. Hartung, THIS JOURNAL, **50**, 3370 (1928).

hydroxide, refluxing and stirring for one hour. Distilled water (100 ml.) was then added, and the alcohol was removed by distillation. The resulting aqueous solution of the potasium salt was cooled to 0° by means of crushed ice, and dilute hydrochloric acid was added until the mixture was acid to congo red. The malonic acid was extracted with ether, the ether solution dried over anhydrous sodium sulfate, and 100 ml. of dry toluene was added. The ether was removed over a steam-bath and the residual toluene solution was cooled overnight. Fifty-three grams (89.5% yield) of 3,4-methylenedioxybenzylmalonic acid was removed by filtration. The colorless product melted[14] with evolution of gas at 143°. The previously reported melting point is 142–143°.[15]

α-Oximino-β-(3,4-methylenedioxyphenyl)-propionic Acid (IV): Method A.—In a 250-ml. 3-neck flask fitted with mechanical stirrer, reflux condenser and dropping funnel was placed 60 ml. of absolute ethanol in which was dissolved 2.3 g. of sodium. To the cooled and stirred solution was added 20.4 g. (0.1 mole) of 3,4-methylenedioxybenzylacetoacetic ester. To the flask, surrounded by a cold (10°) water-bath was added, with rapid stirring, 9.8 g. (0.11 mole) of isopropyl nitrite over a period of fifteen minutes. Stirring was continued for thirty minutes after addition of the nitrite, then the ethanol and isopropanol were removed under reduced pressure at 50°. Crushed ice (35 g.) was added to the residue and the mixture carefully acidified with 6 *N* sulfuric acid, then extracted with ether. The ether solution was then thoroughly extracted with cold 10% sodium hydroxide solution. The alkaline extract was warmed on the steam-bath for fifteen minutes, then chilled and carefully acidified with dilute hydrochloric acid. The α-oximino acid was filtered off, decolorized in hot 30% ethanol with Nuchar and recrystallized from dilute ethanol. The colorless crystalline product melted at 160°. The yield was 62%.

Anal. Calcd. for $C_{10}H_9O_5N$: N, 6.2. Found: N, 6.3 (Kjeldahl).

Method B.—In a beaker surrounded by an ice–salt mixture was placed a solution of 5.6 g. (0.024 mole) of piperonylmalonic acid in 100 ml. of ether, and to it was added 2.2 g. (0.025 mole) of isopropyl nitrite. Dry hydrogen chloride was passed into the stirred mixture at the rate of two to three bubbles per second for about one hour. The reaction mixture, now yellow in color, was allowed to stand at room temperature for four hours, then warmed on the steam-bath until the solvents had evaporated. The residue was dissolved in hot toluene, and the solution was allowed to cool in the ice-box. The colorless crystals of the oxime were collected and dried over sulfuric acid *in vacuo*. A yield of 4.7 g. (89%) of product melting at 160° was obtained.

3,4-Methylenedioxyphenylalanine Hydrochloride (V).—To 7 g. (0.031 mole) of the oxime IV, dissolved in 100 ml. of absolute alcohol containing 2 g. of hydrogen chloride, was added 3 g. of 10% palladium catalyst. The mixture was hydrogenated at atmospheric pressure, the theoretical quantity of hydrogen being taken up in two and one-half hours. The catalyst was removed, the filtrate was concentrated to about 50 ml. under reduced pressure, and 200 ml. of dry ether was added with stirring. Cooling of the ether–alcohol solution produced 6.4 g. (92%) of colorless crystals of 3,4-methylenedioxyphenylalanine hydrochloride which melted at 284° with decomposition.

Anal. Calcd. for $C_{10}H_{11}O_4N{\cdot}HCl$: N, 5.38. Found: N, 5.30 (Kjeldahl).

3,4-Dihydroxyphenylalanine Hydriodide (VI).—In fifty milliliters of hydriodic acid (sp. gr. 1.49) was dissolved 7.4 g. (0.03 mole) of 3,4-methylenedioxyphenylalanine hydrochloride, and the mixture was refluxed for two hours. Toluene (200 ml.) was then added, a Dean–Stark trap equipped with stopcock outlet for removal of the water was inserted between the flask and reflux condenser and the mixture refluxed until no more water collected in the trap (three to four hours). The toluene solution of the dopa-hydriodide was allowed to cool overnight in the ice-box and the amino acid filtered off. The crystals were colorless and did not darken while being dried *in vacuo* over sulfuric acid. The acid melted at 201° (d.)[16] and gave a dark green color with ferric chloride. The yield of dopa-hydriodide was 4.1 g. (88%).

Anal. Calcd. for $C_9H_{11}O_4N{\cdot}HI$: N, 4.32. Found: N, 4.27 (Kjeldahl).

Summary

1. A practical synthesis of *dl*-3,4-dihydroxyphenylalanine (dopa) has been developed.

2. 3,4-Methylenedioxybenzylacetoacetic ester and 3,4-methylenedioxybenzylmalonic acid were nitrosated to give α-oximino β-(3,4-methylenedioxyphenyl)-propionic acid, which was reduced catalytically to give 3,4-methylenedioxyphenylalanine in good yield. The latter was converted into *dl*-dopa by hydrolysis with hydriodic acid.

BALTIMORE, MARYLAND RECEIVED AUGUST 20, 1947

---

[14] All melting points obtained are uncorrected.

[15] "Beilstein," Vol. 19, p. 287.

[16] No constant has been previously reported for the hydriodide of dopa. Stephen and Weizmann (7a) reported the hydrochloride, m. p. 246° (d.) and the hydrobromide, m. p. 212° (d.).

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

The Preparation of Raney Nickel Catalysts and their Use Under Conditions Comparable with Those for Platinum and Palladium Catalysts

BY HOMER ADKINS AND HARRY R. BILLICA[1]

It has been the practice in this and many other laboratories to use a platinum or palladium catalyst if a hydrogenation was to be carried out in glass apparatus at room temperatures. However, improvements in the procedure for the preparation of a catalyst from the Raney nickel–aluminum alloy now makes available a catalyst which appears to be approximately as effective as platinum or palladium for catalysis of hydrogenation at pressures of 45 p. s. i. or lower. It is not implied that any of the three metals is lacking in characteristics which make it uniquely useful. For example, the inactivity of palladium against benzenoid nuclei and nitriles and its relative inactivity toward aldehydes make this catalyst particularly useful in certain selective hydrogenations. Platinum and nickel are more alike in activity in that both, under suitable conditions, are effective against almost all types of carbon-to-carbon double bonds, aldehydes, ketones, nitriles, nitro compounds and oximes. Each of them is preferred to the other for certain situations.

The activity of Raney nickel catalysts under mild conditions has been recognized for some time. In our first publication,[2] its effectiveness at low pressure and room temperature was illustrated with results obtained with styrene, acetone, mesityl oxide and acetoacetic ester among other compounds. G. B. L. Smith and his associates[3] have reported on the effectiveness of Raney nickel with and without a platinum promoter particularly for the hydrogenation of nitro compounds. However, it seemed that the Raney nickel catalysts available were not particularly useful at room temperature, except in the hydrogenation of alkene linkages.

The most active nickel catalyst now known to us is one to which we refer as "W-6 Raney nickel,"[4] It is made by a procedure given later in this paper. The modifications of earlier procedures consist in rapidly carrying out the removal of aluminum from the Raney alloy at a lower temperature and in washing the catalyst under pressure of hydrogen. The use of hydrogen under pressure in the washing process may be advantageous in that it protects the catalyst from contact with air and the loss of the rather large quantity of hydrogen which is adsorbed on the catalyst.

There is summarized in the table the results of applying the W-6 Raney nickel catalyst to the hydrogenation of a variety of organic compounds. The hydrogenations were carried out in glass under the conditions normally used with platinum and palladium catalysts. The absorption of hydrogen was in every experiment within ±4% of that required for the formation of the compounds reported in the last column of the table. Except as noted under the table the hydrogenations went quantitatively to a single product.

Compounds containing a carbon–carbon double bond such as cinnamic acid, ethyl cinnamate and diethyl isopropylidenemalonate, were very rapidly hydrogenated in three to ten minutes to the corresponding saturated compound. Stearolic acid was converted into elaidic acid within less than two minutes. The elaidic acid was then much more slowly converted to stearic acid. Thus it is possible with the W-6 catalyst to selectively hydrogenate an alkyne to an alkene linkage.

Representative aldehydes and ketones were rapidly hydrogenated to the corresponding alcohols. It was found that the addition of a little triethylamine to the reaction mixture approximately cut in half the time required for the hydrogenation of an aldehyde or ketone. Thus through the use of W-6 catalyst with triethylamine all of the aldehydes and ketones tested were hydrogenated to the corresponding alcohol within less than forty minutes, while some of them reacted much more rapidly. The presence of triethylamine retards the hydrogenation of a benzenoid nucleus so that even with a naphthyl ketone there is no danger of hydrogenating the nucleus.

The W-6 catalyst is not only effective against alkene, alkyne and carbonyl linkages, but will also bring about the hydrogenation of benzenoid and pyridinoid nuclei. Diphenyl, hydroquinone, β-naphthol, methyl β-naphthylcarbinol and β-phenylethanol were hydrogenated although more slowly than the types of compounds referred to just above. However, as is shown in the case of hydroquinone, the rate of hydrogenation can be greatly increased through the use of higher ratio of catalyst to compound undergoing hydrogenation. The hydrogenation of the pyridinoid ring in quinoline went rapidly. The hydrogenation of the compounds containing two unsaturated rings was selective, in that under the conditions used only one ring was hydrogenated. The W-6 catalyst was also effective in bringing about a hydrogenolysis of benzhydrol, but not without hydrogenation.

The W-6 catalyst was effective in catalyzing the hydrogenation of nitriles such as benzyl cyanide and stearonitrile. The proportion of primary and secondary amine produced from benzyl cyanide was similar to that observed in a high

---

[1] Monsanto Chemical Co. Fellow, 1946–1947.

[2] Covert and Adkins, THIS JOURNAL, **54**, 416 (1932).

[3] Smith, Scholnik, Reasenberg and Lieber, *ibid.*, **63**, 1192 (1941).

[4] For references and designation of catalysts see Adkins and Pavlic, *ibid.*, **69**, 3040 (1947).

pressure hydrogenation in the absence of ammonia. However, there was no secondary amine formation in the hydrogenation of stearonitrile.

p-Nitrotoluene was converted smoothly and rapidly into *p*-toluidine of excellent quality. The reduction of a nitro group is so exothermic a reaction that precautions must be taken to keep the reaction under control. This is particularly important when a catalyst so active as W-6 is used. As indicated below, there is danger in the use of W-6 Raney nickel under certain circumstances.

The oximino groups in a simple oxime, in an oximinoketone and in an oximinoketo ester were smoothly and rather rapidly hydrogenated to the primary amine group. The keto groups were also hydrogenated to alcohol groups, but the carboethoxy group was stable at the low pressure. Under higher pressure, as will be described in a later paper, the W-6 catalyst catalyzes the conversion of carboethoxy to carbinol.

An alkaline catalyst, referred to as W-7 Raney nickel, has given good results in hydrogenating

Table I

Hydrogenations with W-6 Nickel Catalysts[a]

Compound, g.	Time Hr.	Time Min.	Product
13.0 Ethyl acetoacetate	1	10	Ethyl β-hydroxybutyrate, b. p. 77–78° (15 mm.), $n^{25}\mathrm{D}$ 1.4200, d^{25} 1.0052
13.0 Ethyl acetoacetate[b]	0	34	Ethyl β-hydroxybutyrate
9.1 Benzophenone	0	17	Benzohydrol needles, m. p. 66–69°, phenylurethan, m. p. 138–140°
9.1 Benzophenone[b]	0	8	Benzohydrol
8.5 β-Acetylnaphthalene[b]	0	25	Methyl-β-naphthyl carbinol, needles, m. p. 67–68.5°, b. p. 125–128 (2 mm.); phenylurethan, m. p. 143.5–144.5°
6.6 Cinnamaldehyde[b]	0	39	3-Phenyl-1-propanol, b. p. 82–84° (1 mm.), $n^{25}\mathrm{D}$ 1.5354
6.0 Acetophenone	0	22	Methyl phenyl carbinol, b. p. 103–104° (20 mm.), $n^{25}\mathrm{D}$ 1.5251; phenylurethan, m. p. 93–94°
6.0 Acetophenone[b]	0	10	Methyl phenyl carbinol.
5.3 Benzaldehyde	0	26	Benzyl alcohol, b. p. 104–105 (20 mm.), $n^{25}\mathrm{D}$ 1.5340; phenylurethan, m. p. 74–76°.
5.3 Benzaldehyde[b]	0	12	Benzyl alcohol, b. p. 104–105° (20 mm.), $n^{25}\mathrm{D}$ 1.5340
5.0 *n*-Hexaldehyde	1	50	*n*-Hexyl alcohol, b. p. 67–69° (20 mm.), $n^{25}\mathrm{D}$ 1.4134, phenylurethan, m. p. 40–42°
5.0 *n*-Hexaldehyde[b]	0	40	*n*-Hexyl alcohol
5.8 Acetone	0	38	Isopropyl alcohol
5.8 Acetone[b]	0	23	Isopropyl alcohol
8.8 Ethyl cinnamate	0	3	Ethyl β-phenylpropionate
7.4 Cinnamic acid	0	10	β-Phenylpropionic acid
7.0 Stearolic acid	2	0	Stearic acid, m. p. 67–70°, b. p. 188–190° (1 mm.)
7.0 Stearolic acid	0	2	Elaidic acid, m. p. 42–45°, b. p. 185–187° (1 mm.)
10.0 Diethyl isopropylidene malonate	0	8	Diethyl isopropylmalonate, b. p. 74–76° (3 mm.), $n^{22}\mathrm{D}$ 1.4186; acid, m. p. 86.5–87.5°
5.2 Diphenyl[c]	6	0	Phenylcyclohexane, b. p. 125–128° (30 mm.), $n^{25}\mathrm{D}$ 1.5210
5.5 Hydroquinone	36	0	1,4-Cyclohexanediol, needles, m. p. 98.5–101°[d]
5.5 Hydroquinone[c]	8	0	1,4-Cyclohexanediol
6.1 β-Phenylethanol[c]	96	0	β-Cyclohexylethanol, b. p. 118–120° (36 mm.), $n^{25}\mathrm{D}$ 1.4700; phenylurethan, m. p. 119.5–120.5°
7.2 β-Naphthol	4	0	1,2,3,4-Tetrahydro-2-naphthol (27%), b. p. 118–120° (3 mm.), insoluble in alkali. 5,6,7,8-Tetrahydro-2-naphthol (55%), b. p. 114–116° (3 mm.), soluble in alkali
9.2 Diphenylcarbinol	27	0	$\left\{\begin{array}{l}\text{Diphenylmethane}\\ \text{Benzylcyclohexane}\end{array}\right\}$ b. p. 90–100° (3 mm.), $n^{25}\mathrm{D}$, 1.5600[e]
8.5 β-Acetylnaphthalene	45	0	Methyl-β-tetrahydronaphthylcarbinol[f]
5.9 Benzyl cyanide	1	6	β-Phenethylamine (72%), b. p. 106–107° (37 mm.), $n^{25}\mathrm{D}$ 1.5306; picrate, m. p. 173–174° Di-(β-phenethyl) amine (15%), b. p. 215–220° (38 mm.), $n^{25}\mathrm{D}$ 1.5521; picrate, m. p. 150–151.5°
6.7 Stearonitrile	5	0	*n*-Octadecylamine, b. p. 146–154° (2 mm.), m. p. 51.5–53°; picrate, m. p. 116°; hydrochloride, m. p. 159–161°
6.9 *p*-Nitrotoluene	0	13	*p*-Toluidine, b. p. 107–109° (33 mm.), m. p. 43–44°; picrate, m. p. 179.5–180.5° (dec.)
5.7 Cyclohexanone oxime	0	45	Cyclohexylamine (90%), b. p. 48–52° (30 mm.), $n^{25}\mathrm{D}$ 1.4569; hydrochloride, m. p. 204–206°
8.2 α-Oximinopropiophenone	3	30	2-Amino-1-phenyl-1-propanol, m. p. 99–103°; hydrochloride, m. p. 189–191°; oxalate, m. p. 243–244.5°[g]
8.0 Ethyl α-oximinoacetoacetate	1	20	Ethyl α-amino-β-hydroxybutyrate, b. p. 82–84° (2 mm.), $n^{25}\mathrm{D}$ 1.4495[h]
6.5 Quinoline	0	50	1,2,3,4-Tetrahydroquinoline, b. p. 85–86° (2 mm.), $n^{25}\mathrm{D}$ 1.5910; hydrochloride, m. p. 179–181°

[a] The hydrogenations were carried out at room temperature (25–30°) under a pressure of 15 to 45 p. s. i. in a 250-ml. glass centrifuge bottle shaken at 172 r. p. m. The reaction mixture was made up to a volume of 100 ml. with dry ethanol and contained 2 g. of W-6 Raney nickel, except as noted below. [b] The reaction mixture contained 2 ml. of triethylamine. [c] Nine grams of W-6 Raney nickel was used. [d] Other work has shown the product to be a mixture of the *cis* and *trans* isomers in approximately equal proportions. [e] This value indicates approximately three parts of diphenylmethane and one part benzylcyclohexane. [f] The compound is an alcohol, b. p. 119–119.5° (2 mm.), $n^{25}\mathrm{D}$ 1.5484, $d^{25°}$ 1.0408, M_{R} calcd. 53.33, found 53.3. Phenylurethan, m. p. 230–231.5°. *Anal.* Calcd. for $C_{12}H_{16}O$: C, 81.8; H, 9.14. Found: C, 81.6; H, 9.08. The position of the hydrogens added is not known. [g] A mixture of stereoisomers. [h] The yield of a mixture of stereoisomers was low, probably because of the formation of a piperazine during distillation of product.

ketones, phenols and nitriles, for which alkali in the reaction mixture is beneficial.[5,6] The catalyst is attractive because of the simplicity of the procedure used in washing it. It was somewhat less active than W-6 toward diphenyl and benzyl cyanide, but the proportion of primary to secondary amine was increased. The W-7 catalyst was somewhat more active toward acetophenone than W-6 without triethylamine. The catalyst was remarkably active toward hydroquinone, giving complete hydrogenation within fifteen minutes instead of in eight hours as with W-6.

Preparation of W-6 Raney Nickel Catalyst

WARNING.—The Raney nickel catalysts described below have given reactions proceeding with violence. In one case a hydrogenation proceeding at 125° at 5000 p. s. i. showed a pressure rise to considerably more than 10,000 p. s. i. before the reaction could be stopped or the pressure released. Several instances of sudden increases in pressure have been noted when quantities of catalyst of the order of 10 to 15 g. were being used in the temperature range of 100 to 150° under 5,000 p. s. i. The high activity of the catalysts and the presence of aluminum and rather large amounts of adsorbed hydrogen make it advisable to be *very cautious in their use.* No difficulty has been encountered at temperatures below 100°. Hydrogenations may be carried out safely above 100° if the ratio of catalyst to possible reactants is kept low, *e. g.*, 5% as much nickel as weight of hydrogen acceptor.

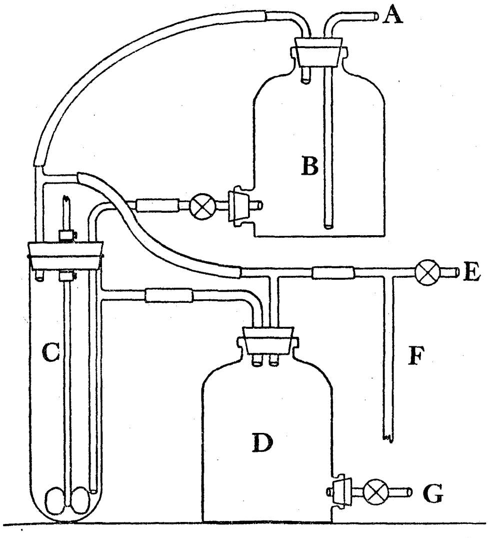


Fig. 1.—Apparatus for washing catalyst: A, distilled water inlet; B, reservoir for distilled water; C, chamber for washing catalyst; D, overflow bottle; E, hydrogen inlet; F, manometer; G, water outlet. It is more convenient to have the inlet tube for wash water sealed into the bottom of the chamber rather than introduced through the stopper as shown.

Procedure.—In a two-liter Erlenmeyer flask equipped with a thermometer and a stainless steel stirrer, is placed 160 g. of sodium hydroxide in 600 ml. of distilled water. The rapidly stirred solution is allowed to cool to 50° in an ice-bath equipped with an overflow siphon. Then 125 g. of Raney nickel–aluminum alloy is added in small portions over a period of twenty-five to thirty minutes. The temperature is maintained at 50 ± 2° by controlling the rate of addition of alloy to the sodium hydroxide and of ice to the cooling bath. When all the alloy has been added, the suspension is digested at 50° for fifty minutes with gentle stirring. It is usually necessary to remove the ice-bath and replace with a hot water-bath. The catalyst, after digestion, is washed three times by decantation and then transferred immediately to the washing tube for further washing.

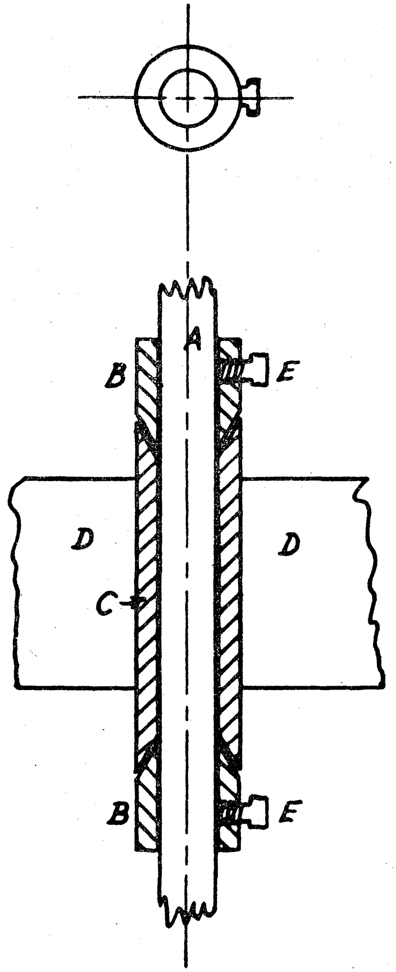


Fig. 2.—Gas tight bushing: The gas tight bushing for the shaft of the stirrer consists of three parts; two cones (B) which fit the shaft snugly and are attached to it by set screws (E); and a bushing (C) so cut that the cones fit into it at top and bottom. The two cones are placed on the 0.25 inch shaft (A) of the stirrer, above and below the bushing and attached to the shaft so that they fit snugly against the bushing. A gas-tight seal is obtained by placing a drop or two of heavy lubricating oil between each cone and the bushing. The over-all dimensions of the bushing are approximately 13 × 65 mm. and it is held in a rubber stopper (D).

---

[5] Delépine and Horeau, *Compt. rend.*, **201**, 1301 (1935).

[6] Fluchaire and Chambert, *Bull. soc. chim.*, **11**, 22 (1944).

A glass test-tube, approximately 5.1 cm. in diameter and 38 cm. in length, with a side arm 6 cm. from the top, is used as the container in washing the catalyst. The tube is equipped with a snugly fitting rubber stopper which is held in place by a suitable device. The stopper carries a gas tight bushing (Fig. 2) through which the 0.25-inch shaft of a stainless steel stirrer projects to the bottom of the washing tube. A 5-liter reservoir for distilled water is so placed that water will flow from it through a stopcock down a glass tube, 8 mm. in diameter, which passes through the stopper and down the side of the washing tube to its bottom. The side arm of the test-tube is connected by rubber tubing to a 5-liter overflow bottle from which the water may be allowed to flow through a stopcock to the drain. A connection from a source of distilled water is made to the reservoir. All connections of rubber and glass tubes should be so fastened that they will withstand the pressures used. The general arrangement of the apparatus is shown in Fig. 1, while certain details of construction are given in Fig. 2.

The catalyst sludge is immediately transferred to the washing tube after the third decantation. The last portions are rinsed from the flask into the tube with distilled water and the tube and reservoir nearly filled with distilled water. The apparatus is then rapidly assembled, and hydrogen introduced so that the water in the reservoir, washing tube and overflow bottle is under a pressure about 0.5 atm. above that of the outside atmosphere. The stirrer is operated at such a speed that the catalyst is suspended to a height of 18–20 cm. Distilled water from the reservoir is allowed to flow through the suspended catalyst at a rate of about 250 ml. per minute. When the reservoir is nearly empty and the overflow bottle full, the drain cock and distilled water inlet are simultaneously opened to an equal rate of flow such that, as the overflow bottle empties, the reservoir is filled, while the pressure in the system remains constant.

After about 15 liters of water has passed through the catalyst, the stirrer and the water are stopped, the pressure released and the apparatus disassembled. The water is decanted from the settled sludge, which is then transferred to a 250 ml. centrifuge bottle with 95% ethanol. The catalyst is washed three times by stirring, not shaking, with 150 ml. of 95% ethanol, centrifuging after each addition. In the same manner, the catalyst is washed three times with absolute ethanol. One to two minutes centrifugation at 1500–2000 r. p. m. is sufficient to separate the catalyst. All operations should be carried out as rapidly as possible if a catalyst of the maximum activity is desired. The catalyst should be stored in a refrigerator in a closed bottle filled with absolute ethanol. The total elapsed time from the beginning of the addition of the alloy to the completion of the preparation, with the catalyst in the refrigerator, should be not more than about three hours.

The volume of the settled catalyst in ethanol is about 75–80 ml. containing about 62 g. of nickel and 7–8 g. of aluminum. It amounts to about twenty-eight "half teaspoonsful" if it is so measured. The catalyst loses some of its special activity upon standing, but seems to be quite active for about two weeks when stored in a refrigerator. After this period it is similar in activity to the Raney nickel made by earlier procedures. The W-3 to W-7 catalysts all lose their special activity rather rapidly when stored under water.

The procedure for the preparation of W-5 Raney nickel, a somewhat less active, but nevertheless excellent catalyst, is the same as that for W-6, except that it is washed at atmospheric pressure without the addition of hydrogen to the system. The W-5 catalyst is similar in method of preparation and activity to the W-4 Raney nickel catalyst as prepared by Pavlic.[4,7] The procedure in the preparation of W-7 Raney nickel, after the digestion and the three decantations, is to transfer the catalyst to a 250 ml. centrifuge bottle with 95% alcohol. It is then washed three times by stirring, not shaking, with 150 ml. of 95% ethanol, centrifuging after each addition. In the same manner, the catalyst is washed three times with absolute ethanol.

Summary

A procedure has been described for the preparation of Raney nickel catalysts, which are useful at room temperatures and low pressures, for the catalysis of the hydrogenation of alkyne and alkene linkages, aldehydes, ketones, nitro compounds, nitriles, oximes and benzenoid and pyridinoid nuclei. While the amount of catalyst required for a given rate of hydrogenation is higher than for platinum and palladium catalysts, it appears that a properly prepared Raney nickel catalyst is effective under as mild conditions of temperature and pressure as are the noble metals. It appears that, under the conditions normally used for the platinum and palladium catalysts, the W-6 Raney nickel catalyst is more selective in action than at higher pressures and temperatures. For example, stearolic acid was converted within two minutes to elaidic without significant reduction of the latter to stearic acid. It has been found that the addition of a small amount of triethylamine to a reaction mixture markedly increases the rate of hydrogenation of aldehydes and ketones over Raney nickel.

MADISON, WISCONSIN RECEIVED AUGUST 18, 1947

---

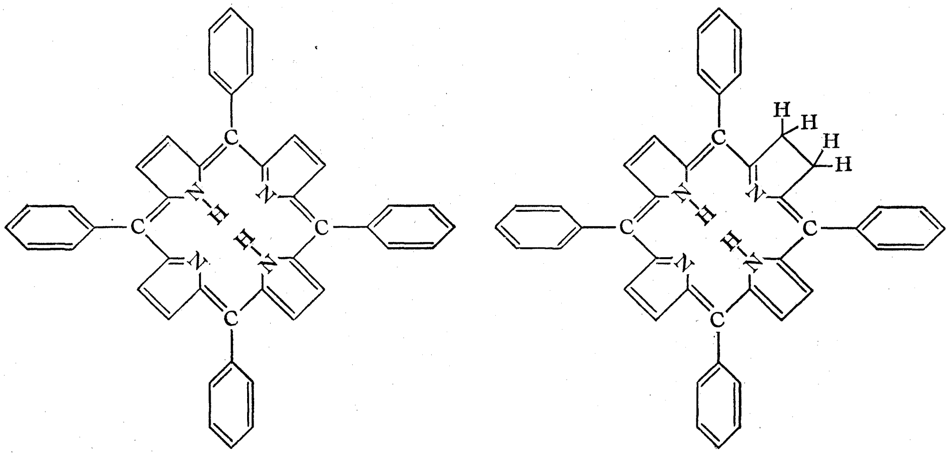
[7] Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946).

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

The Possibility of a Triplet State Intermediate in the Photo-oxidation of a Chlorin

BY M. CALVIN AND G. D. DOROUGH[1]

As part of a rather routine examination of the spectra of a number of tetraphenyl porphin and chlorin compounds (see Fig. 1), the zinc salt of tetraphenyl chlorin was prepared and dissolved in benzene. The solution at first was green in color and showed an intense red fluorescence, but upon standing a few hours this fluorescence died out, and the color of the solution changed from green to yellow. The cause of this curious phenomenon was attributed to a light induced oxidation by molecular oxygen, since it was found that benzene solutions of zinc tetraphenyl chlorin were quite stable if either light or air were excluded, or if the air were replaced by carbon dioxide.



a. Tetraphenyl porphin b. Tetraphenyl chlorin

Fig. 1.

The spectrum of such a degraded zinc chlorin solution is given in Fig. 2. This spectrum, upon reference to the spectra of the zinc complexes of porphin and chlorin (Fig. 3), indicates that some of the zinc chlorin still remains, as evidenced by the remnants of a band at about 6200 Å., that some zinc porphin has been formed, as evidenced by a band at 5500 Å. and that some new substance or substances have been formed, as shown by the high absorption in the region 4650 Å., a region where neither porphin nor chlorin have any appreciable absorption. These conclusions were substantiated by removing the zinc from a sample of the photoöxidation product upon which the spectrum had been run, and chromatographing the resulting free base. Found were tetraphenyl porphin and tetraphenyl chlorin and two substances which appeared as dark blue layers on the talc. No attempt was made to identify these blue materials.

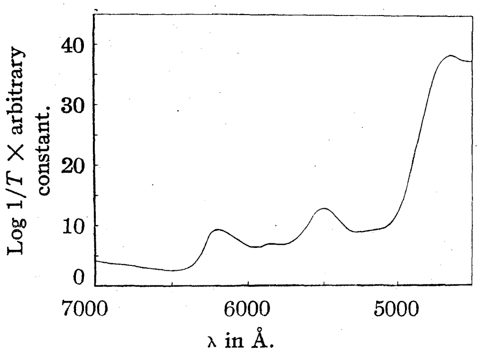


Fig. 2.—Oxygen-degraded zinc chlorin (in benzene).

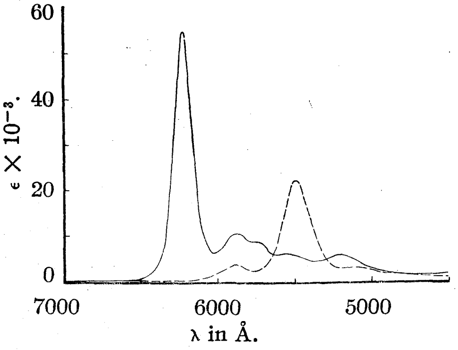


Fig. 3.—Absorption spectra of zinc complexes in benzene: — — — — —, tetraphenylporphin; ————, tetraphenyl chlorin.

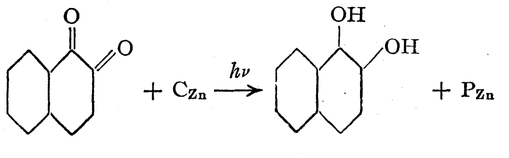
The establishment of a photochemical conversion of chlorin to porphin by molecular oxygen prompted similar experiments with other oxidizing agents. In contrast to the oxygen reaction which gave several products, it was found that a

---

[1] Present address: Department of Chemistry, Washington University, St. Louis 5, Missouri.

number of ortho and para quinones (*p*-benzo, 1,2-naphtho, 1,4-naphtho, and 9,10-phenanthro) in a deoxygenated benzene solution of zinc tetraphenyl chlorin gave quantitatively with light a single product—zinc tetraphenyl porphin. This latter reaction was thus considered to be of the following type where C_{Zn} and P_{Zn} represent zinc tetraphenyl chlorin and porphin, respectively. It was observed further that para quinones as a class seemed to react more slowly than the ortho quinones. Such a result is not unreasonable, for one might very well expect from spatial considerations alone that an ortho quinone might react in a simple bimolecular manner with the simultaneous removal of both hydrogens from the chlorin, while a para quinone could not sterically do so.

(Illustrating with
β-naphthoquinone):



The cleanness of the oxidation of zinc chlorin by the quinones led to a very detailed study of the reaction with one of them, β-naphthoquinone. The reaction was followed by measuring the simultaneous decrease and increase in absorption at 6212 Å. and 5500 Å., respectively, due to the disappearance of chlorin and the formation of porphin as the reaction proceeds (see Fig. 3). By modifying a Beckman spectrophotometer to permit thermostating, it was possible to run the reaction right in this instrument, using the tungsten light of the Beckman both for illumination of the solution and for the measurement of absorption. From rate studies carried out in this manner and other related experiments, it was possible to establish the following facts (see experimental section for details): (1) β-naphthoquinone reacts with zinc tetraphenyl chlorin to give zinc tetraphenyl porphin and β-naphthohydroquinone. (2) Light is required for the reaction—more particularly, only light that is absorbed by the chlorin is required, for illumination was always carried out at 6212 Å. where the naphthoquinone and the zinc porphin have no appreciable absorption. (3) Traces of oxygen inhibit the reaction, *i. e.*, cause the rate to be slower without reacting with the chlorin. (4) The rate of the reaction is independent of the naphthoquinone concentration down to a value of 1.8×10^{-6} *M;* the quantum yield corresponding to this rate is about 0.02. (5) The function of chlorin concentration, $(C_{Zn}) + \log A/\Sigma d$, gives a straight line when plotted against time. (6) The reaction rate increases with decreasing temperature. (7) The reaction rate is directly proportional to the light intensity. (8) There is no evidence for complex formation between the quinone and the chlorin. (9) An ortho quinone of lower oxidation–reduction potential, phenanthro, behaves in a manner identical to the above, but with a rate a factor of three smaller.

The primary step in this reaction must be the absorption of a 6212 Å. photon to give a chlorin molecule excited to the first electronic state. Furthermore, it would appear that the quinone does not react with this excited state, for if it did the rate would be proportional to the quinone concentration. This is due to the fact that the quantum yield is only 2%, and thus 98% of the excited chlorin molecules must be deactivated by a number of processes, fluorescence, solvent and wall deactivation, etc., and it is apparent that if the reaction with quinone were competing with these processes, then the probability of a reaction and thus the rate would increase with increasing quinone concentration. But this is not so; the reaction is independent of the quinone concentration down to a very small value. Thus, if the quinone does not react with the ground state, and does not react with the excited state, then one is forced to the conclusion that it reacts with some intermediate state which is only obtainable from the excited state.

We have considered this intermediate state to be the phosphorescent state, partly because of the ease with which such an assumption will explain the known facts. Figure 4 shows an energy level diagram of this state in relation to the ground and excited states. Now the ground state is a singlet state, that is, there are no unpaired electrons. Since transitions between states of different multiplicity are of low probability, the excited state must also be a singlet, for this transition is obviously of high probability (the extinction coefficient is high). G. N. Lewis[2,3,4] has considered the phosphorescent state to be of a different multiplicity, namely, a triplet state, and accounts for the slow emission of light to the ground state, *i. e.*, phosphorescence, by the low transition probability between these two states. The S′-T transition (dotted line) is a non-radiative transfer, which not being bound by the usual selection rules permits the transition to occur during the very short life time of the S′ state, about 10^{-9} seconds.

Experiments established that zinc tetraphenyl chlorin had a phosphorescence at about 8000 Å. (see Fig. 5) and an intrinsic lifetime of the triplet state of about 8×10^{-3} seconds. If one assumes that every molecule which gets into the triplet state reacts with quinone, then the rate would be independent of the quinone concentration down to the point where the time between collisions became so large as to allow other deactivating processes to occur. Collision number calculations based on the gas laws showed that a triplet state chlorin would, on the average, make an effective collision with quinone in about 10^{-5} second if the quinone concentration were at the point where

---

[2] Lewis, Lipkin and Magel, THIS JOURNAL, **63**, 3005 (1941).

[3] Lewis and Kasha, *ibid.*, **66**, 2100 (1944).

[4] Lewis and Kasha, *ibid.*, **67**, 994 (1945).

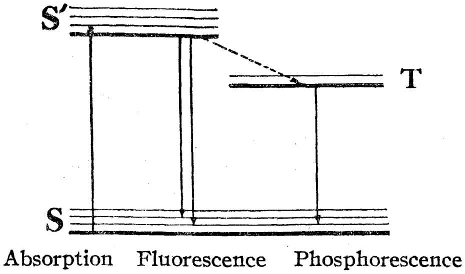


Fig. 4.—Energy level diagram.

quinone independence was experimentally observed to break down. That a triplet state molecule with an intrinsic lifetime of nearly a hundredth of a second could last more than 10^{-5} second in a media where solvent deactivation is inefficient is indeed reasonable.

The inhibitory effect of the oxygen could be accounted for by its paramagnetism. If an excited molecule such as a triplet state chlorin is placed in an inhomogeneous magnetic field, it will radiate due in effect to the breakdown of the selection rules forbidding the transition. Thus a triplet state chlorin approached closely by an oxygen would have a very large probability of being deactivated by radiation to the ground state, due to the magnetic field associated with the oxygen molecule. Thus an observed decrease in the rate of the reaction in the presence of small amounts of oxygen is explained.

The increase in the rate of the reaction with decreasing temperature is not in disagreement with a triplet state mechanism, but neither can it be said that it supports it. What the observation means is that the probability of the S′–T non-radiative transition is increased with decreasing temperature. The direction of change of this probability with temperature depends upon the relative positions of the two states and shapes of their representative potential energy curves, especially at their crossing point. The change may be in either direction.

A mechanism for this reaction may be summarized as

$$C_{Zn} + h\nu \xrightarrow[k_1]{} C^{S'}{}_{Zn} \qquad (1)$$

$$C^{S'}{}_{Zn} \xrightarrow[k_4]{} C_{Zn} + (h\nu \text{ or } kT) \qquad (4)$$

$$C^{S'}{}_{Zn} \xrightarrow[k_2]{} C^{T}{}_{Zn} \qquad (2)$$

$$C^{T}{}_{Zn} + Q \xrightarrow[k_3]{} P_{Zn} + H_2Q \qquad (3)$$

$$C^{T}{}_{Zn} + Q \xrightarrow[k_5]{} C_{Zn} + Q + kT \qquad (5)$$ [5]

k_1 is the primary absorption act

k_2 is the transition from excited singlet to the triplet state

k_3 is the reaction of triplet state molecules with quinone leading to oxidation to porphin

k_4 is the deactivation of excited singlet states by all processes leading to the ground state (fluorescence and thermal deactivation by solvent)

k_5 is the thermal deactivation of triplet state molecules by quinone leading back to ground state chlorin molecules.

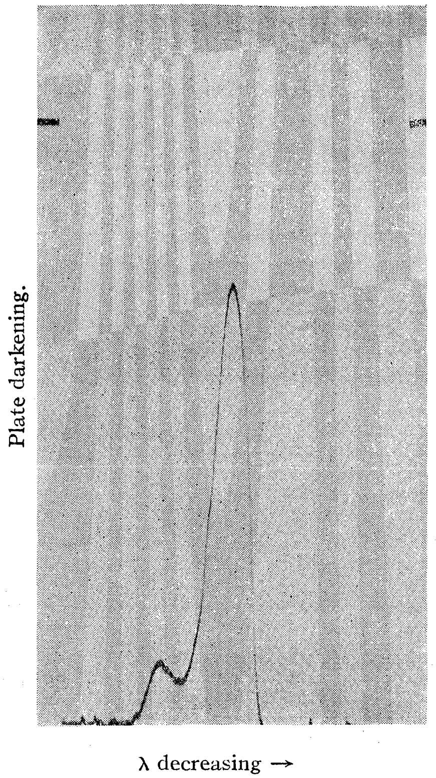


Fig. 5.—Tracing of spectrographic plate showing phosphorescence of zinc tetraphenylchlorin. Peak positions are at approximately 8000 Å. for the tall peak and 9000 Å. for the second peak.

The net rate of disappearance of Zn chlorin is given by

$$-\mathrm{d}(C_{Zn})/\mathrm{d}t = k_3(C^{T}{}_{Zn})(Q) \qquad (6)$$

The steady state expression for $C^{S'}{}_{Zn}$ molecules is

$$K_a I_{\text{absorbed}} = (k_2 + k_4)(C^{S'}{}_{Zn}) \qquad (7)$$

where K_a is a unit conversion factor involving the volume of solution and Avogadro's number to convert photons absorbed per second into moles of photons per liter absorbed per second. And the steady state expression for $C^{T}{}_{Zn}$ molecules is

$$k_2(C^{S'}{}_{Zn}) = k_3(C^{T}{}_{Zn})(Q) + k_5(C^{T}{}_{Zn})(Q) \qquad (8)$$

Combining (7) and (8) for $(C^{T}{}_{Zn})$ and substituting in (6), we have

$$\frac{-\mathrm{d}(C_{Zn})}{\mathrm{d}t} = \frac{k_2}{k_2 + k_4} \times \frac{k_3}{k_3 + k_5} \times K_a I_{\text{abs}} \qquad (9)$$

I_{abs} may be expressed in terms of Beer's and Lambert's law

$$I_{\text{abs}} = I_0 A = I_0(1 - 10^{-\Sigma C_{Zn} d})$$

where I_0 is the impinging light intensity, A is the fraction of the impinging light absorbed, Σ is the molar extinction coefficient for the wave length band used in these experiments, and Σ is the thickness of the solution through which the light passes.

Now it is also readily seen that $k_2/(k_2 + k_4)$ represents the quantum yield of the triplet state,

---

(5) This step was suggested to us by Prof. G. Rollefson and Mr. F. Hueunekens.

and that $k_3/(k_3 + k_5)$ represents the fraction of the triplet state molecules going to porphin. Thus

$$\frac{k_2}{k_2 + k_4} \times \frac{k_3}{k_3 + k_5} = \gamma$$

the quantum yield for the over-all reaction. Using these substitutions in (9) we have

$$-\mathrm{d}(C_{Zn})/\mathrm{d}t = \gamma K_a I_0(1 - 10^{-\Sigma C_{Zn} d})$$

which upon integration gives

$$(C_{Zn}) + \frac{1}{\Sigma d} \log A = \gamma K_a I_0 t + \pi \text{ (integration constant)} \qquad (10)$$

All of our runs showed excellent straight line agreement when the left side of equation (10) was plotted against time.

Another piece of evidence supporting this mechanism was provided by experiments with the copper salt. It was predicted that the copper salt of tetraphenyl chlorin would have a very short lived triplet state due to the magnetic field resulting from the odd electron in the copper orbitals. As a result, it was predicted that copper chlorin, if it reacted with quinone at all, should react very slowly. Experiments were run to test these predictions. It was found that the phosphorescence was so short lived as to be beyond the scope of the phosphoroscope used, which means a life of less than 10^{-5} second. A rate run with copper chlorin and β-naphthoquinone showed the rate to be considerably less than one hundredth that of zinc chlorin. In view of the close chemical similarity between copper and zinc chlorin, and the ease with which the copper chlorin is oxidized by other reagents, we feel this is supporting evidence for the triplet state mechanism.

From equation (9) it is apparent that although the rate of the reaction is independent of the quinone concentration, it is not independent of which quinone is used. The ratio $k_3/(k_3 + k_5)$ will be a characteristic of the quinone used, and increases with the oxidation potential of the quinone and is larger for the ortho quinones than it is for the para quinones. It is interesting to point out the parallelism of these results with those reported by Aronoff[6] on the production of oxygen by illuminated grana using a series of quinones as hydrogen acceptors.

If this reaction of zinc tetraphenyl chlorin is characteristic of the chlorin ring in general, then it may be that the knowledge gained from this reaction may find application in the study of photosynthesis. Using a sample of what we believed to be a pure mixture of chlorophylls *a* and *b*, we found[7] a phosphorescence of fair intensity at about 8000 Å. Whether this phosphorescence was due to chlorophyll is now open to question, for when we extended the work to the separated components of chlorophyll using samples the high purity of which we were absolutely certain, we found that the *b* component phosphoresced weakly at about 8600 Å. with a life of 0.03 second, while no phosphorescence could be detected for chlorophyll *a* below 8600 Å. Nevertheless, the possibility that chlorophyll could act in such a role is not yet excluded, for the S′–T transition under the conditions of the living plant could well be such as to give a high yield of chlorophyll in the metastable state.

It should be pointed out that this photoreduction of quinone by zinc chlorin is in all probability not a conversion of light energy into chemical energy since whatever estimates can be made of its free energy[8] indicate that its value is negative, at least with β-naphthoquinone. However, the reduction by chlorophyll of the pyridine enzymes (TPN or DPN) with the simultaneous formation of the corresponding porphyrin, might be expected to be somewhat endergonic to the extent of about 10 kcal. It could thus be part of the primary photo-chemical transformation.

Experimental

Part I. Apparatus and Materials

The Beckman Spectrophotometer.—The basic unit about which the apparatus was built was a Beckman Quartz Spectrophotometer Model DU. Illumination of the sample was always carried out at a slit width of 0.8 mm. and a wave length setting of 6212 Å., under which conditions the width of the spectral segment was about 300 Å. Absorption measurements which must be run with spectral segments of only a few Ångströms were made at slit width settings around 0.02, where the light intensity was only about 1/1600 of that used for illumination. This light intensity was so low that the reaction was virtually stopped, allowing as many absorption readings to be made as desired with no appreciable light reaction occurring.

Light Source.—The light source for the Beckman is 6–8 v. tungsten filament Mazda 2331 automobile headlight, ordinarily operated at 6 volts. In this work it was run at 9.0 volts, for the intensity from such a lamp is about tripled when the voltage is raised from 6 to 9, thus permitting the use of smaller slit widths and correspondingly narrower spectral ranges for illumination.

Thermostating.—Water from a large reservoir thermostated by conventional means was circulated through a specially designed cell compartment to maintain the temperature within 0.1°. Due to the fact that room temperature was usually below 25°, the benzene in the evacuated cell had the tendency to distil to the upper part of the cell when runs were made at this temperature. To prevent this, the upper part of the cell compartment was heated by a warm stream of air from a heated copper coil (see Fig. 6).

The Reaction Cell.—Figure 6 shows the details of the reaction cell and stirrer. The section in the optical path was constructed from 1-cm. Pyrex square mandrel tubing with one pair of opposite faces ground optically flat. The blank cell for the solvent was a twin to the reaction cell. The reaction cell had to be evacuated in order to exclude oxygen. The solution in the cell had to be stirred since the reaction took place only in the light beam, and thermal diffusion was not fast enough to keep the solution mixed. These two conflicting requirements, evacuation and stirring, were satisfied by the use of an all glass enclosed magnetic stirrer. Since there was no direct mechanical connection between the motor and the reaction cell, this type of stirrer also allowed the blank cell to be placed in the light beam for the balancing of the instrument when taking absorption readings.

---

(6) Aronoff, *Plant Physiol.*, **21**, 393–409 (1946).

(7) Calvin and Dorough, *Science*, **105**, 433 (1947).

(8) Fischer–Orth, "Die Chemie des Pyrroles," Vol. II, Akademische Verlagesellschaft (1937).

Filter Slide.—In addition to the very extensive modifications made on the cell compartment of the Beckman, a minor change was made on the filter slide. This slide has three openings which may be placed in front of the light path. For this work, the first opening was left blank, the second was replaced by a wire screen transmitting 38.0% of the light, and the third was filled with a piece of black cardboard. The filter slide was thus capable of use as a shutter, and as a means of varying the light intensity without varying the special composition of the light.

Preparation of Solutions. Zinc Chlorin.—The preparation was carried out in as dim a light as possible. About 2 mg. of free base chlorin was dissolved in 10 cc. of dioxane and boiled for several minutes with solid zinc acetate. The resulting zinc chlorin was then transferred to benzene, washed and dried, and made up to a volume of 100 cc. This gave a volume of roughly 3×10^{-5} *M*. The exact concentration was determined from the log $1/T$ value of the peak at 6212 Å.

$$C = \frac{\log 1/T}{\epsilon} = \frac{\log 1/T}{5.49 \times 10^4} \quad \text{for a 1 cm. cell}$$

Such solutions were found to be quite stable if stored in the dark and sampled in only the minimum of light.

Preparation of Solutions. β-Naphthoquinone.—Stock aminonaphthol was recrystallized and oxidized by ferric chloride according to "Organic Syntheses."[9] A number of stock benzene solutions were made up with the pure β-naphthoquinone in concentrations varying from 1.89×10^{-5} to 4.72×10^{-3} *M*.

Preparation of Samples for Rate Experiments.—Small aliquots of the order of 1 or 2 cc. of the chlorin and quinone solutions that would give the desired final concentrations were mixed in a small flask. This solution was then used to fill a small delivery cup equipped with an overflow spout. The delivery cup when filled delivered 2.56 cc. of solution, as shown by standardizations with benzene. During the evacuation of the cells, however, a little benzene was usually lost by distillation even though the solutions were frozen during pumping. A correction for this was made by the simple equation

$$V_0 = 2.56\ (C_M/C_O)$$

Where V_0 is corrected volume, C_M is concentration of chlorin when measured into the cell, and C_O is initial value of the chlorin concentration after pumping (determined spectrally). These sampling operations for the reaction mixture were also carried out in the very minimum of light. Solutions for the spectral blank were made with identical quinone concentrations, but without the chlorin.

Evacuation of Samples.—After the sample had been transferred to the reaction cell, the stirrer assembly was attached and the whole unit connected to a vacuum line. The solution was frozen in liquid nitrogen, and the system evacuated. The stopcock on the reaction cell was then closed and the solution thawed out and shaken. The cell was then refrozen, repumped and rethawed in an identical manner. The cell was now filled with hydrogen at nearly atmospheric pressure, and again frozen, pumped and thawed as before. Hydrogen was then twice more admitted. The cell was not thawed the last time; it was taken directly to the Beckman and placed in the thermostated cell compartment.

These operations, too, were carried out in a very minimum of light. As an added precaution, the reaction cell was kept covered by a small "skirt" of black cloth.

Method of Taking Rate Measurements.—After the reaction cell had attained temperature equilibrium, the rate experiments were conducted by illuminating the solution with stirring for intervals of five to fifteen minutes, and recording absorption readings at 6212 Å., 5500 Å., and 4640 Å. before and after each illumination period. The intensity of illumination was determined with a standardized thermopile–galvanometer circuit.

Absorption Spectra.—All absorption spectra were measured on a Beckman Quartz Spectrophotometer Model DU. Points were taken every 50 Å. by even fifties. The curves given represent smooth curves drawn through all points.

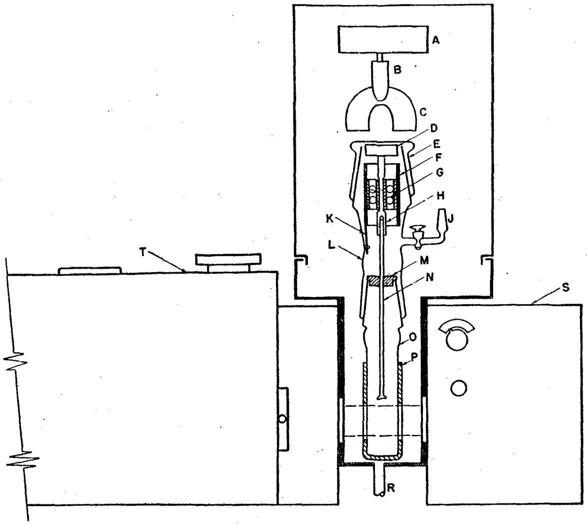


Fig. 6.—Reaction cell and stirrer assembly: A, motor; B, chuck; C, magnet; D, iron bar; E, 29/42 standard taper joint; F, brass column; G, double row ball bearing; H, chuck for stirrer; J, 10/30 standard taper inner joint; K, spring clip to hold column (F); L, Pyrex glass to standard taper 19/38 joint; M, brass bearing; N, glass stirrer; O, Pyrex cell (1 cm. square mandrel tubing); P, cell holder; R, thermostated water inlet; S, photocell compartment of Beckman; T, monochromator case of Beckman.

Phosphorescent Spectra.—The methods and apparatus used to determine spectra were identical to those described by Lewis and Kasha[4]; in fact, it was the same apparatus. The lifetime of the phosphorescences were measured on a photo-electric phosphoroscope.[10] Light from the phosphorescing sample is allowed to impinge on an infrared sensitive photo-multiplier tube, the signal from which is imposed on the vertical plates of an oscillograph. From the resulting decay curve trace and a knowledge of the sweep time, the life time can be calculated.

Part 2. Calculations

Determination of Concentrations During a Run.—In any region of light absorption where the absorption is due to only chlorin and porphin, Beer's law may be used to derive an expression for the chlorin concentration (for a 1.0-cm. cell)

$$C_c = \frac{\log 1/T - \epsilon_p C_T}{\epsilon_c - \epsilon_p}$$

where C_c is the concentration of the chlorin in moles/l, C_T is the total concentration of pigment, $C_c + C_p$; T is the fraction of light transmitted; and ϵ_p and ϵ_c are the molar absorption coefficients for phorphin and chlorin. Two wave lengths could be used

$$\text{at 6212 Å.} \quad C_c = \frac{\log 1/T(\text{obs.}) - 180C_T}{54700}$$

$$\text{at 5500 Å.} \quad C_c = \frac{22200C_T - \log 1/T\ (\text{obs.})}{16{,}300}$$

---

[9] "Org. Syntheses," Vol. XVII, p. 11, paragraph 1, p. 68.

[10] D. M. McClure, to be published.

Since the porphin has practically no absorption at 6212 Å., this wave length was used in most of the calculations. The values from measurements at 5500 Å. were used only for an occasional check.

Determination of Quantum Yield.—From the previously derived rate law (equation 10) it is seen that the quantum yield is easily calculated from the slope of the straight line obtained by plotting the left side of the equation against time

$$\gamma = \text{slope}/K_a I_0 \qquad (11)$$

Now K_a is merely a unit conversion factor, being equal to the reciprocal of the product of Avogadro's number and the volume of the solution in liters. The quantity I_0 is derived from the intensity of the light leaving the Beckman as measured by a standardized thermopile–galvanometer unit (sensitivity of 91.3×10^{-6} watt/sq. cm./cm. of deflection), the area of the light beam at the point of measurement (1.77 sq. cm.), the magnitude of the correction for the amount of light reflected, scattered, and absorbed before reaching the solution (1.6%), and the assumption that the average energy of the photons of the illuminating beam were that of a 6212 Å. photon. Substituting these quantities into equation (11)

$$\gamma = 2.0 \times 10^4 \times \frac{\text{slope} \times V}{D} \qquad (12)$$

V is the volume of the solution in ml., and D is the galvanometer deflection in cm.

It may seem curious that the final rate law should be used for the calculation of the quantum yield, since the quantum yield is an obvious factor in the determination of the rate law. As it turns out, however, the form of the rate law of equation (10) is rather general in character, and will be given by a number of other mechanisms, as well as the one from which it was derived here. In these other cases, however, the quantum yield would be a function of the quinone concentration such that the slope of the line represented by the equation would vary with the quinone. The fact that it does not tells us that these mechanisms are incorrect, but the fact that the equation gives a straight line plot indicates the form of the equation is right, and that we can use the simple equation (12) for calculating quantum yield rather than the more involved and laborious direct calculation which makes no assumption as to mechanism. Comparison of the two methods for a number of runs gave exactly identical results.

Part 3. Experimental Results

Effect of Oxygen and Quinone Concentration.—The first runs that were made (see Table I) were not swept out with hydrogen as is described in the section on the evacuation of samples, but were merely alternately pumped and thawed three times. Now all of these runs individually gave good straight line plots for the function $(C_{Zn}) + (\log Z/\Sigma d)$ against time, and all of the runs showed no trace of an oxygen reaction (no increase in absorption at 4640 Å.). But it is evident from the table that the runs reproduce each other very poorly, and that the rather large variation in quinone concentration has had little effect on the rate (quantum yield). In fact, the data seemed to indicate that the reaction was independent of the quinone concentration, with the quantum yields grouping around 0.015. If one assumed that this were so, then the variance among the different runs might be accounted for by an inhibition of the reaction by oxygen, since the oxygen content of the solutions is the only thing which might logically vary from one run to another. This hypothesis was tested by reducing the oxygen content of the solutions to a very low level, and noting whether or not the rate of the reaction increased. Control experiments were first made to get some sort of measure of the amount of oxygen in the solutions. Table II shows the results of two blank runs which were made in every respect like other runs except that the quinone was left out. Thus the only thing that could occur was the oxygen reaction. Experiment 8 was pumped in a manner identical to those experiments listed in Table I; experiment 9 was swept with hydrogen as described in the section on the evacuation of the reaction cell. Whereas experiment 8 showed a percentage change in the 6212 Å. band of 12.5% in thirty minutes, experiment 9 showed only a change of 13.3% in 105 minutes.

TABLE I

RUNS NOT SWEPT WITH HYDROGEN

Temperature, 25°; chlorine concn. $\cong 10^{-5} M$

Run	Concn. of quinone, M	Quantum yield
1	3.15×10^{-4}	0.019
2	3.15×10^{-4}	.015
3	9.44×10^{-4}	.012
4	9.44×10^{-4}	.010
5	9.44×10^{-4}	.016
6	3.15×10^{-3}	016
7	3.15×10^{-3}	.014

TABLE II

EFFECT OF HYDROGEN SWEEPING

Time, min.	log 1/T 6212 Å.	log 1/T 4640 Å.	% change 6212 Å.
Run 8. No hydrogen sweeping			
0	0.865	0.050	
5	.840	.063	2.9
10	.820	.078	5.2
20	.785	.103	9.2
30	.757	.121	12.5
Run 9. With hydrogen sweeping			
0	0.905	0.050	
10	.880	.068	2.7
35	.855	.090	5.5
60	.830	.106	8.3
105	.785	.136	13.3

Knowing now that the oxygen content could be reduced by sweeping with hydrogen, a new series of experiments were conducted with hydrogen sweeping incorporated into the procedure. Table III summarizes the results of these experiments. It is seen that the reduction in the amount of oxygen has indeed caused a marked increase in the quantum yield, and that over a very wide range in concentration of quinone, the quantum yield remains virtually constant. Undoubtedly these values do not represent the limiting value of the quantum yield, since a trace of oxygen is still present, but they are probably quite close to it.

TABLE III

RUNS SWEPT WITH HYDROGEN AT 25°

Run	Concentration of chlorin, M	Concentration of quinone, M	Quantum yield
10	1.10×10^{-5}	6.65×10^{-6}	0.0204
11	1.2×10^{-5}	1.81×10^{-5}	.0191
12	1.12×10^{-5}	3.99×10^{-4}	.0219
13	1.08×10^{-5}	1.63×10^{-3}	.0215

Run 10 is an extremely interesting one, for the quinone is present in smaller amounts than the chlorin. Yet the rate remained at the same high level until the quinone had fallen to only 1.8×10^{-6} M, and even at that low concentration the rate broke only slightly (see Fig. 7). It was not until the quinone was nearly gone that a reaction with the trace of oxygen present began to occur.

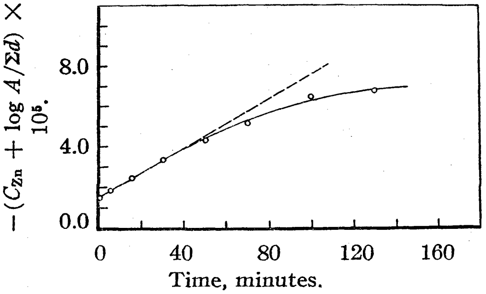


Fig. 7.—Run 10, slope: 5.97×10^{-7}.

Quinone–Chlorin Complex Formation.—An attempt was made to observe complex formation between zinc chlorin and β-naphthoquinone. This was done by running the spectrum of the zinc chlorin in the presence and absence of quinone. Absolutely no deviation was found in the two spectra in the region 6500 to 3000 Å., thus indicating that such complex formation does not exist.

Effect of Temperature.—The effect of temperature was studied by lowering the constant temperature bath from 25 to 10°. The results of two such runs are summarized in Table IV. Although the agreement between the runs is not exceptional, there is no doubt that the rather remarkable result of increasing rate with decreasing temperature has been found.

TABLE IV

RUNS SWEPT WITH HYDROGEN

Temperature, 10°; chlorin concn. $\cong 10^{-5}M$

Run	Quinone concn., M	Quantum yield
14	3.36×10^{-4}	0.0254
15	1.67×10^{-3}	0.0224

Effect of Light Intensity, Run 16.—The variation of the rate with light intensity was measured by the use of the screen described in the section on the filter slide. This screen transmitted 38.0% of light hitting it. A run was started with the screen in the light path, and then about half way through the run, the screen was removed and the run continued. The ratio of the slope of the rate curve for the second part of the run to the first part (see Fig. 8) was 2.65. The ratio of the light intensities for the second part of the run to the first part is

$$\frac{(I_0)_2}{(I_0)_1} = \frac{1}{0.38} = 2.63$$

Thus, the rate is proportional to the light intensity.

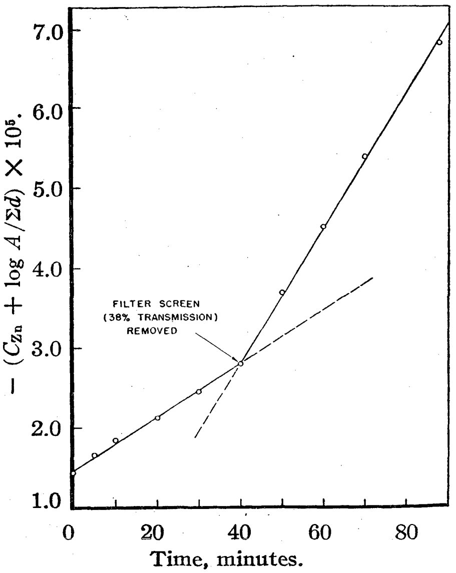


Fig. 8.—Run 16, slopes: 0–40 minutes, 3.2×10^{-7}; 40–88 minutes, 8.52×10^{-7}.

TABLE V

RUN 16

Corrected volume (V)	2.36 ml.
Quinone concn., M	3.42×10^{-4}
Temperature, °C.	10
Av. galv. defl. (D)	1.49 cm.

Time	Experimental log $1/T$ 6212 Å.	5500 Å.	4640 Å.	Chlorin concn., 6212 M	A	Calculated (C_{Zn}) + $(\log A/d)$
38% screen filter in						
0	0.632	0.078	0.025	1.15×10^{-5}	0.365	-1.43×10^{-5}
5	.590	.085	.028	1.07×10^{-5}	.342	-1.67×10^{-5}
10	.562	.095	.029	1.02×10^{-5}	.328	-1.83×10^{-5}
20	.508	.109	.028	0.925×10^{-5}	.303	-2.12×10^{-5}
30	.457	.123	.027	0.832×10^{-5}	.278	-2.44×10^{-5}
40	.404	.137	.027	0.735×10^{-5}	.251	-2.75×10^{-5}
38% screen filter out						
50	0.298	0.168	0.027	0.542×10^{-5}	0.291	-3.69×10^{-5}
60	.222	.188	.025	$.440 \times 10^{-5}$	.146	-4.52×10^{-5}
70	.162	.206	.025	$.295 \times 10^{-5}$	.108	-5.39×10^{-5}
88	.094	.223	.025	$.171 \times 10^{-5}$	.065	-6.80×10^{-5}

Details of Rate Data.—Complete experimental and calculated data for all the completed runs would consume far too much space to serve any useful purpose. To make completely clear our methods, however, Table V has been prepared summarizing the calculations for run number 16 (see also Fig. 8). The data of all completed runs were entirely consistent.

Acknowledgment.—The authors wish to acknowledge the many helpful suggestions and assistance of Prof. G. K. Rollefson, Drs. M. Kasha and R. V. Nauman, and Messrs. F. M. Huennekens and D. M. McClure. The junior author also wishes to express his appreciation for the assistance of the National Research Council.

Summary

1. The photochemical oxidation of a simple chlorin molecule to the corresponding porphin by oxygen and a number of ortho and para quinones is described.

2. From evidence based on rate experiments, a mechanism for the photochemical oxidation of tetraphenyl chlorin by β-naphthoquinone is derived involving the triplet state of the chlorin molecule as an intermediate.

3. A possible significance of the triple state of chlorophyll is indicated.

BERKELEY, CALIFORNIA RECEIVED JULY 8, 1947

[CONTRIBUTION FROM THE METCALF RESEARCH LABORATORY OF BROWN UNIVERSITY]

Properties of Electrolytic Solutions. XXXI. Conductance of Some Electrolytes in Pyridine at 25°[1]

BY DAVID S. BURGESS[2] AND CHARLES A. KRAUS

I. Introduction

In the last paper of this series,[3] it was shown that various quaternary onium salts are normal electrolytes in pyridine. Silver picrate and perchlorate, however, proved to have much larger dissociation constants than was to have been expected. Certain unreported results for sodium and potassium salts were erratic, indicating sources of error that had not been brought under control.

In view of these circumstances a comprehensive study of solutions in pyridine seemed worth-while.

It was suspected that inconsistencies in the results obtained with the alkali metal salts may have been due to the presence of small amounts of alcohol even though the conductance of the solvent was very low. On treating the pyridine with aluminum chloride, solvent was obtained that yielded consistent results with all salts. The marked effect of alcohol and, perhaps, other impurities that were eliminated by aluminum chloride, led to a study of the effect of the addition of small polar molecules, such as water, ammonia and methanol, on the characteristic constants of electrolytes dissolved in pyridine.

An investigation was made of several lithium, sodium and potassium salts and, in view of the unusual behavior of silver salts, silver picrate was included among the salts studied.

Certain quaternary ammonium salts which have been investigated in ethylene chloride and nitrobenzene, were measured for purposes of comparison. These salts were: tetra-*n*-butylammonium nitrate and acetate, tetramethylammonium picrate, ethyltrimethyl-, hydroxyethyltrimethyl-, bromoethyltrimethyl-, bromomethyltrimethyl-, and phenyldimethylhydroxy-ammonium picrate.

Measurements with pyridonium and piperidonium nitrates, as well as with phenylpyridonium picrate, are of obvious interest in view of the strong proton affinity of the solvent.

Measurements were also carried out with ammonium picrate, iodide and nitrate. The nitrate yielded inconsistent values for the conductance of the ammonium ion; publication of results for this salt is withheld pending further investigation.

In order to evaluate ion conductances, measurements have been made with tetrabutylammonium triphenylborofluoride and a value for the conductance of the tetrabutylammonium ion has thus been obtained according to Fowler's[4] method.

II. Experimental

Materials.—Pyridine prepared by the method of Luder[3] failed to yield consistent results; the procedure was, accordingly, modified so as to provide for elimination of residual traces of alcohol. This was accomplished by distillation from aluminum chloride. The distillate was then fractionally distilled, refluxed over aluminum oxide and finally fractionated. Pyridine obtained in this manner had a specific conductance below 1×10^{-9} and reproducible conductance values were obtained with salts which had previously yielded inconsistent results.

Methanol was refluxed over aluminum amalgam and finally distilled. Its specific conductance was 5×10^{-8}; a 0.275 *M*, solution in pyridine showed a specific conductance of 2×10^{-9}.

Ammonia was dried by distillation from sodium amide. A 0.0733 *M* solution of ammonia in pyridine had a specific conductance of 6×10^{-9}.

---

[1] This paper is based on a portion of a thesis presented by David S. Burgess in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in the Graduate School of Brown University, May, 1940.

[2] University Fellow at Brown University, 1938–1939; Metcalf Fellow, 1939–1940. Present address: 1106 N. College Ave., Fayetteville, Arkansas.

[3] Luder and Kraus, THIS JOURNAL, **69**, 2481 (1947).

[4] Fowler and Kraus, *ibid.*, **62**, 2237 (1940).

Sodium and potassium iodides of reagent grade were recrystallized from water and from alcohol.

Lithium, sodium and potassium picrates were prepared from the corresponding bases and recrystallized picric acid. Potassium picrate was recrystallized from water and from ethyl alcohol. The sodium salt was recrystallized from water and from methyl alcohol. It was necessary to heat this salt to 85° in a vacuum before a constant weight was obtained. Lithium picrate was recrystallized from pure ethanol and was dried in the same manner as the sodium salt.

Tetrabutylammonium nitrate was prepared by the method described by Cox,[5] m. p. 118°.

Tetrabutylammonium acetate was prepared by the metathesis of the pure iodide with recrystallized silver acetate in aqueous solution. The solution was filtered off from the silver iodide, concentrated, and pumped to dryness. The residue was dissolved in benzene, the solution filtered and the filtrate pumped to dryness. The salt residue was kept over phosphorus pentoxide in an evacuated tube for several weeks and then used directly in a series of measurements; m. p. 118°. Another sample of the acetate which had been recrystallized from butyl chloride was furnished by Dr. W. E. Thompson.[6]

Pyridinium nitrate was recrystallized from alcohol; m. p. 117.5–118°. Piperidonium nitrate was recrystallized from ethanol–benzene mixtures and was precipitated from ethylene chloride with anhydrous ethyl acetate. It decomposed without melting at 100°.

Phenylpyridonium chloride was prepared by the method of Zincke[7]; m. p. 106°. Metathesis of this salt with silver picrate in alcohol solution yielded phenylpyridonium picrate. This salt was recrystallized from alcohol; m. p 121–122°. An analysis for nitrogen, using catalytic hydrogenation at 350°, gave nitrogen 14.3%; calculated 14.6%.

The remaining salts had been prepared and purified in this laboratory. All were subjected to a final recrystallization from alcohol before use in conductance measurements.

Apparatus and Procedure.—Except for a few details, these were the same as described in earlier papers of this series. Buoyancy corrections (of about 0.1%) were applied in calculating the concentration of solutions of heavier salts.

Ammonia was introduced into the pyridine by attaching the pyridine reservoir (by means of a flexible tube) to a four-liter flask containing air and ammonia in proper proportions at atmospheric pressure. The partial pressure of ammonia was maintained equal to that at which the pyridine was to be saturated. As the ammonia was absorbed by the pyridine, more ammonia was admitted from the tank of purified ammonia, keeping the total pressure in the system constant. The ammoniated pyridine was forced into the conductance cell each time by means of a pressure of air and ammonia over the liquid in the stock flask, thus avoiding change in the composition of the solvent medium.

In order to minimize vapor corrections when working with ammoniated pyridine, the cell used was of small capacity (about 60 ml.) and the side arm leading to the electrode chamber was wide enough to permit mixing when the liquid level in the cell was high. Only a small free volume was allowed above the solution, and diffusion losses were kept low by having a long, narrow neck fitted to the cell. Water and alcohol were added to pyridine in a 500-ml. flask from a micropipet fitted with a drawnout capillary.

III. Results

The experimental data are summarized in Tables I and II in which are given the equivalent conductance Λ and the concentration C of the solution in moles per liter of solution, whose density was taken to be 0.97792.[8] Data for solutions in pure pyridine are given in Table I, while those for solutions containing added dipolar substances are given in Table II. The result of only one series of measurements is reported for each salt although at least two concordant series were carried out. All measurements were carried out at 25±0.01°.

TABLE I

CONDUCTANCE OF SOME SALTS IN PYRIDINE AT 25°

$C \times 10^5$	Λ	$C \times 10^5$	Λ
a. Lithium picrate		b. Sodium picrate	
75.68	18.59	70.90	15.11
26.16	27.23	33.44	20.07
9.901	35.67	13.70	27.46
6.909	38.92	6.196	34.89
3.457	44.63	3.544	40.20
2.607	46.76	1.626	46.94
1.354	51.79		
c. Potassium picrate		d. Silver picrate	
39.46	28.50	145.94	49.93
16.57	36.89	69.53	54.20
6.355	46.31	32.48	58.11
3.244	52.09	14.83	61.30
1.901	56.40	6.242	63.80
		2.261	65.67
e. Sodium iodide		f. Potassium iodide	
474.7	25.05	62.25	39.79
23.25	53.71	27.38	49.39
11.144	60.45	21.26	52.36
8.656	62.40	10.79	59.96
6.481	64.45	6.564	64.68
4.219	66.99	3.328	70.08
g. Ammonium picrate		h. Ammonium iodide	
56.94	44.34	29.23	59.32
30.41	51.58	13.18	70.03
15.20	59.15	7.296	76.96
5.940	63.56	3.749	83.22
3.894	70.60	1.577	88.75
i. Tetra-*n*-butylammonium nitrate		j. Tetra-*n*-butylammonium acetate	
129.50	37.08	114.0	29.18
53.72	46.15	45.81	28.22
23.52	54.75	20.62	46.85
9.655	62.82	11.15	53.37
3.852	68.82		
k. Tetra-*n*-butylammonium triphenylborofluoride		l. Phenylpyridonium picrate	
86.73	33.13	121.94	43.32
32.95	37.94	58.16	48.80
18.92	40.34	32.18	52.86
9.774	42.62	15.10	57.08
5.161	44.33	7.042	60.35
		3.117	62.69

---

(5) Cox, Kraus and Fuoss, *Trans. Faraday Soc.*, **31**, 749 (1935).

(6) Thompson and Kraus, THIS JOURNAL, **69**, 1018 (1947).

(7) Zincke, *Ann.*, **333**, 328 (1904).

(8) Walden, Audrieth and Birr, *Z. physik. Chem.*, **160A**, 337 (1932).

TABLE I (*Concluded*)

$C \times 10^5$	Λ	$C \times 10^5$	Λ
m. Tetramethylammonium picrate		n. Ethyltrimethylammonium picrate	
37.37	56.63	133.7	45.22
15.48	63.72	67.62	51.54
8.345	67.66	32.62	57.91
7.754	68.00	17.14	62.75
5.517	69.80	7.215	67.81
2.822	72.18	3.472	71.03
1.915	73.15		
o. Hydroxyethyltrimethylammonium picrate		p. Bromoethyltrimethylammonium picrate	
62.54	47.19	275.6	32.15
29.07	52.83	128.0	38.43
13.92	57.35	67.65	43.47
7.278	60.35	29.78	49.85
2.552	63.68	13.46	55.32
		6.483	59.39
		3.412	62.39
q. Bromomethyltrimethylammonium picrate		r. Phenyldimethylhydroxyammonium picrate	
37.41	49.15	133.9	40.36
19.55	54.85	64.15	45.58
8.643	60.75	27.51	50.73
3.547	65.41	11.58	55.06
1.944	67.69	6.985	57.44
		3.821	60.48
s. Pyridonium nitrate		t. Piperidonium nitrate	
21.66	42.50	16.92	27.36
10.28	53.82	7.923	36.40
4.109	68.48	4.101	45.50
2.348	76.79	1.736	58.16
1.863	79.79		

TABLE II

CONDUCTANCE OF SALTS IN PYRIDINE IN THE PRESENCE OF ADDED POLAR SUBSTANCES

$C \times 10^5$	Λ	$C \times 10^5$	Λ
a. Tetrabutylammonium picrate (0.0733 *M* ammonia)		b. Tetrabutylammonium picrate (0.146 *M* ammonia)	
59.06	42.48	72.73	41.40
32.69	46.04	55.06	43.26
16.61	49.52	33.78	46.26
8.204	52.36	15.22	50.38
5.547	53.58	8.615	52.66
c. Potassium picrate (0.275 *M* methanol)		d. Sodium picrate (0.0070 *M* water)	
116.4	22.82	65.94	16.27
64.36	27.70	25.15	23.19
24.50	36.81	10.90	30.55
9.605	46.09	6.105	36.15
4.890	52.69	4.258	39.55
		3.164	42.28
		1.931	46.49
e. Sodium picrate (0.733 *M* ammonia)			
157.2	19.82		
73.82	27.27		
29.80	36.50		
13.86	48.10		
8.543	52.71		

IV. Discussion

A. Solutions in Pure Pyridine.—The experimental data have been analyzed by the method of Fuoss[9] so as to obtain values for the limiting conductance and dissociation constant of the electrolytes under consideration. The dielectric constant and viscosity of pyridine were taken as 12.01[10] and 0.008824.[8] Plots were made of F/Λ against $C\Lambda f^2/F$ and values of Λ_0 and K were determined therefrom. These values are given in Table III and plots for some of the salts are shown in Fig. 1. All plots are linear at low concentrations but deviations become apparent a little below the critical concentration, 5×10^{-4}. The strongest electrolytes deviate toward too high a conductance and weaker electrolytes toward too low a conductance.

TABLE III

CONSTANTS FOR SOME SALTS IN PYRIDINE AT 25°

Salt	Λ_0	Λ_0^+	Λ_0^-	$K \times 10^4$
$(C_4H_9)_4NFB(C_6H_5)_3$	48.0	(24.0)	(24.0)	13.2
$(C_4H_9)_4NNO_3$	76.6	..	52.6	3.7
$(C_4H_9)_4NCH_3COO$	76	..	52	1.7
$(CH_3)_4NPi$	76.7	43.0	(33.7)[3]	6.7
$(C_2H_5)(CH_3)_3NPi$	75.5	41.8	..	8.2
$(HOC_2H_4)(CH_3)_3NPi$	67.0	33.3	..	1.5
$(BrC_2H_4)(CH_3)_3NPi$	67.1	33.4	..	5.8
$(BrCH_2)(CH_3)_3NPi$	71.5	37.8	..	4.8
$C_5H_5N(C_6H_5)Pi$	66.3	32.6	..	11.5
$(C_6H_5)(CH_3)_2(OH)NPi$	62.3	28.6	..	12.3
$C_5H_5NHNO_3$	102.2	49.6	..	0.51
$C_5H_{10}NH_2NO_3$	91.1	38.5	..	0.18
$AgNO_3$	86.9[3]	34.3	..	9.3
AgPi	68.0	34.3	..	30.6
LiPi	58.6	24.9	..	0.83
NaPi	60.5	26.8	..	0.43
KPi	65.7	32.0	..	1.0
NH_4Pi	80.5	46.8	..	2.8
NaI	75.2	..	48.4	3.7
KI	80.4	..	48.4	2.1
NH_4I	95.2	..	48.4	2.4

Ion Conductances.—In order to obtain the ion conductances given in columns three and four of Table III, we have assumed, as did Fowler[4] for ethylene chloride, that the conductance of the tetrabutylammonium ion is equal to that of the triphenylborofluoride ion. This gives a value of 24.0 for the conductance of the tetrabutylammonium ion. Using Luder's value for the limiting conductance of tetrabutylammonium picrate,[3] we arrive at a value of 33.7 for the conductance of the picrate ion. The remaining ion conductances are easily evaluated on the basis of these values. It may be noted here that tetrabutylammonium picrate has been reinvestigated and no appreciable error has been found in Luder's data, although traces of alcohol may have been present in his pyridine.

---

(9) Fuoss, THIS JOURNAL, **57**, 488 (1935).

(10) Le Fèvre, *J. Chem. Soc.*, 776 (1935).

Several salt pairs permit intercomparison of ion conductance as derived from different combinations. Thus the conductance of the silver ion, as derived from its picrate, is 34.3; from Luder's value for the conductance of silver nitrate, the same value is obtained for the silver ion. Evaluating the conductance of the sodium, potassium and ammonium ions from the conductance of their picrates, the conductance of the iodide ion may be found from the conductance of the corresponding iodides. The value found is 48.4 for the three salts. This value is not in agreement with Luder's value of 49.1 as found from the conductance of tetrabutylammonium iodide.

The conductance of the simpler negative ions is markedly greater than that of corresponding positive ions. For the perchlorate and bromide ions Luder found conductance values of 47.6 and 51.3, respectively; for the nitrate ion, we have found the value 52.6. In contrast, the conductance of the tetramethylammonium ion is only 43.0, while that of the ammonium ion is 46.8.

The conductance of the pyridonium ion is 49.6, the highest for any cation thus far measured. It seems not unlikely that this high value, considering the size of the ion, is due to proton transfer from one solvent molecule to another, as with the the hydrogen ion in water.

The conductance of the alkali metal ions decreases markedly with decreasing dimensions of the unsolvated ion. Thus, the conductance of the lithium ion is little greater than that of the tetrabutylammonium ion. Obviously, there is strong interaction between the free ion and the solvent molecules as a result of which the mobility of the ion is greatly reduced. There is evidence (to be presented in another paper) that small negative ions likewise have a low conductance. The sodium and potassium ions, also, have low conductances. It will be noted that the conductance of the silver ion is greater than that of the potassium ion.

The introduction of negative elements or groups into the cation results in a marked decrease of conductance. Thus, the conductance of the ethyltrimethylammonium ion is 41.8 while that of the bromomethyltrimethylammonium ion is 37.8 and that of the bromoethyltrimethylammonium ion is 33.4. These effects are significant and indicate increased interaction with the solvent molecules as a result of the presence of the negative atoms or groups in the cations. The conductance of the phenyldimethylhydroxyammonium ion is lower than that of the phenylpyridonium ion. There is reason for believing that the hydrogen of the hydroxyl group interacts strongly with the basic pyridine molecules.

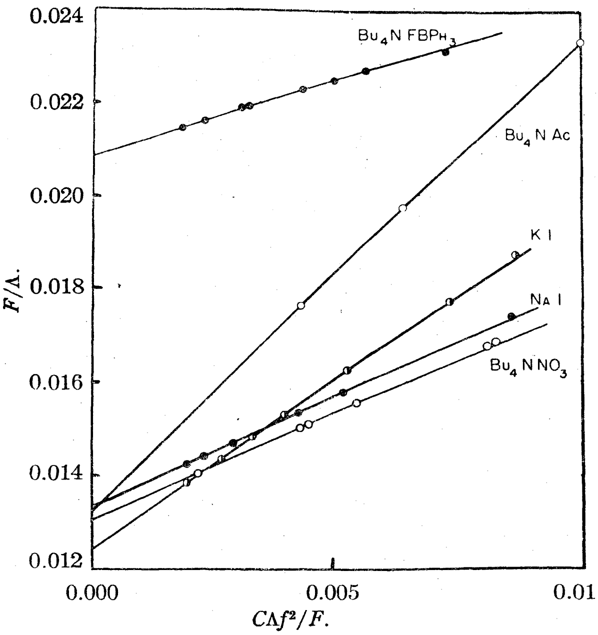


Fig. 1.—Fuoss plots for salts in pyridine at 25°.

Dissociation Constants.—The value of the dissociation constants of normal quaternary ammonium salts are such as might be expected for a solvent whose dielectric constant is 12. It is to be noted, however, that the dissociation constant does not change greatly with increasing dimension of the quaternary ammonium ion. Thus, the constant for tetrabutylammonium picrate[3] is only twice that of tetramethylammonium picrate. The constants of tetrabutylammonium salts of different negative ions follow the order of ion dimensions fairly well, the constants following the order $I^- > NO_3^- > Br^- > Ac^-$. The low value of the constant for the acetate is noteworthy.

The introduction of negative atoms or groups into the quaternary cation structure has a marked effect on the dissociation constant. Substitution of the hydroxyl group in the ethyl group of the ethyltrimethylammonium ion decreases the dissociation constant of the picrate fivefold, while introduction of a bromine atom decreases the constant 25%. Bromomethyltrimethylammonium picrate is a markedly weaker salt than tetramethylammonium picrate. Negative atoms or groups in the positive ions intensify the interaction of such ions with negative ions.

The dissociation constant of an electrolyte is determined by the distance of closest approach of the ions in the ion-pairs. We should, therefore, expect salts of larger ions to have larger dissociation constants, which ions should also have lower conductances. This simple relation usually fails in most solvents that are not of the hydroxylic type. Due to interaction with solvent molecules, ions may have a low conductance, but in their interaction with oppositely charged ions these molecules are not retained in the ion-pairs. This is well illustrated by the salts of lithium, sodium and potassium. The tetramethylammonium ion has a conductance of 43.0, and its picrate has a dissociation constant of 6.7×10^{-4}. On the other hand, lithium, sodium, and potassium ions have conductances of 24.9, 26.8 and 32.0, respectively, while their dissociation constants are, respectively, 0.83×10^{-4}, 0.43×10^{-4} and 1.0×10^{-4}. The picrate of the ammonium ion, whose conductance is 46.8, has a constant of 2.8×10^{-4}. In the case of sodium and potassium iodides, the constants increase in the order of decreasing ion conductance. It is of interest to point out that the dissociation constant of tetrabutylammonium iodide is 4.1×10^{-4}, only one-fourth that of the picrate (12.8×10^{-4})[3]. In the iodide, the sodium ion behaves like a large ion having a constant of 3.3×10^{-4}, but little smaller than that of the tetrabutylammonium salt. It will be recalled that the conductance of the two cations is 26.9 and 24.0, respectively.

An interesting case is that of the phenyldimethylhydroxyammonium ion, whose conductance is 28.6. The dissociation constant of the picrate of this ion is 12.3×10^{-4}, practically the same as that of tetrabutylammonium picrate. The hydrogen of the hydroxyl group evidently interacts strongly with the basic pyridine molecules and these molecules must be, in large measure, retained in the ion-pairs. However we may interpret the result, this ion in its interaction with other ions is effectively nearly as large as the tetrabutylammonium ion.

Pyridonium nitrate is a weak salt with a constant of 0.5×10^{-4}; piperidonium nitrate is an even weaker salt with a constant of 0.18×10^{-4}. Apparently, the additional hydrogen atom attached to nitrogen in the latter cation leads to interaction with the negative ion to yield the lower constant. It is of interest to note that phenylpyridonium picrate has a constant of 11.5×10^{-4} which is practically the same as that of tetrabutylammonium picrate. The geometrical configuration of an ion is an important factor in determining the properties of its salts.

An unexpected and exceptional result of this and the preceding investigation[3] is the high value of the dissociation constant for silver salts. For the nitrate, perchlorate and picrate, the constants are, respectively, 9.3×10^{-4}, 19.1×10^{-4} and 30.6×10^{-4}. Considering that the conductance of the silver ion is 34.4, which corresponds to that of only a moderately large ion, it is surprising to find a constant for silver picrate more than twice that of tetrabutylammonium picrate. If the distance between centers of charge in the ion-pairs is calculated according to the method of Fuoss,[11] the values "*a*" for the above mentioned silver salts are 6.6 Å., 10.6 Å. and 13.2 Å., respectively. The silver ion is exceptional in its interaction with other ions.

B. Solutions Containing Added Polar Molecules.—The results presented in Table II for solutions containing ammonia, water and methanol in small amount have been analyzed by the usual graphical method. Values of Λ_0 and of K for several salts are given in Table IV.

TABLE IV

EFFECT OF ADDED POLAR MOLECULES ON THE CONDUCTANCE OF SALTS IN PYRIDINE

Salt	Concn. added compound	Λ_0	$\Delta\Lambda_0$	$K \times 10^4$
$(C_4H_9)_4NPi$	0.000	57.68	..	12.2
	.073 NH_3	58.12	0.44	12.2
	.146 NH_3	58.58	.90	12.2
NaPi	0.000	60.5	..	0.44
	.007 H_2O	60.5	0.0	.49
KPi	0.000	65.27	..	1.00
	0.275 CH_3OH	64.10	−1.17	1.32
NaPi	0.000	59.98	..	0.44
	.733 NH_3	80	20	.66

As may be seen from the table, the addition of ammonia to a solution of tetrabutylammonium picrate in pyridine causes a small increase in the value of Λ_0 while the dissociation constant remains unchanged. The addition of 0.007 *M* of water to a solution of sodium picrate causes a 10% increase in the dissociation constant while the limiting conductance remains unchanged. The addition of 0.275 *M* methanol to a solution of potassium picrate increases the dissociation constant 32% while it decreases the limiting conductance 1.8%.

A striking result was obtained on the addition of ammonia to a solution of sodium picrate. For an ammonia concentration of 0.733 *M*, the conductance was increased approximately 20 units, or 33%. Since ammonia has but little influence on the conductance of the picrate ion, as shown by the results with tetrabutylammonium picrate, the observed conductance increase of sodium picrate must be due to an increase of approximately 50% in the conductance of the sodium ion.

While the present measurements are preliminary, there is no question as to their authenticity. Subsequent investigations, the results of which will be reported later, have confirmed the present results and have disclosed similar effects for other salts.[12] A comparison of conductance values in Table I, b, and Table II, e, will show that the conductance of sodium picrate in the presence of ammonia is much higher than it is in pure pyridine at all concentrations. This is due to the fact that while the dissociation constant of sodium picrate is not increased greatly (50%) on addition of ammonia, the conductance of the sodium ion is greatly increased. The low conductance of the sodium ion in pyridine is due to its interaction with pyridine molecules; more than one pyridine molecule must be associated with the sodium ion in order to account for its low conductance. The replacement of pyridine by smaller ammonia molecules results in a smaller ion of higher conductance. In the ion-pair equilibrium, however, the ammoniated ion is effectively somewhat larger than is the normal sodium ion in pure pyridine.

---

(11) Fuoss and Kraus, THIS JOURNAL, **55**, 1019 (1933).

(12) C. J. Carignan, unpublished observations in this Laboratory.

V. Summary

1. The conductance of the following salts has been measured in pyridine at 25°: tetrabutylammonium nitrate, acetate and triphenylborofluoride; tetramethylammonium, ethyltrimethylammonium, hydroxyethyltrimethylammonium, bromoethyltrimethylammonium, bromomethyltrimethylammonium, phenyldimethylhydroxyammonium, ammonium, lithium, sodium, potassium and silver picrate; ammonium, sodium and potassium iodide; and pyridonium and piperidonium nitrate.

2. The conductance has also been determined for solutions of tetrabutylammonium picrate in the presence of ammonia; sodium picrate in the presence of ammonia and of water and potassium picrate in the presence of methanol.

3. The experimental results have been analyzed by the usual graphical methods and values of Λ_0 and of the dissociation constant K have been obtained for all the systems investigated. Ion conductances have been evaluated by the method of Fowler.

4. The effect of various interactions on ion conductances and dissociation constants are discussed.

5. It has been shown that the addition of polar molecules to the solvent medium usually causes little change in ion conductance of salts having large ions. With salts of smaller ions, the dissociation constant is often increased. In the case of sodium picrate, the addition of ammonia causes a very large change in Λ_0, up to as much as 33%, with only a small increase in the dissociation constant.

PROVIDENCE, R. I. RECEIVED JUNE 20, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Thallous Sulfoxylate Isomerism[1]

BY J. FENTRESS AND P. W. SELWOOD

The fact that thallous sulfide, Tl_2S, is easily oxidized when exposed to air was first pointed out by Lamy.[1a] At that time it was postulated that the final product of this oxidation was thallous sulfate, Tl_2SO_4. More recent investigation of the oxidation by Iskoldsky[2] has served to confirm much of Lamy's work. It is found that at 720° in air, thallous sulfide is oxidized 90% to thallous sulfate in two and a half hours. Further, the oxidation of the sulfide proceeds step-wise with the intermediate compounds, Tl_2SO_2 and Tl_2SO_3, being identified. Although one might expect to find a compound with the formula Tl_2SO, Iskoldsky was unable to prepare such a compound.

With Case's[3] discovery of the photo-sensitivity of oxidized thallous sulfide, and the more recent improvements on "Thalofide" photo-cells by Cashman[4] and several others,[5–9] new interest has developed in the actual oxidation of thallous sulfide, and the products formed.

The percentage of oxygen in various photosensitive cells[10] varies up to as much as a nearly 1:1 mole ratio of $Tl_2:O_2$, corresponding to the formula Tl_2SO_2. Thus, our interest in thallous sulfide oxidation products, from the point of view of identifying the composition of the photo-sensitive material, only extends as far as Tl_2SO_2 and is not concerned with the complete oxidation to thallous sulfate.

This present study is concerned with the two forms of thallous sulfoxylate[11] that we were able to obtain.

Preparation of Thallous Sulfide.—Thallous sulfide may be prepared either by precipitation at ordinary temperatures, or by direct reaction of thallium metal and sulfur at high temperatures. We selected the former method because early experiments indicated that oxidation proceeds more rapidly with thallous sulfide prepared by precipitation methods.

All the thallous sulfide used in our experiments was prepared by precipitation from alkaline thallous sulfate solution. The thallous sulfate starting material was originally 99% pure commercial material, which was purified by three recrystallizations from aqueous solution. This procedure yielded thallous sulfate which when analyzed by the standard chromate method gave results of satisfactorily high purity, *i. e.*, more than 99.9% of the theoretical thallium content.

A dilute solution of thallous sulfate, under nitrogen atmosphere, was made alkaline with ammonium hydroxide and the thallous sulfide precipitated at 50° with hydrogen sulfide in the pre-

---

(1) This investigation was carried under Contract Nobs. 45068, Bureau of Ships, U. S. Navy. Our thanks are due to Dr. R. J. Cashman at whose suggestion this research was undertaken.

(1a) A. Lamy, *Compt. rend.*, **54**, 1255 (1862); **57**, 442 (1863); *Ann. chim. phys.*, [3] **67**, 385 (1862); [4] **5**, 410 (1865); *Bull. soc. chim.*, [2] **11**, 210 (1869).

(2) I. I. Iskoldsky, *Mineralnoje Syrye*, No. 4, 404 (1931).

(3) T. W. Case, *Phys. Rev.*, **15**, 289 (1920).

(4) R. J. Cashman, N. D. R. C. Report No. 16.4–6 (1943).

(5) R. Sewig, *Tech. physik*, **11**, 269 (1930).

(6) W. Leo and C. Mueller, *Physik. Z.*, **36**, 113 (1935).

(7) Q. Majorana and G. Tedesco, *Atti accad. Lincei*, **8**, 9 (1928).

(8) F. Michelssen, *Tech. physik*, **11**, 511 (1930).

(9) A. A. Sivkov, *J. Tech. Phys. U. S. S. R.*, **8**, 11 (1938).

(10) A. von Hippel, F. G. Chesley, H. S. Denmark, P. B. Ulin and E. S. Rittner, *J. Chem. Phys.*, **14**, 355 (1946).

(11) Both of these compounds were prepared in this Laboratory early in 1943. The publication of parts of this paper has been delayed owing to the war.

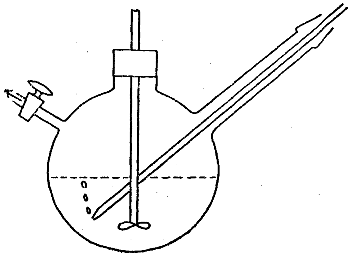


Fig. 1.

cipitation flask (Fig. 1) The filter tube (Fig. 2) was then attached and the thallous sulfide filtered under nitrogen atmosphere. The filter tube was then connected to the sample tube (Fig. 3) which was in place in the vacuum apparatus. While the filter tube was being put in place, a stream of nitrogen was passed through the sample tube to insure that no oxygen was present. The sample tube was evacuated and the sample pumped out until it appeared to be completely dry, two to three days, and then several taps on the side of the filter tube served to dislodge the sample causing it to fall into the sample tube. The sample was evacuated and pumped to a high vacuum, 10^{-3} mm., as measured by a McLeod gage incorporated in the vacuum system. The pumping was continued until the sample was brought to constant weight.

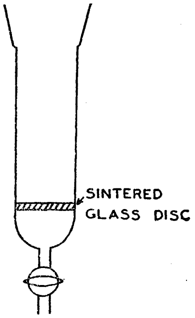


Fig. 2.

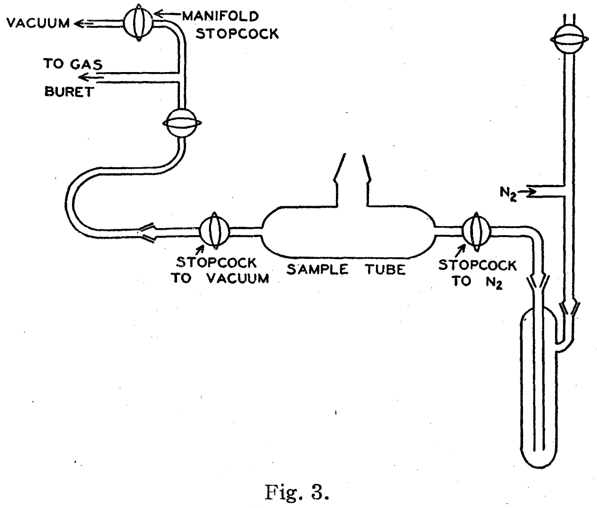


Fig. 3.

In order to carry out an analysis of the thallous sulfide without exposing the sample to the air the sampler (Fig. 4) was attached. The sample was taken by rotating the sample tube 180°, allowing some thallous sulfide to enter the sampler. Then the sample tube was rotated back to its original position leaving a small sample, 0.25–0.50 g., in the sampler. The end of the sampler containing the small sample of thallous sulfide was then sealed off. Once the weight was determined the sealed tube containing the sample was placed in a beaker of sulfuric acid and the tube broken, allowing the thallous sulfide to dissolve. This solution was boiled to remove all the hydrogen sulfide, then made alkaline with ammonium hydroxide, and the thallium determined by precipitation as the chromate. The results of the analyses on a series of thallous sulfide samples gave values from 99.5 to 99.75% pure thallous sulfide. The impurity in these samples was small amounts of water vapor that are not removed by evacuating the sample at room temperature. However, since the reaction between thallous sulfide and oxygen must be catalyzed by water vapor, or some other common catalyst, no attempt was made to remove these last traces of water.

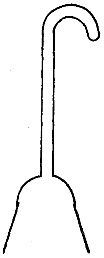


Fig. 4.

Oxidation of Thallous Sulfide.—The bulk of the thallous sulfide which was left in the sample tube was thoroughly pumped out at room temperature and its weight determined. After replacement of the sample tube in the vacuum line the whole system was completely evacuated and the stopcocks to the manifold and nitrogen lines closed. Pure oxygen gas was then introduced into the closed system from a gas buret and the rate at which the oxygen reacted with the thallous sulfide was measured.

In preliminary experiments the oxygen was generated by heating a mixture of potassium chlorate with small amounts of manganese dioxide. Any dust particles of manganese dioxide were filtered out by a sintered glass disc and the gas was stored in a reservoir bulb until it was drawn into the buret. In later experiments the oxygen was generated by direct heating of potassium permanganate. This change in procedure was made because it was felt that small amounts of chlorine gas might be present in the oxygen prepared by the first method.

The nitrogen gas used in these experiments was standard tank nitrogen which was passed over reduced copper at 300°, through soda lime and phosphorus pentoxide before being brought into contact with the thallous sulfide.

The thallous sulfide, with small amounts of water vapor as a catalyst, reacts moderately rapidly with oxygen until a mole ratio of $1:1/Tl_2S:O_2$ is reached. At this point the black thallous sulfide phase has completely disappeared and an olive-brown compound with the formula Tl_2SO_2 is formed. This compound will be designated as *alpha* thallous sulfoxylate, α-Tl_2SO_2. This compound is stable in air at room temperature and thus may be removed from the vacuum system without any decomposition.

The oxidation curves showed no break when a composition corresponding to the formula Tl_2SO was reached, which is in agreement with the observation of Iskoldsky.[2] In order to characterize the *alpha* thallous sulfoxylate the X-ray powder pattern was obtained, and the basic chemistry of the compound was investigated.

Conversion of Alpha Thallous Sulfoxylate to the Beta Form.—Since the *alpha* form of thallous sulfoxylate did not correspond to the greenish yellow compound reported by Iskoldsky,[2] nor to the yellow compound reported by von Hippel[10] as Tl_2SO_2, experiments were undertaken to prepare this yellow form. Since both workers had obtained their compound by oxidation of thallous sulfide at elevated temperatures small samples of the *alpha* form were heated in vacuum in hopes of obtaining the *beta* form. Approximately 1 g. of the *alpha* form in a sample tube was thoroughly evacuated at room temperature. An open-end manometer was included in the system to measure any pressure changes. After the sample was evacuated the stopcock to the vacuum line was closed and the sample was slowly heated in an oil-bath to 250°. In order to get good results the heating must be done slowly and a temperature of 250° must not be exceeded. If the heating is carried out too fast, or if too high a temperature is reached, a grayish powder results which is a mixture of the sulfoxylate with thallous sulfide. If the conversion is carried out as indicated the greenish-yellow form is obtained as a single phase. The small pressure changes noted on the manometer may be satisfactorily explained on the basis of the small amounts of water vapor impurity. This greenish-yellow compound, which also has the formula Tl_2SO_2, will be designated as *beta* thallous sulfoxylate, β-Tl_2SO_2. This compound is also stable in air at room temperatures, and under ordinary conditions shows no tendency to revert back to the *alpha* form. The X-ray powder pattern and basic chemistry of this compound were also investigated.

X-Ray Study of the Two Forms of Thallous Sulfoxylate.—The X-ray patterns of the two forms of thallous sulfoxylate, thallous sulfide and patterns of mixtures of these compounds were taken. These patterns were obtained using the North American Philips Company X-Ray Spectrometer Type No. 12021. In this instrument the conventional camera is replaced by a Geiger counter. A Brown recorder was used in connection with the counting unit to make the machine self-recording. For all the data given a copper target was used, thus all calculations are based on the CuKα line.

A series of patterns of thallous sulfide samples were taken and found to agree closely with the structure of thallous sulfide as proposed by Ketelaar and Gorter.[12] In Fig. 5 a diagram giving the positions and relative intensities of diffraction lines from samples of Tl_2S, α-Tl_2SO_2 and β-Tl_2SO_2 are given. In Table I are given the exact positions of the diffraction lines for *alpha* and *beta* thallous sulfoxylate as determined from the X-ray patterns. Values of d corresponding to measured values of the angle θ are calculated from the expression

$$d = 0.77/\sin\theta$$

for CuKα radiation. It should be noted that the angles given in Table I are equal to 2θ.

TABLE I

X-RAY POWDER DIFFRACTION DATA ON THALLOUS SULFOXYLATE

	Alpha Thallous Sulfoxylate			Beta Thallous Sulfoxylate		
	Line position $2\theta \pm 0.1°$	Rel. int.	d, Å.	Line position $2\theta \pm 0.1°$	Rel. int.	d, Å.
1	19.63	0.1	4.51 ± 0.04	20.50	0.3	4.32 ± 0.04
2	20.75	0.1	4.28 ± .04	24.34	.1	3.65 ± .03
3	22.75	.1	3.91 ± .03	25.25	.6	3.52 ± .03
4	24.34	.2	3.65 ± .03	27.48	.7	3.24 ± .03
5	26.95	.3	3.31 ± .03	28.56	1.0	3.12 ± .03
6	28.63	.3	3.11 ± .03	29.32	1.0	3.05 ± .03
7	29.43[a]	1.0	3.03	30.12	0.6	2.96 ± .02
8	33.01	0.1	2.71 ± .02	32.25	.2	2.77 ± .02
9	34.03	.4	2.64 ± .02	34.13	.1	2.63 ± .02
10	36.19	.1	2.48 ± .01	35.38	.2	2.53 ± .02
11	39.38	.1	2.28 ± .01	36.65	.2	2.46 ± .01
12	39.98	.1	2.25 ± .01	38.98	.1	2.31 ± .01
13	43.75	.1	2.06 ± .01	41.37	.1	2.18 ± .01
14	44.44	.1	2.03 ± .01	41.91	.2	2.16 ± .01
15	46.25	.1	1.96 ± .01	44.06	.1	2.04 ± .01
16	48.81[a]	.4	1.86	46.56	.1	1.95 ± .01
17	52.56	.1	1.75 ± .01	47.25	.1	1.92 ± .01
18	53.62	.1	1.71 ± .01	49.83	.1	1.83 ± .01
19	54.44	.1	1.69 ± .01	51.43	.2	1.78 ± .01
20	56.50	.1	1.62 ± .01	52.87	.1	1.74 ± .01
21	57.95	.3	1.59 ± .01	54.55	.1	1.68 ± .01
22	59.41	.1	1.56 ± .01	59.35	.1	1.56 ± .10
23	60.88	.1	1.52 ± .01	62.91	.1	1.48 ± .01
24	71.40	.1	1.32	65.45	.1	1.42 ± .01
25	72.69	.1	1.30	69.50	.1	1.35
26	77.75	.1	1.23	79.90	.1	1.20
27	79.00	.1	1.21			
28	81.38	.1	1.18			

[a] The positions of these two lines were found by manually moving the Geiger tube until a maximum counting rate was obtained, and thus may be considered accurate to ±0.05°.

The patterns of the two forms of thallous sulfoxylate clearly show that we are dealing with two different structural forms. Further, comparison with the powder pattern of thallous sulfide indicates that both forms are significantly different from thallous sulfide itself.

The data given for *beta* thallous sulfoxylate, although not in exact agreement with the pattern given by von Hippel[10] for the yellow phase that he obtained in oxidized cells, is certainly in satisfactory enough accord to warrant the assumption that *beta* thallous sulfoxylate and von Hippel's yellow phase are one and the same compound. The pattern of the *beta* form was checked by comparison of three samples of β-Tl_2SO_2 prepared from three separate samples of α-Tl_2SO_2. Attempts to change the pattern by further heating of the *beta* form gave negative results. This heating only resulted in decomposition of the compound and the appearance of characteristic Tl_2S lines. Von Hippel[10] has proposed a face-centered cubic structure for the *beta* form. It appears that

---

(12) J. A. A. Ketelaar and E. W. Gorter, *Z. Krist.*, **101**, 367 (1939).

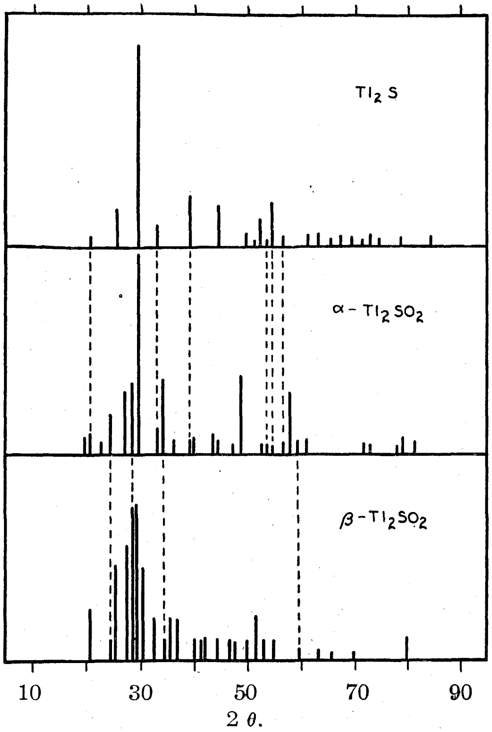


Fig. 5.

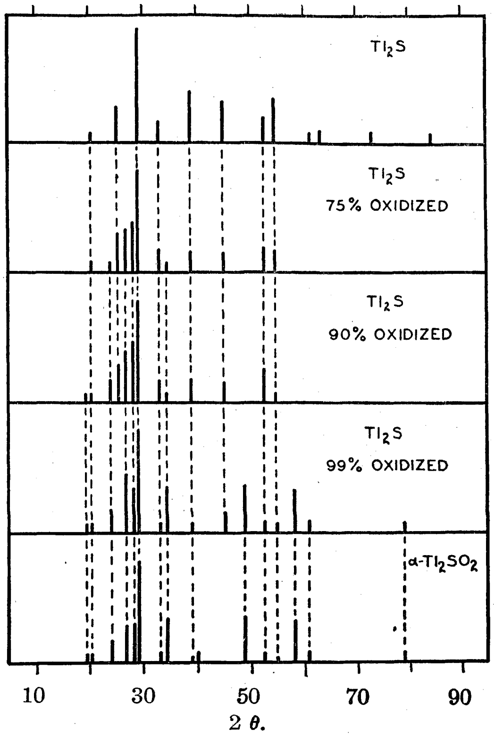


Fig. 6.

the *alpha* form may retain the layer lattice structure of thallous sulfide, but as yet we have failed to obtain sufficient data definitely to give the complete structure of this form, as all attempts to obtain crystals have been unsuccessful.

In Fig. 6 patterns showing different stages of oxidation in the preparation of the *alpha* form are given. These patterns indicate that partially oxidized samples of thallous sulfide do not represent mixtures of Tl_2S and α-Tl_2SO_2. Although some of the characteristic lines of α-Tl_2SO_2 are present in the 75% oxidized samples, at least two of the most intense lines given by the *alpha* form, 48.81° and 57.95°, do not appear until the oxidation is practically complete. This datum is in agreement with our observation that the characteristic brown phase of the *alpha* form does not appear until the reaction is nearly finished These patterns serve to give further evidence for the nonexistence of Tl_2SO at room temperature.

Our inability to obtain evidence of a Tl_2SO phase seems to cast some doubt on the theory advanced by von Hippel and Rittner[13] as to the position of the oxygen atoms in the photo-sensitive phase. These authors state that the most likely sites for the oxygen atoms are in spaces interleaving the Tl–Tl layers in the normal Tl_2S structure. Since the unit cell in the thallous sulfide structure contains twenty-seven Tl_2S units, and the number of possible oxygen positions is equal to the number of sulfur positions, based on the sites proposed by Von Hippel and Rittner, there will be twenty-seven possible locations for the oxygen atoms. If the oxygen atoms actually occupied these proposed sites the saturated structure would be Tl_2SO. The fact that Tl_2SO is so difficult to prepare may indicate that these sites are not as easily available as would at first appear. Calculations indicate that there are fifty-four equivalent positions in the Tl_2S unit cell available to oxygen atoms. Occupation of these would lead to the Tl_2SO_2 arrangement. However, the exact positions of the oxygen atoms cannot be determined without a more detailed X-ray study.

Basic Chemistry of the Thallous Sulfoxylates.—In attempting to elucidate the basic chemistry of the two forms of thallous sulfoxylate two early experiments led us to assign both forms as univalent thallium salts of sulfoxylic acid. Firstly, all evidence indicated that the oxidation of thallous sulfide had not served to oxidize either thallous ion to the thallic valence state. Secondly, all attempts to demonstrate the existence of sulfide ion in either form gave negative results.

Although sulfoxylic acid, H_2SO_2, is not known as the free acid, several inorganic salts have been prepared. The zinc salt $ZnSO_2$ may be prepared either by the action of sulfuryl chloride on zinc dust in absolute ether solution,[14] or by the reaction of

$$SO_2Cl_2 + 2Zn \longrightarrow ZnCl_2 + ZnSO_2$$

zinc metal with sulfur dioxide in absolute alcohol

$$SO_2 + Zn \longrightarrow ZnSO_2$$

---

[13] A. von Hippel and E. S. Rittner, *J. Chem. Phys.*, **14**, 370 (1946).

[14] E. Fromm and J. de S. Palma, *Ber.*, **39**, 3317 (1906).

The cobalt salt, $CoSO_2$, has been prepared by Scholder and Denk[15] by treating cobalt chloride with sodium hyposulfite in ammoniacal solution. Finally, Vogel and Partington[16] have prepared sodium sulfoxylate, Na_2SO_2, by treating sodium ethyl sulfoxylate with sodium hydroxide. In addition to these inorganic derivatives many organic compounds are known which may be considered as organic sulfoxylates.

Modifications of the above methods were attempted to prepare thallous sulfoxylate. Thallium metal turnings were added to a solution of pure sulfuryl chloride in absolute ether. But after prolonged stirring no reaction was observed. The speed with which thallium metal forms a protective oxide film may have been responsible for the failure to obtain any results.

The reaction between several different thallous salts and sodium hyposulfite was attempted under varying conditions. By adding thallous sulfate slowly to a solution of sodium hyposulfite an immediate white precipitate began to form which, however, could not be removed from the solution before it had turned dark gray. Repeated attempts to obtain the white compound which was believed to be $Tl_2S_2O_4$ failed and only Tl_2S and Tl_2SO_4 could be identified in the end-product.

The most satisfactory reaction was that between thallium metal shavings and sulfur dioxide in absolute alcohol. The reaction proceeded slowly yielding a white precipitate. This compound which was rather insoluble in alcohol could be obtained from the solution, and was found on analysis to be $Tl_2S_2O_4$. This compound appeared fairly stable in air, and was found to be rather highly soluble in water. Repeated attempts to convert this salt to thallous sulfoxylate failed to give any results.

However, it was found that *alpha* thallous sulfoxylate prepared from thallous sulfide, readily reacted with sulfur dioxide in alcoholic suspension to give a compound with the formula $Tl_2S_2O_4$ which seemed to be identical with the compound obtained above. It should be noted that *beta* thallous sulfoxylate would not react with sulfur dioxide under the same conditions.

Both forms of the sulfoxylate are only slightly soluble in water, but are quite soluble in dilute sulfuric acid. In the presence of concentrated acids both compounds appear to be decomposed, but concentrated bases have little effect on either compound. Solutions of both compounds containing 10 g. per liter of thallous ion were prepared and subjected to the standard tests for thallous ion. In all cases both compounds reacted as expected yielding both thallium ions immediately in the thallous state. Some difficulty was encountered in oxidizing these solutions to trivalent thallium with mild oxidizing agents, which suggested the presence of some reducing action in the solution.

In more dilute solution, less than 1 g. per liter of thallium, significant differences from normal thallous ion reactions may be noted. Attempts to precipitate the insoluble thallous halides from dilute acid solution gave precipitates only after several minutes, while attempts to precipitate the chromate from ammoniacal solution resulted in failure in most cases. However, it can be stated that there is very little difference in the two forms of the sulfoxylate as regard to the availability of the metal ions.

It was mentioned above that solutions of both forms appear to have a certain degree of reducing action. This fact coupled with the observation that both compounds on treatment with 5 *N* sulfuric acid gave precipitation of sulfur led us to postulate the existence of the thiosulfate ion as an intermediate product of the hydrolysis of sulfoxylic acid. This idea has already been suggested by Foerster[17] who considers sulfoxylic acid as an intermediate product in the formation of polythionates. He suggested that sulfoxylic acid is hydrolyzed according to the equation

$$2H_2SO_2 \longrightarrow H_2S_2O_3 + H_2O$$

The fact that we were able to demonstrate the presence of thiosulfate ion in aqueous solution of both forms lends support to the reaction as given above.

The thiosulfate ion was detected as an intermediate in the hydrolysis of both forms of thallous sulfoxylate by the characteristic reaction given with silver and mercuric ion. In the case of the *alpha* form 5 ml. of 10% solution of silver nitrate added to a saturated aqueous solution of the sulfoxylate gave the expected formation of a series of bright colored precipitates finally going to black silver sulfide. In the case of the *beta* form the reaction did not proceed as far as silver sulfide, but stopped with the formation of an intermediate brown precipitate, which was in part silver sulfite.

The following reactions were carried out in order to more fully investigate any difference in the course of hydrolysis of the two compounds. An aqueous solution containing 10 mg. of β-Tl_2SO_2 was made slightly acid with 2 *N* sulfuric acid. Before any sulfur began to appear this solution was treated with 0.5 ml. of potassium cyanide solution and 5 drops of ferric sulfate solution. The appearance of the familiar red color of the ferric thiocyanate complex indicated the presence of thiocyanate ion. A similar test with α-Tl_2SO_2 gave no color.

This formation of the thiocyanate ion is indicative of the presence of tetra- and pentathionic acid which may react with potassium cyanide according to the reaction

$$S_4O_6^{=} + 3CN^- + H_2O \longrightarrow SO_4^{=} + 2CN^- + S_2O_3^{=} + SCN^- + 2H^+$$

---

[15] R. Scholder and G. Denk, *Z. anorg. allgem. Chem.*, **222**, 17 (1935).

[16] I. Vogel and J. R. Partington, *J. Chem. Soc.*, **127**, 1514 (1925).

[17] F. Foerster, F. Lange, O. Drossbach and W. Seidel, *Z. anorg. allgem. Chem.*, **128**, 268 (1923).

$$S_5O_6^{=} + 4CN^- + H_2O \longrightarrow SO_4^{=} + 2CN^- + S_2O_3^{=} + 2SCN^- + 2H^+$$

Direct treatment of the two forms of thallous sulfoxylate with highly concentrated sulfuric acid gave different results in the two cases. When treated with 18 *N* acid the *beta* form gave off hydrogen sulfide as a decomposition product, and the solution remained clear, *i. e.*, no precipitation of sulfur. As opposed to this the *alpha* form gave no hydrogen sulfide, and sulfur began to precipitate immediately.

The formation of hydrogen sulfide may have been due to direct decomposition of the β-Tl_2SO_2, or may be a result of the hydrolysis of thiosulfate ion in strong acid according to the equation

$$2H_2S_2O_3 \longrightarrow H_2S + H_2S_3O_6$$

Bassett and Durrant[18] suggested the above reaction as one of three possible hydrolysis reactions of thiosulfate. These authors state that the above reaction would be favored in very strong acid.

In view of these results it should be mentioned that our inability to obtain thallous chromate precipitates from dilute solutions of the sulfoxylates in ammonium hydroxide may have been due to the formation of stable thiosulfate complexes in alkaline solution. Strongly complexed salts of this type are well known.

Goehring[19] has proposed that sulfoxylic acid may exist in two isomeric forms: the normal or sulfoxylic form reacting as if it were $S(OH)_2$, while the sulfinic form seems to react as HS(:O)OH. It is proposed by Goehring that the sulfoxylic form may react with thiosulfate ion according to the reaction

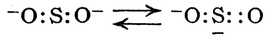
$$S(OH)_2 + 2S_2O_3^{=} + 2H^+ \longrightarrow S_5O_6^{=} + 2H_2O$$

and react with the bisulfite ion

$$S(OH)_2 + 2HSO_3^- \longrightarrow S_3O_6^{=} + 2H_2O$$

while the sulfinic form does not undergo reactions of this type.

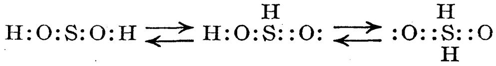
To the present authors such marked differences seem difficult to understand when one realizes that if the sulfoxylate ion is involved the two forms given by Goehring are merely two possible resonance forms and thus could not be distinguished.



$$^{-}O{:}S{:}O^{-} \rightleftarrows {}^{-}O{:}\underset{-}{S}{::}O$$

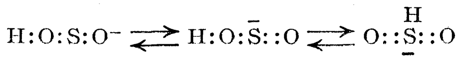
While if the postulated reactions involve the undissociated acid or bisulfoxylate ion it seems highly probable that a labile equilibrium between the two forms will exist.

Such an equilibrium between the two forms proposed by Goehring plus a third possible form could be represented by the equation



$$H{:}O{:}S{:}O{:}H \rightleftarrows H{:}O{:}\overset{H}{S}{::}O{:} \rightleftarrows {:}O{::}\underset{H}{\overset{H}{S}}{::}O{:}$$

for the undissociated acid and



$$H{:}O{:}S{:}O^{-} \rightleftarrows H{:}O{:}\overset{-}{S}{::}O \rightleftarrows O{::}\underset{-}{\overset{H}{S}}{::}O$$

for the bisulfoxylate ion.

From the data obtained it is evident that the primary step in the hydrolysis of both forms of thallous sulfoxylate proceeds according to the equation

$$2Tl_2SO_2 + H_2O \longrightarrow Tl_2S_2O_3 + 2TlOH$$

The noted differences in the end-products of the hydrolysis in each case would then most probably be due to the reaction of the thiosulfate ion, or some further hydrolysis product, with undissociated thallous sulfoxylate.

Summary

Two different forms of thallous sulfoxylate have been prepared and X-ray diffraction patterns of the two forms obtained. The pattern of *beta* thallous sulfoxylate indicates that this compound is identical with a compound obtained by von Hippel and independently by Iskoldsky. No previous reference has been found concerning the *alpha* thallous sulfoxylate.

Conditions are given for converting the *alpha* form into the *beta* form by careful heating *in vacuo* to 250°.

The chemistry of both forms has been investigated and both compounds have been shown to be thallous salts of the hypothetical sulfoxylic acid.

NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS

RECEIVED JUNE 9, 1947

---

[18] H. Bassett and R. G. Durrant, *J. Chem. Soc.*, 1416 (1927).

[19] M. Goehring, *Ncturwiss.*, **32**, 42 (1944).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Kinetics of Activation–Diffusion Controlled Reactions in Solution. The Temperature Dependence of the Quenching of Fluorescence[1,2]

BY BYRON WILLIAMSON[3] AND VICTOR K. LA MER

The quenching of fluorescence in solution is generally considered today to be a diffusion controlled reaction. The most conclusive evidence for this view is the dependence of the empirical rate constant upon the viscosity of the medium. By developing an equation with which they calculated the encounter frequency of ions in solution, and by measuring the quenching constant corrected for various interfering phenomena, Umberger and La Mer[4] showed that only about one encounter in four results in quenching for the reaction involving the quenching of the fluorescence of uranin (the basic form of fluorescein) by iodide ion. Hence the rate of diffusion of the reactants toward each other is the primary, but not the sole factor governing the rate of this and presumably other quenching reactions. It seemed probable that a chemical energy of activation might also be involved in the quenching process and an investigation of this aspect of the problem is the principal objective of this research.

Theory

The development of a rate equation which includes both the energy of activation and the collision frequency is not as simple for liquids as it is for gases. Rabinowitch[5] has shown that collisions in liquids occur in sets, called co-ordinations or encounters. Each encounter consists of many collisions, and the duration of an encounter depends upon the viscosity and the temperature of the liquid under consideration. This concept of diffusion in liquids will be used with the further general provision, namely, that collisions between two reactants, A and B, with each other and with the solvent molecules are not different kinetically when A and B are in an encounter together than when each is alone in an "encounter" with only solvent molecules. The presence of A and B in an encounter thus places no restriction upon either their electronic or thermal activation.

The molar rate constant, k, of a bimolecular reaction in solution can accordingly be represented as the product of the encounter frequency or the rate of diffusion of the reactants together, k_D, times the probability of reaction per *encounter*, p.

$$k = pk_D \qquad (1)$$

The Rate of Diffusion.—An exact and general expression for the encounter rate of molecular solute particles in solution, analogous to gaseous collison frequencies, is not derivable because of the limitations of our knowledge of the nature of liquids. Two different approaches to this problem have been used. Rabinowitch[5] and Fowler and Slater[6] have derived equivalent expressions by considering liquids to have a quasi-crystalline structure, and calculating the probability that two solute particles will occupy adjacent lattice points. Their expressions are especially approximate when the sizes of the solute and solvent molecules differ.

The second approach, and the one that has been used by Sveshnikoff and Wawilow[7] and by Umberger and La Mer[4] in their work with the quenching of fluorescence in solution is the application of Smoluchowski's theory[8] for the coagulation of colloids. Although there are objections to the derivation and to the use of Smoluchowski's expressions in the calculation of encounter frequencies, ample experimental agreement between the rapid coagulation of colloids and Smoluchowski's stationary state solution has been obtained. The stationary state solution, $4\pi DR$, gives very nearly the same numerical values as are obtained from the quasi-crystalline formula and will be used in this paper, *i. e.*

$$k_D = 4\pi DRN/1000f \qquad (2)$$

Sveshnikoff and Wawilow included the transient state term, $R/\sqrt{\tau_0 D}$, of Smoluchowski's theory in their theoretical treatment, substituting τ_0, the mean life of the excited state of the fluorescent molecule for Smoluchowski's general parameter, t. Umberger and La Mer also included the transient state term in their recent work, as has Montroll.[9] The full physical significance of this term needs further clarification. Smoluchowski's boundary conditions are not realized in physical processes, even in the case of colloidal coagulations, for very small or for very large values of t.

The equality of the quenching and diffusion radii also means that static quenching, as discussed by Frank and Wawilow,[10,11,12] will be absent. Static quenching also results from the electronic excitation of a fluorescent molecule while in an encounter with a quencher molecule. This effect is compensated, however, by fluorescence during an

---

(1) Presented at the Sixth Boston Meeting of the American Association for the Advancement of Science, December, 1946, and at the American Chemical Society Meeting, Atlantic City, 1947.

(2) Dissertation submitted by Byron Williamson in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in the Faculty of Pure Science, Columbia University.

(3) Present address: E. I. du Pont de Nemours and Company, Plastics Department, Arlington, New Jersey.

(4) J. Q. Umberger and V. K. La Mer, THIS JOURNAL, **67**, 1099 (1945).

(5) E. Rabinowitch, *Trans. Faraday Soc.*, **33**, 1225 (1937).

(6) R. H. Fowler and N. B. Slater, *ibid.*, **34**, 81 (1938).

(7) B. I. Sveshnikoff, *Acta Physicochim., U. R. S. S.*, **3**, 257 (1935).

(8) P. Debye, *Trans. Electrochem. Soc.*, **82**, 265 (1942).

(9) E. W. Montroll, *J. Chem. Phys.*, **14**, 202 (1946).

(10) B. I. Sveshnikoff, *Compt. rend. Acad. Sci., U. R. S. S.*, **3**, 61 (1936).

(11) J. M. Frank and S. I. Wawilow, *Z. Physik*, **69**, 100 (1931).

(12) E. J. Bowen, *Trans. Faraday Soc.*, **35**, 17 (1939).

encounter. As static quenching is a function of the concentration of quencher, it is eliminated beyond doubt in this work by the necessary extrapolation of the quenching constants to zero concentration quencher.

There remains the problem of the proper values of the diffusion constant to be used in the calculation of k_D. If the Stokes–Einstein expression, $D = kT/6\pi\eta r$, is used the question reduces to that of the proper radius to use. This difficulty has been minimized by Hodges and La Mer[13] who have measured the diffusion constants of the reactants involved using the diaphragm cell method.

The Probability of Reaction per Encounter.—Because collisions in liquids occur in sets, the probability of reaction depends not only upon an energy or an entropy of activation, but also upon the distribution of the collisions, for if a reaction occurs early in an encounter the subsequent collisions of that encounter will be wasted, *i. e.*, they will not be reflected in the reaction rate. To consider these circumstances, let w be the probability of reaction upon collision of reactants A and B, and let x be the probability of the encounter being broken by diffusion between collisions of A and B. If one assumes that an encounter begins with a collision of A and B, the probability of reaction per encounter, p, may be expressed as

$$p = w + (1 - w)(1 - x)p \qquad (3)$$

which, if $xw \ll x$ or w, reduces to

$$p = w/(x + w) \qquad (4)$$

If instead one assumes that diffusion away may occur before the first collision of A and B, equation (4) is derivable directly without the approximation that $xw \ll x$ or w.

The general equation for k, the reaction rate constant in solution, or in media where collisions occur in sets, is then

$$k = (w/x + w)k_{\mathrm{D}} \qquad (5)$$

i. e., the rate of reaction is equal to the rate of formation of encounters times the probability that reaction will occur before the encounter is broken by diffusion away.

Equation (5) is a more general form of equations that have been developed by Rabinowitch[5] and by Fowler and Slater[6] from considerations of the quasi-crystalline structure of liquids.

The probability of reaction per collision may be represented as

$$w = Pe^{-E_{\mathrm{a}}/RT} \qquad (6)$$

where P is an orientation or entropy factor, and E_a is the usual chemical energy of activation.

The probability of a molecule escaping by diffusion between collisions of A and B may also be represented by an exponential term

$$x = Ce^{-E_{\mathrm{d}}/RT} \qquad (7)$$

where E_d is an energy of activation of diffusion, and C consists of an orientation factor together with other small numerical factors to be discussed later.

The relative influence of the chemical energy of activation and the diffusional energy of activation is also shown by rearranging Eq. (4) to the form

$$(1/p) - 1 = x/w \qquad (8)$$

Substituting equations (6) and (7) into the logarithmic form of equation (8) gives

$$\log (1/p - 1) = \log C/P + (E_{\mathrm{a}} - E_{\mathrm{d}})/2.3RT \qquad (9)$$

A plot of $\log(1/p - 1)$ against $1/T$ will have a positive slope if $E_a > E_d$, a negative slope if $E_a < E_d$, and a zero slope if $E_a = E_d$. The intercept of the curve will be a measure of the relative magnitude of the steric factors of diffusion and reaction, and if one is known, the other may be determined.

An expression for the probability, x, of the termination of an encounter between collisions of A and B may be developed and E_a identified with the experimental energy of activation of diffusion. Let x' be the probability that any single attempt at diffusion will be successful, *i. e.*, a collision of a molecule with its cage wall will result in displacement to a new equilibrium position. Diffusion by either of the reactants to a new equilibrium position not adjacent to that occupied by the other reactant will break the encounter so that

$$x = (2n\gamma)x' \qquad (10)$$

where x is the probability that the new equilibrium position will not be adjacent to the other reactant, and $2n$ is the number of attempts at diffusion by the two reactants between collisions with themselves (assuming $n_a = n_b = n/2$).

The number of diffusive collisions per second is $x'Z_1 = 1/\theta$, Z_1 being the collision frequency in liquids and θ is the average time between diffusive collisions. From the Einstein[14] expression for the diffusion constant, the number of diffusive collisions per second in terms of the distance between equilibrium positions in the liquid, λ, is

$$1/t = 2D/\lambda^2 \qquad (11)$$

The relationship between x' and the diffusion constant is then given by equation (12)

$$x' = 2D/\lambda^2 Z_1 \qquad (12)$$

The probability, x', may now be expressed in terms of the experimental energy of activation of diffusion by substituting into Eq. (12) Eyring's[15] expression for D (Eq. 13) and Fowler's[6] expression for Z_1 (Eq. 14)

$$D = (\lambda^2/v_{\mathrm{f}}^{1/3})(k_{\mathrm{B}}T/2\pi m)^{1/2}\, e^{-E_{\mathrm{d}}/RT} \qquad (13)$$

$$Z_1 = 3(2k_{\mathrm{B}}T/\pi m)/a \qquad (14)$$

The factor a is defined as the diameter of the cage, *i. e.*, the diameter of the free volume allowed to any particle, so that a is approximately equal to $v_{\mathrm{f}}^{1/3}$, and Eq. (12) reduces to

$$x' = 1/6e^{-E_{\mathrm{d}}/RT} \qquad (15)$$

---

[13] K. C. Hodges and V. K. La Mer, THIS JOURNAL, **70**, 722 (1948).

[14] A. Einstein, *Ann. Physik*, **17**, 549 (1905).

[15] A. E. Stearn, E. M. Irish and H. Eyring, *J. Phys. Chem.*, **44**, 981 (1940).

Equation (10) now becomes

$$x = (2n\gamma/6)e^{-E_d/RT} \tag{16}$$

The factor n will vary from unity in the case of vibrations of A and B restricted to one coördinate to 11 for random movement in a hexagonal lattice, and γ is of the order of magnitude of $^1/_2$. Orientation or steric factors influencing the diffusion of a molecule from one equilibrium position to the next have not been considered above, and a probability factor, α, which will be unity for spherical molecules should be included in Eq. 16. The constant of Eq. (7) is now seen to be

$$C = \alpha\gamma m/3 \tag{17}$$

and is a small number approximately equal to unity for near spherical molecules. This means that for proper geometrical cases, log C/P, the intercept of equation (9) plotted against $1/T$, will give the order of magnitude of the reaction orientation factor P.

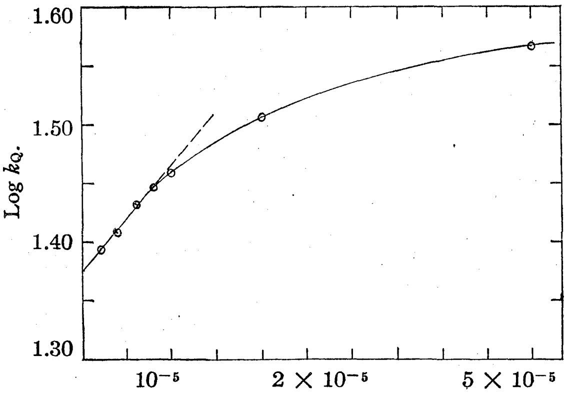


Fig. 1.—The molar quenching constant as a function of the concentration of uranin.

The probability, x', may also be derived as a function of temperature and viscosity, η, by substituting into Eq. (12) another form of Eyring's formula for D,[16] namely

$$D = \frac{\lambda_1}{\lambda_2\lambda_3}\frac{kT}{\eta} \tag{18}$$

The resulting expression for x is

$$x = C_1\sqrt{T/\eta} \tag{19}$$

where C_1 is of the order of magnitude of 10^{-6} to 10^{-5}, depending for the most part upon the mass of the solute particle. Equation (19) is useful because if C_1 can be determined, it will predict more accurately the dependence of x upon T and η than will Equation (7).

The Uranin–Aniline Quenching Reaction.—The quenching of the fluorescence of uranin, $Fl^=$, by aniline, An, has been measured as a function of the concentration of both uranin and aniline, as well as temperature, in order to obtain rate constant values free from absorption effects. The apparatus and procedure used is very similar to that of Umberger and La Mer. The photocells and cuvettes were enclosed in water jacketed housings for temperature control. The Stern–Volmer equation[17] was employed in the initial calculation of the quenching constants.

The decomposition of aniline in basic solution is serious in this work and the solutions, kept in blackened flasks, must be basic no longer than one hour at room temperature before intensity readings are obtained. The decomposition rate increases with temperature, and limits the temperature range employable.

The reabsorption of its own fluorescence by uranin in the presence of 0.01 M aniline at 27° is shown in Table I and Fig. 1, and is in good agreement with the theory and data of Umberger and La Mer.[4]

TABLE I

THE EXPERIMENTAL QUENCHING CONSTANT AS A FUNCTION OF THE CONCENTRATION OF URANIN

Concentration of uranin, m./l.	k_Q	log k_Q
1×10^{-4}	40.5	1.608
2×10^{-5}	32.0	1.505
1×10^{-5}	28.8	1.459
8×10^{-6}	28.0	1.447
6×10^{-6}	27.0	1.431
4×10^{-6}	25.6	1.408
2×10^{-6}	24.8	1.394
zero	(23.7)	(1.375)

At concentrations of aniline above 0.005 M, the quenching constant was found to increase with increasing concentration, Table II and Fig. 2. This

TABLE II

EXPERIMENTAL QUENCHING CONSTANT VALUES FOR THE URANIN–ANILINE REACTION AS A FUNCTION OF THE CONCENTRATION OF ANILINE

Concn. of aniline, m./l.	Quenching, %	k_Q 10^{-5} M $Fl^=$	k_Q Extrap., $C_{Fl^=} = 0$
0.100	70	37.9	31.4
.075	63	36.1	29.9
.040	48	32.7	27.1
.020	31	30.1	24.9
.010	19	28.8	23.7
.004	8	28.1	23.3
zero		(28.0)	(23.2)

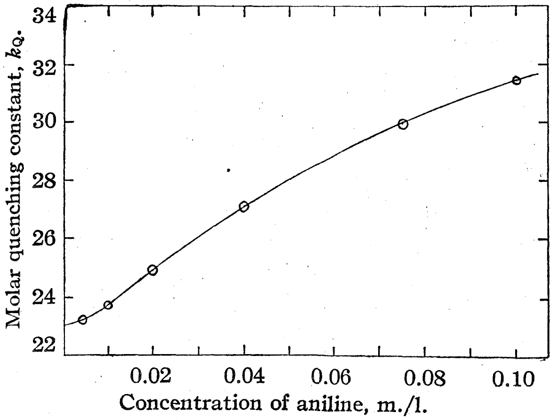


Fig. 2.—The molar quenching constant as a function of the concentration of aniline.

---

(16) H. Eyring, *J. Chem. Phys.*, **4**, 283 (1938).

(17) O. Stern and M. Volmer, *Z. wiss. Phot.*, **19**, 275 (1920).

has been predicted by Sveshnikoff,[10,18] and constitutes the so-called deviations from the Stern–Volmer equation. Some absorption by aniline of the incident and fluorescent light also contribute. The increase is not due to a salt effect on the reaction as evidenced by no change in the quenching constant in the presence of 0.1 *M* NaOH or 0.1 *M* NaCl.

The quenching constant extrapolated to zero concentration of both uranin and aniline is 23.2 ± 0.3 at 27.0 ± 0.5°. The rate of quenching is hence 23.2 times as great as the rate of fluorescence on a molar basis. Using Equation (2), with

$$D = \frac{k_B T\,(1/r_{Fl^-} + 1/r_{An})}{6\pi\eta}$$

the number of encounters between uranin and aniline molecules in the time τ_0 is found to be 43.5 at 27.0°.[20] The probability of quenching per encounter is therefore 0.53 and approximately one out of every two encounters results in quenching.

The Temperature Dependence of the Uranin–Aniline Reaction.—Although much work has been done on the quenching of fluorescence in solution, the temperature dependence of a quenching reaction independent of viscous and other effects has not been determined. Stoughton and Rollefson[19] have been the most recent investigators of the temperature dependence of quenching, but since they did not employ an equation predicting the dependence of the quenching constant upon viscosity they were unable to treat the effect of temperature independently.

In this work the quenching constant of the uranin–aniline reaction has been measured at temperature intervals of five degrees from 7° to 54° using 0.01 *M* aniline and 10^{-5} *M* uranin. The results are given in Table III and Fig. 3. In order to obtain molar quenching constants from the experimental values, the per cent. correction, 19.5%, determined from the two necessary extrapolations at 27° was used at all temperatures. The validity of this procedure was established by measuring the effects of the aniline and uranin concentrations at 40°. The correction was found to be the same per cent. of the experimental value as at 27°.

The intensity of the fluorescence of a uranin solution in the absence of a quencher was found to decrease between 1–2% per 10° increase in temperature. From the work of Lewschin,[20] Jenness[21] and Speas[22] this effect may be shown to be due to a decrease in the extinction coefficient of the dye with increasing temperature. The fluorescence intensity is shown to be a linear function of the extinction coefficient, and the mirror symmetry of the fluorescence and absorption spectra is also maintained over this range of temperature. The average life of uranin in water has been shown to be independent of temperature by Perrin,[23] using polarization measurements. These considerations also show why the correction due to the re-

TABLE III

ANILINE QUENCHING OF THE FLUORESCENCE OF URANIN AS A FUNCTION OF TEMPERATURE

Temp., °C.	k_Q, exptl.	k_Q, cor.	k_D, calcd.	p	Log $(1/p - 1)$
6.5	17.5	14.0	24.2	0.578	−0.138
7.0	18.5	14.9	24.6	.606	− .187
7.4	18.3	14.7	24.9	.590	− .159
8.1	18.8	15.1	25.5	.592	− .161
9.5	18.9	15.2	26.6	.571	− .125
9.8	19.3	15.6	26.9	.580	− .140
11.0	20.0	16.1	27.9	.577	− .134
11.8	20.5	16.5	28.6	.577	− .134
16.0	22.2	17.9	32.5	.551	− .089
19.6	24.4	19.7	36.0	.546	− .082
20.0	24.2	19.5	36.4	.536	− .062
25.0	27.3	22.0	41.7	.527	− .047
30.0	30.5	24.6	47.4	.520	− .035
35.0	34.0	27.4	53.2	.515	− .026
40.0	37.4	30.1	59.9	.503	− .005
44.3	40.5	32.6	66.0	.494	.010
45.6	41.5	33.4	67.4	.496	.007
49.0	44.0	35.7	72.1	.495	.009
52.3	46.8	37.7	77.0	.490	.017
54.0	47.8	38.5	79.4	.485	.026

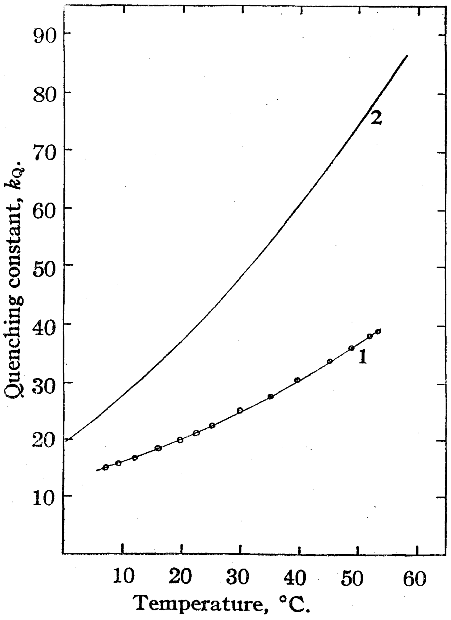


Fig. 3.—The calculated encounter rate (1), and the experimental quenching constant (2) as a function of temperature.

---

(18) B. I. Sveshnikoff, *Acta Physiochim., U. R. S. S.*, **4**, 453 (1936).

(19) R. W. Stoughton and G. K. Rollefson, THIS JOURNAL, **62**, 2264 (1940).

(20) The values used in this computation are:

k_B = 1.38 × 10^{-16}
N_a = 6.02 × 10^{23}
T = 300°
η = 0.00854 poise
t_0 = 0.45 × 10^{-8} sec.
r_{Fl^-} = 6.6 × 10^{-8} cm.
r_{An} = 2.5 = 10^{-8} cm.

(20) V. L. Lewschin, *Z. Physik*, **72**, 368 (1931).

(21) J. R. Jenness, *Phys. Rev.*, **34**, 1275 (1929).

(22) W. E. Speas, *ibid.*, **31**, 569 (1928).

(23) F. Perrin, *Ann. Physik*, 108, **12**, 169 (1929).

absorption of fluorescence is independent of temperature.

Although the radii of these reactants have not been measured as a function of temperature it is expected that they will be constant. The radius of mannitol has been measured as a function of temperature in aqueous solution by Scheffer and Scheffer[24] and discussed by Stearn, Irish and Eyring.[15] Their data show the radius to be independent of temperature to within a few tenths of an Ångström unit. Variations of this order of magnitude are not significant in this work as the value of k_D is not sensitive to small changes in the radii.

Discussion of Temperature Results

The quenching constant measured over a temperature range is a function of two variables, the temperature, T, and the viscosity, η. Equation (2) in terms of these parameters with the constants evaluated for the uranin–aniline reaction is given below

$$k_D = 0.00125T/\eta \tag{22}$$

The usual procedure of determining the energy of activation of a chemical reaction from measurements of the rate constant as a function of temperature is to plot log k *vs.* $1/T$. Such a procedure in this case cannot be used because of the dependence of the encounter frequency upon the temperature and the viscosity.

If Equation (9) is plotted against $1/T$ using the experimental values of p from Table III, the slope will be a measure of the difference in E_a and E_d. This plot is shown as Fig. 4. In accordance with Eq. (9) the slope of the curve shows that the energy of activation of the reaction is of the same order of magnitude as the energy of activation of diffusion, but is about 1000 calories per mole less, or approximately 3000 cal./mole.

The intercept of Fig. 4 is approximately 0.2, which means that $C = 1.5P$. Since C is approximately unity, P is also approximately unity, and hence the orientation and entropy requirements for the formation of an activated complex which will result in quenching are very slight.

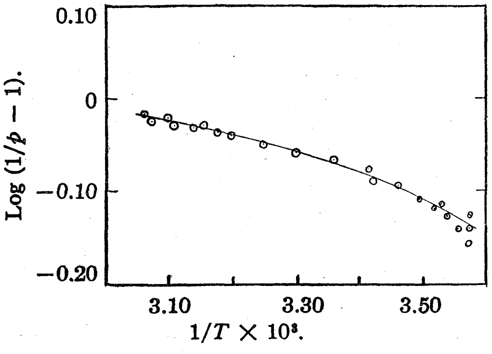


Fig. 4.—The probability of quenching per encounter as a function of temperature.

The average number of collisions per encounter, n, is the reciprocal of x, the probability per collision of an encounter terminating by diffusion of the reactants. The influence of the temperature, and the accompanying viscosity changes, upon the number of collisions per encounter may be calculated from Eq. (7) or Eq. (19). The viscous effect is predominant with the result that while n is nearly 1000 at 0°, it decreases to about 100 at 100°.

A survey of the literature shows that of all the many quenching reactions investigated only a very few are as efficient as the aniline–uranin reaction. The self-quenching of dyes as reported by Umberger and La Mer[4] is the only other type of quenching efficient enough to be a possible exception to the argument being presented. The diffusion constants of all common quenching reactants in solution will be of the same order of magnitude, and it is thus reasonable to expect that the large majority of quenching reactions will require a chemical energy of activation equal to, and in most cases exceeding, that required by uranin–aniline reaction. The quenching of fluorescence in solution in general therefore may be expected to be activation as well as diffusion controlled.

Acknowledgments.—The authors wish to express their appreciation for the suggestions made by Professor G. E. Kimball and by Dr. J. Q. Umberger.

Summary

1. The kinetics of the quenching of the fluorescence of uranin by aniline has been investigated using a precision photoelectric fluorimeter. Molar quenching constants, corrected for reabsorption and other effects, have been measured as a function of temperature.

2. A general equation, utilizing the concept that collisions in liquids occur in sets and introducing an energy of activation term into Smoluchowski's diffusion equation, is presented for reactions in solution whose rates are governed by both an energy of activation and by the interdiffusion of the reactants.

3. Experimental quenching constants for the uranin–aniline reaction, measured as a function of temperature (and necessarily of viscosity also), are interpreted using this equation. Quenching occurs in approximately one out of every two encounters (one out of every 1000 collisions) and hence diffusion alone is not sufficient to explain the observed rate of quenching. An energy of activation of the same order of magnitude as the energy of activation of diffusion suffices for agreement between theory and experiment. In general, the quenching of fluorescence in solution should be expected to be activation as well as diffusion controlled.

NEW YORK, N. Y. RECEIVED OCTOBER 14, 1947

---

[24] J. D. R. Scheffer and F. E. C. Scheffer, *Verslag Akad. Wetenschappen Amsterdam*, **25**, 67 (1916).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Solvent Effects on the Quenching of the Fluorescence of Uranin by Aniline[1,2]

BY KENNETH C. HODGES[3] AND VICTOR K. LA MER

The effects on the quenching of fluorescence produced by changes in viscosity, through the use of different solvents, were noticed early in experimental investigations of this subject.[4,5,6] The theoretical and experimental investigations of Umberger and La Mer[7] showed, however, that it was necessary to apply a number of corrections to the direct measurements of fluorescence quenching in order to convert these data to rate constants. Unfortunately, the necessity of making these corrections was not recognized in the early investigations so that none of the data on solvent effects in the literature can be interpreted unambiguously.

It is the primary purpose of this investigation to interpret rate constants for the quenching of the fluorescence of uranin (basic fluorescein ion) by aniline as a function of the viscosity of the medium. The presently accepted theoretical equations for the calculation of encounter frequencies involve the diffusion coefficients of the reactants. In order to compare the encounter frequencies in liquids with the rate constants, it was necessary to measure these diffusion coefficients. It will be shown that the elementary view that quenching constants will be linear functions of the solvent fluidity is inadequate.

Theory

The application of the cage-model theory of liquids to the study of reaction rates, and the development of rate equations, have been discussed in the previous paper[8] and will not be repeated.

One method of approach to the calculation of encounter frequencies in liquids has been from a model which considers liquids as possessing a lattice structure. Calculations of this type have been made by Rabinowitch,[9] Fowler and Slater,[10] and very recently by Kimball.[11] The molar encounter frequency derived by Kimball is

$$k_{\mathrm{D}} = 4\,\pi R^2 D\,\frac{1}{a}\,\frac{(\mathrm{N})}{1000}\ \text{liters moles}^{-1}\ \text{sec.}^{-1} \qquad (1)$$

where "a" is the distance between lattice points, and all other symbols have their usual values. Rewriting equation (1) as

$$k_{\mathrm{D}} = \frac{4\pi DR(\mathrm{N})}{1000}\,\frac{R}{a}$$

it is evident that k_{D} will be larger than the value given by the stationary state term of Smoluchowski's equation (ref. 8, eq. 2) since in general R will be larger than "a." The dependence of the encounter rate on the viscosity of the medium, eta, is evident if the relation

$$D = \frac{kT}{6\pi\eta}\left(\frac{1}{r_{\mathrm{d}}} + \frac{1}{r_{\mathrm{q}}}\right)$$

is substituted into either equation.

Equation 1 predicts a dependence of k_{D} on the solvent structure through the inclusion of the factor "a" which will be roughly proportional to the size of the solvent molecules. However, an exact value of "a" is not known. It is equivalent to λ, the distance between equilibrium positions of the molecules involved in viscous flow, as defined by Eyring.[12]

The results in this investigation are interpreted in terms of eq. 1. The effects of different solvents on the rate of fluorescence quenching reactions will be discussed on the basis of the relation presented for the probability of reaction per encounter by Williamson and La Mer.[8]

Experimental

Quenching Constants.—Quenching constants have been measured with the sensitive photoelectric fluorimeter developed by Umberger and La Mer,[7] and the experimental techniques described therein. The volume-molar quenching constants for the quenching of the fluorescence of uranin by aniline have been measured in the following solutions: water and glycerol, water and sucrose, water and methanol, and methanol, ethanol and isopropanol.

Uranin was chosen as the fluorescent material since its average life in the excited state, τ, was constant within the solvent ranges chosen.[13,14] Aniline was chosen as the quencher since its electrical neutrality in alkaline solution reduced very greatly primary kinetic salt effects. These have been shown to be zero by Williamson and La Mer.[8]

All quenching measurements were made within the temperature range 24.5–26.5°, with most falling between 24.5 and 25.5°. However, the actual temperature in the cell was recorded at the time of the measurement to $\pm 0.2°$, and the viscosity of the solution experimentally determined at this temperature with an Ostwald viscometer. The concentration of quencher used was 0.0100 molar, and the concentration of uranin 10^{-5} molar, with the pH of all solutions approximately 12. The results are given in Table I, and are plotted in Fig. 1 as a function of the solvent fluidity.

To correct for the reabsorption of the fluorescent light,[7] it was necessary to obtain the value of the quenching con-

---

(1) Presented in part at the A. A. A. S. Boston meeting, December, 1946, and at the American Chemical Society, Atlantic City, 1947.

(2) Dissertation submitted by Kenneth Charles Hodges in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in the Faculty of Pure Science, Columbia University.

(3) Present address: E. I. du Pont de Nemours & Co., Cellophane Research, Buffalo, N. Y.

(4) J. M. Frank and S. I. Wawilow, *Z. Physik*, **69**, 100 (1931).

(5) B. I. Sveshnikoff, *Acta Physicochim., U. R. S. S.*, **3**, 257 (1935).

(6) R. W. Stoughton and G. K. Rollefson, THIS JOURNAL, **62**, 2264 (1940).

(7) J. Q. Umberger and V. K. La Mer, *ibid.*, **67**, 1099 (1945).

(8) B. Williamson and Victor K. La Mer, *ibid.*, **70**, 717 (1948).

(9) E. Rabinowitch, *Trans. Faraday Soc.*, **33**, 1228 (1937).

(10) R. H. Fowler and N. B. Slater, *ibid.*, **34**, 81 (1938).

(11) G. E. Kimball, private communication.

(12) H. Eyring, *J. Chem. Phys.*, **4**, 283 (1936).

(13) F. Perrin, *Ann. Physik*, [10S] **12**, 169 (1929).

(14) B. Sveshnikoff, *Acta. Physicochim., U. R. S. S.*, **7**, 755 (1939).

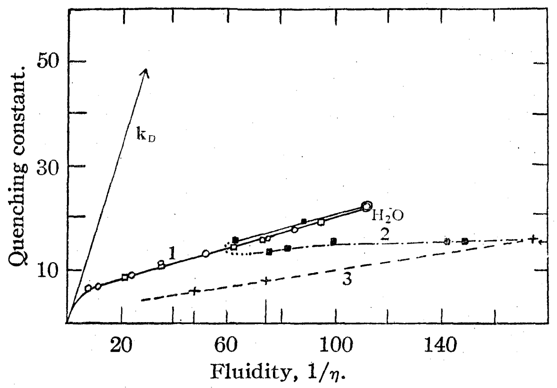


Fig. 1.—Quenching constants as a function of solvent fluidity: O, glycerol–H_2O; □, sucrose–H_2O; ■, methanol–H_2O.

stant extrapolated to zero uranin concentration. A plot of log k_Q against the concentration of dye shows a linear relation between 10^{-5} and 2×10^{-6} molar uranin. Extrapolation to the zero concentration intercept gives the quenching constant corrected for reabsorption. The slope of this line for the quenching reactions uranin and aniline and uranin and potassium iodide was determined in water at 25° as 8500 ± 500 l./m. In the glycerol–water and sucrose–water mixtures the slopes were found to be less than that in water; for example, 5600 ± 500 for 36.8% glycerol, and 6400 ± 600 for 18.6% sucrose, respectively. This decrease is probably due to a difference in the amount of overlap of the fluorescence and absorption spectra as the solvents are changed. Hence the correction to be applied to the 10^{-5} molar quenching constant decreased as the concentration of the glycerol and the sucrose increased. The slopes in the alcohols were the same as in water.

TABLE I

ANILINE QUENCHING OF THE FLUORESCENCE OF URANIN AS A FUNCTION OF SOLVENT FLUIDITY

Solvent composition Wt. % glycerol	Viscosity (poises × 10^3)	Fluidity (poise^{-1})	k_Q exp. (l./m.)	k_Q corr. (l./m.)
0.00	8.95	112	26.9	22.0
9.8	11.7	85.5	21.5	17.7
14.6	13.1	76.5	19.6	16.2
28.2	19.2	52.0	15.8	13.3
36.8	28.2	35.4	13.0	11.4
45.4	39.8	25.1	11.0	9.8
61.5	81.3	12.3	8.1	6.9
69.0	120	8.25	7.8	6.8
Wt. % sucrose				
9.65	10.6	94	22.6	18.5
14.2	13.6	73.5	19.4	16.0
18.6	16.1	62.1	17.3	14.4
31.1	28.6	35.0	13.0	11.2
39.2	45.5	22.0	10.0	8.7
Wt. % methanol				
8.1	11.2	89.3	24.1	19.6
43	15.9	63.0	19.5	15.8
66	13.15	76.0	16.8	13.4
76	12.0	83.5	17.6	14.2
87	10.0	100	19.4	15.6
94	7.04	142	19.1	15.4
95.5	6.75	148	19.1	15.4
Methanol	5.71	175	19.8	15.9
Ethanol	13.4	74.5	10.3	8.1
Isopropanol	20.8	48.1	8.0	6.2

A small correction was also necessary for the absorption of the incident light by the aniline, as reported by Williamson and La Mer.[8] Their experiments were repeated in various solvents and the absorption remained constant. Hence, as the k_Q decreased, the correction became relatively greater. Quenching independent of diffusion, known as static quenching, may occur when the uranin is excited while in an encounter.[15] This complication is removed by extrapolation to zero concentration of quencher.

Since the addition of sodium hydroxide to aniline hydrochloride produced a precipitate of sodium chloride in the alcoholic solvents, it was necessary to use freshly distilled aniline as quencher in these solvents. In 10^{-5} molar uranin, and 0.01 molar sodium hydroxide in excess of the aniline hydrochloride concentration, the same value of the quenching constant was obtained whether aniline or aniline hydrochloride was used as the quencher.

Diffusion Coefficients.—In order to calculate the molar encounter frequencies for the reaction, values of the diffusion coefficients D, of both dye and quencher are required. A search of the literature revealed that no values were recorded for uranin and aniline at 25°, in the solvents used. Hence, it was necessary to determine the diffusion coefficients in systems closely approximating those occurring during quenching measurements. The "diaphragm cell" method of measurement was employed,[16] using as a standard that value proposed by Gordon, $D = 1.838 \times 10^{-5}$ sq. cm./sec. for 0.10 molar potassium chloride for which $\Delta c_f/\Delta c_0$ is almost unity.

Analysis of the solutions in the upper and lower compartments was carried out as follows:

Potassium Chloride and Hydrochloric Acid.—Volumetric titration using standard procedures ("Elementary Quantitative Analysis" by Willard and Furman).

Uranin.—The uranin concentrations were measured in the fluorimeter after appropriate dilutions with solvent, until upper and lower intensities were comparable and in a range where reabsorption effects did not interfere.

Aniline.—Because of the decomposition which occurs in basic aniline with time, and the consequent shifting of absorption bands, it was necessary to do considerable trial work with basic aniline solutions, making periodic analyses at different wave lengths in the Beckman Ultraviolet Spectrophotometer. The absorption of aniline over a seventy-two hour period at wave lengths between 240 and 300 mμ was found to be sufficiently constant if the diffusion cells were painted black and the solutions protected as well as possible from the light.

The results for uranin and aniline in different solvents are given in Table II. The diffusion coefficients of 10^{-5} molar uranin in glycerol–water and sucrose–water solutions are plotted in Fig. 2 as a function of the weight percentage and mole fraction of glycerol or sucrose.

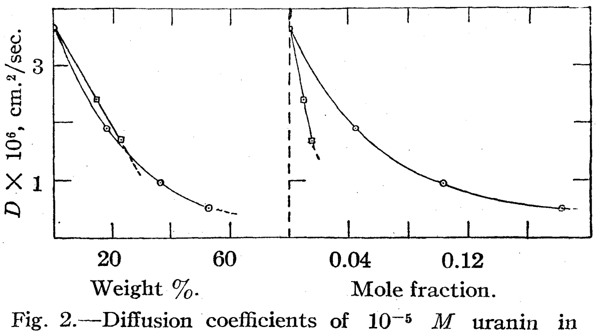


Fig. 2.—Diffusion coefficients of 10^{-5} M uranin in glycerol–water, ⊙, and in sucrose–water, ⊡, solution.

---

(15) E. J. Bowen, *Trans. Faraday Soc.*, **35**, 17 (1939).

(16) A. R. Gordon, *Ann. N. Y. Acad. Sci.*, p. 285 (1945).

TABLE II

DIFFUSION COEFFICIENTS, *D*, OF URANIN AND ANILINE IN VARIOUS SOLVENTS AT 25°

Solvent composition[a] Wt. % glycerol	M./l.	Mole fraction	$D \times 10^6$ (cm.²/sec.)	$r = kT/6\pi\eta D$ (Å. units)
Solute, 10^{-5} *M* Uranin				
0.0	0.0	0.0	3.67	6.6
19.2	2.18	.044	1.91	7.7
36.8	4.35	.103	0.95	8.8
53.1	6.52	.182	0.51	8.6
Sucrose				
14.2	0.44	0.0087	2.40	6.65
22.9	.73	.0153	1.71	6.7
43% Methanol			2.08	6.6
Methanol			5.64	6.5
Isopropanol			2.18	4.7
Ethanol			3.20	5.0
10^{-4} *M* Uranin in water			3.60	6.8
Solute, 0.010 *M* aniline				
Water			9.7	2.5
19.2% Glycerol			5.8	2.5
Methanol			19.3	2.0
Ethanol			10.0	1.6
Isopropanol			6.6	1.6

[a] All solutions *p*H 12.

Discussion of Results

Diffusion Coefficients.—Kinetic theory when applied to suspended particles in a medium yields,[17] $D = RT/NaF$. Here *R*, *T*, and *Na*, have their usual meanings and *F* is the frictional resistance, to movement of a particle. According to Stokes' law the frictional resistance for spherical particles, large compared to the molecules of solvent, is $F = 6\pi\eta r$, where "*r*" is the radius of the particle, and eta is the viscosity of the medium. Combining the equations yields

$$D = \frac{RT}{Na} \times \frac{1}{6\pi\eta r} \qquad (2)$$

The methods of testing the reliability of this equation have been to observe the constancy of the products $D\eta$, and Dr, as the other variables are changed. Excellent constancy is obtained when the viscosity is varied by changing the temperature in a fixed solvent. On the other hand, less quantitative agreement is obtained when the viscosity is varied by changing the solvent at a given temperature. The explanation, very likely, is that the frictional resistance given above is less applicable when the solute molecules approach the size of the solvent molecules. In the limit, for very small solute molecules, Sutherland[18] expressed the frictional resistance as $4\pi\eta r$. The radius for uranin is consequently more reliable than that for the smaller aniline molecule.

The effective diffusion radius of the uranin and the aniline, calculated from the Stokes–Einstein relation(2), are reported in Table II. In the glycerol–water mixtures the values of "*r*" for uranin increase slightly with increasing glycerol content. Solvation of the uranin by the glycerol could account for this increase. It is believed that the smaller values of the radii obtained in the alcohols may be due to the inadequacies of the Stokes–Einstein relation rather than to an actual radius decrease. Hence, in calculating encounter frequencies in the alcohols, the values of the radii obtained in water have been used for the reaction radius, *R*.

The radius value obtained for uranin in water, 6.6 Å. (*p*H 12), checks well with the value, 6.8 Å., reported by Marenesco[19] for neutral fluorescein, but differs somewhat from his value, 5.5 Å., for uranin in 0.75 molar sodium hydroxide. Both of Marenesco's values were obtained from viscosity measurements.

Marenesco measured the diffusion coefficients for other dyes—Rhodamine B, Eosin—(see Table III) which are similar in structure to uranin, in solutions of *p*H 6.2–7. In this range of *p*H these dyes are not appreciably ionized. There is disagreement between the results of Marenesco and the authors in respect to the trend in radii resulting from the change of solvent from water to alcohols. This divergence probably results from the fact that the two sets of measurements involve substances of different electric charge type, namely, Marenesco's are on a molecule, and these upon ion. Likewise, all of the present measurements were carried out in solutions of 0.01 *M* sodium hydroxide concentration, and the dye was several hundred-fold more dilute. In addition, the differences of the dielectric constants in the solvents used may effect the diffusion in the case of the uranin.

TABLE III

COMPARISON OF DIFFUSION COEFFICIENTS IN DIFFERENT SOLVENTS

Solvent	Marenesco, 20°C. Base concn. = 10^{-7}–10^{-8} *M* $D \times 10^6$ (sq. cm./sec.)		*r* in Å.	This investigation, 25°C. Base concn. = 10^{-2} *M* $D \times 10^6$ (sq. cm./sec.)		*r* in Å.
Water	3.3	Rhodamine B	6.5	3.7	Uranin	6.6
	3.3	Eosin	6.5			
Methanol				5.64	Uranin	6.5
Ethanol	2.4	Rhodamine B	7.5	3.20	Uranin	5.0
	2.1	Eosin	8.6			
Isopropanol				2.18	Uranin	4.7

Quenching Constants.—It may be seen from Table I and Fig. 1 that the results for the dependence of k_Q on η for the different types of solvents do not coincide with each other. The results show a decided dependence on the type of solvent used to obtain the macroscopic viscosity. Sveshnikoff[14] measured I_0/I values for the same reaction in a series of alcohols at various temperatures and reported no specific solvent effects.

---

(17) A. Einstein, *Z. Electrochem.*, **14**, 235 (1908).

(18) W. Sutherland, *Phil. Mag.*, [6] **9**, 781 (1905).

(19) N. S. Marenesco, *J. Chim. Phys.*, **24**, 593 (1927).

Unfortunately, it is impossible to correct his measurements for the various interfering effects mentioned previously. Hence, we are unable to report properly corrected quenching constants from his data.

The present results follow three general paths. Starting with water and increasing the viscosity by additions of either glycerol or sucrose, the quenching constants decrease along what has been labelled—path 1—in Fig. 1. The results in methanol, ethanol and isopropanol fall in a series by themselves—path 3—running more or less parallel to the water–glycerol series. However, in changing solvent from methanol to water through a series of methanol–water mixtures, the quenching constants follow path 2. The essentially different nature of methanol-rich mixtures and water-rich mixtures of the same macroscopic viscosity accounts for the effect of these solutions on the quenching constants.

The effect of solvent on the quenching constant, other than that caused by the macroscopic viscosity, may be partially interpreted by the effect of the solvent changes on the lattice distance "*a*." The larger value of "*a*" which one would expect in alcohols over that value in water will reduce k_D, the encounter frequency. For example, if the lattice distance be assumed equal to the cube root of the volume per molecule in the following solvents, the decreases in k_D are evident:

Solvent	Molar vol.	"*a*" in Å.	k_D ("*a*" const.)	k_D ("*a*" from column 3)
Water	18	3.1	122 (a = 3.1)	122
Methanol	40	4.1	226 (a = 3.1)	171
Ethanol	58	4.6	120 (a = 3.1)	81
Isopropanol	77	5.0	79 (a = 3.1)	50

Part of the specific solvents effects on the quenching of fluorescence may not have been recognized in the calculation of k_D, the encounter frequency, because the method of measurement of the diffusion coefficients in the various solvents involves the determination of large concentration differences. The true driving force of diffusion is not concentration gradient, but rather gradient of chemical potential or its index, the activity. This may necessitate corrections in k_D which cannot be made easily and it has been necessary to ignore them when treating the data.

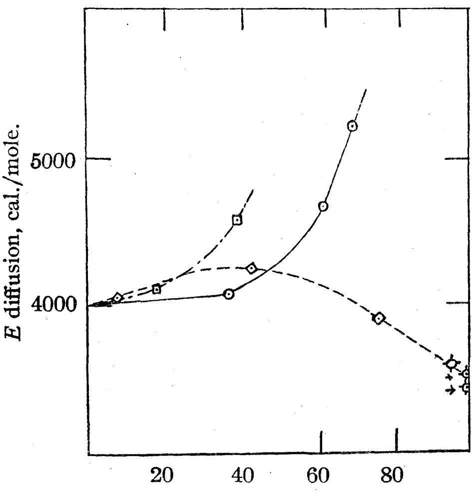


Fig. 3.—Energy of activation of diffusion as a function of solvent: —, ⊙, glycerol–water; – – –, ⊡, sucrose–water; — — —, ◇, methanol–water.

The probability of reaction per encounter, "p"[8] may change with changing solvent. This probability may be equated to the ratio of the probability of reaction per collision to the sum of the probabilities of reaction per collision plus the probability of diffusion out of the encounter by either reactant between collisions

$$p = \frac{P \exp.\ (-E\ \text{act.}/RT)}{P \exp.\ (-E\ \text{act.}/RT) + C \exp.\ (-E_{\text{diff.}}/RT)} \qquad (3)$$

It seems reasonable to assume that the solvent forming the cage will have only a small effect on the chemical energy of activation. However, it is well known that the energy of activation of diffusion, $E_{\text{diff.}}$, varies considerably in different solvents. It is at once apparent that the lower the value of the energy of activation of diffusion, the more likely an encounter is to be broken by diffusion between collisions. Thus the probability of reaction per encounter must diminish.

From the "p" values obtained from comparison of measured quenching constants with the calculated encounter frequencies, the energies of activation of diffusion have been calculated. The chemical energy of activation has been calculated to be 3900 cal./mole by the method of Williamson and La Mer[8] with k_D from equation 1. The energy of activation of diffusion in water was chosen as 4000 cal./mole at 25°. The ratio C/P (equation 3) equals 5, and for the $E_{\text{diff.}}$ calculations the steric factor P has been assumed unity. Selected $E_{\text{diff.}}$ values are given in Table IV. The energies of activation of diffusion of the solvents used are plotted as a function of solvent composition in Fig. 3.

The glycerol–water and sucrose–water solutions yield values of the energy of activation of diffusion of 4000 cal./mole or more in all cases. The solvents methanol, ethanol and isopropanol give values around 3500 cal./mole. The energies of activation of diffusion pass through a maximum in the methanol–water mixtures.

The literature gives the following information on energies of activation of diffusion. Quantitative data on energies of activation of diffusion are relatively scarce due to the difficulties of measurement. Scheffer and Scheffer's[20] data on the diffusion of mannitol in water yield an $E_{\text{diff.}}$ of 4460 cal./mole in the temperature range 20–30°. Other data calculated from the "International Critical Tables" for the solvent water gives $E_{\text{diff.}}$

---

(20) J. Scheffer and F. Scheffer, *Proc. Acad. Sci. Amsterdam*, **19**, 148 (1916).

at 15° as about 5000, while for iodine in methanol at 15° $E_{\text{diff.}}$ is 4100, and iodine in ethanol in the range 8–18° is 3700 cal./mole. In general when the solute molecules are large, $E_{\text{diff.}}$ is a function of the solvent rather than the solute.

Eyring[21] states that the energy of activation of diffusion is related to the energy of evaporation by a factor ranging between 3 and 4. For water and the alcohols these values have been calculated and are given in Table IV, assuming a constant factor of 3. The energy of activation of viscosity has been calculated from the temperature dependence of measured viscosities.

TABLE IV

OBSERVED AND CALCULATED VALUES OF THE ENERGY OF ACTIVATION OF DIFFUSION

Solvent	k_D (calcd.)	k_Q (meas.)	p	E_D (obs.) (cal./mole)	$E_{\text{visc.}}$ (calcd.) (cal./mole)	
36.8 Wt. % glyc.	55.9	11.4	0.20	4070	20%	4620
61.5 Wt. % glyc.	16.8	6.9	.41	4670	40%	5570
69 Wt. % glyc.	10.9	6.8	.63	5210	60%	7110
18.6 Wt. % sucrose	67.8	14.4	.21	4110	20%	4620
39.2 Wt. % sucrose	23.6	8.7	.37	4590	40%	6110
8.1 Wt. % methanol	98	19.6	.20	4070	47.4%	4560
43 Wt. % methanol	62.4	15.8	.25	4260	71.6%	3700
76 Wt. % methanol	87.0	14.2	.16	3910		
Methanol	171	15.9	.09	3540	2430	
Ethanol	81	8.1	.10	3580	$E_{\text{vap.}}/3$-3140	
Isopropanol	79	6.2	.08	3440	$E_{\text{vap.}}/3$-3170	
Water	122	22.0	.18	4000	$E_{\text{vap.}}/3$-3520	
					$E_{\text{visc.}}$	3700

The trends shown are all in agreement with the experimental results. Better quantitative agreement would be fortuitous, considering the original assumptions. Note that in Table IV, when p is small, the $E_{\text{diff.}}$ is small. This means that the probability of reaction during an encounter will be less the more easily the reactants can diffuse out of the encounter between collisions.

The dependence of quenching constants on the viscosity of the solvent will vary depending on the choice of solvent, and the chemical energy of activation for the particular fluorescent material and quencher. A linear relationship between quenching constant and fluidity will be the exception.

The data of this investigation have been recalculated on the basis of the normalized mole fraction concentration scale.[22] No advantage has been gained by such a change in this reaction.

Acknowledgments.—The authors wish to express their appreciation for the suggestions made by Professor G. E. Kimball and Dr. J. Q. Umberger.

The award of a National Research Council Predoctoral Fellowship to one of us (K.C.H.) made possible the completion of this work.

Summary

1. The kinetics of the quenching of the fluorescence of uranin by aniline has been investigated as a function of the viscosity of the solvent in which the reaction is carried out.

2. The diffusion coefficients, D of uranin and aniline have been measured using the diaphragm-cell method in the solvents water, methanol, ethanol, isopropanol, water–glycerol and water–sucrose. They are reported and discussed in terms of the theories pertaining to diffusion.

3. The molar quenching constants are dependent on properties other than the macroscopic viscosity of the solvent. Hence, the previously expected linear relationship between quenching constants and the reciprocal of viscosity need not hold. The data are interpreted in terms of both the diffusion of the reactants together and the probability of reaction when the two are in an encounter. This latter quantity is controlled by an energy of activation of diffusion. The functional dependence of quenching constants on viscosity will depend on the choice of solvent used to vary the viscosity.

---

[21] Glasstone, Laidler and Eyring, "Theory of Rate Processes," The McGraw-Gill Book Co., New York, N. Y., 1941, p. 523.

[22] H. G. Davis and V. K. La Mer, *J. Chem. Phys.*, **10**, 585 (1942).

NEW YORK, N. Y. RECEIVED OCTOBER 14, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL CHEMISTRY, THE HEBREW UNIVERSITY]

Some Catalytic Hydrogen Exchange Reactions of Hydrocarbons

BY J. AMAN, L. FARKAS AND A. FARKAS[1a]

The catalytic exchange reaction of hydrocarbons with molecular hydrogen has been the subject of a large number of investigations.[1b-8] Two different mechanisms have been proposed for the reaction: (a) the dissociative and (b) the associative mechanism. The dissociative mechanism may be formulated as

$$RH_2 \xrightarrow[-H]{+K} RH - K \xrightarrow[+D]{-K} RHD \qquad (1)$$

On the other hand Polanyi and Horiuti have suggested the following associative mechanism for the exchange reaction

$$RH_2 \xrightarrow[+D]{+K} RH_2D - K \xrightarrow[-H]{-K} RHD \qquad (2)$$

(K = catalyst)

The half-hydrogenated compound which is formed by the first step in (2) is according to these authors responsible for the connection between the hydrogenation and exchange reaction, since it is an intermediate compound for both processes.

While all experiments on the exchange of saturated hydrocarbons indicate that in these cases the dissociative mechanism is operative[4,5,9,10] the exact mechanism of the exchange reactions of unsaturated hydrocarbons has not yet been definitely settled.

The present paper reports some results on the exchange of the following pairs of compounds: ethylene and water, *n*-butene and water, *n*-butane and water, *n*-butene and ethylene, and *n*-butane and ethylene. The mechanism of the catalytic exchange reactions is discussed in the light of these findings.

Experimental

Material

Ethylene was obtained either from a cylinder from the Ohio Chemical Co. or by dehydration of ethyl alcohol in the presence of alumina at 400°.

***n*-Butene** was prepared by the dehydration of *n*-butyl alcohol by means of alumina at 400°. The two isomers butene-1 and butene-2 thus obtained were used without separation.

***n*-Butane** was prepared by the hydrogenation of *n*-butene with an excess of hydrogen on a nickel or palladium catalyst.

Heavy *n*-butane was prepared by hydrogenating *n*-butene with deuterium in the presence of either nickel or palladium.

All the above mentioned hydrocarbons were purified by fractional distillation under low pressure.

Palladium Catalyst.—This was prepared by passing hydrogen through a suspension of 5 g. of activated charcoal (lumps) in a concentrated solution of 1 g. of palladium chloride at 50–60° until the solution was completely decolorized. The lumps of catalyst were washed with distilled water, neutralized with a dilute solution of sodium hydroxide, and again washed with distilled water until free of chloride ions. The catalyst was then dried at 100° in vacuum. The catalyst thus obtained contained about 10% palladium by weight.

Nickel Catalyst.—Raney nickel in the form of either powder or lumps was used. It was prepared in the usual way by dissolving out the aluminum with a concentrated solution of sodium hydroxide. The catalyst was protected from contact with air prior to use (for method of handling, see below).

Apparatus and Procedure

Two methods were used: (1) a static method in which the apparatus consisted essentially of a large reaction bulb, and (2) a circulating method in which the reacting gases were circulated over the catalyst by means of a pump.

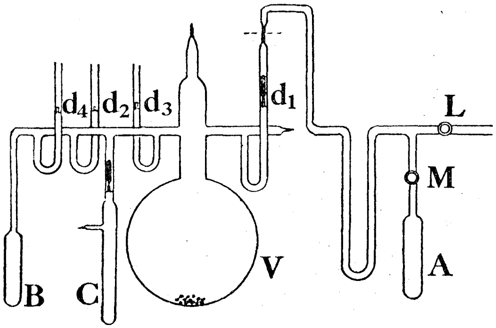


Fig. 1.—Reaction vessel (static method).

(1) In the static method (Fig. 1) reaction vessels 1 to 5 l. capacity were used. They were fitted with one or more break-seals, *d*, for the introduction or withdrawal of samples. The side-arm, B, served for the condensation of the reactants. If water was one of the reactants, it was previously degassed in a small glass tube and sealed off under vacuum. This tube, C, was connected to the reaction vessel via a break-seal. The palladium catalyst was introduced directly into the reaction vessel. When a nickel catalyst was used the following procedure was adopted: the nickel powder or lumps were washed by decantation with distilled water until free of alkali and transferred, while still wet, to a thin-walled glass tube. This tube was then connected via a trap cooled in an acetone–Dry Ice slush to a high vacuum system and the water distilled off. The catalyst was then degassed by heating to 200° for several hours, sealed off, and introduced carefully into the reaction vessel which was then evacuated. Grease and mercury vapors were excluded during this operation by a Dry Ice trap. Known amounts of the gaseous reactants were then distilled into the side-arm, B, by cooling it with liquid air, and the reaction vessel was sealed off. Water, if one of the reactants,

---

[1a] Present address: The Barrett Division, Allied Chemical & Dye Corporation, Philadelphia.

[1b] A. Farkas, L. Farkas and E. K. Rideal, *Proc. Roy. Soc.* (*London*), **A146**, 630 (1934).

[2] A. Farkas and L. Farkas, THIS JOURNAL, **60**, 22 (1938).

[3] I. Horiuti and M. Polanyi, *Trans. Far. Soc.*, **30**, 1164 (1934).

[4] K. Morikawa, W. S. Benedict and H. S. Taylor, THIS JOURNAL, **58**, 1145 (1936).

[5] K. Morikawa, N. R. Trenner and H. S. Taylor, *ibid.*, **59**, 1103 (1937).

[6] A. Farkas and L. Farkas, *Trans. Far. Soc.*, **33**, 827 (1937).

[7] G. H. Twigg and E. K. Rideal, *Proc. Roy. Soc.* (*London*), **171**, 55 (1939).

[8] G. K. Conn and G. H. Twigg, *ibid.*, **171**, 70 (1939).

[9] A. Farkas and L. Farkas, *Trans. Far. Soc.*, **35**, 917 (1929).

[10] A. Farkas, *ibid.*, **36**, 522 (1940).

was then admitted into the reaction vessel by breaking the appropriate break-seal. If nickel was used as a catalyst, the reaction vessel was shaken vigorously at this stage, until the thin-walled tube containing the catalyst was broken. The reaction vessel was then heated in an electric furnace at a constant temperature for a definite time, after which it was connected through one of its break-seals to the evacuating system, thus enabling a sample of the contents to be withdrawn into A and analysed.

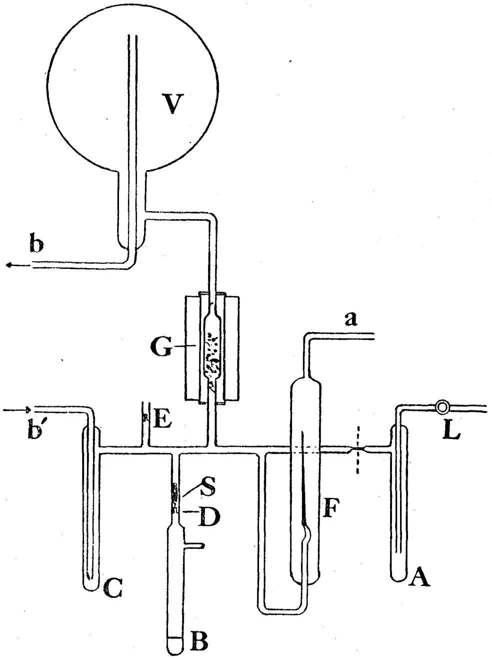


Fig. 2.—Reaction apparatus (circulating method).

(2) In the circulating method (Fig. 2) an all glass electromagnetic pump was used for circulating the reactants over a palladium catalyst heated to the desired temperature in an electric furnace, G. At the start of an experiment, the reaction system was evacuated and the catalyst outgassed at 150°. The reacting gas was then introduced through a trap, A, cooled in an acetone–Dry Ice slush into the tube, C, which was cooled in liquid air. After sealing off from the evacuating system, the break-seal D was broken, so that the water in B distilled over into C; the circulating pump was then started. The temperature of the catalyst was fixed at the desired value and the gas allowed to evaporate and bubble through the water in C which was kept at a constant temperature. After a certain time the reacting gas and water were withdrawn through the break-seal E and analysed. An all glass Bourdon type gage, F, was used to measure the change of pressure in the apparatus.

The electromagnetic pump (Fig. 3) differed in the following details from those described previously.[11,12]

(a) Only one electromagnet E was used for lifting the piston (consisting of an iron rod 25 mm. in diameter and 300 mm. long enclosed in a glass tube) and (b) a mercury switch M instead of an electric motor was used for interrupting the current. The pump works as follows: when a direct current from a 220 v. source is switched on, the electromagnet E lifts the piston; at the same time two small electromagnets, D, connected in parallel with E work against the spring, L, and tip the mercury switch, M, so that the current is interrupted. The piston then falls down freely while the spring L brings the switch M back to its initial position. The cycle is then repeated. With a current of 0.3 ampere the pump could circulate 1.1 l., of gas per minute against a back pressure of 110 mm. When only gaseous reactants were used the pump could work for several hundred hours without interruption. When water vapors were circulated, the piston stuck to the glass wall after about fifty hours and had to be cleaned.

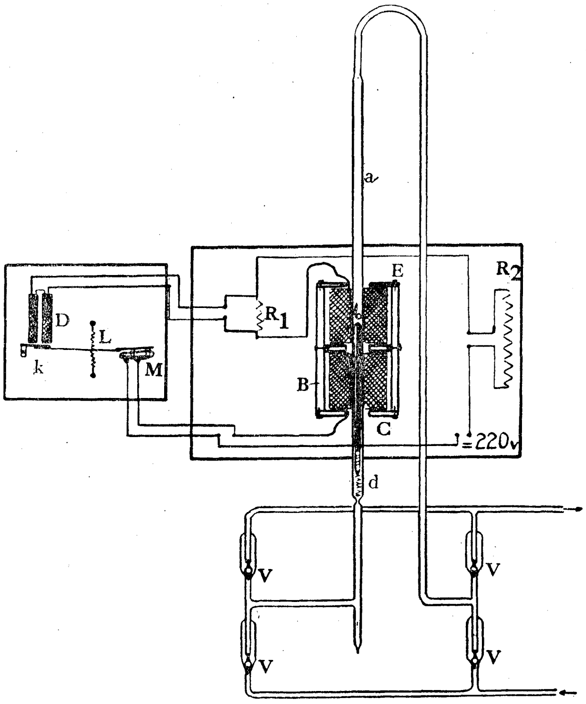


Fig. 3.—All glass electromagnetic circulating pump.

Analytical

The water was separated from the hydrocarbon by distillation in vacuum. It was further purified by the addition of anhydrous sodium carbonate and potassium permanganate and redistilling in vacuum. It was then analyzed for its deuterium content by the float method with an accuracy of 1 part of D_2O in 5×10^4 parts of H_2O. If 0.5 to 1 g. of the hydrocarbon were available, it was burnt over platinized asbestos and the water obtained after purification was analyzed by the float method. If only small samples of the hydrocarbon (3–5 mg.) were available, the analysis was carried out by a method described previously[13] consisting of burning the hydrocarbon to water over copper oxide and bringing this water into equilibrium with a minute amount of hydrogen by means of a glowing platinum filament. The deuterium content of the hydrogen was then analyzed by the microconductivity method.

Experimental Results

Exchange between Ethylene and Water.—The results of these experiments are given in Table I. Experiments 1, 2, 3, 15 and 16 were performed by the circulating method, and 4 and 5 by the static method. In Expt. 16 both the water and the ethylene were analyzed, in the others the deuterium content of the ethylene was calculated from the change in the deuterium content of the water. The last column of Table I shows the values of the partition

$$K = (D/H)\text{ ethylene}/(D/H)\text{ water}$$

---

[11] R. Livingstone, *J. Phys. Chem.*, **33**, 955 (1929).

[12] W. Brenschende, *Z. physik. Chem.*, **A178**, 74 (1937).

[13] A. Farkas, *Trans. Far. Soc.*, **32**, 413 (1936).

TABLE I

EXCHANGE BETWEEN ETHYLENE AND WATER

				Water				Ethylene				
Expt.	Catalyst	Temp., °C.	Reac. time, hours	Moles	Partial pressure, mm.	% D-content initial	% D-content final	Moles	Partial pressure, mm.	% D-content initial	% D-content final	Partition, *K*
15	Pd (0.5 g.)	110	190	0.047	300	9.8	9.6	...	...	..	..	..
3	Pd (2 g.)	80	30	.10	17.5	1.00	0.99	0.076	500	0.00	0.00	0.00
1	Pd (2 g.)	120	20	.11	17.5	1.22	1.21	.069	400	.00	.00	.00
16	Pd (1 g.)	110	45	.31	17.5	9.9	9.5	.090	600	.00	.11	.01
2	Pd (2 g.)	170	21	.11	17.5	1.24	1.14	.070	500	.00	.07	.06
4	Pd (1.5 g.)	110	118	.083	350	1.05	0.44	.062	260	.00	.41	.93
5	Ni (5 g.)	110	140	.083	350	4.43	1.69	.088	370	.00	1.29	.76

It is seen from Table I that no exchange, or at most only a very slow one, occurred when the circulating method was used, even at a temperature of 170°. On the other hand, equilibrium was almost reached in the static method experiments. The longer reaction time in Expts. 4 and 5 cannot explain the higher deuterium values observed in the ethylene, and we have to assume that the much higher partial pressure of water (350 mm.) as compared with that in the circulating method experiments (17.5 mm.) is responsible for the higher rate of exchange. The dependence of the rate of exchange on the partial pressure of water and ethylene has not yet been investigated further.

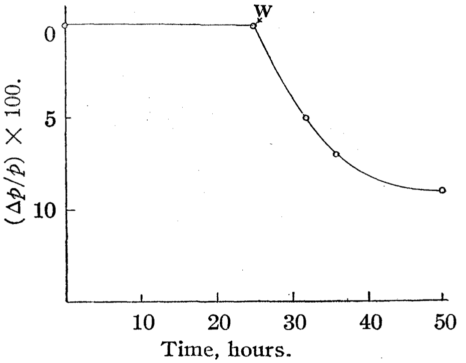


Fig. 4.—Polymerization of ethylene in the presence of water.

It was noticed that, in those experiments in which there was no appreciable exchange, a decrease of the pressure in the reaction system occurred due to polymerization. In Fig. 4 the change of pressure in Expt. 16 is given. It will be seen that the pressure change occurred only in the presence of water but not in the absence of water during the first twenty-five hours. After a certain reaction time, the catalyst becomes poisoned by traces of a high polymer and its activity considerably reduced. By determining the vapor pressure of the polymerization product at eight different temperatures between −60 and −25°, it was found to be butene-2. In Expts. 4 and 5 with high partial pressure of water no polymerization was observed. Besides the polymerization two side reactions also occurred in the presence of the palladium catalyst: the formation of small amounts of ethyl alcohol and acetic acid.

Exchange between Butene and Water.—The experimental results are given in Table II. In Column 13 the equilibrium values of the deuterium content of the butene are given. They were calculated on the assumption that all the eight hydrogen atoms are exchangeable and that the partition coefficient for this reaction is 0.8 (*i. e.*, the same as in the case of the ethylene and water). Column 14 gives the first order velocity constant

$$k = \frac{1}{t} \ln \frac{D_e}{D_e - D_t}$$

where D_e and D_t denote the deuterium content at equilibrium and at time t, respectively. It can be seen that in all cases an exchange between the hydrogen atoms of the water and the hydrogen atoms of the butene took place. Figure 5 shows the course of the exchange in Expt. 21. It can be seen that here also the catalyst gradually lost its activity.

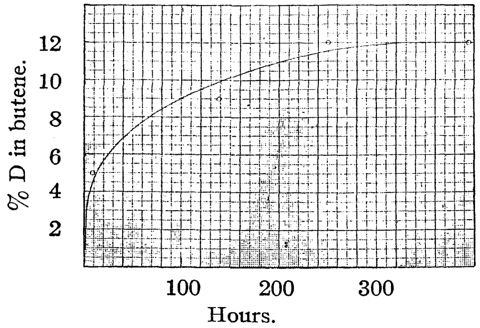


Fig. 5.—Exchange between butene and water at 120°.

The water recovered after exchange in the presence of the palladium catalyst contained an unidentified acid and also a solid polymer which remained behind on evaporating off the water.

Exchange between Butane and Water.—No exchange between butane and water was observed under conditions under which the exchange between butene and water took place readily (catalyst: 2 g. palladium; temperature, 120°; reaction time, 160 hours; p_{H_2O} = 220 mm.; $p_{C_4H_{10}}$ = 20 mm.). This negative result was not due to (accidental) inactivity of the catalyst, since the same catalyst was used in a subsequent experiment (Expt. 20, Table II) for the reaction between butene and water in which an exchange was observed.

TABLE II

EXCHANGE BETWEEN BUTENE AND WATER

				Water				Butene					
Expt.	Catalyst	Temp., °C.	Reacn. time, hours	Moles	Partial pressure, mm.	% D-content initial D_0	% D-content final D_t	Moles	Partial pressure, mm.	% D-content initial D_0	% D-content final D_t	D-content of butene at equilib. %	$k \times 10^3$/hr.
7	Ni (8 g.)	110	166	0.08	320	4.43	1.43	0.09	360	0.0	0.68	0.77	13.2
9[a]	Pd (2 g.)	110	159	.073	280	96.0	53.3	.016	61	0.0	23.8	47.3	4.4
11	Pd (2 g.)	110	235	.058	230	96.0	66.0	.021	83	0.0	21.0	36.3	3.7
12	Pd (2 g.)	110	284	.056	220	96.0	80.2	.018	70	21.0	32.6	51.9	1.7
13	Pd (1 g.)	110	307	.054	200	96.0	85.0	.016	59	32.6	40.2	59.4	1.1
14	Pd (0.5 g.)	110	314	.061	240	96.0	85.0	.0046	18	0.0	21.5	70.4	1.2
20	Pd (0.5 g.)	120	17.5	.058	230	99.6		.0054	21	0.0	3	65.5	2.6
20a	Pd (0.5 g.)	120	61	.058	230	99.6		.0054	21	0.0	8	65.5	2.1
21	Pd (0.5 g.)	120	7.75	.058	230	99.6		.0057	23	0.0	5	68	9.3

[a] In Experiments 9, 13 and 14 the increase of the D-content of butene does not quite correspond to the decrease of the D-content of the water.

TABLE III

EXCHANGE BETWEEN BUTENE AND ETHYLENE

				Ethylene				Butene					
Expt.	Catalyst	Temp., °C.	Reacn. time, hours	Moles	Partial pressure, mm.	% D-content initial D_0	% D-content final D_t	Moles	Partial pressure, mm.	% D-content initial D_0	% D-content final D_t	% D-content at equilib.	$k \times 10^3$/hr.
6	Ni (5 g.)	110	140	0.058	220	1.29	0.77	0.045	170	0	0.34	0.50	
8	Ni (6 g.)	110	211	.061	175	0	0.21	.047	135	0.68	0.54	0.41	3.4
10	Pd (2 g.)	110	123	.0052	125	0	5.5	.0067	150	23.8	21.7	17.1	3.2
17	Pd (0.5 g.)	110	300	.0047	100	0	17	.0116	250	40.2	36.7	33.5	2.4
18	Pd (0.5 g.)	120	10.75	.0011	25	0	7	.0026	60	36	30.4	29.6	25
23	Pd (0.5 g.)	120	90	.0030	70	0	5	.0047	12	12	11.0	9.1	6.3

Exchange between Butene and Ethylene.—The results are given in Table III. In all these experiments, except in Expt. 6, "heavy" butene was used in order to exclude the possibility of an apparent exchange reaction due to dimerization of "heavy" ethylene. Column 13 gives the equilibrium values of the deuterium content of the two hydrocarbons assuming a partition coefficient of 1. All the hydrogen atoms in the butene were assumed to be exchangeable. Column 14 gives the first order velocity constant. In all cases only the deuterium content of the ethylene was determined. Ethylene was chosen rather than butene, since the change in its deuterium content is relatively higher. In Expt. 18, a series of measurements on the progress of the exchange reaction was also made (see Fig. 6). During the reaction no change of pressure occurred.

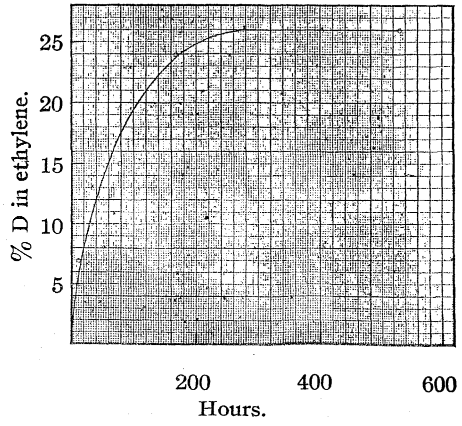


Fig. 6.—Exchange between butene and ethylene.

Exchange between Butane and Ethylene.—The exchange between butane and ethylene was tested by the same procedure as used in Expt. 18 of Table III: 0.0052 mole of butane (D-content 45%) and 0.0021 mole of "light" ethylene were allowed to interact on the palladium catalyst for one-hundred fifteen hours at 120°. After this treatment the deuterium content of the ethylene was found to be 1%. This increase was within the limits of experimental error. After this period, a small amount of "light" butene (0.0002 mole) was introduced into the reaction vessel in order to test whether the exchange between butane and ethylene proceeds via butene. After a period of one-hundred thirteen hours, the deuterium content of the ethylene rose to 1.5%. The possibility that these negative results were due to an accidental inactivation of the catalyst was excluded by using the same catalyst for the exchange of butene and ethylene in Expt. 23 of Table III.

The activity of the same catalyst was also tested for the exchange reaction of butane with deuterium. The catalyst which was used in the butane–ethylene exchange (one-hundred fifteen hours), butane–ethylene–butene exchange (one-hundred thirteen hours) and butene-ethylene (ninety hours; Expt. 23) was brought into contact with 0.0043 mole of "light" butane and 0.0028 mole of deuterium (99.6% D_2) in the same reaction vessel at 120°. The deuterium content in the butane was found to be 6 and 9% after thirteen and one-half and thirty-five and one-half hours, respectively.

Discussion

The exchange of water with ethylene has been observed by Horiuti and Polanyi,[3] and the present experiments are in qualitative agreement with their results. In the experiments of these authors, the ratio $p_{H_2O}/p_{C_2H_4}$ was 2.6. In the present experiments this ratio was about 1 when the static method was used and only 0.029 to 0.044 in the circulating method. These experiments show a strong dependence of the rate of exchange on the ratio of the partial pressures of water and ethylene and the simplest assumption is that water is displaced from the surface of the catalyst by ethylene if the ratio $p_{H_2O}/p_{C_2H_4}$ is low. On the other hand, the absence of dimerization of ethylene in the presence of a high partial pressure of water would suggest that under these conditions the ethylene concentration on the surface layer is low, so that ethylene–ethylene interaction becomes slow. At low partial pressures of water, the dimerization of ethylene could be explained by the well-known mechanism of carbonium ion formation

$$C_2H_4 + H_2O \longrightarrow C_2H_5^+ + OH^- \qquad (3)$$

$$C_2H_5^+ + C_2H_4 \longrightarrow C_4H_8 + H^+ \qquad (4)$$

If the first step goes only in a forward direction and the second step in this scheme is rapid, it would explain the absence (or relatively slow rate) of exchange of ethylene with water under these conditions. According to this mechanism the deuterium content of the dimer (butene) should have the value of 12.5% (one deuterium atom out of eight hydrogen atoms) if the dimerization were catalyzed by deuterons from pure deuterium oxide. In Expt. 16 of Table I, in which the content decreased from 9.86–9.6% a butene with 1.14% D-content should be obtained. The D-content of the butene formed by dimerization was not determined.

In the case of the exchange reaction between ethylene and water, the possibility that the reaction $C_2H_4 + H_2O \rightleftarrows C_2H_5OH$ contributes substantially to the exchange must be considered. However, a quantitative consideration shows that this is improbable. The equilibrium constant of this reaction is at 110° about 0.068,[14,15] so that at the equilibrium in Expts. 4 and 5 about 1.5% of ethyl alcohol should be formed. In fact only in Expt. 4 in the presence of palladium catalyst was the formation of ethyl alcohol detectable. Nevertheless the exchange also takes place on a nickel catalyst at a similar rate, and in this case there is no evidence that ethyl alcohol is formed.

This observation, together with the fact that ethyl alcohol and water on a platinum catalyst[16] exchange only the hydrogen atom of the hydroxyl group, show that the above reaction is a slow one and does not play an important role in the exchange process under our experimental conditions.

The general features of the butene–water exchange are similar to those of the ethylene–water exchange. In these experiments the $p_{H_2O}/p_{C_2H_4}$ ratio was between 0.9 and 10. These extreme values of the ratio do not influence the rate of exchange to a great extent. On the basis of the present experiments it is not possible to decide whether those hydrogen atoms attached to the double bonded carbon atoms exchange more readily than the remainder. Of particular significance is the absence of exchange between butane and water under conditions under which the exchange between butene and water takes place readily.

Horrex, Greenhalgh and Polanyi[17,18] found that the rate of exchange of benzene with water is about the same as that of cyclohexane and isopentane with water, and inferred that in general the exchange rate of saturated and unsaturated hydrocarbons with water is the same. Our observations indicate that this generalisation is not permissible, and that the similarity in the rates of exchange in the cases investigated by Horrex, Greenhalgh and Polanyi is accidental and dependent upon certain particular experimental conditions (partial pressures and temperature). The experiments on the exchange of ethylene with water show clearly that the ratio of partial pressures has a decisive influence on the rate of exchange of this pair, and it is probable that a more or less pronounced dependence on the ratio of partial pressures of the reactants may also occur in other cases. The comparison of the rate of exchange of butene and butane with water on the same catalyst under identical conditions suggests that in the case of the butane–water pair the absence of exchange is due to a complete displacement of butane by water from the catalyst. This mutual displacement strongly influences the rate of interaction on the catalyst, and it has already been emphasized in previous publications that this effect has to be taken into account.

The same authors also discussed the two possible mechanisms of exchange in the light of their findings that the rate of exchange between water and saturated hydrocarbons was similar to the rate of exchange between hydrogen and saturated hydrocarbons and came to the conclusion that the dissociative mechanism can be operative only if the first step in the scheme

$$RH_4 \underset{-H}{\overset{+K}{\longrightarrow}} RH_3 - K \underset{+H}{\overset{-K}{\longrightarrow}} RH_4$$

---

(14) A. W. Francis, *Ind. Eng. Chem.*, **20**, 283 (1928).

(15) A. W. Francis and R. V. Kleinschmidt, *Oil Gas J.*, **27**, 118 (1929).

(16) A. Farkas and L. Farkas, *Trans. Far. Soc.*, **33**, 628 (1937).

(17) C. Horrex, R. K. Greenhalgh and M. Polanyi, *ibid.*, **35**, 511 (1939).

(18) R. K. Greenhalgh and M. Polanyi, *ibid.*, **35**, 520 (1939).

is the rate determining step. It was assumed that the chemisorbed hydrogen atoms on the catalyst arising from the presence of molecular hydrogen must be greater than that arising from the presence of water and therefore the second step should be much faster in the former case than in the latter. Actually we have found this to be the case in our exchange experiments with butane and water and butane and hydrogen so that the above conclusion that the second step cannot be the rate determining step can be upheld in its general form.

The experiments on the exchange of hydrogen atoms between ethylene and butene are of particular interest, in connection with the question as to whether or not unsaturated hydrocarbons undergo dissociation on the surface of the catalyst. Conn and Twigg[8] investigated the interaction of C_2H_4 and C_2D_4 on a nickel catalyst at 76° and 330–360°, but found that no ethylene molecules containing both hydrogen and deuterium atoms were formed, even if the time of interaction was much longer than the half life time of the exchange of ethylene with deuterium on the same catalyst. They considered these experiments as a direct proof that no dissociation of unsaturated compounds takes place to any appreciable extent, and concluded that the exchange of ethylene and deuterium must follow the associative mechanism.

It has been pointed out,[19] however, that this negative result might be due to the fact that under the experimental conditions of these authors the stationary concentration of hydrogen atoms on the surface of the catalyst was so low that the mutual exchange of C_2H_4 with C_2D_4 was inappreciable. The hydrogen concentration on the catalyst might be very low if the atoms formed by dissociation are removed from the catalyst by reaction with ethylene.

The present observations on the exchange of butene with ethylene show directly that unsaturated hydrocarbons can exchange their hydrogen atoms and although the observed rates were not very great (the same order of magnitude as the exchange rates with water) they show that there is only a quantitative difference in the behavior of unsaturated and saturated hydrocarbons. The negative result of the exchange experiment with ethylene and butane is presumably due to the displacement of the butane from the surface of the catalyst by ethylene.

Summary

The following exchange reactions of hydrogen atoms on palladium and nickel catalysts at pressures of 20–700 mm. and in the temperature range of 80–170° were investigated: water and ethylene, water and butene, water and butane, butene and ethylene and butane and ethylene.

It was found that exchange of hydrogen atoms between ethylene and water, butene and water and butene and ethylene does occur while under the same experimental conditions no exchange between butane and water or butane and ethylene was observed.

The experimental results are discussed and the importance of the mutual displacement of the reactants on the catalyst surface is emphasized. The two possible mechanisms for the exchange reactions are discussed in the light of the new experimental evidence.

JERUSALEM, PALESTINE RECEIVED SEPTEMBER 23, 1947

---

[19] A. Farkas, *Trans. Far. Soc.*, **35**, 910 (1939).

[CONTRIBUTION FROM THE NATIONAL BUREAU OF STANDARDS]

The Effect of Substituents upon the Rate of Fading of Some Sulfonphthalein Indicators in Alkaline Solutions

BY ELIZABETH E. SAGER, ARTHUR A. MARYOTT AND MARJORIE R. SCHOOLEY

I. Introduction

The usefulness of an indicator in the measurement of *p*H depends, in part, on its chemical stability. Phenolphthalein and some of the substituted phenolphthaleins show a pronounced tendency to fade, particularly in alkaline solutions. Replacement of the carboxyl group in the phenolphthaleins by the sulfonic acid group to form the phenolsulfonphthaleins greatly increases the stability. Sulfonphthaleins covering practically the entire useful *p*H range are available commercially and form one of the most satisfactory series of indicators for colorimetric and spectrophotometric measurements. In the course of a program concerning the application of precise spectrophotometric methods in the determination of ionization constants of indicators, it seemed desirable to examine quantitatively the alkaline stability of a rather complete series. Although the fading rates of certain of the sulfonphthaleins have been the subject of a number of investigations,[1-6] data are lacking in some cases and have been obtained under varied experimental conditions in others, so that an extensive intercomparison of the effect of substituents upon the fading rates cannot be made.

---

(1) A. Thiel, *Monatsh.*, **54**, 1008 (1929).

(2) F. W. Panepinto and M. Kilpatrick, THIS JOURNAL, **59**, 1871 (1937).

(3) E. S. Amis and V. K. LaMer, *ibid.*, **61**, 905 (1939).

(4) S. Hochberg and V. K. LaMer, *ibid.*, **63**, 3110 (1941).

(5) M. D. Barnes and V. K. LaMer, *ibid.*, **64**, 2312 (1932).

(6) M. H. Hubacher, *ibid.*, **65**, 2097 (1943).

The mechanism of the fading reaction has been established.[3] A study of the Brønsted primary salt effect showed that the bivalent, alkaline form of the indicator, $[\mathrm{R}^{=}]$, adds a hydroxyl ion to form the colorless carbinol, $[\mathrm{ROH}^{=}]$. As the reaction is reversible, the extent of fading depends on the alkali concentration. The equilibrium between the colored and faded forms is illustrated for phenolsulfonphthalein in Fig. 1. The bimolecular rate constants, k_1 and k_2, represent the fading and color-regenerating reactions, respectively.

In the present work, phenolsulfonphthalein and nine of its derivatives which have various substituents in the two chromophoric rings were studied.

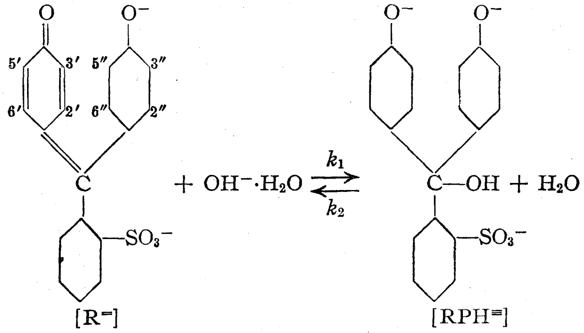


Fig. 1.—Alkaline fading of the phenolsulfonphthaleins.

II. Experimental

Brom phenol red was obtained from Hynson, Westcott and Dunning and the other indicators were obtained from W. A. Taylor and Company. Preliminary experiments were first made to determine the limiting spectral curves which represent the neutral yellow form and the reddish purple to blue alkaline form of each indicator. The molar absorbancy index, a_{M}, is calculated for any given wave length according to the equation

$$a_{\mathrm{M}} = -\log_{10} T_{\mathrm{s}}/(b \times M) \qquad (1)$$

in which T_{s} is the transmittancy of the solution, b is the length of the absorbing path between the boundary layers of the solution (cell-length in cm.), and M is the molar concentration of the indicator.

The maximum values of a_{M} were found for the alkaline forms of the indicators and vary from about 36,000 for thymol blue to 73,000 for brom cresol purple. As two-cm. absorption cells were used for the experiments, odd concentrations of each indicator were used to give an initial transmittancy value of 25 to 30% at the wave length of maximum absorption.

All of the fading reactions were conducted in relatively strong alkali, 1.12 *M*. At lower concentrations of alkali, the time required to follow some of the fading reactions is prohibitively long. The spectral transmittancies at the wave length of maximum absorption were observed throughout the course of the reactions at various intervals of time depending upon the rates of fading. The duration of the reactions ranged from less than an hour for brom phenol blue to a month and more for the more stable indicators. The transmittancies were measured with a Beckman quartz photoelectric spectrophotometer after revision of the cell compartment as described in a previous publication.[7] The temperature of the room containing the spectrophotometer and the solutions was maintained at 25° to within ±1°. In several instances the fading reaction continued to completion, but in a majority of cases a finite equilibrium between colored and colorless forms was reached. When there was no further change in the transmittancy at the wave length of maximum absorption, the spectral curve was taken at 5 mμ intervals from 220 to 750 mμ. These curves represented either the colorless carbinol form in cases of complete fading or an equilibrium mixture of colored and colorless forms. The solutions were again examined later to determine whether any changes in the spectral curves had occurred which might indicate irreversible decomposition.

III. Calculation of Rate Constants

Where the fading continues only until some definite equilibrium is established between the colored and the colorless forms of the indicator, the rate of disappearance of the colored form is given by

$$-\mathrm{d}[\mathrm{R}^{=}]/\mathrm{d}t = k_1[\mathrm{R}^{=}][\mathrm{OH}^{-}] - k_2[\mathrm{ROH}^{=}] \qquad (2)$$

As the alkali concentration is much greater than that of the indicator and does not change much during the reaction, the bimolecular rate constant, k_1, may be replaced by the first-order rate constant, $k_1' = k_1[\mathrm{OH}^{-}]$. The integrated rate equation is then

$$k_1' + k_2 = 2.303/t \log [x_{\mathrm{e}}/(x_{\mathrm{e}} - x_{\mathrm{t}})] \qquad (3)$$

where x_{t} is the fraction of $[\mathrm{R}^{=}]$ which has reacted at time, t, and x_{e} is the fraction reacted at equilibrium. From the relationship between the concentration and spectral transmittancy in accordance with Beer's law

$$x_{\mathrm{e}} = \frac{\log T_{\mathrm{s,o}} - \log T_{\mathrm{s,e}}}{\log T_{\mathrm{s,o}}}$$

and

$$x_{\mathrm{t}} = \frac{\log T_{\mathrm{s,o}} - \log T_{\mathrm{s,t}}}{\log T_{\mathrm{s,o}}}$$

where $T_{\mathrm{s,o}}$, $T_{\mathrm{s,t}}$, and $T_{\mathrm{s,e}}$ are the transmittancies at zero time, at time t, and at equilibrium, respectively. Equation 3 then becomes

$$k_1' + k_2 = \frac{2.303}{t} \log \frac{\log T_{\mathrm{s,o}} - \log T_{\mathrm{s,e}}}{\log T_{\mathrm{s,t}} - \log T_{\mathrm{s,e}}} \qquad (4)$$

From the transmittancies measured at intervals during the course of the fading and the observed equilibrium transmittancy, the forward and reverse rate constants and the equilibrium constant were evaluated in the following manner. The composite rate constant, $k_1' + k_2$, was determined from the slope of the straight line obtained by

---

(7) Elizabeth E. Sager, Marjorie R. Schooley, Alice S. Carr and S. F. Acree, *J. Research N. Bur. Standards*, **35**, 521 (1945), RP1686.

TABLE I

Common name	Abbr.	Substituents	Fading rates $k_1 \times 10^3$ min. × M	Fading rates $k_2 \times 10^3$ min. × M	Substituent effect A_x Obsd.	Substituent effect A_x Calcd.	Equilibrium constant K	Ionization constant pK^*	$\frac{[ROH^=]^a}{[R^=]}$
Brom phenol blue	BPB	3′,5′,3″,5″ Br	84	....	+1.69	+1.78	(34,000)	4.0	0.003
Chlor phenol red	CPR	3′,3″ Cl	12.5	....	+ .86	....	(500)	6.0	.005
Brom phenol red	BPR	3′,3″ Br	13.5	....	+ .89	....	(540)	6.2	.008
Brom cresol purple	BCP	3′,3″ CH_3; 5′,5″ Br	1.87	0.06	+ .03	+0.03	33	6.3	.001
Phenol red	PR	None	1.73	.25	....	....	7.9	7.9	.006
Brom cresol green	BCG	2′,2″ CH_3; 3′,5′,3″,5″ Br	0.80	....	− .32	− .08	(10,000)	4.7	.005
Cresol red	CR	3′,3″ CH_3	.24	.52	− .86	....	0.5	8.3	.001
Brom thymol blue	BTB	2′,2″ CH_3; 3′,3″ Br; 5′,5″ C_3H_7	.0280	.0016	−1.79	−1.79	20	7.0	.002
Meta cresol purple	MCP	2′,2″ CH_3	.0261	.0085	−1.82	....	3.1	8.3	.006
Thymol blue	TB	2′,2″ CH_3; 5′,5″ C_3H_7	(.004)	....	−2.6	−2.68	(.22)	8.9	.002

[a] At $pH = pK^* + 3$.

plotting log (log $T_{s,e}$ − log $T_{s,t}$) as a function of time according to equation 4. The equilibrium constant was evaluated from

$$K = \frac{[ROH^=]}{[R^=][OH^-]} = \frac{\log T_{s,o} - \log T_{s,e}}{\log T_{s,e}\,[OH^-]} \qquad (5)$$

In general $T_{s,o}$ could not be obtained directly because measurable fading occurred during the time interval between the start of the reaction and the first experimental observations. It was obtained from the intercept of the above plot corresponding to zero time. The separate rate constants were then obtained from the equations

$$k_1 = \frac{k_1' + k_2}{[OH^-] + 1/K} \text{ and } k_2 = k_1/K$$

In cases where fading goes practically to completion, equation 4 assumes the simplified form

$$k_1' = \frac{2.303}{t} \log (\log T_{s,o}/\log T_{s,t}) \qquad (6)$$

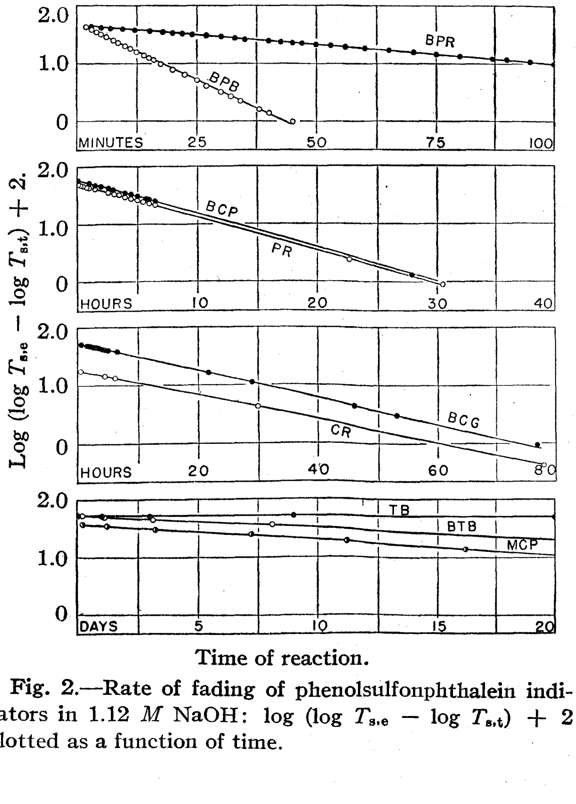


Fig. 2.—Rate of fading of phenolsulfonphthalein indicators in 1.12 M NaOH: log (log $T_{s,e}$ − log $T_{s,t}$) + 2 plotted as a function of time.

IV. Experimental Results

The ten sulfonphthaleins are listed in Table I and their common names as indicators, substituent groups, fading rates, effect of substituents upon the fading rates, as well as their equilibrium and ionization constants are also given. The indicators are given in the order of their fading rate constants, k_1, and the reverse rate constants, k_2, are calculated for the cases where they could be obtained. The substituent effects are defined and discussed in the next section. The experimental data plotted in accordance with equation 4 or equation 6 are shown in Fig. 2. The plots are linear over the entire range of fading. Additional data for TB, BTB, and MCP extended well beyond the twenty days given in the figure. TB fades extremely slowly and only an approximate value of k_1 could be obtained. Data for CPR are not shown. In this case the plot was linear only up to about 50% faded. Beyond this region the points fell above the straight line in a manner suggesting a small amount of colored impurity, presumably some other sulfonphthalein, having similar absorption but greater alkaline stability. In this case k_1 was evaluated from the initial, linear portion of the curve.

In addition to reversible fading similar to the sulfonphthaleins, the phenolphthaleins undergo gradual irreversible decomposition which has been attributed to oxidation by the air.[8] No definite evidence of irreversible decomposition, however, was found for any of the sulfonphthaleins during the course of the present observations. Any substantial irreversible change should be apparent as a gradual change in the transmittancy curves after fading had become complete or had reached an equilibrium. Figure 3 shows the spectral curves for BCG during various stages of the fading. In this case the fading goes to completion. Curves numbered 4 and 5 were taken after five and thirteen days, respectively, and indicate that no detectable change in spectral absorption of the colorless carbinol had occurred during this interval. Corresponding data for PR, which does not fade completely, are shown in Fig. 4.

---

[8] E. S. Amis and R. G. Overman, THIS JOURNAL, **66**, 941 (1944).

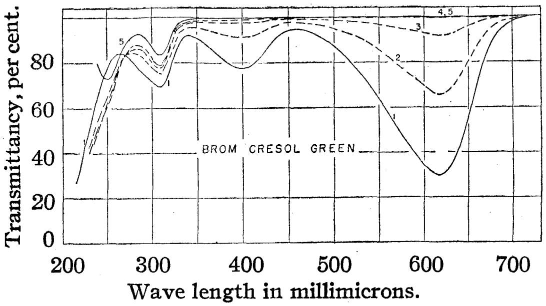


Fig. 3.—Per cent. transmittancy of brom cresol green in alkaline solutions plotted as a function of wave length: curve 1, unfaded at pH 8.2; curves 2, 3, 4 and 5, fading in 1.12 M NaOH after one, five, seven and thirteen days, respectively.

V. Discussion of Results

Substituents introduced into the rings of the parent substance, PR, have pronounced effects upon both the forward and the reverse rate constants, as shown in Table I. Qualitatively, the variations in k_1 are in accord with the general inductive influences of these substituents. Replacement of a hydrogen atom by the more electronegative halogen makes the effective charge on the reactive central carbon atom more positive, and thus increases its rate of reaction with the negative hydroxyl ion. The opposite inductive effect of a methyl or other alkyl group leads to a decrease in the rate of reaction, compared to PR. The inductive influence of a given substituent should have opposite effects upon the forward and reverse rate constants. An increase in effective positive charge on the reacting carbon atom should make more difficult the removal of the hydroxyl ion from the carbinol and thus decrease k_2. For substituents sufficiently removed from the point of reaction, that is, in the meta position with respect to the central carbon atom, such is the case. For example, CR, with a meta methyl group in each of the chromophoric rings, has a lower value of k_1 and a higher value of k_2 than PR. On the other hand, MCP, with a methyl group in the ortho position, has lower values for both k_1 and k_2, indicating that some other factor predominates over the inductive effect. In terms of the collision theory, this behavior would be attributed to a steric effect associated with the proximity of the substituent to the reacting center of the molecule, which would play a similar role in lowering both k_1 and k_2.

In the cases of the indicators which have more than one substituent in the chromophoric rings, it is of interest to ascertain whether they act more or less independently of each other in influencing the rate constants. According to the method of Hammett,[9] the effect of a substituent upon a given type of reaction may be defined by $A_x = \log k_x - \log k_0$, where k_0 is the rate for the unsubstituted compound, and k_x is the corresponding rate constant when a given substituent is introduced. On the basis of the transition state theory, A_x is related to the change in free energy of activation, ΔF, by $A_x = \Delta F/(2.3RT)$ and consequently reflects a change in either the energy of activation or the entropy of activation, which is characteristic of the nature and location of the substituent introduced. It has been found that, in general, substituents relatively far removed from the reacting center affect primarily the energy of activation, whereas neighboring groups influence both the energy and the entropy of activation. For example, from a thermodynamic study of the alkaline fading of several sulfonphthaleins Hochberg and LaMer[4] found that meta substituents influenced the energy of activation while ortho substituents influenced both the energy and the entropy of activation.

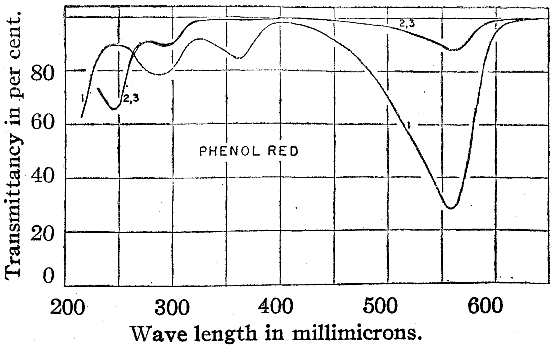


Fig. 4.—Per cent. transmittancy of phenol red in alkaline solutions plotted as a function of wave length: curve 1, unfaded at pH 11.8; curves 2 and 3, partially faded in 1.12 M NaOH after seven and twelve days, respectively.

Only three substituents need be considered for the present comparisons. These are a bromine in the meta position, an alkyl group (methyl or isopropyl) in the meta position, and a methyl group in the ortho position. No distinction is made between a methyl and an isopropyl group in the meta position, because their inductive effects should be practically the same and they are sufficiently removed from the reacting center to minimize any differences due to size. Only the fading rates will be considered in detail since the values of k_2 are more approximate and could not be obtained in some instances.

From the values of k_1 for BCP, CR, MCP, and PR the separate substituent effects are given by $A_{m\text{-Br}} = +0.89$, $A_{m\text{-alkyl}} = -0.86$, and $A_{o\text{-CH}_3} = -1.82$. These values represent the effect of two identical substituents, one in each of the chromophoric rings. For the five remaining cases which have two or three substitutents in each ring, the observed values of A_x should be the same as the values calculated by summation of the individual substituent effects provided these groups exert independent effects on the reaction. The seventh and eighth columns of Table I show a comparison of the observed and calculated values of A_x. The

---

[9] Louis P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940.

agreement is exact for BCP and BTB, both of which have two groups of opposite inductive effect, bromine and alkyl, in the meta positions. For BPB and BCG with two bromines in the meta positions, the observed values of A_x are lower than the calculated values by 0.09 and 0.24, respectively, and suggest a tendency toward saturation when both meta substituents have inductive influences in the same direction. As the fading of TB was extremely slow it is conceivable that some mechanism other than the formation of the carbinol, which might be too slow to be observable in the other cases, might be the controlling factor. That the mechanism is the same, is supported by the agreement between the observed and calculated values of A_x. The reasonably good agreement between the two values of A_x for the five cases listed shows that the total change in the free energy of activation is nearly an additive function of the contributions of the separate substituents. It should be possible to make satisfactory estimates of the alkaline stability of other poly-substituted sulfonphthaleins from a knowledge of the individual substituent effects.

It is of interest to note that the accelerating effect of a *m*-halogen on the fading rate of a sulfonphthalein is practically the same as the retarding effect of a *m*-alkyl group. On the basis of the generally observed inductive influences of these groups, a much larger effect might be expected from the *m*-halogen atom. Hammett correlated substituent effects quantitatively for a wide variety of aromatic reactions where the substituent is in the meta or para position, so that the entropy of activation remains substantially independent of the nature of the substituent for a given type of reaction. A_x may then be regarded as the product of two factors, $A_x = \rho\sigma_x$, where ρ is characteristic only of the type of reaction and σ_x depends only on the nature of the substituent. If the reaction under consideration conformed to this general rule, the observed values of A_x, $A_{m\text{-Br}} = +0.89$, $A_{m\text{-Cl}} = +0.86$, and $A_{m\text{-alkyl}} = -0.86$ should be proportional to the substituent constants listed by Hammett which are $\sigma_{m\text{-Br}} = +0.39$, $\sigma_{m\text{-Cl}} = +0.37$, and $\sigma_{m\text{-alkyl}} = -0.07$. Although the relative values for the two halogen atoms are normal with bromine having a slightly larger effect, the proportionality does not hold when the halogen and alkyl groups are compared. That Hammett's rule does not apply is not surprising in view of the high degree of benzenoidal–quinoidal resonance in the indicator ion. This resonance affects and may largely determine the effective charge on the central carbon atom. A given substituent, consequently, may influence this effective charge not only by exerting its normal inductive effect but also by modifying the resonance. Since the possibilities for this sort of resonance do not exist in the carbinol, the individual effects of the meta substituents in the case of k_2 might be expected to follow the order observed by Hammett. From the reverse rate constants, $A'_{m\text{-Br}} = -1.0$, $A'_{m\text{-alkyl}} = +0.3$, and $A'_{o\text{-methyl}} = -1.5$. Although the agreement is none too good, possibly because of the greater experimental uncertainties in determining k_2, a meta bromine has a definitely greater effect than a meta alkyl group in accordance with the general inductive influences of these groups.

The rate studies may be used to make a rough estimate of the maximum amount of reversible alkaline fading which might be encountered during the normal use of these indicators in the measurement of *p*H. The upper limit of the interval of color transformation may be taken as a *p*H three units higher than the pK^* of the indicator corresponding to 99.9% of the colored alkaline form. The values for pK^*, representing the ionization constants for each indicator, are given in Table I, column 10. The ninth column lists the values of K for the equilibrium eventually established between the colored alkaline form and the colorless carbinol form. The values in parentheses could not be determined directly from the experimental data but are approximate values obtained from the known values of k_1 and values of k_2 estimated from the substituent constants listed in the preceding paragraph. The eleventh column shows the ratio of carbinol to colored form of each indicator, $[\text{ROH}^=]/[\text{R}^=]$, which would be reached at the above limit of *p*H after sufficient time had elapsed for the equilibrium to be established. The extent of reversible fading is of the same order for all of the indicators and does not exceed 1% in any case although the fading rate constants vary by a factor greater than 10^4. It is evident that the indicators which fade the most rapidly and have the largest equilibrium constants have a compensating factor in that their color transformations occur at lower values of *p*H.

Summary

A quantitative examination by precise spectrophotometric methods of the stability in 1 *M* alkali of phenolsulfonphthalein and nine of its derivatives with alkyl and halogen substituents in the ortho and meta positions has been made. Some of the indicators faded completely, but in general the reaction continued only until some finite equilibrium was established between the colorless carbinol and the colored quinoid forms. The fading rate constants k_1, and, where possible, approximate values of the color regenerating rate constants, k_2, were calculated. The substituents were found to exert nearly independent effects upon the fading rate constants in cases where more than one substituent was present in the two chromophoric rings.

WASHINGTON, D. C. RECEIVED AUGUST 2, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

Tetraphenylphosphonium and Tetraphenylstibonium Chloride

BY HOBART H. WILLARD, L. R. PERKINS[1] AND F. F. BLICKE

Tetraphenylarsonium chloride[2,3] has been found to have unique and very valuable analytical applications[4] inasmuch as it can be used satisfactorily for the determination of perchlorate, periodate, perrhenate, mercury, cadmium, tin and zinc.

In the hope that a substance might be found which would be equally useful as an analytical reagent, but available at a lower cost, we have studied the preparation and properties of tetraphenylphosphonium and tetraphenylstibonium chloride.

Tetraphenylphosphonium chloride had been prepared by Dodonov and Medox[5] by interaction of triphenylphosphine, phenylmagnesium bromide and oxygen, conversion of the tetraphenylphosphonium bromide produced into the phosphonium hydroxide, and treatment of the latter substance with hydrochloric acid. We found that tetraphenylphosphonium chloride could be obtained by successive recrystallizations of the corresponding bromide from saturated sodium chloride solutions. However, a far more advantageous process was elution of the bromide through a chloride-charged resin; Amberlite IR-4-B[6] proved to be satisfactory for this purpose.

In order to obtain the required tetraphenylphosphonium bromide it is not necessary to prepare and isolate triphenylphosphine since the phosphonium bromide can be obtained in one operation, and in good yield, from phosphorus trichloride merely by allowing the latter substance to react with phenylmagnesium bromide, and then passing oxygen into the mixture.[7]

The only tetraphenylstibonium salt known hitherto is the stibonium bromide which had been synthesized by Chatt and Mann[8] from triphenylstibine, bromobenzene and aluminum chloride. We prepared the bromide by interaction of triphenylstibine dichloride with phenylmagnesium bromide. The stibonium bromide was converted into the chloride by elution through chloride-charged Amberlite resin.

Experimental Part

Tetraphenylphosphonium Chloride.—In order to obtain tetraphenylphosphonium bromide, a solution of phenylmagnesium bromide was prepared from 160 g. (1.02 moles) of bromobenzene, 20.9 g. (0.86 mole) of magnesium and 600 ml. of ether in an atmosphere of nitrogen. The solution was cooled with ice, stirred rapidly, and 18 g. (0.13 mole) of phosphorus trichloride, dissolved in 50 ml. of ether, was added slowly. The material was stirred and refluxed for one hour. Dry oxygen, at the rate of about 250 ml. per minute, was then passed into the mixture while it was stirred and cooled; the gas was passed through a sintered glass disc in order to obtain fine bubbles. After the mixture had been treated with 250 g. of ice and 80 ml. of concentrated hydrochloric acid, the ether layer was separated and discarded. To the product, which had separated as an oil, and the aqueous layer, water was added until the total volume was 1 liter; the mixture was then heated until practically all of the oil had dissolved. After treatment with Norite, the mixture was filtered, and 250 g. of sodium chloride was added to the hot filtrate. The solution was cooled with ice, the precipitated crystalline bromide filtered, dried and washed with ether. The crude bromide weighed 50.0 g. (91%).

Fifty grams of the crude bromide was dissolved in 2 liters of boiling water, the solution cooled to room temperature, and then passed, successively, through two tubes; each tube was 25 mm. in diameter and 120 cm. long, and each contained 250 g. of the chloride-charged anion-exchange resin (Amberlite IR-4-B). The effluent solution was concentrated to a volume of 500 ml., 150 g. of sodium chloride was added, the precipitated phosphonium chloride filtered and dried. It was then dissolved in 50 ml. of hot ethanol, the mixture filtered, and the filtrate concentrated to a volume of 15 ml. The product was precipitated by addition of 500 ml. of dry ether; yield 39 g. or 79% based on the phosphorus trichloride used; m. p. 265–267°.[9]

Tetraphenylstibonium Chloride.—Crude triphenylstibine[10] (23.0 g.), dissolved in 35 ml. of carbon tetrachloride, was treated with chlorine until the solution became yellow; most of the solvent and excess chlorine were then removed on a steam-bath. The triphenylstibine dichloride (40.3 g., 94%), which separated from the cold, concentrated solution, melted at 142–144°.[11]

Phenylmagnesium bromide was prepared from 30.0 g. (0.19 mole) of bromobenzene, 4.4 g. (0.18 mole) of magnesium and 200 ml. of ether in a flask provided with a stirrer. After the addition of 25.4 g. (0.06 mole) of triphenylstibine dichloride, dissolved in a mixture of 30 ml. of dry benzene and 270 ml. of dry ether, the material was stirred occasionally, and allowed to remain at room temperature for at least three days. The mixture was treated with 30 g. of ice and 20 ml. of 48% hydrobromic acid, the ether–benzene layer separated, and the aqueous layer extracted four times with 100 ml. portions of ether. The combined ether–benzene layer and the extracts were heated on a steam-bath until the solvents had been removed; the viscous, brown, oily residue solidified when cooled. It was dissolved in 1 liter of boiling water, the solution filtered through glass wool, the filtrate concentrated to a volume of 250 ml., and 25 g. of sodium bromide was added to the hot solution. The stibonium bromide, which pre-

---

[1] This paper represents part of a dissertation presented to the Horace H. Rackham School of Graduate Studies by L. R. Perkins in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

[2] Blicke and Marzano, THIS JOURNAL, **55**, 3056 (1933); Blicke and Monroe, *ibid.*, **57**, 720 (1935); Blicke, Willard and Taras, *ibid.*, **61**, 88 (1939).

[3] This product can be purchased from the Standard Sample Company, Ames, Iowa.

[4] Lamprey, Doctoral Dissertation, University of Michigan, 1935; Willard and Smith, *J. Ind. Eng. Chem., Anal. Ed.*, **11**, 186, 269, 305 (1939).

[5] Dodonov and Medox, *Ber.*, **61**, 907 (1928).

[6] This resin can be obtained from the Resinous Products Chemical Company, Philadelphia, Pa.

[7] The analytical applications of tetraphenylphosphonium chloride will be described soon by Willard and Perkins.

[8] Chatt and Mann, *J. Chem. Soc.*, 1192 (1940).

[9] The reported m. p. is 165° (ref. 5).

[10] The stibine was obtained by the method described by Morgan and Mickelthwaite (*J. Chem. Soc.*, **99**, 2290 (1911)). For our purpose it was merely necessary to remove the ether from the solution of the crude product.

[11] Pfeiffer (*Ber.*, **37**, 4621 (1904)) reported 141.5°.

cipitated from the cold solution, was washed with 5 ml. of water; yield 28.0 g.; m. p. 210–215°[12].

Anal. Calcd. for $C_{24}H_{20}SbBr$: Br^-, 15.7. Found: Br^-, 15.6.

The bromide (50 g.) was converted into the chloride by one passage through the anion-exchange resin in the manner which has been described; yield 40 g. (87%); m. p. 202–205°.

Anal. Calcd. for $C_{24}H_{20}SbCl$: Cl^-, 7.62. Found: Cl^-, 7.65.

The stibonium chloride can be recrystallized from water or ethyl acetate. It is only slightly soluble in ether or benzene.

Summary

New procedures have been developed for the preparation of tetraphenylphosphonium and tetraphenylstibonium chloride and bromide. The analytical applications of tetraphenylphosphonium chloride will be described in an early publication.

Ann Arbor, Michigan Received September 17, 1947

---

[12] The reported m. p. is 210–218° (ref. 8).

[Contribution from the Research Laboratories of Parke, Davis and Co.]

Hydroxyalkylamides of 4-Arsonophenoxy- and 4-Arsonoanilinoacetic Acids

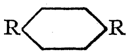
By C. K. Banks, D. F. Walker, John Controulis, E. W. Tillitson[1] and L. A. Sweet

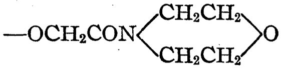
Study of the derivatives of 4-amino- and 4-hydroxybenzenearsonic acid has indicated that certain of them are of greater interest for therapeutic purposes than the parent arsenicals. 4-Arsonophenylurea (carbarsone-U.S.P.),[2] 4-arsonophenylglycineamide (tryparsamide-U.S.P.)[3] and others have become accepted therapeutic agents. Investigations of two types of derivatives, the carbamylmethyl[3,4] and the hydroxyalkyl,[5,6] have led to a number of interesting compounds. In order to determine the effect of incorporating both the hydroxyalkyl and carbamido functions in the same molecule, the hydroxyalkylamides of 4-arsonophenoxyacetic and 4-arsonophenylglycine were prepared.

4-Arsonophenoxyacetic acid[7] and 4-arsonophenylglycine[8] were converted to their methyl esters.[3,4] Reaction of these esters with hydroxyalkylamines yielded the desired amides. The substituted arsonic acids were reduced to the corresponding arsonous acids.

Table I

Arsonic Acids[a]



R	R′	Yield, %	Empirical formula	Arsenic, %[b] Calcd.	Found
$-AsO_3H_2$	$-NHCH_2CONHCH_2CH_2OH$	61	$C_{10}H_{15}AsN_2O_5$	23.54	23.35
$-AsO_3H_2$	$-NHCH_2CON(CH_2CH_2OH)_2$	76	$C_{12}H_{19}AsN_2O_6$	20.67	20.80
$-AsO_3HNa$	$-N(CH_2OH)CONHCH_2OH$	52	$C_9H_{12}AsN_2NaO_6$	21.89	21.89
$-AsO_3HNa$	$-N(CH_2OH)CH_2CONHCH_2OH$	95	$C_{10}H_{14}AsN_2NaO_6$	21.04	21.25
$-AsO_3H_2$[c]	$-NHNH_2$	50	$C_6H_9AsN_2O_3$	32.30	31.98
$-AsO_3H_2$[d]	$-NHN{=}C(CH_3)_2$	42	$C_9H_{13}AsN_2O_3$	27.53	27.80
$-AsO_3H_2$	$-OCH_2CONHCH_2CH_2OH$	50	$C_{10}H_{14}AsNO_6$	23.48	23.85
$-AsO_3HNa$	$-OCH_2CONHCH_2CH_2OH$	89	$C_{10}H_{13}AsNNaO_6$	21.96	22.12
$-AsO_3H\cdot H_3NCH_2CH_2OH$	$-OCH_2CONHCH_2CH_2OH$	94	$C_{12}H_{21}AsN_2O_7$	19.67	19.72
$-AsO_3H\cdot H_3NCH_2CHOHCH_3$	$-OCH_2CONHCH_2CHOHCH_3$	97	$C_{14}H_{25}AsN_2O_7$	18.35	18.54
$-AsO_3H_2$	$-OCH_2CONHC(CH_2OH)_3$	82	$C_{12}H_{18}AsNO_7$	20.62	20.55
$-AsO_3H\cdot H_3NC(CH_2OH)_3$	$-OCH_2CONHC(CH_2OH)_3$	78	$C_{16}H_{29}AsN_2O_{11}$	14.97	15.00
$-AsO_3H_2$	$-OCH_2CONHCH_2OH$	32	$C_9H_{12}AsNO_6$	24.55	24.48
$-AsO_3HNa$	$-OCH_2CONHCH_2OH$	85	$C_9H_{11}AsNNaO_6$	22.90	22.90
$-AsO_3H_2$	 $-OCH_2CON\left\langle{}^{CH_2CH_2}_{CH_2CH_2}\right\rangle O$	43	$C_{12}H_{16}AsNO_6$	21.75	21.79

[a] All compounds are colorless unless otherwise noted. [b] Arsenic determined by a modification of the method of Cislak and Hamilton, This Journal, 52, 638 (1930). [c] Light brown. [d] Yellow.

Methylolamides could not be prepared by the above procedure but it was found that formaldehyde would condense with the unsubstituted amides to yield the desired products. 4-Arsonophenoxyacetamide gave a monomethylol compound while 4-arsonophenylurea and 4-arsonophenylglycineamide lead to dimethylol derivatives. It would appear from these data that one

---

[1] Present address: Department of Chemical Engineering, Wayne Univ., Detroit, Michigan.

[2] German Patent 213,155.

[3] Jacobs and Heidelberger, This Journal, 41, 1587 (1919).

[4] Jacobs and Heidelberger, *ibid.*, 41, 1440, 1581, 1600, 1610, 1809, 1822, 1826, 1834 (1919).

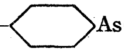
[5] Hamilton, *ibid.*, 45, 275 (1923).

[6] Sweet and Hamilton, *ibid.*, 56, 2409 (1934).

[7] Palmer and Kester, "Org. Syn.," 8, 4 (1928).

[8] German Patent 204,664.

TABLE II

ARSENOUS ACIDS,[a] R—  As(OH)$_2$

R	Yield, %	Empirical formula	Arsenic, %[b] Calcd.	Arsenic, %[b] Found
—NCN	46	$C_7H_7AsN_2O_2$	33.13	32.81
—NHNH$_2$	32	$C_6H_9AsN_2O_2$	34.60	34.52
—NHCH$_2$SO$_3$Na	86	$C_7H_9AsNNaO_5S$	23.60	23.20
—NHCH$_2$CONHCH$_2$CH$_2$OH	64	$C_{10}H_{15}AsN_2O_4$	24.77	24.67
—NHCH$_2$CON(CH$_2$CH$_2$OH)$_2$	72	$C_{12}H_{19}AsN_2O_5$	21.62	21.38
—OCH$_2$CONHCH$_2$CH$_2$OH	73[c]	$C_{10}H_{14}AsNO_5$	24.71	24.78
—OCH$_2$CON(CH$_2$CH$_2$OH)$_2$	62	$C_{12}H_{18}AsNO_6$	21.54	21.37
—OCH$_2$CONHC(CH$_2$OH)$_3$	55	$C_{12}H_{18}AsNO_7$	20.63	20.55

[a] All compounds are colorless. [b] Determined by the method of Banks and Sultzaberger, THIS JOURNAL, 69, 1 (1947). [c] The same compound was also obtained from methyl 4-arsonosophenoxyacetate and ethanolamine, yield 92%.

methylol group was formed on the amide nitrogen and one on the arylamino nitrogen in the last two instances. The position of the methylol group on nitrogen rather than on the benzene ring was proved by hydrolysis to 4-arsonophenoxyacetic acid and N-4-arsonophenylglycine.

4-Aminobenzenearsonous acid reacted with sodium formaldehyde bisulfite to yield a sulfomethyl derivative. 4-Cyano- and 4-hydrazinobenzenearsonous acid[9,10] were obtained by reduction of the corresponding arsonic acids.

Experimental

Acetamides.—The methyl ester of 4-arsonophenoxyacetic acid or 4-arsonophenylglycine (0.1 mole) was dissolved in an excess of the amine (100 ml.) and heated to 80° for two hours. On adding the reaction mixture to an excess of alcohol (2 l.), the amine salt of the hydroxyalkylacetamide crystallized. It was filtered off and dried *in vacuo*. The free arsonic acids were liberated when the amine salts were dissolved in a small amount of water and made strongly acid to congo red paper with hydrochloric acid. The arsonic acids were recrystallized from water.

Arsonous Acids.—The arsonous acids were prepared from the corresponding arsonic acids by previously published methods.[11]

Methylol Amides.—The arsono-substituted acetamide (0.1 mole) or urea was dissolved in water (25 ml.) by the addition of sodium hydroxide to pH 7, or the sodium salt was dissolved in water, and 37% aqueous formaldehyde (1 ml. per gram) added. The mixture was heated to 80° for two hours, then concentrated *in vacuo* to a solid. The residue was dissolved in a minimum of water, filtered and the sodium salt crystallized upon the addition of alcohol and ether. The free arsonic acids could be obtained by carefully acidifying cold aqueous solutions of the salts.

Acetone 4-Arsonophenylhydrazone.—4-Hydrazinobenzenearsonic acid[10] (5.8 g.) was warmed with 25 ml. of acetone and 5 ml. of water until solution occurred. On chilling, a mass of pale red crystals was obtained. After two recrystallizations from water–acetone (1:2), a nearly white crystalline product was obtained. Unlike the initial material, the product did not give a silver mirror test with ammoniacal silver nitrate.

Summary

1. Four new N-hydroxyalkyl derivatives of 4-arsonoanilinoacetic acid and five corresponding derivatives of 4-arsonophenoxyacetic acid are reported. Representative salts are described.

2. The arsonic acids were reduced to the corresponding arsonous acids.

3. Several miscellaneous related arsenicals are also reported.

DETROIT 32, MICH. RECEIVED AUGUST 27, 1947

---

[9] Banks, Controulis and Holcomb, THIS JOURNAL, **68**, 2102 (1946).

[10] U. S. Patent 2,390,529 (1945).

[11] Banks, Gruhzit, Tillitson, Controulis, Walker and Sultzaberger, THIS JOURNAL, **66**, 1771 (1944); **69**, 5 (1947).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

C-Alkylation and O-Alkylation in the Synthesis of Substituted Furoic Acids

BY CHARLES D. HURD AND KENNETH WILKINSON

In the alkylation of ethyl sodio-oxaloacetate with ethyl bromopyruvate Sutter[1] claimed to have prepared 2,3,5-furantricarboxylic acid. That is to say, he assumed that C-alkylation had occurred followed by ring closure and the elimination of water. However, Reichstein[2] prepared the same tricarboxylic acid by partially decarboxylating furantetracarboxylic acid, and since pyrolysis of such acids causes preferential decarboxylation in the *alpha* position he contended that Sutter had experienced O-alkylation and had obtained 2,3,4-furantricarboxylic acid. Archer and Pratt[3] demonstrated that O-alkylation was the course followed in the analogous condensation between ethyl bromopyruvate and ethyl sodio-β-ketosuberate, since subsequent ring closure yielded 5-(3,4-dicarboxyfuryl)-valeric acid.

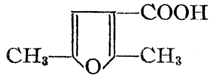
Similar interaction of acetoacetic ester and chloroacetone should produce 2,5-dimethyl-3-furoic acid (I) by C-alkylation, and 2,4-dimethyl-3-furoic acid (II) by O-alkylation. On the basis of

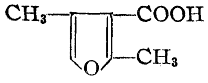
---

[1] Sutter, *Ann.*, **499**, 56 (1932).

[2] Reichstein, *Helv. Chim. Acta*, **16**, 276 (1933).

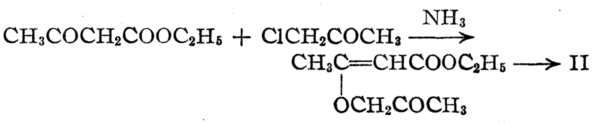
[3] Archer and Pratt, THIS JOURNAL, **66**, 1656 (1944).


I

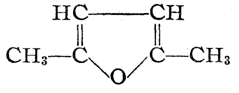

II

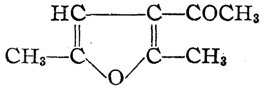
Archer and Pratt's work one might guess that chloroacetone and ethyl sodio-acetoacetate, followed by ring-closure, would yield II. Actually, this experiment was performed by Paal.[4] His acid, m. p. 136°, has been assigned structure I rather than II, but it must be said that the evidence regarding structure may be questioned.

A few years later, Feist[5] carried out a similar reaction between chloroacetone and acetoacetic ester, the base being ammonia instead of sodium ethoxide. His product melted at 122°. He suggested structure II, again without adequate proof. These steps would apply if O-alkylation occurred


$$CH_3COCH_2COOC_2H_5 + ClCH_2COCH_3 \xrightarrow{NH_3} \underset{\displaystyle OCH_2COCH_3}{\underset{|}{CH_3C}}{=}CHCOOC_2H_5 \longrightarrow \mathrm{II}$$

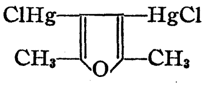
We have repeated and confirmed both Paal's and Feist's observations. To establish conclusively the structures of the acids formed, we have synthesized I by an unequivocal method. For this work, 2,5-dimethylfuran (III) was chosen as a source material of unquestioned structure. It was converted into 3-acetyl-2,5-dimethylfuran (IV) by means of acetic anhydride and stannic chloride. Since the only previous synthesis[6] of IV involved autoclaving a mixture of succinic acid, acetic anhydride, sodium acetate and zinc chloride at 200°, the present synthesis of IV places the structure on a secure basis. Oxidation of this ketone by sodium hypoiodite yielded an acid melting at 135° and obviously of structure I.

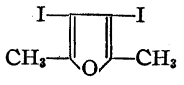

III

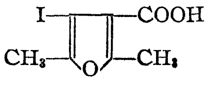

IV

This proof of structure I fixes structure II as well, and establishes the fact that C-alkylation is involved in the reaction of chloroacetone with acetoacetic ester and sodium ethoxide, whereas O-alkylation occurs if ammonia is used as the base. That the initial products of C- and O-alkylation were different was evident also in the reactions of cyclization. The former, $CH_3COCH(CH_2COCH_3)COOC_2H_5$, which is a 1,4-diketone, undergoes ring closure promptly on treatment with concentrated sulfuric acid. The latter, $CH_3C(OCH_2COCH_3){=}CHCOOC_2H_5$, undergoes practically no cyclization under these conditions. The method of cyclizing this material is to saponify, then acidify, a method not applicable to the C-alkylated compound since it promotes decarboxylation instead.

Other reactions of dimethylfuran were developed during this work. Both mono- and dimercuration (V) products were obtained by reaction with mercuric chloride. Both of these compounds reacted readily with iodine to yield 3-iodo-2,5-dimethylfuran and 3,4-diiodo-2,5-dimethylfuran (VI), respectively. Compound VI could not be brought into reaction with magnesium even by using butyl ether and temperatures[7] up to 140° or by employing a special magnesium alloy.[8] It was inert also toward potassium cyanide when an attempt was made to form the nitrile. A small amount of Grignard exchange was observed between methylmagnesium iodide and VI, since the product yielded 2,5-dimethyl-4-iodo-3-furoic acid (VII) on carbonation. On the other hand, methylmagnesium iodide did not cause substitution of magnesium into the nucleus of 2,5-dimethylfuran. Instead, a coördination compound precipitated.


V


VI


VII

Experimental

3-Acetyl-2,5-dimethylfuran.—A mixture of 46 g. of 2,5-dimethylfuran, 64 g. of acetic anhydride, and 0.2 ml. of stannic chloride was refluxed for four hours and then distilled. The yield of product boiling at 196° was 53.3 g. or 77%. The oxime[6] melted at 77°.

2,5-Dimethyl-3-furoic Acid.—A solution of iodine in aqueous potassium iodide was added to 1 g. of 3-acetyl-2,5-dimethylfuran and 4 ml. of 50% sodium hydroxide until there was an excess of iodine. The reaction was maintained at 60° for one-half hour, then the iodoform which formed in the reaction was extracted with ether. After warming off the ether, acidification and use of a small amount of bisulfite to remove the excess iodine yielded 2,5-dimethyl-3-furoic acid which was recrystallized from water, m. p. 135.4°. The neutral equivalent of this acid was found to be 139.8 (calcd., 140).

2,5-Dimethyl-3-furylmercuric Chloride.—A mixture of 10 g. of 2,5-dimethylfuran, 27 g. of mercuric chloride, 13 g. of sodium acetate trihydrate and 300 g. of water was warmed to 50° and shaken occasionally for three hours. The 14 g. of yellow cream solid which separated was dissolved in 50–60 ml. of hot acetone, filtered and precipitated by pouring into three volumes of water. This process was repeated before analysis.

Anal. Calcd. for C_6H_7ClHgO: Hg, 60.60. Found: Hg, 60.64.

A product analyzing 64.0% mercury was obtained by using relatively more sodium acetate. From a mixture of 5 ml. of 2,5-dimethylfuran, 13.6 g. of mercuric chloride, 10 g. of anhydrous sodium acetate and 50 g. of water, kept at 40–50° for thirty minutes, was obtained 5.4 g. of a cream-colored product after filtration and rinsing with water till free of mercuric chloride. It still analyzed 64.0% after dissolving nine-tenths of it in 80 ml. of hot acetone, filtering, and precipitating with 150 ml. of water.

The mercury analysis is satisfactory for a compound

---

(4) Paal, *Ber.*, **17**, 2765 (1884).

(5) Feist, *ibid.*, **35**, 1540, 1551 (1902).

(6) Magnanini and Bentivoglio, *Gazz. chim. ital.*, **24**, I, 435 (1894).

(7) Marvel, Blomquist and Vaughn, THIS JOURNAL, **50**, 2810 (1928).

(8) Sheppard, Winslow and Johnson, *ibid.*, **52**, 2086 (1930).

of the structure C_6H_7O-Hg-C_6H_6O-HgCl (calcd. 64.1% Hg). At least, it appeared that both monomercurated and dimercurated furan nuclei were produced since iodination (I_2–KI reagent) yielded an oily mixture containing a substantial amount of solid 3,4-diiodo-2,5-dimethylfuran, m. p. 60.5°. Also, this mercurated product was much more soluble in hot acetone than compound (V), described below.

3-Iodo-2,5-dimethylfuran.—A mixture of 6.6 g. of 2,5-dimethyl-3-furylmercuric chloride (containing 60.6% Hg) and 50 g. of 2,5-dimethyl-3-furylmercuric chloride (containing 60.6% Hg) and 50 g. of water was shaken with an aqueous solution of iodine and potassium iodide until there was an excess of iodine. This was decolorized with sodium bisulfite. The mixture was treated with 0.5 g. of sodium bicarbonate and the oily product was steam distilled, ether extracted, dried over sodium sulfate and distilled; yield, 2.6 g. (62%) of b. p. 85.5–86° (20 mm.); $n^{22.6}_{D}$ 1.5388; d^{20}_{4} 1.699. The compound decomposes in two weeks if exposed to light.

Anal. (by J. Anderson): Calcd. for C_6H_7IO: C, 32.45; H, 3.16. Found: C, 32.56; H, 3.20.

2,5-Dimethyl-3,4-furan-bis-(mercuric chloride) (V).—By heating 18.4 g. (0.19 mole) of 2,5-dimethylfuran and 108.4 g. (0.4 mole) of mercuric chloride in 150 ml. of water at 70° with intermittent shaking for one hour, 2,5-dimethyl-3,4-furan-bis-(mercuric chloride), a white solid, was formed. It was filtered and dried at 50° since temperatures above 80° caused extensive decomposition. This material is only slightly soluble in hot acetone.

Anal. Calcd. for $C_6H_6Cl_2Hg_2O$: Hg, 70.87. Found: Hg, 70.6.

3,4-Diiodo-2,5-dimethylfuran.—An aqueous solution of iodine and potassium iodide was added to 33.1 g. of 2,5-dimethyl-3,4-furan-bis-(mercuric chloride) suspended in 100 ml. of water until there was an excess of iodine which persisted after an hour of intermittent shaking. Thiosulfate was then added to remove the excess of iodine. Any acids in the solution were neutralized by treatment with excess bicarbonate, after which the solution was steam distilled. The bicarbonate treatment removes traces of hydrodic acid which would promote resinification of the product. The oily distillate was extracted with ether, dried over anhydrous sodium sulfate, and the ether evaporated. The yield was 13 g. (41%) of white crystalline 3,4-diiodo-2,5-dimethylfuran, m. p. 60.8°. Its odor is similar to iodoform. It is stable in alcoholic solution, but in a crystalline state it completely decomposes in less than two months.

Anal. (by P. Craig): Calcd. for $C_6H_6I_2O$: C, 20.70; H, 1.72. Found: C, 20.93; H, 1.62.

2,5-Dimethyl-4-iodo-3-furoic Acid.—To a solution of 0.1 mole of methylmagnesium iodide in 25 ml. of ether was added 2.2 g. of 3,4-diiodo-2,5-dimethylfuran in 10 ml. of ether. The mixture was refluxed for one hour and then carbonated by pouring over solid carbon dioxide. The mixture was acidified with 30% sulfuric acid and extracted with ether, then the ether was extracted with 5% potassium hydroxide. Evaporation of the ether yielded 1.9 g. or 87% of the starting material. Acidification of the alkaline solution and extraction with ether gave 0.2 g. of 2,5-dimethyl-3-iodo-4-furoic acid which was recrystallized from 50% methanol: m. p. 208.8°.

Anal. (by P. Craig): Calcd. for $C_7H_7IO_3$: C, 31.59; H, 2.63; neut. equiv., 266. Found: C, 31.43; H, 2.48; neut. equiv., 265.

2,4-Dimethyl-3-furoic Acid *via* O-Alkylation.—A stream of ammonia gas was passed through a flask containing 100 ml. of ether, 28 g. of chloroacetone and 39 g. of ethyl acetoacetate. After thirty minutes the reaction was stopped, the ammonium chloride which had formed was filtered off, and the ether evaporated. The residual oil was fractionated under reduced pressure yielding 15 g. (27%) of a fraction boiling at 95–98° at 14 mm.; n^{25}_{D} 1.482. This alkylation product was saponified by warming with a slight excess of 5% sodium hydroxide for thirty minutes. Acidification of the hot solution yielded upon cooling pure 2,4-dimethyl-3-furoic acid, m. p. 123°; reported[5] 122°.

2,5-Dimethyl-3-furoic Acid *via* C-Alkylation.—After dissolving 7 g. of sodium in 100 ml. of absolute alcohol, 40 g. of ethyl acetoacetate was added and the solution was brought to refluxing temperature. To it was added 28 g. of chloroacetone over a period of two hours. After refluxing for an additional hour, the mixture was cooled, the sodium chloride filtered off and washed with alcohol, and the alcohol distilled away from the high boiling product. Fractionation under reduced pressure yielded 29 g. (43%) of a liquid boiling at 126–128° at 14 mm.; n^{25}_{D} 1.4385. This boiling point is considerably higher and the refractive index significantly lower than the analogous constants from the ammonia reaction.

Three grams of this alkylation product was poured into 10 ml. of concentrated sulfuric acid. After five minutes it was poured over cracked ice. The mixture was extracted with ether, the ether evaporated, and the oil remaining saponified with 5% sodium hydroxide solution on a steam-bath for ten minutes. Acidification yielded 0.4 g. (18%) of 2,5-dimethyl-3-furoic acid, m. p. 135.4°. A mixed melting point with an authentic sample prepared from the acetylation of 2,5-dimethylfuran followed by a hypoiodite oxidation showed no depression.

Summary

The synthesis of 2,5-dimethyl-3-furoic acid from 2,5-dimethylfuran is described by a method which proves its structure. The same acid is made starting with chloroacetone and ethyl sodio-acetoacetate, a process involving C-alkylation of the acetoacetic ester. A different acid, 2,4-dimethyl-3-furoic acid, results from reaction of chloroacetone and ethylacetoacetate in the presence of ammonia. This involves O-alkylation of the acetoacetic ester.

Mercuration studies on 2,5-dimethylfuran are reported.

3,4-Diiodo-2,5-dimethylfuran was inactive toward magnesium, but did undergo an exchange reaction with methylmagnesium iodide to yield upon carbonation, 2,5-dimethyl-4-iodo-3-furoic acid.

2,5-Dimethylfuran did not undergo a Grignard exchange with methylmagnesium iodide.

EVANSTON, ILLINOIS

RECEIVED OCTOBER 7, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, GENERAL MILLS, INC.]

Hydroxylated Stearic Acids. II. The Periodate Oxidation of the 9,10-Dihydroxystearic Acids and the 1,9,10-Trihydroxyoctadecanes[1a]

BY HAROLD WITTCOFF, OWEN A. MOE AND MARJORIE H. IWEN

The quantitative oxidative cleavage of vicinal hydroxyl groups by the action of periodic acid to yield two carbonyl compounds was first demonstrated by Malaprade,[1b] and it was later postulated by Criegee[2] and co-workers that the reaction proceeded through an acidic cyclic ester which decomposed with water to yield the observed products.

That a cyclic diester is an intermediate in this reaction has likewise been postulated by Price and co-workers[3] who further pointed out that if ring formation is the rate-controlling factor then so-called *cis* glycols would be expected to oxidize faster than the corresponding *trans* isomers. This follows since the requisite double inversion which must necessarily occur in cyclic ester formation does not change the relative positions in space of the *cis* and *trans* hydroxyl pairs.

Criegee[2] had previously shown this to be so in compounds in which the space relationships of the adjacent hydroxyl groups were determined and rigidly maintained by the cyclic nature of the compounds. Price and co-workers[3] extended the work to the open chain compounds, ethylene glycol and pinacol, and showed that the hydroxyl groups are on the average more proximal in acidic than in basic medium probably because of association with a proton at a lower *p*H. Furthermore, this difference in space relationship was readily detectable by the difference in rate of oxidation by periodate.

Thus previous work has shown that periodate oxidation is a valuable tool for the determination of configuration of glycols when the configuration depends either on a cyclic structure or on the *p*H of the medium. It was postulated, therefore, that this reagent would be valuable, likewise, in indicating the proximity of the hydroxyl groups in the diastereoisomeric open chain glycol pairs. That lead tetraacetate was an adequate reagent for this purpose had previously been reported by Hilditch and Jasperson[4a] and Dorée and Pepper[4b] who had shown respectively that the low-melting forms of 9,10-dihydroxystearic acid and 13,14-dihydroxybehenic acid are oxidized more rapidly than the high-melting forms.

In the case of alicyclic glycols the so-called *cis* and *trans* relationship arises from a combination of the repulsive effects of the hydroxyl groups and of the groups attached to the hydroxyl-bearing carbon atoms. In such instances it is interesting to note that free rotation is probably reduced to what may be regarded as a sort of oscillation within a restricted area.

Accordingly, periodate oxidation was applied to each of the forms of the 9,10-dihydroxystearic acids and the 1,9,10-trihydroxyoctadecanes in the hope that there would be a detectable difference in the rate of oxidation which in turn would provide additional evidence for the configuration of these compounds.

King[5] had previously oxidized with periodate both forms of the 9,10-dihydroxystearic acids in order to obtain the expected scission products without, however, noting a difference in the rates of oxidation. In the present investigation it was observed that low-melting 9,10-dihydroxystearic acid (95°) consumed periodate at a much more rapid rate than did the high-melting form (132°) when the oxidations were carried out in aqueous media in the presence of an emulsifying agent consisting of sodium β-alkylaminopropionate in which the alkyl moiety was derived from soybean oil fatty acids. This is indicated in Table I.

TABLE I

OXIDATION OF THE 9,10-DIHYDROXYSTEARIC ACIDS IN AQUEOUS MEDIA AT 24°

Time, min.	Moles of acid oxidized	
	Low-melting form	High-melting form
5	0.29	..
15	.60	..
30	.91	0.02
45	.94	..
60	1.04	.10
90	1.05	.30
105	..	.42
120	1.03	.54
180	..	.74
240	..	.89
300	..	.95

Since there was a possibility that the results might have been influenced by a difference in the solubilities of the two forms, the oxidations were carried out in the homogeneous medium provided by 75 volume per cent. aqueous ethanol. Although homogeneity greatly accelerated the reaction rates, a very marked difference in behavior was still demonstrated by the two forms.

Similarly the low melting form of 1,9,10-trihydroxyoctadecane was oxidized at a more rapid rate

---

[1a] Paper No. 83, Journal Series, Research Laboratories, General Mills, Inc.

[1b] L. Malaprade, *Bull. soc. chim.*, [4] **43**, 683 (1928); [5] **1**, 833 (1934); [5] **4**, 906 (1937).

[2] R. Criegee, *Sitzber. Ges. Beförder. ges. Naturw. Marburg*, **69**, 25 (1934).

[3] (a) C. C. Price and H. Kroll, THIS JOURNAL, **60**, 2726 (1938); (b) C. C. Price and M. Knell, *ibid.*, **64**, 552 (1942).

[4] (a) T. P. Hilditch and H. Jasperson, *Nature*, **147**, 327 (1941); (b) C. Dorée and A. C. Pepper, *J. Chem. Soc.*, 447 (1942).

[5] G. King, *ibid.*, 1826 (1938).

than the high melting form in 75 volume per cent. aqueous ethanol. These results are indicated in Table II.

TABLE II

OXIDATION OF THE 9,10-DIHYDROXYSTEARIC ACIDS AND THE 1,9,10-TRIHYDROXYOCTADECANES IN 75 VOLUME PER CENT. ETHANOL–WATER AT 24°

	Moles acid oxidized in			
	9,10-Dihydroxystearic acids		1,9,10-Trihydroxyoctadecanes	
Time, min.	Low melting	High melting	Low melting	High melting
2	0.8	0.37	..	..
5	.9	.47	0.78	0.47
10	.9	.63	.87	.61
15	...	.74	.96	.80

From the scission products of the low melting form of 1,9,10-trihydroxyoctadecane, pelargonic aldehyde was isolated as the 2,4-dinitrophenylhydrazone, indicating that the desired reaction had taken place.

The structural feature responsible for these results also comes into play when one determines which form is capable of yielding an acidic cyclic complex with boric acid by the classical procedure. Boëseken and Couvert[6] had shown that *cis* glycols of rigid systems form a complex possessing an acidic hydrogen atom which is readily demonstrable by conductivity measurements.

This technique was shown to be applicable to diastereoisomeric open chain glycols by Lees and co-workers[7] and by Knowlton and co-workers[8] who showed that the *dl* form of 2,3-butanediol formed a borate complex whereas the *meso* form did not. With the 9,10-dihydroxystearic acids conductivity measurements in absolute ethanol indicated that the low melting form was amenable to complex formation with boric acid since the specific conductivity increased with increasing concentration of the acid. On the other hand, successive increase of the concentration of the high melting form had no effect on the specific conductivity of the borate mixture. The data are presented in Table III.

TABLE III

SPECIFIC CONDUCTIVITY MEASUREMENTS FOR THE 9,10-DIHYDROXYSTEARIC ACIDS AT 25° IN ABSOLUTE ETHANOL

Low-melting form		High-melting form	
Moles of acid/liter of 1 *N* H_3BO_3	Specific conductivity	Moles of acid/liter of 1 *N* H_3BO_3	Specific conductivity
0	8.37×10^{-5}	0	8.37×10^{-5}
0.0106	1.58×10^{-4}	0.0112	1.04×10^{-4}
.0269	1.88×10^{-4}	.0275	1.03×10^{-4}
.0446	2.09×10^{-4}	.0510	1.02×10^{-4}
.0936	2.97×10^{-4}	.0989[a]	1.04×10^{-4}

[a] This was a supersaturated solution which started to crystallize as the reading was taken.

All of these data, then, indicate that the vicinal hydroxyl groups in the low-melting forms of 9,10-dihydroxystearic acid and 1,9,10-trihydroxyoctadecane possess a closer spatial relationship than those in the high-melting form. Accordingly it follows that the normal hydroxylation products of oleic acid and oleyl alcohol (*cis* double bond) are the high-melting forms of 9,10-dihydroxystearic acid and 1,9,10-trihydroxyoctadecane, whereas the normal hydroxylation products of elaidic acid and elaidyl alcohol (*trans* double bond) are the low-melting forms. These conclusions are in accord with those of Esafov,[9] King[10] and Wittcoff and Miller[11] but are at variance with those of Atherton and Hilditch.[12]

Acknowledgment.—The authors are indebted to Prof. Richard T. Arnold for several helpful discussions.

Experimental

Materials.

The low-melting form of 9,10-dihydroxystearic acid was prepared by the hydroxylation of U. S. P. oleic acid as described by Scanlan and Swern.[13] After numerous crystallizations from ethyl acetate it melted sharply at 94–95°.[14]

The high-melting form of 9,10-dihydroxystearic acid was prepared by the hydroxylation of U. S. P. oleic acid by action of permanganate as described by Lapworth and Mottram[15] save that considerably less water was used. Thus a solution of oleic acid (20 g.) and potassium hydroxide (10 g.) in water (3 l.) reacted at 0–5° with a solution (400 ml., 2%) of potassium permanganate. The product was isolated as indicated by the previous workers. During crystallization from ethyl acetate, however, an insoluble crystalline material separated. This was shown by melting point, neutral equivalent and elementary analysis to be one of the high melting forms of 9,10,12,13-tetrahydroxystearic (sativic) acid.[16] Thus from three runs there was obtained, in addition to 13 g. of 9,10-dihydroxystearic acid (m. p., 129–30°), 2.0 g. of sativic acid melting at 172–173°.

Anal. Calcd. for $C_{18}H_{36}O_6$: C, 62.07; H, 10.44; neut. eq., 348.5. Found: C, 61.89; H, 10.44; neut. eq., 345.

The low-melting form of 1,9,10-trihydroxyoctadecane was prepared according to the procedure of Scanlan and Swern,[13] employing commercial oleyl alcohol from which all of the C_{14} and C_{16} compounds had been removed by stripping through a Podbielniak column. The product was crystallized successively from absolute ethanol, ethyl acetate and isopropyl ether and melted at 75–76°.

The high-melting form of 1,9,10-trihydroxyoctadecane was prepared by hydroxylating with permanganate the half acid phthalate of oleyl alcohol and saponifying the resultant product as described by Collin and Hilditch.[17] Pure oleyl alcohol[18] was used and the crude hydroxylation

---

[6] J. Boëseken and H. Couvert, *Rec. trav. chim.*, **40**, 354 (1921).

[7] T. M. Lees, E. I. Fulmer and L. A. Underkofler, *Iowa State Coll. J. Sci.*, **18**, 359 (1944).

[8] J. W. Knowlton, N. C. Schieltz and D. MacMillan, THIS JOURNAL, **68**, 208 (1946).

[9] (a) V. I. Esafov, *J. Gen. Chem.* (*U. S. S. R.*), **6**, 1818 (1936); (b) V. I. Esafov, *ibid.*, **7**, 1403 (1937).

[10] G. King, *J. Chem. Soc.*, 37 (1943).

[11] H. Wittcoff and S. E. Miller, THIS JOURNAL, **69**, 3138 (1947).

[12] D. Atherton and T. P. Hilditch, *J. Chem. Soc.*, 204 (1943); *cf.* ref. 11 for a discussion of Hilditch's conclusions.

[13] J. T. Scanlan and D. Swern, THIS JOURNAL, **62**, 2305 (1940).

[14] Melting points are uncorrected.

[15] A. Lapworth and E. N. Mottram, *J. Chem. Soc.*, 1628 (1925).

[16] R. W. Riemenschneider, D. H. Wheeler and C. E. Sando, *J. Biol. Chem.*, **127**, 391 (1939).

[17] G. Collin and T. P. Hilditch, *J. Chem. Soc.*, 246 (1933).

[18] D. Swern, H. B. Knight and T. W. Findley, *Oil and Soap*, **21**, 133 (1944). The authors are indebted to Mr. David E. Terry for the preparation of the pure alcohol.

product was saponified by refluxing it (5.5 g.) with a solution of potassium hydroxide (3.0 g.) in ethanol (50 ml.) for two hours. The potassium phthalate was filtered from the cooled mixture, and the filtrate was made exactly neutral by addition of dilute hydrochloric acid. Evaporation to dryness *in vacuo* yielded a residue which was taken up in ethyl acetate and was filtered to remove inorganic salt. From the filtrate there resulted on standing 2.5 g. of product which, when crystallized from the same solvent, melted at 125–126°.

The Periodate Oxidation of the 9,10-Dihydroxystearic Acids in Aqueous Suspension.—All of the oxidations by periodate were performed at 24° using aqueous 0.05 *M* periodate (buffered, *p*H 4.2) prepared from trisodium paraperiodate and acetic acid.[19] The periodate oxidations of both forms of 9,10-dihydroxystearic acid were carried out in aqueous suspension in the presence of a known quantity of sodium β-alkylaminopropionate in which the alkyl moiety was derived from soybean oil fatty acids. The titrations of the aliquot portions of the reaction mixtures were carried out according to the method of Fleury and Lange[20] as modified by Grangaard, Gladding and Purves.[21] Corrections were made for blanks. The results of the periodate oxidation in aqueous suspension are given in Table I.

The Periodate Oxidation of the 9,10-Dihydroxystearic Acids and the 1,9,10-Trihydroxyoctadecanes in Ethanol–Water.—Since ethanol proved to be a suitable solvent for all of the glycols under investigation, the oxidations by periodate in homogeneous medium were carried out at 24° in the following manner: The compounds (0.0200 g.) were dissolved in absolute ethanol (15 ml.); a solution of periodate (0.05 *M*, 5 ml.) was added and the oxidations were permitted to continue for the periods of time indicated in Table II. The titrations were performed as previously described and corrections were made for blanks. Perfectly clear reaction mixtures resulted in all oxidations of this type. The results obtained are given in Table II.

Identification of Pelargonic Aldehyde among the Scission Products of 1,9,10-Trihydroxyoctadecane.—1,9,10-Trihydroxyoctadecane (5.0 g., m. p. 75–76°) was dissolved in absolute ethanol (100 ml.), and 0.5 *M* periodate (50 ml.) was added. After one hour at room temperature the reaction mixture was poured into water and was extracted with ether. From the ether solution there resulted an oil (4.8 g.) which was converted, during refrigeration, to a pasty solid. This crude product was dissolved in warm Skellysolve B. Cooling yielded a small amount of solid which was probably unreacted glycol. From the filtrate there was obtained an oil which was treated with 2,4-dinitrophenylhydrazine in the conventional manner. The crude dinitrophenylhydrazone first obtained melted at 91–96°. After three recrystallizations from ethanol the product melted at 104–5° (uncor., lit. 100°).[22]

Anal. Calcd. for $C_{15}H_{22}O_4N_4$: C, 55.9; H, 6.8; N, 17.4. Found: C, 55.8; H, 6.9; N, 17.7.

Conductivity of the Borate Complexes of the 9,10-Dihydroxystearic Acids.—The conductivity measurements were carried out in a one normal solution of boric acid in absolute ethanol with the aid of an alternating current, 1000 cycle, conductivity Wheatstone bridge. The results are contained in Table III.

Summary

The results of periodate oxidation have been used to show that the hydroxyl groups are more proximal in the low-melting forms of the 9,10-dihydroxystearic acids and the 1,9,10-trihydroxyoctadecanes than in the high-melting forms.

The low-melting form of 9,10-dihydroxystearic acid has been shown to form a cyclic, acidic complex with boric acid, whereas the high-melting form does not.

---

[19] (a) D. H. Grangaard, J. H. Michell and C. B. Purves, THIS JOURNAL, **61**, 1290 (1939); (b) O. A. Moe, S. E. Miller and M. H. Iwen, *ibid.*, **69**, 2621 (1947).

[20] P. Fleury and J. Lange, *J. pharm. chim.*, [8] **17**, 107, 196 (1933).

[21] D. H. Grangaard, E. K. Gladding and C. B. Purves, *Paper Trade J.*, **115**, no. 7, 41 (1942).

[22] H. H. Strain, THIS JOURNAL, **57**, 758 (1935).

MINNEAPOLIS, MINNESOTA RECEIVED AUGUST 28, 1947

[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY OF WESTERN RESERVE UNIVERSITY]

The Reaction of Amines with Phosphorus Pentasulfide; Thiophosphoric Amides

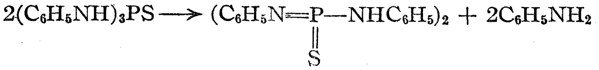
BY ALLEN C. BUCK,[1a] JOHN D. BARTLESON[1b] AND HERMAN P. LANKELMA

Previous investigations of products obtained by the action of amines on phosphorus pentasulfide have been limited to a single reaction. Knop[1c] observed that six moles of aniline and one mole of phosphorus pentasulfide heated at a temperature not exceeding 150° evolved hydrogen sulfide and gave a pungent smelling product in the form of monoclinic crystals which melted at 153°. Rudert[2] prepared the same product from aniline and thiophosphoryl chloride and showed it to be thiophosphoric trianilide, $(C_6H_5NH)_3PS$.

Knop's results were repeated in this Laboratory. A 50% yield of thiophosphoric trianilide melting at 153–154° was obtained. This product did not depress the melting point of thiophosphoric trianilide prepared from aniline and thiophosphoryl chloride. Although Knop regarded temperatures in excess of 150° to be detrimental, we obtained the maximum yield at a reaction temperature of 180°.

The anilide was not hydrolyzed upon refluxing with dilute acid or with aqueous or alcoholic potassium hydroxide, but was by heating with concentrated phosphoric acid at 130°, for two hours, and with glacial acetic acid for twenty hours.

When thiophosphoric trianilide was heated at 225° *in vacuo*, it lost aniline and formed dimeric thiophosphoric anil anilide:



$$2(C_6H_5NH)_3PS \longrightarrow (C_6H_5N{=}\underset{\underset{\displaystyle S}{\|}}{P}{-}NHC_6H_5)_2 + 2C_6H_5NH_2$$

Upon refluxing the anil anilide in aniline the reaction was reversed. This reaction will be discussed in a future paper.

[1a] Standard Oil Co. (Ohio) Fellow in Chemistry, Western Reserve University, 1946–1947. Present address: E. I. du Pont de Nemours and Co., Parlin, N. J.

[1b] Standard Oil Co., Cleveland, Ohio.

[1c] Knop, *Ber.*, **20**, 3352 (1887).

[2] Rudert, *ibid.*, **26**, 565 (1893).

The addition of four moles of aniline to one mole of phosphorus pentasulfide at 30° gave a copious evolution of hydrogen sulfide and rapidly formed thiophosphoric dianilide, $(C_6H_5NH)_2PSSH$. Thiophosphoric dianilide formed salts with silver, lead and mercury ions. These salts were insoluble in water and in organic solvents and could not be purified. The dianilide, unlike the trianilide, was immediately hydrolyzed by refluxing in water, dilute acids or bases.

Thiophosphoric dianilide was converted to thiophosphoric trianilide by refluxing in aniline. This reaction indicates that the formation of thiophosphoric trianilide from six moles of aniline and one mole of phosphorus pentasulfide involves the rapid formation of thiophosphoric dianilide followed by the slower formation of the trianilide at the higher reaction temperatures.

The reaction of two moles of aniline and one mole of phosphorus pentasulfide did not give a monoanilide, $C_6H_5NHPS(SH)_2$. Instead the dianilide and unreacted phosphorus pentasulfide were obtained.

The reaction of phosphorus pentasulfide was studied with a number of additional amines both aromatic and aliphatic.

With *p*-chloroaniline excellent yields of thiophosphoric tri-*p*-chloroanilide were obtained. With *o*-chloroaniline, however, no triamide could be obtained either from phosphorus pentasulfide or thiophosphoryl chloride. Excellent yields of the diamide were obtained using a 4:1 molar ratio of *o*-chloroaniline to phosphorus pentasulfide. The failure of the trianilide to form here may be ascribed to the much weaker basic character of the *o*-chloroaniline.

With 2-naphthylamine, the product obtained was phosphoric tri-2-naphthalide instead of thiophosphoric tri-2-naphthalide. It is probable that thiophosphoric tri-2-naphthalide was first formed but was hydrolyzed to the phosphoric 2-naphthalide in the purification process which included steam distillation. Rudert[2] also obtained phosphoric tri-2-naphthalide upon recrystallizing the reaction product of 2-naphthylamine and thiophosphoryl chloride from acetic acid.

With a high boiling aliphatic amine, benzylamine, 43% yields of tribenzyl thiophosphoric amide were obtained. Low boiling aliphatic amines, such as *n*-propyl amine, would not permit sufficiently high reaction temperatures at atmospheric pressure. However, in a sealed tube, low yields of tri-*n*-propyl thiophosphoric amide were obtained.

With a secondary amine, oily products which could not be purified were usually obtained. However, two crystalline secondary amine thiophosphoric triamides were obtained. Tetrahydroquinoline gave low yields of a crystalline triamide and piperidine gave a crystalline triamide by reaction with thiophosphoryl chloride according to the method of Michaelis.[3]

The secondary amine thiophosphoric triamides, exhibited stability to prolonged reflux in dilute acids, bases, and in glacial acetic acid.

Experimental

Materials.—The phosphorus pentasulfide was a commercial grade purified by extraction with carbon bisulfide using a Soxhlet extractor. The purified product melted at 273–277°. *Anal.* Calcd. for P_2S_5: P, 27.90; S, 72.09. Found: P, 27.64; S, 69.6. The amines were purified by distillation and where necessary, previously dried over potassium hydroxide. Tetrahydroquinoline was prepared from quinoline by the method of Hoffman and Koenigs[4] and purified by the method of Rupe, *et al.*[5]

Preparation of Thiophosphoric Triamides from Amine and Phosphorus Pentasulfide.—A mixture of phosphorus pentasulfide and amine, in a molar ratio of 1:6 with a small excess of amine, was heated in a three-neck round-bottom flask equipped with a stirrer and reflux condenser. The reaction was usually highly exothermic. After the initial reaction had subsided, the mixture was heated from two to four hours at a temperature of 180° to complete the reaction. (In the case of the volatile *n*-propylamine, the mixture was heated in a sealed tube.) The excess amine was removed by steam distillation or by treatment with dilute hydrochloric acid and the residual amide was purified by crystallization from alcohol. The yields and melting points of the products were:

Amide	Yield, %	M. p., °C.
Triphenyl	50	153–154
Tri-*p*-chlorophenyl	97	225–226
Tribenzyl	43	125–126
Tripropyl	10	73–74
Tri-tetrahydroquinolyl	15	190–192

Tri-*p*-chlorophenylthiophosphoricamide. *Anal.* Calcd. for $C_{18}H_{15}Cl_3N_3PS$: N, 9.49; P, 7.01; S, 7.2. Found: N, 9.24; P, 7.42; S 7.35.

Preparation of Thiophosphoric Diamides from Amine and Phosphorus Pentasulfide.—The amine was added dropwise to a mixture of phosphorus pentasulfide in 5 to 10 parts of toluene, with stirring. A small excess over 4 moles of amine to 1 mole of phosphorus pentasulfide was employed. The temperature was kept at 30° for two hours. The diamide separated as a white solid. It could be purified by dissolving in ice cold sodium hydroxide solution and extracting with ether to remove the amine. The diamide was then precipitated with dilute ice cold hydrochloric acid, washed with ether and carbon disulfide and dried.

Diphenylthiophosphoricamide, yield 47%, m. p. 161°–163°. *Anal.* Calcd. for $C_{12}H_{13}N_2PS_2$: N, 10.00; P, 11.07; S, 22.85. Found: N, 10.50; P, 10.90; S, 22.61. Di-*o*-chlorophenylthiophosphoric amide, yield 95%, m. p. 183–190°. It could not be recrystallized without decomposition.

Hydrolysis and Aminolysis of Thiophosphoric Diamides.—Thiophosphoric dianilide and *o*-chloroanilide, unlike the triamides were very sensitive to hydrolyses. Upon exposure to air, hydrolysis occurred slowly; rapid hydrolysis occurred upon boiling with water or treatment with aqueous acid or alkali.

The aminolysis of thiophosphoric dianilide was carried out with aniline, and of thiophosphoric di-*o*-chloroanilide with benzylamine. A mixture of 5.0 g. of thiophosphoric dianilide and 10 g. of aniline was heated at 180° for four hours. Three grams of thiophosphoric trianilide, melting point 150–153°, was obtained. It was identified by a mixed melting point.

Fifty grams of thiophosphoric di-*o*-chloroaniline was dissolved in 10.7 g. of benzylamine with cooling. The mixture was then heated to 180° for three hours. The crude product was washed with dilute hydrochloric acid to remove excess benzylamine and the residue recrystallized

---

(3) Michaelis, *Ann.*, **326**, 129–258 (1903).

(4) Hoffman and Koenigs, *Ber.*, **16**, 728 (1883).

(5) Rupe, Seiberth and Kussmaul, *Helv. Chim. Acta*, **3**, 75 (1920)

from alcohol. One and six-tenths grams of tribenzyl thiophosphoric amide, melting point 121–123°, was obtained. It was identified by a mixed melting point.

Thermal Decomposition of Thiophosphoric Triamides to Dimeric Thiophosphoric Acid Imide Amides.—Thiophosphoric trianilide and thiophosphoric tribenzylamide were converted to the imide amide. Twenty-three grams of thiophosphoric trianilide was heated at 215–225° for two hours under a vacuum of 30 mm. mercury. Six grams of aniline distilled over. The residual solid was recrystallized from alcohol and gave 10 g. of thiophosphoric anil anilide, m. p. 233–235°. This product did not depress the melting point of a sample of the material prepared by the method of Michaelis and Karstens.[6] The anil anilide was readily converted back to the triamide by heating with an excess of aniline at the boiling point for four hours.

Tribenzylthiophosphoric amide was converted to the imide amide by the same method, yield 70%, m. p. 197–199°. *Anal.* Calcd. for $C_{28}H_{30}N_4P_2S_2$: N, 10.22; P, 11.31; S, 11.68; mol. wt., 548 Found: N, 10.34; P, 11.01; S, 11.68; mol. wt., 560.

The Reaction of 2-Naphthylamine and Phosphorus Pentasulfide.—A mixture of 9.2 g. of phosphorus pentasulfide, 45 g. of 2-naphthylamine and 70 g. of diethylbenzene was heated for two hours at 185° with stirring. The diethylbenzene was removed by steam distillation and the excess amine by extraction with cold alcohol. The residue was recrystallized from alcohol and gave 7 g. of phosphoric tri-2-naphthalide, m. p. 168–170°. A mixed melting point with a sample of the material prepared from 2-naphthylamine and phosphorus oxychloride by the method of Rudert[2] gave no depression.

Summary

The reaction of six moles of a primary aliphatic or aromatic amine with one mole of phosphorus pentasulfide at 130–180° gave crystalline thiophosphoric triamides. Secondary amines usually gave oily products, piperidine and tetrahydroquinoline being exceptions.

The reaction of four moles of aniline with one mole of phosphorus pentasulfide at room temperature gave thiophosphoric dianilide. This dianilide appears to be an intermediate in the formation of the trianilide. The thiophosphoric triamides are very stable toward hydrolysis; the phosphorus sulfur linkage of thiophosphoric tri-2-naphthalide is an exception. The triamides of primary amines are hydrolyzed on prolonged heating with 85% phosphoric acid or glacial acetic acid.

Thiophosphoric diamides are very sensitive to hydrolysis.

The primary amine triamides upon heating to 225°, *in vacuo*, lose amine to form a dimeric imide amide. This reaction is easily reversible.

The preparation of thiophosphoric monoanilide from aniline and phosphorus pentasulfide was unsuccessful.

CLEVELAND, OHIO RECEIVED SEPTEMBER 8, 1947

---

[6] Michaelis and Karstens, *Ber.*, **28**, 1237, 1895.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

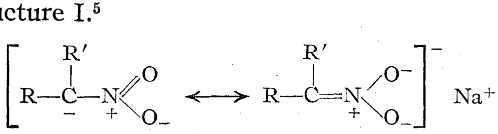
The Basis for the Reported Optical Activity of the Salts of Aliphatic Nitro Compounds: 2-Nitrobutane[1]

BY NATHAN KORNBLUM, JOHN T. PATTON[2] AND JOSEPH B. NORDMANN

The experimental basis for the report that 2-nitrobutane gives an active sodium salt[3] has been reëxamined in view of the recent finding that the optical activity attributed to the salts of 2-nitrooctane is really due to the presence of 2-octyl nitrate.[4] It has now been found that the 2-nitrobutane previously employed was contaminated with 2-butyl nitrate and that the activity ascribed to the sodium salt of 2-nitrobutane is due to this impurity.

Dextrorotatory-2-nitrobutane prepared according to the earlier workers[3] is only partially soluble in aqueous sodium hydroxide. The resulting aqueous alkaline solution, which contains the sodium salt of 2-nitrobutane, is devoid of activity whereas the insoluble portion is still *dextro*rotatory. Examination of the alkali insoluble material reveals that it is *d*-2-butyl nitrate $[\alpha]^{24}\text{D}$ +7.0°.

The "*d*-2-nitrobutane" was freed of *d*-2-butyl nitrate, and any other contaminants, by treatment with cold 96% sulfuric acid. Thus purified, *d*-2-nitrobutane has $[\alpha]^{20}\text{D}$ +7.2°, gives a negative test for nitrate esters, and is completely soluble in aqueous sodium hydroxide; the resulting solution is inactive. When sodium methoxide is used as the base the sodium salt is again devoid of activity and the 2-bromo-2-nitrobutane produced by brominating this salt is also inactive. These results, as well as the various other properties of the salts of aliphatic nitro compounds, lead to the conclusion that they possess the hybrid structure I.[5]



$$\left[R-\overset{R'}{\underset{-}{C}}-\overset{+}{N}\begin{smallmatrix}O\\O^-\end{smallmatrix}\longleftrightarrow R-\overset{R'}{C}=\overset{+}{N}\begin{smallmatrix}O^-\\O^-\end{smallmatrix}\right]^- Na^+$$

I

In addition to establishing I as the structure of the salts of aliphatic nitro compounds the present investigation corroborates the recent observation[4] that, contrary to the accepted view, the reaction of an alkyl halide with silver nitrite (The Victor

---

[1] Presented at the Atlantic City meeting of the American Chemical Society, April, 1947.

[2] Allied Chemical and Dye Fellow 1945–1947.

[3] Kuhn and Albrecht, *Ber.*, **60**, 1297 (1927).

[4] Kornblum, Lichtin, Patton and Iffland, THIS JOURNAL, **69**, 307 (1947).

[5] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 67.

Meyer reaction) yields not only the anticipated nitroparaffin and alkyl nitrite but also a number of other products. As detailed in the experimental portion of this paper, the reaction of 2-iodobutane with silver nitrite gives 2-nitrobutane, 2-butyl nitrite, 2-butyl nitrate, 2-butanol and butanone.[6] Just as with 2-nitroöctane, the yield of pure 2-nitrobutane is very low, *ca.* 15%.

Experimental

Racemic 2-Iodobutane.—This compound was prepared according to Clarke.[7] It was rectified through a 12-inch modified Widmer column[8] fitted with a variable take-off head[8a]; yield 80–87%, b. p. 118°, n^{20}_D 1.4959, d^{20}_4 1.5962; literature values, b. p. 117–118°[9]; b. p. 118–119°; d^{20}_4 1.5952[10]; b. p. 121°, d^{20}_4 1.585, n^{19}_D 1.4945.[11]

Racemic "2-Nitrobutane."—Using 120 g. of racemic 2-iodobutane and following as closely as possible the directions of the previous investigators[3] 4 g. of "2-nitrobutane" was obtained; b. p. 30–31° (36 mm.); n^{20}_D 1.4042; lit. values,[3] b. p. 35–36° (17 mm.), n^{21}_D 1.4057. An authentic sample obtained from the Commercial Solvents Corporation had n^{20}_D 1.4040.

That the "2-nitrobutane" thus prepared is a mixture was demonstrated by shaking it with 10% aqueous sodium hydroxide; about 33% of the "2-nitrobutane" failed to dissolve even after prolonged shaking. This insoluble material was taken up in low boiling petroleum ether and dried over magnesium sulfate. The solvent was removed at atmospheric pressure leaving a colorless liquid, b. p. 121°, n^{20}_D 1.4016. Synthetic 2-butyl nitrate (see below) has b. p. 124°, n^{20}_D 1.4015. In contrast, 2-butyl nitrite (see below) has b. p. 68°, n^{20}_D 1.3710.

The aqueous alkali insoluble material gave a positive test for nitrates esters[12] and a negative test for nitrite esters.[13]

***d*-2-Butanol.**—Eastman Kodak Co. White Label 2-butanol was resolved according to Ingersoll.[14] The *d*-2-butanol distilled at 99°, n^{20}_D 1.3954, d^{20}_4 0.809, $[\alpha]^{25}_D$ +10.9° (no solvent); lit. values[15]: b. p. 99°, n^{20}_D 1.3954, d^{20}_4 0.808, $[\alpha]^{20}_D$ +13.87°.

***l*-2-Iodobutane.**—Following the procedure of Clarke,[7] 89 g. of *d*-2-butanol ($[\alpha]^{22}_D$ +10.9°) was treated with 138 g. of iodine and 24 g. of red phosphorus. The product was rectified[8a]; yield 199 g. (90%), b. p. 117.5–118°, n^{20}_D 1.4948, d^{20}_4 1.5959, M_D (calcd.) 33.47, M_D (found) 33.61; $[\alpha]^{24}_D$ −15.9° (no solvent); lit. values,[15] b. p. 117–118°, d^{17}_4 1.5970, $[\alpha]^{17}_D$ −31.98°.

Pure *d*-2-Nitrobutane.—One hundred and forty grams of *l*-2-iodobutane ($[\alpha]^{24}_D$ −15.9°) was treated with 175 g. of recrystallized silver nitrite[16] and 60 g. of freshly ignited quartz sand following, as closely as possible, the directions of the previous investigators.[3]

The silver nitrite and sand were placed in a 500 ml. round-bottom flask fitted with a condenser (the outlet of which led to a dry ice–acetone cooled trap), a tantalum Hershberg stirrer and a dropping funnel. The flask was submerged in an ice–salt mixture and the *l*-2-iodobutane was added dropwise over the course of one and one-half hours. Upon the addition of the first few ml. of iodide copious evolution of brown fumes was observed. When addition of the 2-iodobutane was complete the reaction mixture was allowed to come to room temperature and to stand overnight (*ca.* twelve hours). The flask was then heated at 90° for one hour and at the end of this period was fitted with a condenser set for downward distillation. Twenty-four grams of material distilled at atmospheric pressure when the reaction product was heated on a steam-bath (Fraction A). Further heating on the steam-bath under reduced pressure (60 mm.) gave an additional 38 g. of distillate (Fraction B). The Dry Ice trap contained 9 g. of a blue liquid, the color of which was discharged upon standing overnight at Dry Ice temperature.

Thirty-six grams of Fraction B, upon rectification[8a] at 188 mm., gave several fractions (Table I).

TABLE I

Fract.	B. p., °C.	Wt., g.	n^{20}_D
1	29	4.0	1.3762
2	30–51	1.0	1.3780
3	52–58	4.0	1.3891
4	60–61	5.0	1.3960
5	62–78	1.5	1.3970
6	79–80	6.0	1.4015
7	81–85	1.2	1.4029
8	86–87	10.5	1.4043
Dry Ice trap		1.4	1.3743

To 8 g. of Fraction 8 (Table I) was added 30 ml. of 96% sulfuric acid (precooled to 0°) at such a rate that the temperature did not rise above 3°. The solution was shaken for five minutes at 0° and then poured onto 50 g. of ice which was covered with 50 ml. of 30–60° petroleum ether. The aqueous layer was separated and extracted with fresh portions of petroleum ether. The extracts were combined, washed with water and dried over "Drierite." The solvent was removed at atmospheric pressure and the residue distilled under reduced pressure. The yield of pure 2-nitrobutane was 4.2 g., b. p. 60° at 70 mm., 137° at 760 mm. (Emich); n^{20}_D 1.4040, d^{20}_4 0.9627, M_D (calcd.) 26.21, M_D (found) 26.21, $[\alpha]^{20}_D$ +7.20° (no solvent); lit. values,[3] b. p. 35–36° at 17 mm., n^{21}_D 1.4057, d^{17}_4 0.9854, $[\alpha]^{22}_D$ +8.83°. An authentic sample of 2-nitrobutane obtained from Commercial Solvents Corporation was rectified and a middle cut taken; b. p. 140° (Emich), n^{20}_D 1.4040, d^{20}_4 0.9633.

Anal.[17] Calcd. for $C_4H_9NO_2$: C, 46.53; H, 8.79; N, 13.58. Found: C, 46.78, 46.87; H, 8.74, 8.69; N, 13.85, 13.90.

In contrast to "2-nitrobutane" prepared according to the earlier workers,[3] 2-nitrobutane thus purified is readily and completely soluble in aqueous alkali, gives a negative nitrate test,[12] and also gives a negative test for nitrite esters.[13]

Experiments with Pure *d*-2-Nitrobutane

(a) Racemization of *d*-2-Nitrobutane by the Action of Sodium Methoxide.—To a solution of 2 g. of *d*-2-nitrobutane ($[\alpha]^{20}_D$ +7.20°) in 5 ml. of absolute methanol was

---

(6) It should be pointed out that both instances in which products other than the nitro compound and alkyl nitrite were isolated involved secondary halides. It seems likely that the same result will be obtained with primary and tertiary halides; this point is being investigated.

(7) Clarke, THIS JOURNAL, **30**, 1149 (1908).

(8) Smith and Adkins, *ibid.*, **60**, 657 (1937).

(8a) Subsequent use of this column will be indicated by the superscript 8a.

(9) DeLuynes, *Ann.*, **132**, 276 (1864).

(10) Lieben, *ibid.*, **150**, 96 (1869).

(11) Kenyon, Phillips and Pittman, *J. Chem. Soc.*, 1080 (1935).

(12) S. P. Mulliken, "A Method of the Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1916, Vol. II, p. 27. We have found that with Mulliken's diphenylamine–sulfuric acid reagent 2-butyl nitrate gives a purple color, 2-nitrobutane a blue color and 2-butyl nitrite a slight yellow color. Mulliken, it should be noted, reports that alkyl nitrites, alkyl nitrates and nitroparaffins all give an intense blue color.

(13) Bose, *Analyst*, **56**, 504 (1931).

(14) A. W. Ingersoll, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1944, Vol. II, p. 403.

(15) Pickard and Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

(16) Mallinckrodt silver nitrite was purified as described previously[4] except that 60 g. of impure silver nitrite was used instead of 84 g. per four liters of water. From 300 g. of crude silver nitrite 250 g. of purified product was obtained.

(17) All analyses are microanalyses by Miss Theta Spoor of the University of Illinois unless otherwise stated.

added 15 ml. of 1.56 *N* methanolic sodium methoxide. The resulting solution was optically inactive $[\alpha]^{23}_{\mathrm{D}}$ 0.00 ($C = 10$).

(b) **Racemic 2-Bromo-2-nitrobutane from the Sodium Salt of *d*-2-Nitrobutane.**—The optically inactive methoxide solution obtained from *d*-2-nitrobutane (see preceding paragraph) was treated with an excess of bromine–water, care being taken to prevent the reaction mixture from becoming acidic. The alcoholic solution was then poured into water whereupon the brominated product separated as an oil. The mixture was then extracted with diethyl ether and the ether solution dried over "Drierite"; the resulting solution of crude 2-bromo-2-nitrobutane showed no optical activity, $[\alpha]^{24}_{\mathrm{D}}$ 0.00°; $l = 1$ dm. The ether was then removed by warming in an air stream, following which the residual oil was chromatographed on an aluminum oxide–Celite column using low boiling petroleum ether to develop the chromatogram. The solvent was removed and the residue chromatographed once again, this time on Darco; low boiling petroleum ether was used to develop the chromatogram. Most of the solvent was removed by blowing a stream of dry air over the solution at room temperature and the remainder by shaking at 30° in a vessel evacuated to 15 mm. The 3 g. (85% yield), of colorless product was still optically inactive, $[\alpha]^{24}_{\mathrm{D}}$ 0.00 (no solvent) $l = 1$ dm., n^{20}_{D} 1.4678, d^{20}_{4} 1.4927, M_{D} (calcd.) 34.05, M_{D} (found) 33.95.

Anal. Calcd. for $C_4H_8NO_2Br$: C, 26.37; H, 4.39; N, 7.69; Br, 43.90. Found: C, 26.25, 26.39; H, 4.41, 4.52; N, 7.69, 7.39; Br, 43.89, 43.67.

(c) **Racemization of *d*-2-Nitrobutane by the Action of Aqueous Sodium Hydroxide.**—Two-tenths gram of *d*-2-nitrobutane, ($[\alpha]^{20}_{\mathrm{D}}$ +7.20°) was shaken for ten minutes with 1 ml. of 20% aqueous sodium hydroxide. The mixture was then diluted with 1 ml. of water and shaken for an additional ten minutes. The *d*-2-nitrobutane had now dissolved completely and the resulting solution was devoid of optical activity ($C = 10$, $l = 1$ dm.).

(d) **Preparation of a Solid Derivative of 2-Nitrobutane. [2-(4-carboxyphenylazo)-2-nitrobutane].**—Immediately after neutralization, the aqueous alkaline solution of *d*-2-nitrobutane from the preceding section was coupled with diazotized *p*-aminobenzoic acid. The product was recrystallized from 85% ethanol, m. p. 128–128.7°; mixed m. p. undepressed; lit. values,[18] m. p. 128–129°.

Similar experiments were carried out with pure *l*-2-nitrobutane of $[\alpha]^{23}_{\mathrm{D}}$ −1.95°. In all instances the results agree with those obtained above but since the initial specific rotation is relatively low, the results are not as conclusive as those reported for the *dextro*rotatory isomer.

By-products of the Reaction between 2-Iodobutane and Silver Nitrite.—The reaction between 2-iodobutane and silver nitrite gives not only 2-nitrobutane and 2-butyl nitrite but also 2-butyl nitrate, 2-butanol and butanone. Their isolation from fractions A and B (see earlier section entitled "Pure-*d*-2-Nitrobutane") is described below.

(a) ***d*-2-Butyl Nitrate.**—Fraction 6 (Table I) was shaken by hand with 10 ml. of 20% aqueous sodium hydroxide for twenty minutes following which 10 ml. of water was added and the shaking continued for an additional twenty minutes; the organic phase was isolated and the treatment repeated. The organic layer was then washed with water and finally shaken with 10 ml. of 85% phosphoric acid for thirty minutes after which the mixture was allowed to stand until separation of the two layers was complete (*ca.* twelve hours.). The acid was drawn off and the organic layer was washed with water and dried over "Drierite." There was obtained 4 g. of colorless liquid, n^{20}_{D} 1.4016. Upon distillation at atmospheric pressure there was collected 3.7 g. of a colorless product, b. p. 124°, d^{20}_{4} 1.026, n^{20}_{D} 1.4016, M_{D} (calcd.) 28.80, M_{D} (found) 28.90, $[\alpha]^{24}_{\mathrm{D}}$ +7.02°, $l = 1$ dm. (no solvent); lit. values,[19] b. p. 124°, d^{0} 1.0382. Synthetic 2-butyl nitrate (see below) has b. p. 124°, d^{20}_{4} 1.029, n^{20}_{D} 1.4015.

The *d*-2-butyl nitrate thus isolated from the Victor Meyer reaction gave a positive nitrate ester test[12] and a negative nitrite test.[13]

Anal. Calcd. for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.77. Found: C, 40.46, 40.57; H, 7.64, 7.72; N, 11.72, 11.63.

(b) ***d*-2-Butyl Nitrite.**—Fraction A (24 g.) was dried over sodium sulfate and rectified at 200 mm. pressure using ice-water in the condenser.[8a] There was obtained 6.3 g. of *d*-2-butyl nitrite boiling at 30°. At atmospheric pressure the b. p. is 68° (Emich), d^{20}_{4} 0.8720, n^{20}_{D} 1.3710, M_{D} (calcd.) 27.01, M_{D} (found) 27.04, $[\alpha]^{24}_{\mathrm{D}}$ +0.44° (no solvent); lit. values[20] b. p. 68°, d^{0} 0.8981. Synthetic 2-butyl nitrite (see below) has b. p. 68° (Emich), d^{20}_{4} 0.8728, n^{20}_{D} 1.3710. The *d*-2-butyl nitrite thus isolated from the Victor Meyer reaction gives a positive test for nitrite esters.[13] The fact that this compound was a nitrite was further demonstrated by diazotizing *p*-toluidine with it and then coupling the diazonium salt with alkaline beta-naphthol according the procedure described for 2-octyl nitrite.[4] The crude azo compound after three recrystallizations from glacial acetic acid melted 132–132.7° and a mixed m. p. with an authentic sample showed no depression. The yield of pure azo compound was 40%. Under the same conditions 2-nitrobutane and 2-butyl nitrate did not diazotize *p*-toluidine.

(c) **2-Butanol.**—Two grams of Fraction 4, Table I (n^{20}_{D} 1.3960) was passed through a short column of aluminum oxide–Celite without the use of any solvent. The 1.1 g. of liquid thus obtained gave only a faint nitrite ester test[13] and had n^{20}_{D} 1.3967. This material was heated at reflux for five hours with 2.7 g. of phthalic anhydride and 3 g. of dry pyridine. No brown deposit was formed in the condenser nor was there any evolution of oxides of nitrogen as in the case when 2-butyl nitrite is subjected to the same treatment. At the end of this time the resulting solution was cooled to room temperature and poured into an excess of 37% hydrochloric acid. The oil which separated was taken up in benzene and the solution filtered. The solvent was removed and the remaining solid recrystallized from 60–90° petroleum ether. There was obtained 2.4 g. (67% yield) of 2-butyl hydrogen phthalate, m. p. 56–57°, $[\alpha]^{23}_{\mathrm{D}}$ 0.00, $l = 1$ dm. ($C = 20$); lit. values,[15] m. p. 56–57° (racemic), 46–47° (active). A mixed m. p. with racemic 2-butyl hydrogen phthalate showed no depression. The mother liquor was checked for optical activity, $[\alpha]^{23}_{\mathrm{D}}$ 0.00. It is interesting to note that whereas the 2-octanol produced in the Victor Meyer reaction between 2-bromoöctane and silver nitrite is optically active[4] the 2-butanol obtained here is completely racemic.

When 2-butyl nitrite is subjected to the phthalic anhydride–pyridine treatment 2-butyl hydrogen phthalate is formed; on the other hand 2-butyl nitrate does not give any phthalate ester.

(d) **Butanone.**—Fraction 1, Table I (n^{20}_{D} 1.3762) was passed through a silicic acid–Celite column. There was obtained, without the aid of a solvent, 1.8 g. of product, n^{20}_{D} 1.3785. This was treated with 1.5 g. of 2,4-dinitrophenylhydrazine.[21] A yellow, amorphous precipitate formed at once. It was filtered off while the solution was still hot. Upon cooling the filtrate, yellow needles of the 2,4-dinitrophenylhydrazone of butanone were deposited. After recrystallization from ethanol the derivative melted at 110–111° and showed no depression in a mixed m. p.; lit. value,[22] m. p. 111°. The yellow, amorphous material which came out of the hot solution does not melt below 200°. When 2-butyl nitrite was subjected to the same treatment only the amorphous material was obtained. With 2-butyl nitrate there was no evidence of any reaction.

Racemic 2-Butyl Nitrate.—A 500-ml. three-neck flask was fitted with a stirrer, condenser and dropping funnel and then immersed in a salt–ice mixture. In the flask was placed 190 g. of finely powdered silver nitrate and 137

---

[18] Degering and Feasley, *J. Org. Chem.*, **8**, 12 (1943).

[19] Bertoni, *Gazz. chim. ital.*, **20**, 374 (1890).

[20] Bertoni, *Gazz. chim. ital.*, **18**, 434 (1888).

[21] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 143.

[22] Ref. 21, p. 221.

g. of 2-bromobutane was added dropwise over a period of two hours. At the end of this time the reaction mixture was allowed to come to room temperature and then to stand for twelve hours. It was then heated at 60° until the organic layer gave a negative test for halogen. The flask was then fitted with a condenser set for downward distillation and heated to 80° at 60 mm. pressure; there was obtained 61 g. of distillate. This was shaken for one hour with 75 ml. of 85% phosphoric acid, and then allowed to stand in contact with the acid overnight. The acid layer was withdrawn, the organic layer was washed with water, dried over magnesium sulfate and then rectified.[8a] There was obtained 58 g. (49% yield) of 2-butyl nitrate boiling at 59° (80 mm.). At atmospheric pressure the nitrate boils at 124° (Emich), n^{20}_D 1.4015, d^{20}_4 1.029, M_D (calcd.) 28.80, M_D (found) 28.81, lit. value,[19] b. p. 124°, d^0 1.0382.

Anal.[23] Calcd. for $C_4H_9NO_3$: C, 40.33; H, 7.62. Found: C, 40.68, 40.34; H, 7.62, 7.79.

Racemic 2-Butyl Nitrite.—(a) Thirty-nine grams of racemic 2-butanol was treated with 38 g. of sodium nitrite and 15.5 ml. of 96% sulfuric acid according to the method of Noyes.[24] Upon rectification[8a] there was obtained 49 g. (83% yield) of a pale yellow liquid; b. p. 28° at 180 mm. At atmospheric pressure the nitrite ester boils at 68° (Emich), n^{20}_D 1.3710, d^{20}_4 0.8726, M_D (calcd.) 27.01, M_D (found) 27.02; lit. values,[20] b. p. 68°, d^0 0.8981.

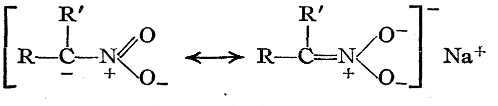
(b) Following the procedure described by Kornblum and Oliveto[25] 30 g. of racemic 2-butanol was treated with 40 g. of nitrosyl chloride. One modification was made, namely, the omission of the use of petroleum ether in working up the product; yield 21 g. (50%) boiling at 27° under 180 mm. pressure. At atmospheric pressure the nitrite boils at 68° (Emich); n^{20}_D 1.3710, d^{20}_4 0.8728.

Anal.[26] Calcd. for $C_4H_9NO_2$: N, 13.58. Found: N, 13.67, 13.70.

Summary

Contrary to an earlier report, optically active 2-nitrobutane does not give an active sodium salt upon treatment with sodium methoxide. Furthermore, 2-bromo-2-nitrobutane prepared from this salt is optically inactive.

It is concluded that the correct structure for the salts of aliphatic nitro compounds is



The action of silver nitrite on 2-iodobutane has been shown to form 2-nitrobutane, 2-butyl nitrate, 2-butyl nitrite, 2-butanol and butanone.

---

(23) Microanalyses by Dr. Carl Tiedcke, New York, N. Y.

(24) Noyes, THIS JOURNAL, **55**, 3888 (1933).

(25) Kornblum and Oliveto, *ibid.*, **69**, 465 (1947).

(26) "The Pharmacopaeia of the United States of America," Mack Printing Co., Easton, Pa., 1942, 12 revision, p. 597.

LAFAYETTE, INDIANA RECEIVED AUGUST 1, 1947

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

The Stereochemistry of Complex Inorganic Compounds. VIII. Configurations of Some Compounds as Revealed by Rotatory Dispersion Curves[1]

BY THOMAS D. O'BRIEN,[2] JAMES P. MCREYNOLDS[3] AND JOHN C. BAILAR, JR.

The determination of configuration of ions of the type $[M(AA)_2b_2]$ and $[M(AA)_2bc]$[4] by chemical means presents several difficult problems and no general method has yet been suggested. It is often stated that the *cis* compounds are more highly colored and more soluble than the *trans*, but there are so many exceptions to these rules that no reliance can be placed in them. Differences in reactivity of *cis* and *trans* isomers have been observed in several cases, but they are so scattered that generalization cannot be drawn from them. Finally, the fact that a compound is prepared from another of known structure is of no value in determining configuration because molecular rearrangements are common in such reactions.

Unless one or more of the coördinating groups is optically active, *trans* complexes are not resolvable, while those of the *cis* configuration are. Thus, it is definite that the optically active (violet) form of $[Co\ en_2\ Cl_2]^+$ (Ib) must have the *cis* configuration, while the inactive (green) form must be *trans* (Ia). If, on the other hand, the coördinating groups are optically active, both isomers of the complex will rotate the plane of polarized light, so that the presence of optical activity does not serve to distinguish one isomer from the other. As will be shown in this paper, however, the rotatory dispersion curves often give the desired information.

It has previously been pointed out[5] that the rotatory dispersion curves of resolved *cis*-dichloro-bis-ethylenediamine cobaltic chloride, $[Co\ en_2\ Cl_2]Cl$ (Ib) and the corresponding compound of *levo*-propylenediamine, $[Co(l\text{-}pn)_2Cl_2]Cl$, (IIb) are strikingly alike in general shape and in the positions of maxima, minima and points of zero rotation. The same is true of the carbonato complexes. Several investigators have shown that *cis* cobaltic complexes containing optically active diamines do not exist in all the possible stereo-

---

(1) Constructed from portions of the doctorate theses of James P. McReynolds (1938) and Thomas D. O'Brien (1941).

(2) Present address, Chemistry Department, University of Minnesota, Minneapolis, Minn.

(3) Died, June 19, 1943.

(4) The following abbreviations are used: AA = a group occupying two coördination positions; en = ethylenediamine; pn = propylenediamine; a, b and c = groups occupying one coördination position; Y = group occupying two coördination positions. The various compounds referred to are designated for convenience by Roman numerals, those of the ethylenediamine series being assigned odd numbers and those of the propylenediamine series, even numbers. For *trans* isomers, the Roman numeral is followed by the letter "a," for *cis* isomers, by "b."

(5) Bailar and McReynolds, THIS JOURNAL, **61**, 3199 (1939).

chemical forms but only in certain preferred configurations.[6] The optical activity is mainly due to the arrangement of the groups about the central atom, so the rotatory dispersion curves of complexes of similar configuration should have the same characteristics whether the coördinating base be active or not. Should the non-basic constituents be in the *trans* positions in the di-active-propylenediamine compounds, then one might expect their dispersion characteristics to be similar to those of active propylenediamine itself (Fig. 2). There is, of course, the possibility of having additional isomers due to the position of the methyl group in the active propylenediamine, *i. e.*, in *cis*-[Co(*l*-pn)$_2$Cl$_2$]$^+$ (IIb) the methyl groups could be adjacent to the plane containing the chlorine and cobalt or distant from it. Similar relations hold for the *trans* salt. However, it is assumed here that the contribution of the methyl groups in the different positions to the rotatory dispersion curve would be very small compared to the contribution of the central atom itself. It is also possible that both diastereoisomers [Co(*l*-pn)$_2$a$_2$]*d*$^+$ and [Co(*l*-pn)$_2$a$_2$]$_L$$^+$ (or [Co(*l*-pn)$_2$Y]^+_D and [Co(*l*-pn)$_2$Y]^+_L might form, although it is known that these are of different stabilities. Such a pair has been reported by Bailar and McReynolds for the carbonato-bis-propylenediamine cobaltic ion (XIV).[5] They found that the rotatory dispersion curves of the two differ widely. Even if the two *cis* diastereoisomers form in equal quantity, therfore, the dispersion curve of the mixture will not resemble the curve of the *trans* isomer.

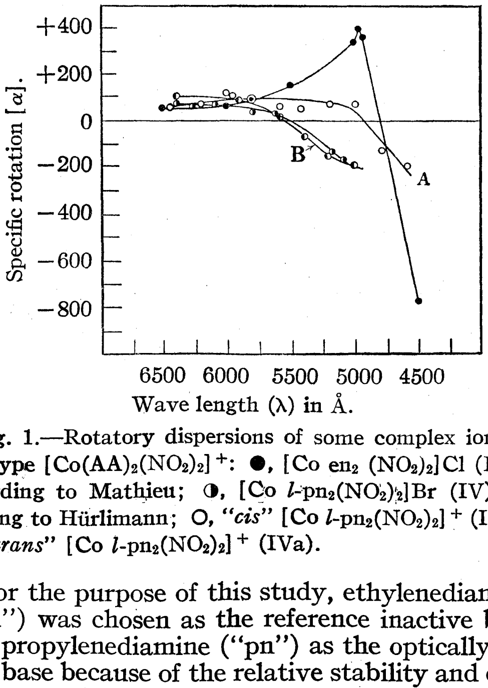


Fig. 1.—Rotatory dispersions of some complex ions of the type [Co(AA)$_2$(NO$_2$)$_2$]$^+$: ●, [Co en$_2$ (NO$_2$)$_2$]Cl (IIIb) according to Mathieu; ◑, [Co *l*-pn$_2$(NO$_2$)$_2$]Br (IV) according to Hürlimann; ○, "*cis*" [Co *l*-pn$_2$(NO$_2$)$_2$]$^+$ (IVb); ◐, "*trans*" [Co *l*-pn$_2$(NO$_2$)$_2$]$^+$ (IVa).

For the purpose of this study, ethylenediamine ("en") was chosen as the reference inactive base and propylenediamine ("pn") as the optically active base because of the relative stability and ease of preparation of most of their coördination compounds, and because Mathieu[7] has determined the rotatory dispersion curves of many diethylenediamine cobaltic complexes.

Hurlimann[6a] has reported the dispersion curve of dinitro-bis-*levo*-propylenediamine cobaltic bromide, [Co(*l*-pn)$_2$(NO$_2$)$_2$]Br (IV), which he obtained from the reaction of trinitro-triammine-cobalt and *levo*-propylenediamine. Hurlimann was of the opinion that his product was the pure *cis* isomer (IVb) and that none of the *trans* (IVa) form resulted from this reaction. This conclusion was based upon the fact that the compound gave a green color when heated with hydrochloric acid (a test which has been reported to distinguish the *cis* and *trans* isomers in both the ammonia and ethylenediamine series).[8] However, the dispersion curve which Hurlimann obtained (Fig. 1) shows no similarity to the one given by Mathieu for *cis*-dinitro-bis-ethylenediamine cobaltic ion (IIIb). We therefore studied Hurlimann's reaction further, and found that in addition to the product reported by him another material is formed in even larger amount. It gives a dispersion curve somewhat resembling that for *cis* [Co en$_2$(NO$_2$)$_2$]$^+$ (IIIb). The lack of greater similarity here may possibly be due to the fact that this was not the pure *cis* isomer. At least, this curve definitely differs from the curve of the *trans* isomer. The compound also gives the test which Hurlimann considered distinctive for the *cis* form. The *cis*-ethylenediamine compound is known to be slowly converted to the *trans* form on boiling in water. Our *levo*-propylenediamine complex which gave the "*cis*" rotatory dispersion curve was gradually converted by long boiling into a material which gave a curve resembling that reported by Hurlimann. As the curves show, the material which Hurlimann studied must have been largely the *trans* isomer. There are numerous examples in which *cis* compounds of the type [Ma$_4$b$_2$]$^+$ (when a and b are groups occupying one coördinate position) when heated in water are converted to the *trans* isomer. As the *cis* compound has only one form there is no possibility of getting a mixture of *cis* isomers. If A$_2$ groups (pn for example) are substituted for the a$_4$ ones, the same reaction occurs on heating in water. In addition, as no one has reported a mixture of *d* and *l* forms in which both were stable with respect to each other, it seems logical to assume that when a change occurs on refluxing the *cis* compound, it is the *trans* that is formed.

Again, it is possible that the two forms of the *levo*-propylenediamine compound might be diastereoisomers, [Co *l*-pn$_2$ (NO$_2$)$_2$]$_D$$^+$ and [Co *l*-pn$_2$(NO$_2$)$_2$]$_L$$^+$ (IVb). To test this point, each of the diastereoisomers of [Co *l*-pn$_2$ CO$_3$]$^+$ (XIVb)[5] was treated at room temperature with calcium nitrite. The curves for the two materials obtained were much alike, the product from the stable carbonato form apparently being all *trans*,

---

[6] (a) Hurlimann, "Dissertation," Zurich, 1918; (b) Jaeger, *Rec. trav. chim.*, **38**, 170 (1919).

[7] Mathieu, *Bull. soc. chim.*, [5] **3**, 463–475 (1936).

[8] Jorgensen, *Z. anorg. Chem.*, **17**, 468, 472 (1898); Werner, *Ber.*, **34**, 1709 (1901).

and that from the unstable form being predominately *trans*. It seems safe to say that the isomers of [Co *l*-$pn_2(NO_2)_2]^+$ (IV) which were obtained from trinitro-triamminecobalt were the stable *cis* form and the *trans* form.

The dispersion curve for chloro-ammino-bis-*dextro*-propylenediamine cobaltic chloride (VI) (Fig. 2) is quite smooth and regular, very similar to the curve for active propylenediamine itself, and very unlike the curve for the corresponding active ethylenediamine salt (Vb). Identical curves were obtained regardless of whether the material was prepared from the *cis* or from the *trans*-dichloro-bis-*dextro*-propylenediamine cobaltic chloride (II), and from their shape one concludes that the product has the *trans* configuration (VIa). The dichloro-bis-propylenediamine salt (II) evidently acts differently than the corresponding dichloro-bis-ethylenediamine salt (I), because the latter, whether *cis* or *trans*, always yields the *cis*-chloro-ammino salt (Vb) when treated with aqueous ammonia.

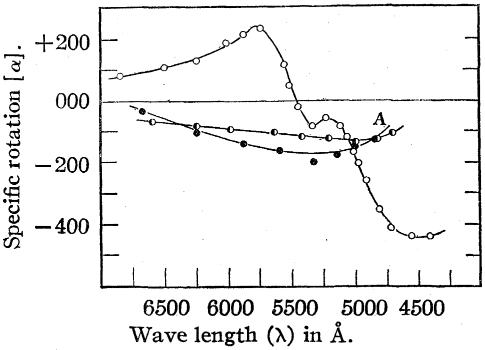


Fig. 2.—The rotatory dispersion of [Co $en_2(NH_3)Cl]Cl_2$, [Co *d*-$pn_2(NH_3)Cl]Cl_2$ and of propylenediamine: ○, [Co $en_2(NH_3)Cl]Cl_2$ (Vb) (Mathieu); ●, [Co *d*-pn_2 $(NH_3)Cl]Cl_2$ (VI) prepared from *cis*-[Co *d*-pn_2 $Cl_2]Cl$; ◐, *levo*-propylenediamine.

The configurations of the diammino and dithiocyanato complexes $[Co(AA)_2(NH_3)_2]^{+++}$ and $[Co(AA)_2(NCS)_2]^+$ can be related through the conversion of the latter to the former by the action of chlorine or perhydrol. These reagents destroy the thiocyanato group, eliminating the carbon and sulfur and leaving the nitrogen (as ammonia) coördinated to the cobalt. The fact that this takes place in acid solution shows that the nitrogen–cobalt bond is not broken during the reaction, and that the diammine must therefore have the same configuration as the dithiocyanato complex from which it is derived.

No rotatory dispersion curve for [Co en_2 $(NCS)_2]^+$ (IXb) was found in the literature, so a sample of the material was resolved and a curve prepared (Fig. 3). The rotations in all parts of the spectrum were low and the absorption high, so no great accuracy can be attached to the values given. However, they are sufficiently exact for our present purpose.

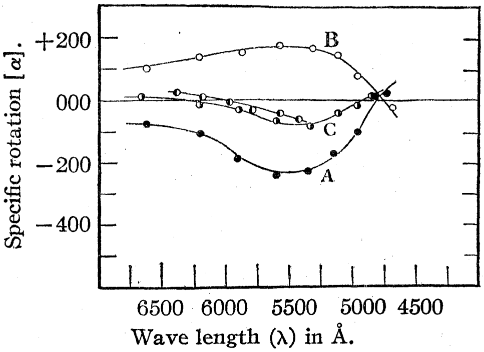


Fig. 3.—The rotatory dispersions of some complex ions of the type $[M(AA)_2(NCS)_2]^+$: ○, [Co *l*-$pn_2(NCS)_2]NCS$ (X) prepared from *cis*-[Co *l*-$pn_2Cl_2]Cl$; ●, [Co *d*-pn_2 $(NCS)_2]NCS$ (X) prepared from *trans*-[Co *d*-$pn_2Cl_2]Cl$; ◐, *cis*-[Co $en_2(NCS)_2]Cl$ (IX); ◑, [Cr *d*-$pn_2(NCS)_2]NCS$ (XVI).

The dithiocyanato-bis-propylenediamine cobalt compounds (X) used in this study were prepared by the reaction of potassium thiocyanate with [Co pn_2 $Cl_2]Cl$ (II).[9]

The products obtained from the *cis* and *trans* dichloro salts were evidently the same, as shown by the curves of Fig. 3. Here again, the rotations were low and absorptions high, so the values are not very exact. A comparison of the curves of Fig. 3, however, indicates that the propylenediamine complex (X) is quite different from the ethylenediamine compound (IXb) so must have the *trans* configuration.

Diammino-bis-*levo*-propylenediamine cobaltic chloride (VIII) was prepared by substitution of ammine groups for chlorine in *cis* and *trans* dichloro-bis-*levo*-propylenediamine cobaltic chloride (II) by allowing the salt to react with liquid ammonia at −35° and with ammonia gas at +80°, and by oxidation of the thiocyanato groups in [Co (*l*-pn)$_2$ $(NCS)_2]NCS$ (X) with chlorine gas.[9] The products of all procedures gave almost identical rotatory dispersion curves. Comparison of these curves with that obtained by Mathieu for *cis*-diammino-bis-ethylenediamine cobaltic chloride (Ib) (Fig. 4) shows marked differences, in that the curve for the ethylenediamine compound shows a sharp inflection at about 5200 Å. and crosses the zero axis at about 5100 Å., while the others are positive at all wave lengths. It was therefore concluded that all of the products of our reactions were of the *trans* form. Data are given in the Experimental Section for several different reactions, but to avoid crowding on the diagram, only the results of the reaction between [Co *l*-$pn_2Cl_2]Cl$ (II) and gaseous ammonia are shown in Fig. 4.

The sulfito salts in both series crystallize as hydrates, so might conceivably have the structure $[Co(AA)_2(SO_3)H_2O]Cl$, in which the sulfito group occupies but one coördination position, as it does,

---

[9] Werner and Dawes, *Ber.*, **40**, 791 (1907).

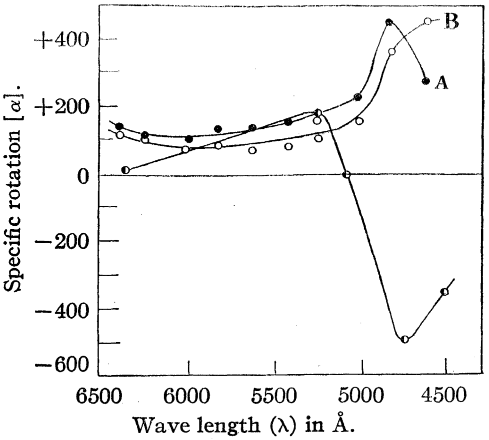


Fig. 4.—Rotatory dispersion curves of some complex ions of the type $[Co(AA)_2(NH_3)_2]^{+++}$: ●, [Co *l*-$pn_2(NH_3)_2]Cl_3$ (VIII) from *cis*-[Co *l*-$pn_2Cl_2]Cl$ and NH_3 gas; ○, [Co *l*-$pn_2(NH_3)_2]Cl_3$ (VIII) from *trans*-[Co *l*-$pn_2Cl_2]Cl$ and NH_3 gas; ◐, [Co $en_2(NH_3)_2]Cl_3$ (VII) according to Mathieu.

for example, in $NH_4[Co(NH_3)_4(SO_3)_2]$. Such a complex ion might have either the *cis* or *trans* configuration, and for a time we thought our propylenediamine complex to have the *trans* [Co $pn_2(SO_3)H_2O]^+$ structure because the dispersion curves (Fig. 5) differ markedly from the curves shown by other salts containing bidentate groups but resemble those of *trans* [Co *l*-pn_2 $X_2]^+$ salts. However, the discovery that the ethylenediamine compound is optically active proved that it must have the *cis* configuration; the striking similarity of the curves for the two series indicates that the propylenediamine compounds are also *cis*. Finally, the fact that the ethylenediamine sulfito compound can be dehydrated without change in color or loss of optical activity indicates that the water is not an integral part of the complex ion, which must, therefore, have the structure [Co en_2 $SO_3]^+$ (XI). On account of the great solubility of the corresponding propylenediamine salt, pure samples could not be obtained. The similarities between the members of the two series are so great, however, that there is little doubt that they have the same structure.

The physical properties of corresponding complex ions of cobalt and chromium are strikingly similar, as many investigators have observed. While we have not studied the reactions of chromic complexes in detail, the curves of Figs. 3 and 6 indicate that the rotatory dispersion curves of complex ions of the two elements are of the same general shape. Even though the points of inflection and points of zero rotation differ by several hundred Ångstrom units, the similarity of the curves is great enough to allow one to decide whether a complex ion of either metal is *cis* or *trans* if the configuration of an analogous complex of the other is known.

It is interesting to note that the thermal decomposition of tris-propylenediamine chromic thiocyanate leads to *cis*-dithiocyanato-bis-propylenediamine chromic thiocyanate. The corresponding reaction in the ethylenediamine series apparently yields the *trans* dithiocyanato compound.[10] This reaction is being investigated further.

Experimental

Rotatory Dispersion Curves.—The observed rotations were taken on a Schmidt–Haensch polarimeter with a prism monochromator and using a 1000-watt projection bulb as a light source. The wave lengths reported are not strictly monochromatic, but represent an average which covers about 100 Å. The polarimeter scale is graduated to 0.001°, although an accuracy of 0.01° was the best that could be obtained due to the high light adsorption by the colored solutions. Every time the wave length setting was changed the zero point of the instrument was checked, and it was found that there was some change due to the change in focus of the light source and to the different openings of the monochromator slit. The observed rotations are an average of at least five readings, and in some cases, where the light adsorption was high and the accuracy low, as many as ten readings were taken. A 1-dm. tube was used unless otherwise noted.

Dichloro-bis-ethylenediamine cobaltic chloride (I) was prepared by the usual method,[11] and the corresponding propylenediamine compound according to the directions given earlier [12]

***cis*-Dinitro-bis-*levo*-propylenediamine cobaltic nitrite (IVb)** was prepared from *levo*-propylenediamine and trinitro-triammine-cobalt as carried out by Watts.[13] The first fraction only was used. As has been pointed out in the discussion, this reaction leads to a mixture of *cis* and *trans* forms which can be separated by careful fractionation. The *trans* form was obtained in solution by refluxing the *cis* form in water for twenty-six hours. The *trans* form was also prepared by allowing the stable carbonato-bis-*levo*-propylenediamine complex (XIV) to stand in solution with a 10% excess of calcium nitrite for one week at room temperature. A mixture of *cis* and *trans* forms was obtained from a similar procedure using the unstable diastereoisomer of the carbonato compound.[5]

***cis*-Dinitro-bis-*levo*-propylenediamine Cobaltic Nitrite (IVb)**.—The readings were taken upon a solution containing 0.16 g. of the salt in 100 cc. of water in the regions of higher transmission and upon a solution of one-half this concentration for the regions of higher absorption. This solution was found to be stable over several days so that all the readings could be taken upon a single solution (readings taken with 0.16% are marked with an asterisk), Curve A, Fig. 1.

Wave length	Observed rotation	Specific rotation
6400*	+0.08	+ 50
6200*	+ .09	+ 56
6000*	+ .17	+106
5900*	+ .16	+100
5800*	+ .15	+ 94
5600*	+ .10	+ 63
5400*	+ .08	+ 50
5200*	+ .12	+ 75
5000	+ .06	+ 75
4800	− .10	−125
4600 (0.04%)	− .08	−200

---

(10) Rollinson and Bailar, THIS JOURNAL, **66**, 641 (1944).

(11) Bailar, "Inorganic Syntheses," Vol. II, McGraw-Hill Book Co., New York, N. Y., 1946, p. 222.

(12) Bailar, Stiegman, Balthis and Huffman, THIS JOURNAL, **61**, 2402 (1939).

(13) Watts, "Dissertation," Zurich, Switzerland, 1912.

A solution containing 0.16 g. per 100 cc. of the *cis* dinitro compound was refluxed in water for seven hours. The rotation was then taken at selected wave lengths.

Wave length	Observed rotation	Specific rotation
5400	+0.07	+ 45
5200	+ .04	+ 25
5000	− .14	− 88

The solution was then refluxed for another ten hours.

5400	+ .04	+ 25
5200	− .06	− 38
5000	− .16	−100

The solution was then refluxed for another nine hours (Curve B, Fig. 1).

Wave length	Observed rotation	Specific rotation
6400	+0.16	+100
5900	+ .13	+ 80
5800	+ .11	+ 70
5600	+ .03	+ 20
5400	− .05	− 30
5200	− .26	−160
5000	− .32	−200

Further refluxing gave no further change. This material is evidently the pure *trans* isomer (IVa).

Dinitro-bis-*levo*-propylenediamine cobaltic nitrite (IV), prepared from the stable diastereoisomer of carbonato-bis-*levo*-propylenediamine cobaltic carbonate (XIV), was used in a solution of 0.2% concentration. Readings were taken only in the range at which the values changed from positive to negative.

Wave length	Observed rotation	Specific rotation
5800	+0.14	+ 70
5600	+ .04	+ 20
5400	− .06	− 30
5200	− .33	−165

It will be noted that this series of readings checks well with those given above for the *trans* form (IVa).

Dinitro-bis-*levo*-propylenediamine cobaltic nitrite (IV) prepared from the unstable diastereoisomer of carbonato-bis-*levo*-propylenediamine cobaltic carbonate (XIV) was used in a solution of 0.3% concentration. It was found necessary to dilute this solution for the reading at 5200 Å.

Wave length	Observed rotation	Specific rotation
6000	+0.27	+90
5600	+ .15	+50
5400	+ .10	+30
5200 (0.15%)	− .09	−60

The dispersion characteristics of the solution indicate that this reaction leads to a mixture of *cis* and *trans* forms. From the shape of the curve at the point at which the sign of the rotation changes it would seem that more of the material is of the *trans* form than the *cis*.

Chloro-amino-bis-*dextro*-propylenediamine cobaltic chloride (VI) was prepared by the method of Watts.[13] This consisted of adding aqueous ammonia to *cis*-dichloro-bis-*dextro*-propylenediamine cobaltic chloride (IIb) until the resulting solution turned deep red. This was evaporated to dryness and the residue extracted with alcohol. The extract was then evaporated to dryness, and the resulting purple-red powder dried at 105° for two hours. The salt contains one molecule of water of hydration.

Anal. Calcd.: Cl, 30.58; N, 20.10. Found: Cl, 30.56; N, 20.09.

The rotatory dispersion curve was measured on a 0.05% solution (Curve A, Fig. 2). Due to the high adsorption at the lower wave lengths, reproducible readings could not be obtained below 4800 Å.

Wave length in Å.	Observed rotation	Specific rotation
6625	−0.02	− 40
6225	− .06	−120
5892	− .07	−140
5615	− .08	−160
5360	− .10	−200
5160	− .09	−180
4985	− .08	−160
4850	− .07	−140

Dithiocyanato-bis-*dextro*-propylenediamine cobaltic thiocyanate (X) was made from dichloro-bis-*dextro*-propylenediamine cobaltic chloride (II) and potassium thiocyanate by the method of Werner and Dawes.[9] Both the *cis* and the *trans* starting material were used, and, as was shown later, both yielded the *trans* dithiocyanato salt (Xa).

Anal. Calcd.: C, 28.35; H, 5.25. Found: C, 28.57; H, 5.50. The optical rotations were taken on a 0.1% solution in a 0.5-dm. tube (Curve A, Fig. 3).

Wave length in Å.	Observed rotation	Specific rotation
6625	−0.035	− 70
6225	− .05	−100
5892	− .095	−190
5615	− .12	−240
5360	− .11	−220
5160	− .09	−180
4985	− .045	− 90
4850	00	00
4720	+ .01	+ 20

Readings were also taken on a 0.1% solution of dithiocyanato-bis-*levo*-propylenediamine cobaltic thiocyanate (X), Curve B. At the wave length marked with one asterisk, the solution was diluted with an equal volume of water, giving a 0.05% solution. At those wave lengths marked with two asterisks, the solution was again diluted with an equal volume of water, resulting in a 0.025% solution.

Wave length in Å.	Observed rotation	Specific rotation
6625	+0.10	+100
6225	+ .13	+130
5892	+ .15	+150
5615	+ .18	+180
5360	+ .17	+170
5160*	+ .07	+140
4985**	+ .02	+ 80
4850**	.00	00
4720**	− .005	− 20

Diammine-bis-*levo*-propylenediamine cobaltic chloride (VIII) was prepared from dithiocyanato-bis-*levo*-propylenediamine cobaltic thiocyanate (X) by oxidation with chlorine as reported by Werner and Dawes.[9] Further samples of diammino-bis-*levo*-propylenediamine cobaltic chloride (VIII) were prepared from *cis* and *trans* dichloro-bis-*levo*-propylenediamine (II) by allowing them to react with liquid ammonia at −33°. Samples were also prepared by passing ammonia gas over the dry *cis* and *trans* dichloro compounds at 80°. After recrystallization, the compound contains one molecule of water. *Anal.* Calcd. N, 23.01. Found for sample from *cis* dichloro and ammonia gas: N, 22.70; for sample from *trans* dichloro and liquid ammonia: N, 22.62.

The complete curves for the samples prepared from the

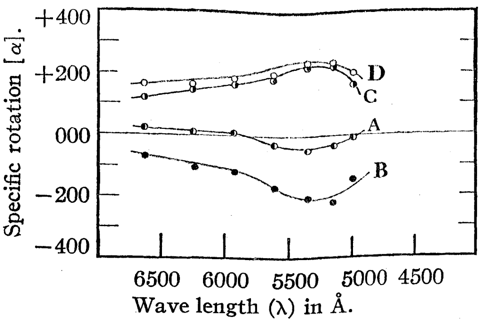


Fig. 5.—The rotatory dispersion of some complex ions of the type $[Co(AA)_2SO_3]^+$: ○, $[Co\ l\text{-}pn_2SO_3]^+$ (XII) prepared from *cis*-$[Co\ l\text{-}pn_2Cl_2]Cl$ and Na_2SO_3; ◑, $[Co\ l\text{-}pn_2SO_3]^+$ (XII) prepared from *trans*-$[Co\ l\text{-}pn_2Cl_2]Cl$ and Na_2SO_3; ●, $[Co\ d\text{-}pn_2SO_3]^+$ (XII) prepared from *trans*-$[Co\ d\text{-}pn_2Cl_2]Cl$ and Na_2SO_3; ◐, $[Co\ en_2SO_3]^+$ (XI) prepared from *levo-cis*-$[Co\ en_2Cl_2]Cl$ and Na_2SO_3.

dichloro compounds with dry ammonia at 80° were obtained. The other samples were examined only at intervals throughout the spectrum. The product of the reaction of dry ammonia upon the *cis* dichloro compound was run at a concentration of 0.1% at all wave lengths except those marked with an asterisk. The marked wave lengths were run at a concentration of 0.05% (Curve A, Fig. 4).

Wave length in Å.	Observed rotation	Specific rotation
6400	+0.13	+130
6200	+ .11	+110
6000	+ .10	+100
5800	+ .12	+120
5600	+ .13	+130
5400	+ .15	+150
5200	+ .10	+100
5000	+ .23	+230
4800*	+ .23	+460
4600*	+ .14	+280

The product prepared from the *trans* dichloro compound with dry ammonia was studied in the same manner. All readings except those marked with an asterisk were taken at 0.1%. Those marked were taken at 0.05% (Curve B, Fig. 4).

Wave length, Å.	Observed rotation	Specific rotation
6400	+0.11	+110
6200	+ .11	+110
6000	+ .08	+ 80
5800	+ .09	+ 90
5600	+ .08	+ 80
5400	+ .09	+ 90
5200	+ .16	+160
5000*	+ .08	+160
4800*	+ .19	+380
4600*	+ .23	+460

The product from the liquid ammonia and *trans* dichloro reaction was examined in a 0.1% solution. Only three wave lengths were used since the points fell well within the range of error for the curves already found.

Wave length, Å.	Observed rotation	Specific rotation
5800	+0.11	+110
5200	+ .20	+200
4800	+ .38	+380

The product of the liquid ammonia and *cis*-dichloro reaction was not isolated from the solution as it had been contaminated with sodium dithionate in an unsuccessful attempt to isolate the *trans* form as the dithionate. The concentration was approximately 0.1%. This solution was examined at only four wave lengths as the readings checked well with the curves already obtained.

Wave length, Å.	Observed rotation	Specific rotation
6400	+0.11	+110
5600	+ .12	+120
5200	+ .19	+190
4800	+ .45	+450

The product from the oxidation of the dithiocyanato complex was not isolated from solution since it was found that the solution was strongly acid and the compound decomposed on evaporation. The concentration used was approximately 0.16%. Only three wave lengths were examined since the points found fall close to the curves already obtained.

Wave length, Å.	Observed rotation	Specific rotation
6000	+0.15	+ 90
5400	+ .21	+130
4800	+ .60	+360

Sulfito-bis-ethylenediamine cobaltic chloride (XI) was prepared by the procedure of Werner and Pokrowska,[14] using optically active dichloro-bis-ethylenediamine cobaltic chloride (Ib). The material can be recrystallized from warm water and dried at 100° with only partial loss of optical activity. In order to get the largest readings possible, however, the material on which the dispersion curve was obtained was not isolated from the solution. Two hundred milligrams of optically active $[Co\ en_2Cl_2]Cl$(Ib) in 100 cc. of water was treated with 1 g. of sodium sulfite and the solution was diluted to 204 cc. Readings were taken as soon as the characteristic brown-yellow color of the sulfito salt appeared (Curve A, Fig. 5).

Wave length, Å.	Observed rotation	Specific rotation
6625	+0.04	+40
6225	+ .02	+20
5892	+ .02	+20
5615	− .02	−20
5360	− .04	−40
5160	− .02	−20
4985	− .01	−10

All attempts to isolate the sulfito propylenediamine salt (XII) in pure crystalline form proved fruitless, so the readings were made on a solution prepared by adding 1 g. (an eight-fold excess) of sodium sulfite to 200 mg. of *trans*-dichloro-bis-*dextro*-propylenediamine cobaltic chloride (II). This should yield 209 mg. of the sulfito complex, and it was on this assumption that the solution was diluted to 209 cc. to give a 0.1% solution (Curve B, Fig. 5).

Wave length in Å.	Observed rotation	Specific rotation
6625	−0.07	− 70
6225	− .10	−100
5892	− .11	−110
5615	− .17	−170
5360	− .20	−200
5160	− .22	−220
4985	− .14	−140

The same procedure as described above was used to prepare sulfito-bis-*levo*-propylenediamine cobaltic ion (XII). A 0.1% solution was used (Curve C).

---

(14) Werner and Pokrowska, *Ann.*, **386**, 81 (1912).

Wave length in Å.	Observed rotation	Specific rotation
6625	+0.11	+110
6225	+ .14	+140
5892	+ .16	+160
5615	+ .19	+190
5360	+ .22	+220
5160	+ .22	+220
4985	+ .17	+170

The following points were obtained from a 0.1% solution of sulfito-bis-*levo*-propylenediamine cobaltic ion (XII) made by the above procedure, with the exception that the *cis*-dichloro-bis-*levo*-propylenediamine cobaltic chloride (IIb) was used as a starting material rather than the *trans* (Curve D).

Wave length in Å.	Observed rotation	Specific rotation
6625	+0.16	+160
6225	+ .16	+160
5892	+ .18	+180
5615	+ .20	+200
5360	+ .24	+240
5160	+ .24	+240
4985	+ .20	+200

Dithiocyanato-bis-*dextro*-propylenediamine chromic thiocyanate (XVI) was prepared accordingly to the directions of Rollinson and Bailar.[14] Readings were taken on a 0.1% solution (Curve C, Fig. 3). At those wave lengths marked with an asterisk the solution had to be diluted with an equal volume of water because of high absorption.

Wave length in Å.	Observed rotation	Specific rotation
6625	+0.01	+10
6225	− .01	−10
5892	− .04	−40
5615	− .07	−70
5360	− .08	−80
5160*	− .02	−40
4985*	− .01	−20
4850*	+ .01	+20

While the rotations of the chromic salt (Fig. 3) are less negative at all wave lengths than those of the corresponding cobalt salt, the similarity of the curves is striking.

The curves for the dichloro-bis-ethylene (XVb) and bis-propylenediamine chromic (XVI) salts are shown in Fig. 6. The salts were prepared according to Rollinson and Bailar[10] and the former was resolved by the method of Werner.[15] Readings were taken on a 0.083% solution. At those wave lengths marked with an asterisk a 0.042% solution was used, made by diluting the original solution with an equal volume of water (Curve A, Fig. 6).

Wave length in Å.	Observed rotation	Specific rotation
6625	−0.15	−160
6225	− .07	− 84
5892	+ .03	+ 36
5615	+ .15	+180
5360	+ .33	+396
5160*	+ .18	+432
4985*	+ .10	+240
4850*	− .05	−120

Rotations of the dichloro-bis-*levo*-propylenediamine chromic salt (XVI) were taken on a 0.033% solution (Curve B).

Wave length in Å.	Observed rotation	Specific rotation
6625	+0.04	+120
6225	+ .02	+ 60
5892	− .01	− 30
5615	− .02	− 60
5360	− .12	−360
5160	− .13	−390
4985	− .06	−180
4850	+ .02	+ 60

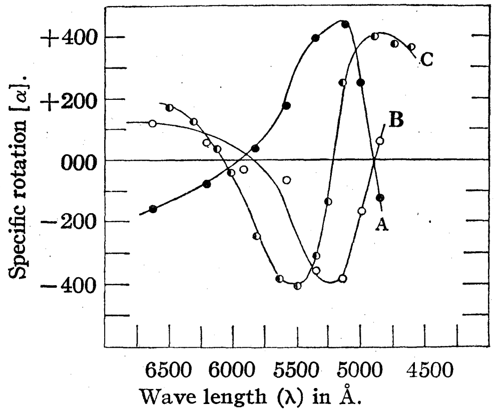


Fig. 6.—The rotatory dispersions of some complex ions of the type *cis*-$[M(AA)_2Cl_2]^+$: O, [Cr *l*-pn_2Cl_2]Cl (XVIII); ●, *levo*-[Cr en_2Cl_2]Cl (XVII); ◐, [Co *l*-pn_2Cl_2]Cl (II) (for data, see ref. 5).

Summary

Rotatory dispersion curves have been plotted for several ethylenediamine and propylenediamine cobaltic complexes of the types $[Co(AA)_2a_2]^+$ and $[Co(AA)_2Y]^+$. These can be used to distinguish between *cis* and *trans* isomers in the propylenediamine series.

It is shown that the reaction of $[Co(NH_3)_3(NO_2)_3]$ with propylenediamine leads to a mixture of *cis* and *trans* [Co $pn_2(NO_2)_2$]NO_2(IV). Either *cis* or *trans* [Co pn_2Cl_2]Cl(II), reacting with potassium thiocyanate, leads to *trans* [Co $pn_2(NCS)_2$]$^+$ (Xa). The reaction of either *cis* or *trans* [Co pn_2Cl_2]Cl (II) with aqueous ammonia yields *trans* [Co $pn_2(NH_3)Cl$]Cl_2 (VIa) and with anhydrous ammonia, *trans* [Co $pn_2(NH_3)_2$]Cl_3 (VIIIa). The reaction with aqueous ammonia is particularly interesting, as the corresponding reaction in the ethylenediamine series leads to the *cis* isomer (VIIb).

The reaction of sodium sulfite with *trans* [Co pn_2Cl_2]Cl (IIa) gives [Co pn_2SO_3]$^+$ (XII), in which the sulfite ion acts as a bidentate group.

The similarity between the rotatory dispersion curves shown by analogous complexes of cobalt and chromium is pointed out, with the suggestion that it may serve as a means of determining configurations.

URBANA, ILLINOIS RECEIVED DECEMBER 26, 1946

---

[15] Werner, *Ber.*, **44**, 3132 (1911).

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

The Sterochemistry of Complex Inorganic Compounds. IX. The Diastereoisomers of *dextro*-Tartrato-*bis*-ethylenediamine Cobaltic Ion

BY HANS B. JONASSEN, JOHN C. BAILAR, JR., AND E. H. HUFFMAN[1]

The stereochemistry of the octahedral complex ions offers many problems for which there is no counterpart in the better known stereochemistry of carbon. For example, the union of a metallic ion with three molecules of an optically active bidentate coördinating agent would be expected to lead to a large number of stereoisomeric complex ions.[2] The case of tris-propylenediamine cobaltic ion, $[\mathrm{Co\ pn_3}]^{+++}$[3] offers an interesting example. Considering optical activity only, the complex ion would be expected to exist in eight isomeric forms. Taking D and L to represent the signs of rotation of the complex as a whole (at the sodium D line) and *d* and *l* the signs of rotation of propylenediamine, these are D*lll*, D*lld*, D*ldd*, D*ddd*, L*lll*, L*lld*, L*ldd*, L*ddd*. (In addition, there might be several racemoids or partial racemoids.) Experiment has shown, however, that these combinations are not all of equal stability; in fact, only two of the isomeric ions are stable enough to be isolated. They are L*lll* and D*ddd*.[4]

A similar effect is observed if the complex contains only two optically active coördinating groups. It has been shown that such ions as *cis* $[\mathrm{Co\ pn_2\ Cl_2}]^+$ and *cis* $[\mathrm{Co\ cptdin_2\ Cl_2}]^+$ exist[6] in only two of the six possible forms—D*ll*$\mathrm{Cl_2}$ and L*dd*$\mathrm{Cl_2}$.[4b] If dichloro-bis-*levo*-propylenediamine cobaltic ion, $[\mathrm{Cl}\ l\text{-}\mathrm{pn_2\ Cl_2}]^+$, be treated with *dextro*-propylenediamine, the ion $[\mathrm{Co}\ l\text{-}\mathrm{pn_2}\ d\text{-}\mathrm{pn}]^{+++}$ apparently forms, but immediately rearranges to a mixture of the more stable L$[\mathrm{Co}\ l\text{-}\mathrm{pn_3}]^{+++}$ and D$[\mathrm{Co}\ d\text{-}\mathrm{pn_3}]^{+++}$.[4a,5]

These selective effects, while pronounced, are not absolute but only relative. Lifschitz[6] found evidence that cobalt and chromium tris-*dextro*-alanine exist in D*ddd* and L*ddd* forms. Bailar and McReynolds[7] have shown that the ion $[\mathrm{Co}\ l\text{-}\mathrm{pn_2\ CO_3}]^+$ exists in both D*ll* $\mathrm{CO_3}$ and L*ll* $\mathrm{CO_3}$ forms, but that the latter is unstable, rearranging to the former when warmed gently.

When only one molecule of the optically active base is present in the coördination sphere, there is some tendency toward the formation of preferred orientations, but not enough to completely fix the configurations. Thus, when Jaeger and Blumendal[4b] allowed racemic *trans*-cyclo-pentanediamine to react with $[\mathrm{Co\ en_2\ Cl_2}]^+$, they obtained a true racemic mixture of D$[\mathrm{Co\ en_2}\ l\text{-}\mathrm{cptdin}]^{+++}$ and L$[\mathrm{Co\ en_2}\ d\text{-}\mathrm{cptdin}]^{+++}$ without detecting any of the other two possible forms. When, however, they used *levo*-cyclopentanediamine, they observed that the base entered both the D and L forms of the complex, yielding D and L$[\mathrm{Co\ en_2}\ l\text{-}\mathrm{cptdin}]^{+++}$.[8]

This paper is concerned with another case in which the complex ion contains one optically active bidentate coördinating group—the tartrate ion. It has been found that *dextro* tartaric acid reacts readily with carbonato-*bis*-ethylenediamine cobaltic ion, $[\mathrm{Co\ en_2\ CO_3}]^+$ to give the two diastereoisomers D$[\mathrm{Co\ en_2}\ d\text{-}\mathrm{tart}]^+$ and L$[\mathrm{Co\ en_2}\ d\text{-}\mathrm{tart}]^+$, which differ strikingly in stability, reactivity and solubility.

The *dextro*-tartrato-bis-ethylenediamine cobaltic ion was prepared by the interaction of equivalent quantities of $[\mathrm{Co\ en_2\ CO_3}]\mathrm{Cl}$ or $[\mathrm{Co\ en_2\ CO_3}]\ \mathrm{Br}$ and *dextro*-tartaric acid. It makes no difference whether the carbonate salt is racemic or optically active; the final product is the same. Solutions of these substances react rapidly at room temperature with the evolution of carbon dioxide, but the primary product of the reaction is $[\mathrm{Co\ en_2\ (H_2O)_2}]^{+++}$. In order to insure complete replacement of the water molecules by tartrate, the solution must be evaporated to dryness and the residue heated on the steam-bath for several hours. The tartrato halides $[\mathrm{Co\ en_2}\ d\text{-}\mathrm{tart}]\ \mathrm{X}$ are extremely soluble, and form deep red glasses which cannot be crystallized.[9] *Anal.* of $[\mathrm{Co\ en_2}\ d\text{-}\mathrm{tart}]\mathrm{Br{\cdot}2H_2O}$, calcd.: N, 13.23; Br, 18.04. Found: N, 13.28; Br, 17.56. The rotation of a 0.1% solution at the sodium D line is about $-0.19°$.

On account of its high solubility, the mixture could not be completely fractionated into the D and L components. Partial fractionation was achieved, however, by dissolving the substance in water and reprecipitating about half of it by the addition of alcohol. The portion remaining in the filtrate was precipitated by addition of a large excess of ether. These fractions were again dissolved and reprecipitated. Repetitions of the process gave specific rotations as high as $+2°$ and as low as $-46°$.

Reaction of DL$[\mathrm{Co\ en_2}\ d\text{-}\mathrm{tart}]^+$ with Ethylenediamine.—A mixture of 20 g. of $[\mathrm{Co\ en}\ d\text{-}\mathrm{tart}]\mathrm{Br}$, 60 ml. of 56% ethylenediamine and 15 ml. of water was shaken at room temperature for definite time intervals. After each time interval, the solution was poured into 75 ml. of ice-cold ethyl alcohol, and the precipitate was removed by filtration. The filtrate was evaporated to 55 ml. in a current of air (to remove the alcohol), 10 ml. of ethylenediamine was added (to compensate for that lost by evaporation and reaction) and the mixture was returned to the shaker for another time interval. The precipitate was thrice dis-

---

[1] Most of the work reported in this article was taken from the doctorate theses of Hans B. Jonassen (1946) and E. H. Huffman (1936) at the University of Illinois. The remainder was done by Mr. Jonassen at Tulane University. For the previous paper in this series, see THIS JOURNAL, **70**, 749 (1948).

[2] Jaeger gives a full discussion of the various possibilities in his book "Optical Activity and High Temperature Measurements," McGraw-Hill Book Co., New York, N. Y., 1928.

[3] The following abbreviations are used: pn = propylenediamine, en = ethylenediamine, cptdin = *trans*-cyclopentanediamine, tart = tartrate ion.

[4] For other examples, see (a) Smirnoff, *Helv. Chim. Acta*, **3**, 177 (1920), and (b) Jaeger and Blumendal, *Z. anorg. allgem. Chem.*, **175**, 161 (1928).

[5] Bailar, Stiegman, Balthis and Huffman, THIS JOURNAL, **61**, 2402 (1939); ref. 2, p. 155.

[6] Lifschitz, *Z. physik. Chem.*, **114**, 493 (1925).

[7] Bailar and McReynolds, THIS JOURNAL, **61**, 3199 (1939).

[8] See also Werner, *Helv. Chim. Acta*, **1**, 5 (1918).

[9] Duff, *J. Chem. Soc.*, **119**, 388 (1921).

solved in 15 ml. of water and reprecipitated by adding 15 ml. of methyl alcohol. This kept the unchanged tartrato salt in solution but precipitated the bright yellow tris-ethylenediamine salt. The filtrates were saved, and the complex in them was finally recovered by evaporation at room temperature to 50 ml. and addition of 150 ml. of a 2:1:1 mixture of methyl and ethyl alcohols and ether. The results are shown in Table I.

TABLE I

Time of shaking	Color of ppt.	Color of filtrate	α(obs.) 1-dm. tube	Yield, g.
10 min.	Pink	Red	+0.13 (0.1% soln.)	0.15
40 min.	Yellow	Red	+0.05 (0.5% soln.)	3.2
100 min.	Yellow	Red	+0.08 (0.5% soln.)	3.5
12 hours	....	Red	....	0.0

From the filtrate, after twelve hours of shaking, it was possible to recover 9 g. of $[\text{Co en}_2\ d\text{-tart}]\text{Br}$; 2 g. was also recovered from the filtrates obtained upon recrystallization of the precipitates. It is evident that the reaction proceeds rapidly for something over an hour, then stops completely.

A similar experiment was carried out at a higher temperature, the procedure differing only in that after each removal of tris-ethylenediamine salt the unchanged tartrato salt was completely precipitated by adding 100 ml. of a 2:1:1 mixture of methyl and ethyl alcohols and ether. This precipitate was then dissolved in twice its weight of water, and twice this volume of ethylenediamine was added. A small portion of the resulting solution was used each time for a determination of the rotation. The results are shown in Table II.

TABLE II

Time of shaking, hr.	Temp., °C.	Yield of $[\text{Co en}_3]^{+++}$ salt, g.	α observed ppt. (0.5%) 1-dm. tube	% purity of D$[\text{Co en}_3]^{+++}$	Filtr. (0.1%) 1-dm. tube
0	20				−0.07
0.25	20	2.2	+0.43	90	− .08
0.75	20	2.3	+ .38	85	− .13
2	20	4.7	+ .35	80	− .17
12	20	0.6	+ .40	85	− .20
28	50	2.3	+ .45	90	− .26
48	50	2.0	+ .30	75	− .33
68	50	0.5	+ .25	70	− .40
82[a]	50	1.1	+ .01		− .45
106[a]	50	0.2	+ .02		− .06

[a] Two grams of activated charcoal was added in each of the last two time intervals. This greatly catalyzes the reaction, but the product is racemic. The filtrate from each of the last two filtrations was orange or brown (the color of $[\text{Co en}_3]^{+++}$), while the filtrates from the earlier shakings were a brilliant cherry red (as is $[\text{Co en}_2\ \text{tart}]^+$).

The fact that the $[\text{Co en}_3]^{+++}$ fractions all show positive rotations, while the material which has not reacted shows an increasing negative rotation, indicates that the original material is a mixture of two isomers rather than a single individual, D or L $[\text{Co en}_2\ d\text{-tart}]^+$.

The filtrate from the precipitate obtained after one-hundred six hours of shaking could not be precipitated by addition of 100 ml. of 2:1:1 mixture of methyl and ethyl alcohols and ether. The excess of ethylenediamine was therefore removed by bubbling gaseous hydrogen chloride through the ice cold solution until most of the ethylenediamine was precipitated as the hydrochloride and before the solution began to change to a purple color (indicative of the formation of $[\text{Co en}_2\ \text{Cl}_2]^+$). The ethylenediamine hydrochloride was filtered off, and the filtrate was evaporated in a stream of air. The residue was dried for four hours at 65°; yield about 3.5 g. The rotation was −0.06 for a 0.5% solution.

Similar results were obtained in several other runs although no exact duplications of the rotations were obtained. The tris-ethylenediamine salt obtained in the sixty-eight hours represents a little more than 12 g. of optically pure tris-ethylenediamine cobaltic bromide. Since 1.3 g. of almost inactive $[\text{Co en}_3]\text{Br}_3$ was recovered, as well as 3.5 g. of unchanged starting material, it is evident that an asymmetric synthesis has taken place.

In the best run, a 70% yield of *dextro*-$[\text{Co en}_3]^{+++}$ was obtained (out of a possible 100% for *dextro*- and *levo*-combined). Either the two isomers of $[\text{Co en}_2\ d\text{-tart}]^+$ are not present in equal amount or the less reactive is converted to the more reactive as the latter is used up by the reaction with ethylenediamine. The fact that the DL-$[\text{Co en}_2\ d\text{-tart}]^+$ mixture has a high negative rotation would suggest that the L isomer is somewhat more abundant and therefore more stable than the D. This leads to the conclusion that the D form is the more reactive and so is the one which reacts with ethylenediamine the more readily. Whether the difference in rate of reaction takes place in the formation of the tartrato complex or in its conversion to the *tris*-ethylenediamine salt, we have here a partially asymmetric synthesis of $[\text{Co en}_3]^{+++}$.

Reaction of DL-$[\text{Co en}_2\ d\text{-tart}]^+$ with Hydrochloric Acid.—A solution of ten grams of the tartrato salt in ten milliliters of water was treated with 10 ml. of concentrated hydrochloric acid. At given time intervals the mixture was poured into 50 ml. of ice cold methanol, which caused precipitation of the unchanged tartrato salt, but kept the violet colored *cis*-dichloro salt in solution. After filtration, the red precipitate was again treated with hydrochloric acid. The violet filtrate was treated with 75 ml. of concentrated nitric acid to precipitate the dichloro salt. This precipitate was filtered as quickly as possible, washed with ether and dried in a vacuum desiccator over potassium hydroxide for two weeks. This long drying is essential to remove the last traces of acid. Without it, the crystals turn green (*trans*-dichloro salt) when exposed to moist air. Table III shows the results of two runs. It will be observed that samples of the *cis*-dichloro salt obtained in the second run showed no optical activity. This is probably due to the fact that the acid was not entirely removed, and caused very rapid racemization. This *cis*-dichloro salt racemizes rapidly even under the best conditions, and the measurements of optical rotation must be made immediately. While the rotations of the *cis*-$[\text{Co en}_2\ \text{Cl}_2]\text{Cl}$ could never be duplicated, the increasing negative rotation of the unchanged tartrato salt was demonstrated repeatedly. Here again, the results show that $[\text{Co en}_2\ d\text{-tart}]^+$ is not a single individual, but is a mixture of two forms which differ greatly in reactivity.

Optical rotations were taken on 0.1% solutions at the sodium D line in a 1-dm. tube. *Anal.* Calcd. for $[\text{Co en}_2\ \text{Cl}_2]\text{Cl}$: Cl, 37.3. Found for sample B: first run, Cl, 37.21; second run, Cl, 37.45.

Reaction of DL-$[\text{Co en}_2\ d\text{-tart}]\text{Br}$ with Calcium Nitrite.—Four grams of the DL tartrato salt, in about 10 ml. of water, was mixed with 2.4 g. (100% excess) of calcium nitrite. Reaction was very slow, but over a period of several weeks calcium tartrate and a brown powder of $[\text{Co en}_2\ (\text{NO}_2)_2]\text{Br}$ gradually precipitated. This was recrystallized from water containing a little ammonium bromide. It was dextrorotatory; analysis showed 23.06% bromine; calcd., 22.77%. The reaction can be greatly accelerated by heating the mixture near the boiling point for five minutes and cooling immediately, or by heating to 50–60° for three hours. For the best sample prepared by the first of these techniques $[\alpha]_D$ was found to be +50°. Werner[10] reports $[\alpha]_D$ for $[\text{Co en}_2\ (\text{NO}_2)_2]\text{Br}$ to be +44°. For a typical sample prepared by the second technique, $[\alpha]_D$ was found to be +42°, and the percentage of bromine, 22.84.

In every case the filtrate still had the brilliant red color of the tartrato salt, and it was evident that much of this remained. When the reaction mixture was heated long enough to bring about complete reaction, the product was always racemic, probably because of the easy racemization

---

[10] Werner, *Ber.*, **44**, 2450 (1911).

TABLE III

Sample	Total time of reaction, hours	First run			Second run		
		cis-Dichloro, g.	[α] of *cis*-dichloro	[α] of filtrate	*cis*-Dichloro, g.	[α] of *cis*-dichloro	[α] of filt.
Original				(−0.09)			(−0.09)
A	1	1.92	+0.06	− .13	1.13	+0.01	−0.12
B	5	3.64	+ .05	− .18	4.30	.00	− .19
C	12	0.96	+ .05	− .26	0.75	.00	− .24
D	24	0.88	+ .02	− .34	0.80	.01	− .33
E	48	0.24	+ .04	− .40	0.34	.00	− .40

of [Co en_2 $(NO_2)_2$]$^+$. The best yield of optically active dinitro product that was ever obtained was 40%. It is apparently possible to convert one form of the [Co en_2 *d*-tart]Br to the dinitro salt without affecting the other form. When the reaction is allowed to proceed at room temperature, the precipitation of calcium tartrate goes on slowly but steadily until about half is precipitated; the reaction then stops unless the temperature is raised.

Summary

The presence of two or three optically active chelate groups in an octahedral complex tends to fix a definite configuration upon the complex ion as a whole, and in some cases the number of stereoisomers which can be isolated is limited to a small fraction of those theoretically possible. No such effect has been observed in complex ions containing only one asymmetric chelate group. It is now shown that while both the D and L forms of *dextro*-tartrato-*bis*-ethylenediamine cobaltic ion, [Co en_2 *d*-tart]$^+$, form when *dextro*-tartaric acid reacts with [Co en_2 CO_3]$^+$, they differ greatly in reactivity. When the mixture of the two is shaken with ethylenediamine at room temperature, part of the material reacts within two hours, giving *dextro*-[Co en_3]$^{+++}$. The remainder does not react even in twelve hours and can be recovered. At 50°, a 70% yield of *dextro*-[Co en_3]$^{+++}$ is obtained, and very little of the original material can be recovered. Evidently the less reactive form changes to the more reactive as the latter is used up. The reaction with hydrochloric acid seems to follow a similar course, and gives a large yield of *dextro*-rotatory *cis*-[Co en_2 Cl_2] Cl.

Reaction with calcium nitrite gives similar results; at room temperatures or slightly above, about half of the tartrato salt reacts, yielding *dextro*-[Co en_2 $(NO_2)_2$]$^+$. The remainder will not react at room temperatures. At higher temperatures the product is racemized.

These are evidently the first examples of asymmetric synthesis in the field of inorganic complex ions.

URBANA, ILLINOIS
NEW ORLEANS, LA.
RECEIVED JUNE 21, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

Hydrofluorination in the Presence of Boron Fluoride

BY ALBERT L. HENNE AND ROBERT C. ARNOLD

The addition of hydrogen fluoride to an olefinic hydrocarbon occurs with great ease[1]; addition also takes place easily with asymmetrically halogenated olefins such as $CH_2{=}CHX$, $RCH{=}CX_2$ or $RCX{=}CH_2$,[2] while the presence of the vinylic halogens on both sides of the double bond impedes or prevents it.[2] We have now observed that when the addition is carried out in the presence of small quantities of boron fluoride the reaction is greatly hastened, and even occurs where it had failed in the absence of boron fluoride.

Besides plain hydrofluorination, an alternation of HF additions and HX removals is observed, so that $RCH{=}CX_2$ gives not only RCH_2CX_2F, but also $RCH{=}CFX$, RCH_2CXF_2, $RCH{=}CF_2$ and RCH_2CF_3 in sequence. The presence of the boron fluoride increases the number of these steps and the extent to which they occur; the net effect is to increase the fluorine content of the final product.

The use of boron fluoride is particularly advantageous with heavily halogenated olefins, or with olefins bearing a CF_3 group which slows down the reactivity of their double bond. For more reactive olefins, boron fluoride may not be so desirable because it hastens resinification as well as addition; the economy of each case should be individually considered. The literature statement[1] that BF_3 is of no help should be restricted to non-halogenated olefins, where addition is so easy that it does not need any help.

Eleven different olefins were treated with hydrogen fluoride in the molar ratio of 1/2; when BF_3 was added, it was in the concentration shown in grams per mole of olefin in the table of experimental results.

The observed improvements can be explained by the formation of a coördinated complex $HF \rightarrow BF_3$, which enhances the percentage of ionic character of the H–F bond; this facilitates the separation of hydrogen as a proton, and makes it more available for addition to the more negative of the

---

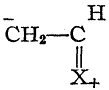
(1) Grosse and Lind, *J. Org. Chem.*, **3**, 26 (1938).

(2) Henne and Plueddeman, THIS JOURNAL, **65**, 1271 (1943), also Renoll, *ibid.*, **64**, 1115 (1942).

EXPERIMENTAL RESULTS

°C.	Hours	BF_3, g./mole	mole % A	mole % B	mole % recovery
$CHCl{=}CCl_2 + HF \rightarrow CH_2ClCCl_2F$ (A) $+ CH_2ClCClF_2$ (B)					
60	24	12	18	0	88
95	12	3	16	3	92
95	3	6	19	2	90
95	12	6	35	9	82
95	1	12	16	2	93
95	3	12	20	3	90
95	12	12	45	10	84
95	24	12	60	9	86
95	3	24	38	2	87
120	20	20	35	22	57
160	12	0	0	0	95
$CHCl{=}CHCl + HF \rightarrow CH_2ClCHClF$ (A) + polymer (B)					
25	21	12	3	10	83
60	21	6	17	17	80
60	11	12	26	25	82
60	21	12	26	33	68
95	3	3	10	9	82
95	3	6	21	17	80
95	11	6	20	29	54
95	1	12	19	26	79
95	3	12	24	29	63
160	11	0	0	0	60
$CF_2{=}CCl_2 + HF \rightarrow CF_3CHCl_2$ (A) + polymer (B)					
95	10	24	0	0	97
150	12	24	42	traces	87
150	12	0	0	traces	80
$CFCl{=}CFCl + HF \rightarrow CF_2ClCHClF$ (A) + polymer (B)					
95	18	24	0	0	89
150	12	24	trace	trace	96
180	17	24	43	trace	87
180	17	0	0	trace	95
$CFCl{=}CCl_2 + HF \rightarrow CF_2ClCHCl_2$ (A) $+ CF_2{=}CCl_2$ (B)					
180	17	24	33	17	82
180	17	0	0	0	89
$CCl_2{=}CCl_2 + HF \rightarrow CCl_2FCHCl_2$ (A) $+ CFCl{=}CCl_2$ (B)					
95	13	30	0	0	82
140	7	24	7	trace	82
160	14	24	15	3	77
180	17	24	trace	20	87
180	17	0	0	0	97
$CHCl{=}CF_2 + HF \rightarrow CH_2ClCF_3$ (A)					
25	0.5	3	90	0	90
95	3	0	70	0	90
$CF_3CCl{=}CCl_2 + HF \rightarrow CF_3CHClCCl_2F$ (A) $+ CF_3CCl{=}CClF$ (B)					
95	18	14	0	0	88
150	12	24	9	trace	91
180	17	24	22	7	90
180	17	30	21	10	91
180	17	0	0	0	92
$CF_3CH{=}CClF + HF \rightarrow CF_3CH_2CClF_2$ (A)					
95	24	5	65	0	85
120	24	0	0	0	85
$CH_3CH{=}CHCl + HF \rightarrow CH_3CH_2CHClF$ (A) $+ CH_3CHFCH_2Cl$ (B)					
60	6	2	12	20	56
100	4	0	10	20	60
$CH_3CCl{=}CHCl + HF \rightarrow CH_3CClFCH_2Cl$ (A) $+ CH_3CF_2CH_2Cl$ (B)					
25	5	2	35	4	76
95	4	0	5	10	92

doubly bonded carbons. In support of this interpretation is the opposite fact that hydrogen fluoride addition to alkynes is *slowed down* by an oxygenated solvent such as ether or acetone[3]; in this case, complex formation with the solvent involves hydrogen bonding to the unshared electrons of the oxygen atom and obstructs separation as a proton for the first stage of addition to the triple bond.

The **direction** of addition was always that expected from the ionic character of the olefin. The vinylic halides acted as if entirely in their resonating form  $:\overset{-}{C}H_2{-}\overset{H}{C}{=}X^{+}$, so that RR′C=CR″X lead exclusively to HRR′C=CR″XF. By induction, a CF_3 group attached to a doubly bonded carbon caused a polarization opposed to that created by a CH_3 group, so that the polarization of propene and trifluoropropene could be represented as $CH_3\underset{+}{C}H{=}\underset{-}{C}H_2$ and $CF_3\underset{+}{C}H{=}\underset{-}{C}H_2$, respectively.

The **ease** of addition was not determined solely by the extent of polarization of the double bond. $CH_2{=}CCl_2$ accepted hydrogen fluoride more readily than $CHCl{=}CHCl$ and $CCl_2{=}CF_2$ more than $CClF{=}CClF$; $CH_3CCl{=}CClH$ was more easily hydrofluorinated than $CF_3CH{=}CClF$, yet the latter compound should be much more polarized than the former due to the combination of the eletronegative character of the CF_3 group and the vinylic character of the $=CFCl$ group. It is proposed that the *absolute* electron density around the double bond should also be taken into account; if this is done, it is to be expected that all ethylenes bearing a CF_3 group should be slowed down by the electron drainage away from the double bond; in agreement, $HCCl{=}CCl_2$ was found more easily hydrofluorinated than $CF_3CCl{=}CCl_2$. This explanation would be similar to that used for the meta-directing effect of an electronegative group on a benzene ring, and its retarding influence.

Experimental Details

Reaction Equipment.—For relatively low pressure, an 800-ml. steel vessel fitted as previously described[4] was used; for the higher pressures prevailing with more boron fluoride, a 200 cc. Aminco bomb was used, with super-pressure fittings. Heating was done by immerging in a hot water-bath, or by strapping to the electrically heated mantle of a mechanical rocking devise.

Reagents.—Commercial grades.

---

(3) Henne and Plueddeman, THIS JOURNAL, **65**, 587 (1943).

(4) Henne and Flannagan, *ibid.*, **65**, 2362 (1943).

Loading Procedure.—As previously described.[5,6]

Metering of Boron Fluoride.—A steel cylinder of known capacity was connected to a commercial tank of boron fluoride; the gas was admitted and the pressure created was noted. Next, this loaded steel cylinder was connected to the reaction vessel and the amount of boron fluoride delivered was computed from the observed drop in pressure. For very small additions of boron fluoride, a stream of the gas was passed through weighed liquefied hydrogen fluoride cooled to −70°.

Treatment of Reaction Products.—Gaseous products were released through a washing train and collected in a Dry Ice cooled receiver. Liquids were poured on cracked ice, neutralized, steam distilled, dried and separated by fractional distillation. In the few cases where the olefin and its addition product boiled practically at the same temperature, the composition of the distillate was estimated from the index of refraction, but this procedure was avoided as much as possible by using efficient dephlegmators.

Summary

The addition of hydrogen fluoride to halogenated olefins is accelerated or made possible by using small amounts of boron fluoride as a catalyst. The action is attributed to the formation of a coördinate compound HF → BF_3, in which the H to F bond is weakened; this favors the supply of protons for the first step of the addition to the double bond. The direction and ease of addition are discussed. Eleven olefins have been tried and the results are tabulated.

COLUMBUS, OHIO RECEIVED SEPTEMBER 22, 1947

---

[5] Henne and Haeckl, This Journal, **63**, 2692 (1941).

[6] Henne and Whaley, *ibid.*, **64**, 1157 (1942).

[CONTRIBUTION FROM GENERAL MILLS, INC., RESEARCH DEPARTMENT]

Polyamide Resins from Dilinoleic Acid and Ethylenediamine. Molecular Weight–Viscosity Relationships[1a]

BY R. H. ANDERSON AND D. H. WHEELER

Introduction

In 1941, Bradley and Johnston[1b] isolated dilinoleic acid in a pure state as the methyl ester by fractional molecular distillation of the heat-polymerized methyl esters of the acids from dehydrated castor oil. They prepared polyesters of triethylene glycol with molecular weights of about 4300. Cowan and Wheeler[2] prepared polyesters with various glycols having molecular weights up to 20,000 to 30,000.

Polyamides have been prepared by Falkenburg, Teeter, Skell and Cowan[3] from various diamines and the residual polymeric fatty acids or esters (mixtures of dimer and trimers of linoleic and linolenic acids). The polyamide from ethylenediamine and these mixed polymeric fatty acids was proposed as a new synthetic coating material[4] under the name *Norelac*. The molecular weights of these resins were 3,000 to 5,000, determined by the method of end-groups. The same type of polyamide has been commercially prepared on a pilot plant scale,[5] and is apparently finding some use as a coating for heat-sealing and laminating paper.

No description has appeared of polyamides from pure dilinoleic acid and ethylenediamine. The present investigation describes the preparation and some properties of such linear polyamides having molecular weights from 2,000 to 15,000.

Viscosities were determined on solutions in 1:1 butanol-toluene solvent at concentrations from 0.2 to 9.8 g. per 100 cc. and intrinsic viscosities were calculated. The intrinsic viscosity was found to be related to molecular weight by the formula

$$[\eta] = KM^{a} \qquad (1)$$

Flory and Stickney[6] have pointed out the fact that a relationship such as equation (1) really relates to *viscosity* average (M_v) rather than *number* average (M_n) molecular weights of non-homogeneous polymers, and that M_v is greater than M_n, but less than M_w, the weight average molecular weight.

Now, the molecular weights, as determined by end-group titration in the present study, are actually *number* average molecular weights. The fact that the determined molecular weights and viscosities of these polyamides agree with equation (1) is interpreted to mean that these polymers, as prepared, have essentially a constant ratio of M_v to M_n. Flory[7] has shown on theoretical grounds that for bifunctional condensation polymers, M_w/M_n approaches 2 for higher polymers. Taylor[8] has shown that the ratio is very nearly 2 for 66-nylon polyamide, and that the value of M_v is close to that of M_w. The weight average can therefore be used interchangeably with M_v without introducing serious error.

When mixtures of condensation polyesters or polyamides are considered, the importance of considering a weight average rather than a number average in calculating viscosity is apparent. The viscosity in the molten state of a mixture of polyesters was shown by Flory[7] to agree with the M_w,

---

[1a] Paper No. 79, Journal Series, General Mills, Inc., Research Department.

[1b] Bradley and Johnston, *Ind. Eng. Chem.*, **33**, 86 (1941).

[2] Cowan and Wheeler, This Journal, **66**, 84 (1944).

[3] Falkenburg, Teeter, Skell and Cowan, *Oil and Soap*, **22**, 143 (1945).

[4] Cowan, Lewis and Falkenburg, *ibid.*, **21**, 101 (1944).

[5] Cowan, Schwab and Falkenburg, *Modern Packaging*, [9] **17**, 103 (1944).

[6] Flory and Stickney, This Journal, **65**, 372 (1943).

[7] Flory, *ibid.*, **62**, 1057, 3032 (1940).

[8] Taylor, *ibid.*, **69**, 635, 638 (1947).

but not with the M_n, of the mixture. Similarly, the molecular weight of a mixture of polyamides calculated from its $[\eta]$ is shown in the present study to agree with a weighted average rather than the number average of the mixture.

Experimental

Dilinoleic acid was prepared from a commercial dehydrated castor oil of Z-3 Gardner viscosity by conversion to methyl esters, which were heated for twelve hours at 300° under nitrogen. Unpolymerized methyl esters were removed by ordinary vacuum distillation. The residue of dimer and trimer was fractionally distilled in an alembic flask similar to that used by Cowan, Falkenburg and Teeter.[9] The fractional distillation was repeated three times, taking a middle cut of about 80% on the second and third distillations. On the second and third distillations, the methyl dilinoleate distilled at 20 μ pressure with a vapor temperature of 225–235° and a pot temperature of 255–265°. The pure dimer fraction from the third distillation had a spread in refractive index of 10 units in the fourth place between the first and last small fraction. Continuation of the distillation until the pot temperature was 300° left about 1.2% of undistilled residue having a refractive index only slightly higher than the pure dimer. The pure ester showed the following analytical values: sapn. equiv. 295 (calcd. 294), iodine value 75.2 (calcd. 86.8), mol. wt. (ebul., acetone), 545, 571 (calcd. 588), density 0.943 (25°).

The ester was converted to acid in the usual manner. The acid showed: neutr. equiv., 285; sapn. equiv., 283 (calcd. 280.2). Aqueous ethylenediamine from Carbide and Carbon Co. was redistilled, b. p. 115.5–117.5°, and titrated with standard acid using methyl red indicator. It contained 67.5% ethylenediamine.

Preparations of the polyamides were carried out in a three-necked flask with stirrer, thermometer, dropping funnel and simple side arm take-off for distillate. Dilinoleic acid (70 to 100 g.) was heated to 120° and stirred under vacuum to remove dissolved gases, pure nitrogen was admitted and the calculated amount of ethylenediamine was added over a period of one-quarter hour at a temperature of 120–130°. After addition of the amine, the temperature was raised to 200° at a rate such that the vapor temperature never exceeded 100°. The mixture was then held at 200° for four hours (six hours for polymers no. 8 and 9) under nitrogen and for an additional hour at 200° under vacuum with a Dry Ice trap in the vacuum line to catch any amine. The resin was then cooled to 160°, and poured into containers under inert gas. Samples were stored under nitrogen when not in use.

The distillate plus trap material was titrated for amine lost, which was quite small, −0.1 to 0.2% of original amine.

Carboxylic end-groups were determined by titration of the resin in a 50–50 butanol–toluene mixture with 0.1 *N* alcoholic potassium hydroxide (phenolphthalein). Amine end-groups were determined by titration with freshly standardized 0.1 *N* alcoholic hydrochloric acid (brom cresol green). Average molecular weights were calculated from the combined acid and amine end-groups. The molecular weights as determined were in close agreement with those expected on the basis of the excess of acid used. A balance of the free acid and amine groups in the polymer against the amount of acid and amine used as starting materials showed less than 1% discrepancy in every case. This would indicate that not over 1% loss of acid groups occurred by decarboxylation, unless amine were lost in equivalent amounts. Some properties of the resins are given in Table I.

TABLE I

POLYAMIDES OF DILINOLEIC ACID AND ETHYLENEDIAMINE

Polymer	Acid no.[a]	Amine no.[a]	Mol. wt.[a]	Soft pt. °C.[b]	Viscosity[c]	Penetration[d]	Gel time[e]
1	51.00	0.00	2,200	94.6	A-3	31.4	1440
2	27.20	.00	4,125	111.0	A-1 to A	6.8	650
3	18.30	.00	6,130	112.5	A	4.1	513
4	16.20	.24	6,800	117.8	B	3.7	465
5	13.23	.43	8,216	118.2	B	3.3	356
6	11.10	.65	9,544	119.2	B to C	2.0	306
7	10.65	.58	10,000	118.4	C	2.8	347
8	3.00	4.91	14,200	122.0	E to F	1.1	70
9	5.51	1.78	15,370	121.5	F	1.9	0

[a] Acid no. and amine no. equal milligrams of KOH equivalent to the acid and amine groups, respectively, in 1 g. of material, whence: Mol. Wt. = 2 × 56,100/acid no. + amine no. [b] Ball and ring. [c] Gardner bubble viscosity at 25° of a 35% solution in 1–1 (wt.) *n*-butanol–toluene solvent. [d] Tenths of a mm. with A.S.T.M. standard penetrometer needle, 200 g. load, thirty seconds at 25°. [e] Time in seconds for 0.03 inch film to gel in air on a hot-plate at 200°. Gelation is indicated by the drawing of a string upon touching with a pin point.

As shown by the data, with increasing molecular weight, the melting point increases rapidly at first and then levels off somewhat. Viscosity increases regularly and hardness increases (penetration decreases), whereas gel time decreases regularly with increased molecular weight. Gelation is caused by cross-linking induced by oxygen, since the resins are stable at this temperature in the absence of oxygen. The greater the chain length, the fewer cross-links should be necessary to cause gelation, and the shorter the gel time should be.

Solution viscosities of the polyamides were determined at concentrations ranging from 0.2 to 9.8 g. per 100 cc. of solution in 1–1 (wt.) *n*-butanol–toluene. The viscosities were determined in an Ostwald viscometer of 3.16 cc. volume, 9.5 cm. capillary with a diameter of 0.057 cm. Viscosities were calculated by the following equation which corrects for kinetic energy losses[10]

$$\eta = \rho C t - (\rho/8\pi l)(v/t) \qquad (2)$$

where C is a calibration constant, ρ is the density and t the time in seconds for efflux of volume v. The viscometer was calibrated with water (t = 82.4) using 0.00894 poise as the value for water at 25°. Most of the measurements were made in a constant temperature bath at 25°, controlled to ±0.02°. Several series were also run at 30°. The values for ηr at 30° were identical with those at 25° within experimental error. The solutions were quite stable, good checks being obtained on samples which had stood for a number of weeks. The solvent had a viscosity of 0.00973 poise at 25° ($t = 108.7$, $\rho = 0.832$).

The viscosity data for the polyamides (and for dimer acid) are shown in Fig. 1, where $\ln \eta r/c$ is plotted *vs.* concentration. Up to a concentration of 1.5% the values are constant within experimental error, with the values at higher concentrations for the polymers of higher molecular weights showing a progressive tendency to be lower than those obtained up to 1.5% concentration (accentuated in Fig. 1 by the change in scale beyond 2.0).

---

(9) Cowan, Falkenburg and Teeter, *Ind. Eng. Chem.*, **16**, 90 (1944).

(10) E. C. Bingham, "Fluidity and Viscosity," McGraw-Hill Book Co., New York, N. Y., 1922, p. 17.

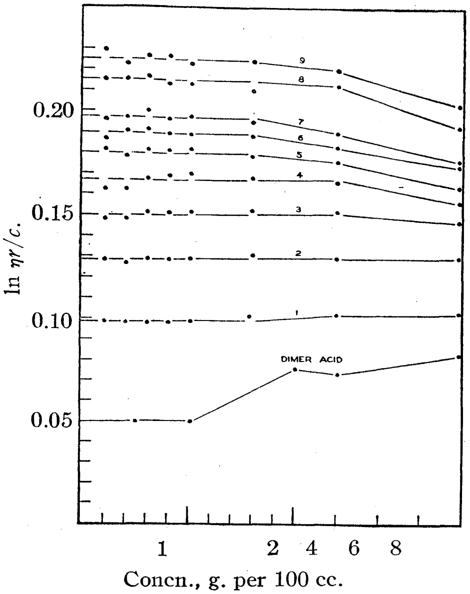


Fig. 1.—ln $\eta r/c$ *vs.* concentration.

The intercepts of the lines with the zero concentration axis, as determined from Fig. 1, are recorded in Table II as [η], with the corresponding molecular weights.

TABLE II

INTRINSIC VISCOSITIES AND MOLECULAR WEIGHTS OF POLYAMIDES

Polymer	Mol. wt.	[η]
1	2,200	0.0986
2	4,125	.129
3	6,130	.150
4	6,800	.167
5	8,220	.180
6	9,640	.190
7	10,000	.197
8	14,200	.215
9	15,370	.225

The relationship of molecular weight to intrinsic viscosity was best represented by a log–log plot of these values, as shown in Fig. 2. The largest deviation, that of no. 4, is 10% while the other samples were within 1 to 6% of the values for the line. The equations for the line in Fig. 2 are

$$[\eta] = 4.06 \times 10^{-3} M_n{}^{0.42} \qquad (3)$$

$$M_n = 5.50 \times 10^{5} [\eta]^{2.4} \qquad (4)$$

where K of equation 1 is seen to be 4.06×10^{-3} and a is 0.42. Taylor's values on 66 nylon in formic acid were 1.1×10^{-3} and 0.72, respectively.

Intrinsic viscosities of mixtures of high and low molecular weight polymers were determined in the same manner. Mixtures were made of the 2000 mol. wt. polymer with the 10,000 and 15,000 mol. wt. polymers. The mixtures had values for [η] which agreed fairly well with the weighted averages of [η] and with the [η] determined from the weighted number averages ("M_w") by means of Fig. 2, but did not agree with the [η] determined from the number average by Fig. 2. The results are shown in Table III.

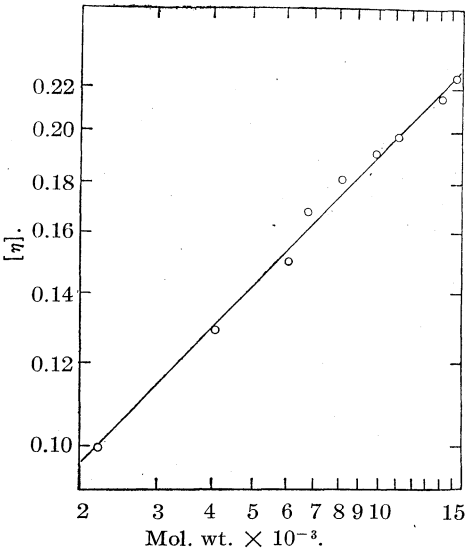


Fig. 2.—Molecular weight *vs.* intrinsic viscosity on log–log scale.

TABLE III

INTRINSIC VISCOSITIES OF MIXTURES OF POLYAMIDES

M. W. 2200 and 10,000

% of 2200	Obs.	Wtd.[a] av.	From "Mw"[b]	From Mn[c]
75	0.131	0.123	0.131	0.109
50	.156	.148	.153	.124
25	.182	.172	.172	.145
M. W. 2200 and 15,370				
50	0.163	0.162	0.179	0.125

[a] $[\eta]$ (weighted av.) = $[\eta]_1 w_1 + [\eta]_2 w_2$. [b] "$M_w$" (Mixt.) = $M_1 w_1 + M_2 w_2$. [c] M_n(Mixt.) = $1/(w_1/M_1 + w_2/M_2)$, where w_1 and w_2 refer to the weight fraction of polymers with determined molecular weights of M_1 and M_2, respectively.

It should be noted that the values for "M_w" referred to in Table III are really weighted number average values rather than true M_w values, since the molecular weights used are the determined number average values. However, the comparisons in Table III are valid if the determined M_n values of the components have a constant ratio to their M_w values, as is believed to be the case. Calculations based on an equation of Flory,[7] relating M_w to M_n for polyesters, indicate that M_w/M_n for the lowest polymer is about 1.86, while for the next higher polymer it is 1.93, with values more nearly approaching 2 for the higher polymers.

Discussion

All of the polyamides except no. 8 had acid end-groups almost exclusively (see Table I). The linear relationship of ln η_r to concentration, up to at least 1.5%, would indicate that association of acid end-groups is not an appreciable factor at these concentrations. Polymer 8, with a more nearly equal number of amino and acid end-groups, also shows no appreciable deviation of ln η_r in Fig. 1, and its general viscosity characteristics are similar to those of no. 9, which is of similar molecular weight, but which has a high ratio of acid to amino end-groups. The dimeric acid did show a slight increase in ln η_r/c with increasing concentration, and the polymer of lowest molecular weight, no. 1, also showed a slight similar increase of this value at concentrations above 1.5%, whereas the higher polymers often showed a slight decrease. These phenomena would indicate some association of acid end-groups at higher concentrations in the cases of polymers with a high concentration of acid end-groups.

Summary

1. Polyamides of dilinoleic acid and ethylenediamine have been prepared with molecular weights from 2,200 to about 15,000.

2. The relationship of molecular weight to intrinsic viscosity can be expressed by the equation

$$[\eta] = 4.06 \times 10^{-3} M^{0.42}$$

3. The nature of this relationship, and the results of a study of the viscosities of mixtures of polymers indicate that the number average molecular weights of the polymers, as prepared, bear a constant ratio to the viscosity and the weight average molecular weights.

4. Except at higher concentrations with polymers of high acid values, association of terminal end-groups is not very significant.

MINNEAPOLIS, MINN. RECEIVED MAY 17, 1947

[CONTRIBUTION FROM THE THOMPSON LABORATORY OF THE PHILLIPS EXETER ACADEMY]

The Addition of Halogens to an Acetylenic Ketone

BY CHARLES L. BICKEL

Diaryl acetylenic ketones undergo many addition reactions; one of the simplest of these would appear to be the addition of the halogens. The halogenation of a diaryl acetylenic ketone has, however, been investigated in only one case—that of phenylbenzoylacetylene. Nef[1] obtained phenylbenzoylacetylene diiodide by the addition of iodine in ether solution. Later, Dufraisse[2] studied the addition of both bromine and iodine to phenylbenzoylacetylene and obtained phenylbenzoylacetylene dibromide, as well as the diiodide previously described by Nef.

Recent papers from this Laboratory describe the preparation of *o*-chlorophenylbenzoylacetylene,[3,4] a substance which can be obtained in excellent yield from simple starting materials. This acetylenic ketone crystallizes well from oily mixtures and can therefore be isolated more easily than the unsubstituted analogue. These facts suggested the present study of the action of the halogens on *o*-chlorophenylbenzoylacetylene.

Nef stated that an ethereal solution of phenylbenzoylacetylene easily absorbs iodine while Dufraisse stated only that an ethereal solution of the acetylene, treated with an ethereal solution of iodine, gives the iodine addition product. Neither author indicated that the reaction was sluggish. *o*-Chlorophenylbenzoylacetylene, on the other hand, gives no apparent reaction with iodine at room temperature. When a chloroform solution of iodine and the acetylene is heated, there is no evidence of reaction until the solvent has been completely evaporated. Further heating of the residual mixture of iodine and *o*-chlorophenylbenzoylacetylene gives a solid cake from which the iodine addition product can be isolated in good yield.

Although the melting point of phenylbenzoylacetylene diiodide has been variously reported,[1,2] there is no indication in the literature that the melting of this substance is attended by decomposition. *o*-Chlorophenylbenzoylacetylene diiodide, however, decomposes slowly at about 145° and rapidly at 172°, the temperature at which it appears to melt. The decomposition is a clean reaction, iodine and the original acetylenic ketone being the only products. In fact, the thermal decomposition of the diiodide provides the best method of analysis.

o-Chlorophenylbenzoylacetylene, like the unsubstituted analogue, reacts readily with bromine to give a dibromide, a substance which is stable at a temperature one hundred degrees above its melting point. The same dibromide is obtained by treating the diiodide with bromine.

In view of the successful addition of iodine and bromine to *o*-chlorophenylbenzoylacetylene, no difficulty was anticipated in the addition of chlorine. However, attempts to prepare the dichloride have so far met with no success. The acetylenic ketone is recovered unchanged when chlorine is bubbled through its chloroform solution, either at room temperature or at the boiling point of the solution, and even when a trace of iodine is added. When chlorine is bubbled through the molten acetylenic ketone, a red oil is obtained which has as yet given no solid products. Chlorine does not displace bromine from the di-

---

[1] Nef, *Ann.*, **308**, 277 (1899).

[2] Dufraisse, *Ann. chim.*, **17**, 133 (1922).

[3] Bickel, THIS JOURNAL, **69**, 73 (1947).

[4] Bickel, *ibid.*, **69**, 2134 (1947).

bromide, the dibromide being recovered unchanged.

When chlorine is bubbled into a chloroform solution of the diiodide, iodine is liberated and a single crystalline product is obtained. The analysis of this substance indicates that only one of the iodine atoms of the diiodide has been displaced. This product presumably has the structure A-CI=CCl-B or A-CCl=CI-B, where A is the *o*-chlorophenyl group and B is the benzoyl group. Prolonged treatment of the diiodide with chlorine at a higher temperature gives a mixture of substances. The analytical results indicate that one component of this mixture is a saturated compound formed by the addition of chlorine to the monochloride described above, which may be tentatively assigned the structure A-CICl—CCl$_2$-B or A-CCl$_2$—CICl-B.

The author is indebted to the Marine Biological Laboratory of Woods Hole, Mass., for the chemicals needed in preparing the starting materials used in this problem and also for the use of the facilities of the Marine Biological Laboratory.

Experimental

***o*-Chlorophenylbenzoylacetylene Diiodide.**—A suspension of 15 g. of *o*-chlorophenylbenzoylacetylene and 18.5 g. of iodine in 50 cc. of chloroform was heated until the solvent was completely removed. The residual solid cake was cooled, about 100 cc. of ether added and the solid cake pulverized, filtered and washed with ether. The ether solution, washed with sodium thiosulfate solution to remove excess iodine, gave 1.5 g. of the diiodide. The solid diiodide not dissolved by the ether weighed 26 g., a total yield of 89%.

o-Chlorophenylbenzoylacetylene diiodide is moderately soluble in chloroform and acetone, sparingly soluble in ether and very sparingly soluble in petroleum ether. It crystallizes as colorless needles from ether. When heated slowly, the diiodide begins to lose iodine at 140–145°; when heated rapidly, it appears to melt at about 172°. The diiodide was analyzed by heating a weighed sample in a platinum crucible at 160–170° until iodine was no longer liberated. The residue in the crucible solidified on cooling and melted at 94°, a mixed melting point proving it to be *o*-chlorophenylbenzoylacetylene.

Anal. Calcd. for $C_{15}H_9OClI_2$: $C_{15}H_9OCl$, 48.7; I, 51.3. Found: $C_{15}H_9OCl$, 49.0; I, 51.0.

***o*-Chlorophenylbenzoylacetylene Dibromide. A. By the Action of Bromine on *o*-Chlorophenylbenzoylacetylene.**—Bromine was added to a solution of 5 g. of *o*-chlorophenylbenzoylacetylene in 20 cc. of chloroform until the color of free bromine was apparent, considerable heat being liberated. The chloroform was then boiled off and the solid residue was taken up in about 100 cc. of ether. The ether solution gave 7.1 g. of the dibromide, a yield of 85%.

B. By the Action of Bromine on the Diiodide.—Six grams of bromine was added to a suspension of 8 g. of the diiodide in 30 cc. of chloroform. Evaporation of the chloroform gave a solid product which was taken up in ether. The ether solution, washed with sodium thiosulfate solution, gave 3.5 g. of the dibromide described above, a 54% yield. The residual orange-red oil has as yet given no solid products.

o-Chlorophenylbenzoylacetylene dibromide is readily soluble in chloroform, moderately soluble in ether and sparingly soluble in petroleum ether. It crystallizes as colorless prisms from ether and melts at 142°, with no sign of decomposition up to 250°.

Anal. Calcd. for $C_{15}H_9OClBr_2$: C, 44.9; H, 2.3. Found: C, 44.8; H, 2.5.

The Action of Chlorine on the Diiodide.—Dry chlorine was bubbled into a suspension of 5 g. of the diiodide in 25 cc. of chloroform at room temperature. The color of free iodine appeared immediately and the diiodide rapidly went into solution. After about one hour the delivery of gas was discontinued and the solvent evaporated. The product, which solidified on cooling, was dissolved in ether and the free iodine removed with sodium thiosulfate. The ether solution gave 2.5 g. of massive, colorless prisms melting at 125–126°.

Anal. Calcd. for $C_{15}H_9OCl_2I$: C, 44.7; H, 2.3. Found: C, 44.3, 44.5; H, 2.5, 2.5.

In a second experiment, dry chlorine was bubbled into a suspension of 10 g. of the diiodide in 50 cc. of chloroform, heated to the boiling point. After about two hours the solvent was evaporated, the flow of gas being maintained throughout. The product, after the removal of the iodine, was a mixture from which was obtained about 3 g. of colorless prisms, melting at 172.5° after repeated recrystallization from ether.

Anal. Calcd. for $C_{15}H_9OCl_4I$: C, 38.0; H, 1.9. Found: C, 38.5; H, 2.2.

Summary

Iodine and bromine give addition products with *o*-chlorophenylbenzoylacetylene, the diiodide losing iodine near its melting point and regenerating the acetylenic ketone.

Attempts to prepare the dichloride of *o*-chlorophenylbenzoylacetylene were unsuccessful. Two substances formed by the action of chlorine on the diiodide are reported.

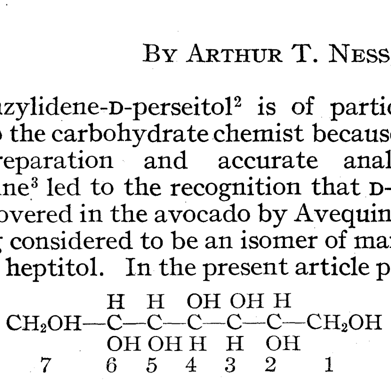
EXETER, NEW HAMPSHIRE RECEIVED AUGUST 23, 1947

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE][1]

The 1,3:5,7-Dibenzylidene and 1,3:5,7-Dimethylene Acetals of the D-, L- and D,L-Perseitols

BY ARTHUR T. NESS, RAYMOND M. HANN AND C. S. HUDSON

Dibenzylidene-D-perseitol[2] is of particular interest to the carbohydrate chemist because its original preparation and accurate analysis by Maquenne[3] led to the recognition that D-perseitol (I), discovered in the avocado by Avequin[4] in 1831 and long considered to be an isomer of mannitol, is indeed a heptitol. In the present article proofs are presented for the structure of dibenzylidene-D-perseitol and for that of a corresponding dimethylene-D-perseitol which we have prepared. The structures agree with those expected from perseitol as predicted by the generalizations[5] correlating the configuration of polyhydric alcohols with the structures of the benzylidene and methylene acetals derived from them.



$$\begin{array}{ccccccc} & \mathrm{H} & \mathrm{H} & \mathrm{OH} & \mathrm{OH} & \mathrm{H} & \\ \mathrm{CH_2OH}- & \mathrm{C}- & \mathrm{C}- & \mathrm{C}- & \mathrm{C}- & \mathrm{C}- & \mathrm{CH_2OH} \\ & \mathrm{OH} & \mathrm{OH} & \mathrm{H} & \mathrm{H} & \mathrm{OH} & \\ 7 & 6 & 5 & 4 & 3 & 2 & 1 \end{array}$$

D-Manno-D-*gala*-heptitol (D-Perseitol)

(I)

Maquenne[3] prepared dibenzylidene-D-perseitol by mixing benzaldehyde and a finely divided suspension of D-perseitol in aqueous-alcoholic solution which had been saturated with gaseous hydrochloric acid, and in his original description of the crystalline diacetal he stated that it softened at 215° but did not show a sharp melting point; in a later article[6] he recorded the softening point as 219° and this value is also given in his book on sugars.[7] Lobry de Bruyn and Alberda van Ekenstein[8] recorded a melting point of 230–235°. In our initial preparation of dibenzylidene-D-perseitol we dissolved the heptitol in 50% sulfuric acid and added benzaldehyde and alcohol; the diacetal which crystallized melted at the much lower temperature of 153–155°; it rotated $[\alpha]^{20}\mathrm{D}$ −58.2° in pyridine solution. Upon recrystallization from a pyridine–alcohol mixture the melting point of the compound increased progressively and after three recrystallizations it attained a maximum value of 280 ± 2°[9] but the substance still showed a rotation of −58.1° in pyridine. Next we prepared dibenzylidene-D-perseitol by Maquenne's procedure. In three experiments the products melted initially over ranges of 230–240°, 240–248° and 225–235°; after several recrystallizations from a pyridine–alcohol mixture the melting point reached the maximum value of 280 ± 2° and the specific rotation was −57.9°. The fact that recrystallization from pyridine–alcohol of dibenzylidene-D-perseitol, regardless of its method of preparation or its initial melting point, yields a final product melting at 280 ± 2° and rotating about −58° suggests that the products obtained initially by the different procedures of preparation may be mixtures of diastereomers in various proportions. Fischer[10] first called attention to the possibility of the occurrence of diastereomers in cyclic benzylidene acetals, due to different configurations of the acetal carbon atom of the benzylidene group, in his discussion of the formation of the labile and stable forms of what is now known to be 3,5-benzylidene-gluco-*gulo*-heptitol.[11] In the case of dibenzylidene-D-perseitol four diastereomers are theoretically possible. Whether the product melting in a range of 150–155° obtained by the sulfuric acid method and that melting at 280 ± 2° represent two relatively pure diastereomeric forms must await further evidence. As mentioned in the experimental part, these two products yield identical tribenzoyl-dibenzylidene-D-perseitols upon benzoylation in pyridine solution and identical trimethyl-dibenzylidene-D-perseitols upon methylation with thallous hydroxide and methyl iodide; it therefore seems evident that their isomerism is not due to different positions of the acetal linkages, but is to be ascribed to the stereoisomerism of the benzylidene groups. Ordinary crystalline dimorphism seems improbable.[11] An interconversion of the configurations present in the asymmetric carbon atoms of the benzylidene groups is possibly favored by the basic conditions attending the recrystallization, benzoylation and methylation.

Proof of the Structure of 1,3:5,7-Dibenzylidene-D-perseitol.—In initial tests to determine the structure of dibenzylidene-D-perseitol a solution of the diacetal (m. p. 280 ± 2°) in 2-methoxyethanol ("methyl cellosolve") was found to be fully resistant to oxidation by aqueous sodium

---

[1] Presented Sept. 18, 1947, at the New York meeting of the American Chemical Society.

[2] For a review of the reasoning leading to the selection of the D-symbol in naming natural perseitol see Hudson, "Advances in Carbohydrate Chemistry," Vol. I, p. 14, Academic Press, Inc., New York, N. Y., 1945.

[3] Maquenne, *Compt. rend.*, **107**, 583 (1888).

[4] Avequin, *Journal de chimie mèdicale, de pharmacie et de toxicologie*, [1] **7**, 467 (1831).

[5] Hann and Hudson, THIS JOURNAL, **66**, 1909 (1944).

[6] Maquenne, *Ann. chim. phys.*, [6] **19**, 16 (1890).

[7] L. Maquenne, "Les sucres et leurs principaux dérivés," Carré and Naud, Paris, 1900, p. 183.

[8] Lobry de Bruyn and Alberda van Ekenstein, *Rec. trav. chim.*, **18**, 151 (1899).

[9] The melting points of the higher-melting forms were determined on a Berl and Kullmann copper block and are corrected; melting points below 250° were determined in a Hershberg apparatus with the stem of the calibrated thermometer in the rapidly stirred bath. All the crystalline compounds described in the experimental part were recrystallized to constant melting point and specific rotation $[\alpha]^{20}\mathrm{D}$; c is the concentration in 100 ml. of solution; the tube length was 4 dm.

[10] E. Fischer, *Ber.*, **27**, 1524 (1894).

[11] Hann, Ness and Hudson, THIS JOURNAL, **68**, 1769 (1946).

metaperiodate; this fact indicates that the structure of the compound does not include an α-glycol grouping. However, this limitation is by no means sufficient for establishing the structure since many conceivable structures conform with it. Additional evidence was sought through methylation studies. Attempts to methylate the dibenzylidene-D-perseitol melting at 153–155° with Purdie's reagents (silver oxide and methyl iodide) were unsuccessful, the diacetal being recovered almost quantitatively as the 280 ± 2° isomer by hot pyridine extraction of the silver oxide residues from the attempted methylation, but the methylation of the higher-melting isomer with Purdie's reagents gave nearly quantitative yields of a sirup showing the correct methoxyl content for a trimethyl-dibenzylidene-perseitol. Crystalline trimethyl-dibenzylidene-D-perseitol (m. p. 121–122°; $[\alpha]^{20}D$ $-43.5°$ in chloroform) was eventually obtained by methylation with thallous hydroxide and methyl iodide[12] of either the lower or higher melting dibenzylidene-D-perseitol. The hydrolysis of either the sirupy or the crystalline trimethyl-dibenzylidene-D-perseitol gave a crystalline trimethyl-D-perseitol (m. p. 120–121°; $[\alpha]^{20}D$ $+11.8°$ in water) which is not oxidized by sodium metaperiodate in aqueous solution. This evidence discloses the structure of the trimethyl derivative. Inspection of the formula of D-perseitol (I) shows that to fulfill the condition of absence of an α-glycol grouping in the trimethyl-D-perseitol, one methyl group must be at carbon atoms 1 or 2 and another at carbon atoms 6 or 7; of the four possible combinations of these positions, 1,6-, 1,7- and 2,7 are excluded because no combination of three methylated hydroxyl groups which includes such a pair can fulfill the condition that the trimethyl derivative be free of an α-glycol grouping; in the remaining 2,6-combination the third methyl group can be only at position 4 to exclude such a grouping, and therefore the compound is 2,4,6-trimethyl-D-perseitol. Accordingly, dibenzylidene-D-perseitol is a 1,3,5,7-diacetal and there can be little doubt that it is specifically 1,3:5,7-dibenzylidene-D-perseitol. The trimethyl ether of the diacetal is to be formulated as 2,4,6-trimethyl-1,3:-5,7-dibenzylidene-D-perseitol.

Proof of the Structure of 1,3:5,7-Dimethylene-D-perseitol.—The treatment of D-perseitol with aqueous formaldehyde solution and concentrated hydrochloric acid yielded a crystalline dimethylene-D-perseitol which melted at 251–253° and rotated $[\alpha]^{20}D$ $-19.3°$ in water. This dimethylene acetal was not oxidized by aqueous sodium metaperiodate, a result which shows that it possesses no α-glycol grouping. It formed a tritosyl ester which did not react when heated with sodium iodide in acetone solution at 100° for two hours, an indication by the Oldham–Rutherford rule that tosyl groups are not attached at carbon atoms 1 or 7, which accordingly must be involved in the acetal linkages. Proof that the hydroxyl groups in the diacetal are secondary and at positions 2, 4 and 6 follows from the fact that methylation of the dimethylene-D-perseitol with thallous hydroxide and methyl iodide gave a crystalline trimethyl-dimethylene-D-perseitol (m. p. 140–141°; $[\alpha]^{20}D$ $-6.2°$ in water) which was identical with the product resulting from the methylenation of authentic 2,4,6-trimethyl-D-perseitol (obtained through the benzylidene series as described) with aqueous formaldehyde solution and concentrated hydrochloric acid. Accordingly, the acetal linkages in the dimethylene perseitol must be at positions 1, 3, 5 and 7 and there can be little doubt that the substance is specifically 1,3:5,7-dimethylene-D-perseitol. Its tritosyl derivative is to be formulated as 2,4,6-tritosyl-1,3:5,7-dimethylene-D-perseitol and its methyl ether as 2,4,-6-trimethyl-1,3:5,7-dimethylene-D-perseitol.

Does the 1,3:5,7-diacetal structure that is present in the dibenzylidene- and dimethylene-D-perseitols conform with the previously mentioned generalizations regarding cyclic acetal structures of polyhydric alcohols?[5] An inspection of the formula of perseitol (I) shows according to the generalizations that the only pair of secondary hydroxyl groups favored to enter into methylene or benzylidene acetal formation consists of those at positions 3 and 6, which are *gamma* in position and *trans* in configuration. This combination was regarded as favorable to the formation of an acetal of the dioxepane seven-atom ring type when the generalizations were proposed because such an acetal was a prominent feature in the mannitol series. Later, it was also found in the closely similar L-rhamnitol (6-desoxy-L-mannitol) series.[13] Subsequent studies in the iditol[14] and talitol[15] series and the present one in the perseitol series fail to disclose the presence of such a dioxepane acetal although the configurations in each case seem favorable for its occurrence. However, in the iditol, talitol and perseitol configurations there are favorable positions for one or more dioxane six-atom ring acetals which conflict with the dioxepane ring acetal. Thus in perseitol the 1,3-acetal obviously competes with a 3,6-acetal. There is no such competition in the mannitol and rhamnitol series. We would accordingly extend the original generalizations by stating that formation of the dioxepane ring may not occur if competing dioxane-ring acetals are indicated by favorable positions in the configuration. It is readily evident that such competition will always occur in the case of any heptitol.

Using some L-perseitol which had been made by the reduction of D-gala-L-*manno*-heptose, we have prepared the enantiomorphous 1,3:5,7-dibenzylidene-L-perseitol and 1,3:5,7-dimethylene-L-perseitol, following the procedures already described. The L-perseitol behaved precisely like its enantio-

---

[12] The procedure of Fear and Menzies, *J. Chem. Soc.*, 937 (1926).

[13] Haskins, Hann and Hudson, THIS JOURNAL, **67**, 1800 (1945).

[14] Hann and Hudson, *ibid.*, **67**, 602 (1945).

[15] Hann, Haskins and Hudson, *ibid.*, **69**, 624 (1947).

morph and it was especially noted that the indications of lability in the dibenzylidene acetal were duplicated.

A 1,3:5,7-dibenzylidene-D,L-perseitol melting at 271–272° was obtained by one recrystallization of a mixture of equal amounts of the higher-melting (280°) D- and L- forms from pyridine–alcohol solution. In an effort to obtain a D,L-compound from the low-melting (153–155°) D- and L- forms, cold solutions of equal amounts of them in 2-methoxyethanol were mixed and concentrated to crystallization at room temperature by an air current. The product melted at 235–237° and two recrystallizations from the same solvent raised the melting point to 271–272° which did not change on further recrystallization. The optical-crystallographic measurements which Mr. George L. Keenan reports (see Table I) show that the crystals of 1,3:5,7-dibenzylidene-D,L-perseitol (m. p. 271°) represent a true racemate having indices of refraction that are different from those of the crystals of its components.

An aqueous solution of equal amounts of the enantiomorphous dimethylene-perseitols deposited crystals of a dimethylene-D,L-perseitol hemihydrate melting at 236–237° and showing no detectable rotation in aqueous solution. The fact that it is a hydrate indicates that the crystals are a true racemate because the component enantiomorphs crystallize in anhydrous condition. The measurements of Mr. Keenan (see Table I) verify the true racemic character.

We thank Mr. Charles A. Kinser and Mrs. Betty Mount for the microchemical analyses and Mr. George L. Keenan for the optical-crystallographic measurements.

Experimental

1,3:5,7-Dibenzylidene-D-perseitol and Some of its Derivatives

1,3:5,7-Dibenzylidene-D-perseitol.—(A) To a solution of 5.0 g. of D-perseitol in 25 ml. of 50% sulfuric acid 25 ml. of benzaldehyde and 25 ml. of ethanol were added; needle-like crystals appeared in the clear solution in a few minutes. After three hours at 25° the magma was thinned with 100 ml. of ethanol, filtered and the precipitate washed with water and alcohol. The product (8.2 g., 89%) melted at 153–155° and there was no change in its weight or melting point upon digesting it with 200 ml. of hot water for two hours. It was insoluble in usual organic solvents except pyridine and 2-methoxyethanol. Its $[\alpha]^{20}\mathrm{D}$ value in pyridine (*c*, 0.5) was −58.2°. In four repetitions products were obtained which melted at 152–154°, 153–155°, 151–154° and 150–152°.

Anal. Calcd. for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23. Found: C, 64.74; H, 6.29.

The dibenzylidene-D-perseitol (m. p. 153–155°) was recrystallized by solution in 15 parts of pyridine and the addition of 40 parts of alcohol. The melting point of the once-recrystallized product was 268 ±2°; after a second recrystallization it melted at 277 ±2° and after a third it reached a maximum value of 280 ±2°. Its $[\alpha]^{20}\mathrm{D}$ value was then −58.1° in pyridine (*c*, 0.9), and its analysis showed that there had been no change in its elementary composition.

(B) The dibenzylidene-D-perseitol was prepared by the procedure of Maquenne.[3] A slurry of suspended D-perseitol, prepared by adding 5 ml. of ethanol to a solution of 2.5 g. of the heptitol in 5 ml. of hot water, was cooled to 0° and saturated with dry hydrochloric acid gas; 5 ml. of benzaldehyde was added and the mixture agitated until solution was complete. Small needles soon separated and the magma which formed on allowing the reaction mixture to stand at 25° for three hours was thinned with 100 ml. of ethanol and the crystalline product was separated by filtration, washed with water and alcohol and dried. The yield was 3.9 g. (83%). The compound, which melted at 230–240°, was recrystallized by solution in 12 parts of pyridine and the addition of 20 parts of alcohol and it formed small needles which melted at 280 ±2° and rotated −57.9° in pyridine (*c*, 0.9). A mixed melting point determination with the dibenzylidene-D-perseitol (m. p. 280 ±2°) prepared by the pyridine–alcohol recrystallization of dibenzylidene-D-perseitol (m. p. 153–155°) showed no depression. A second preparation of the dibenzylidene-D-perseitol by Maquenne's method gave a yield of 97% of a product which melted at 240–248°. A quantitative yield of diacetal showing a melting point of 225–235° was deposited from a homogeneous solution of 2.0 g. of D-perseitol, 10 ml. of concentrated hydrochloric acid, 5 ml. of benzaldehyde and 5 ml. of ethanol which was allowed to stand at 5° for four hours. The melting point of these products was raised to 280 ±2° by recrystallization from pyridine–alcohol mixtures.

Stability of 1,3:5,7-Dibenzylidene-D-perseitol against Oxidation by Sodium Metaperiodate.—To a solution of 0.1086 g. of 1,3:5,7-dibenzylidene-D-perseitol (m. p. 280 ±2°) in 90 ml. of 2-methoxyethanol 3.0 ml. (5.73 molecular equivalents) of aqueous 0.534 *M* sodium metaperiodate solution was added and the volume was adjusted to 100 ml. at 25° with 2-methoxyethanol. Analysis of 10-ml. aliquots at the expiration of one, six and forty-eight hours showed that no oxidant had been consumed, indicating that dibenzylidene-D-perseitol has no pair of contiguous hydroxyl groups in its structure.

2,4,6-Tribenzoyl-1,3:5,7-dibenzylidene-D-perseitol.—To an ice-cold solution of 2.0 g. of 1,3:5,7-dibenzylidene-D-perseitol (m. p. 280 ±2°) in 20 ml. of pyridine, 3.0 ml. (50% excess) of benzoyl chloride was added dropwise. The reaction mixture was allowed to stand three days at room temperature (22–25°) and then poured into 500 g. of crushed ice. The gummy precipitate which formed was washed with water and upon trituration with 50 ml. of ethanol it yielded 3.2 g. (90%) of a crystalline product which melted at 181–182°. The compound was recrystallized from 100 parts of ethanol as long prismatic rods which melted at 181–182° and showed an $[\alpha]^{20}\mathrm{D}$ value +76.8° in chloroform (*c*, 0.85). It is soluble in pyridine, acetone, benzene and hot ethanol and nearly insoluble in water, cold ethanol and methanol, and hexane. Benzoylation of the dibenzylidene-perseitol (m. p. 153–155°) under the same conditions gave the same tribenzoate in a yield of 90%. This result is in agreement with the conclusion that these two dibenzylidene-D-perseitols are not ring-position isomers.

Anal. Calcd. for $C_{42}H_{36}O_{10}$: C, 71.99; H, 5.18; C_6H_5CO, 45.0. Found: C, 71.95; H, 5.19; C_6H_5CO, 44.7.

2,4,6-Trimethyl-1,3:5,7-dibenzylidene-D-perseitol.—Repeated attempts to obtain a trimethyl derivative of the 1,3:5,7-dibenzylidene-D-perseitol (m. p. 280 ±2°) by methylation of the diacetal with silver oxide and methyl iodide (Purdie's reagents) gave nearly quantitative yields of a stiff brown sirup which showed a methoxyl content of 21.82% (theory 21.63%). A crystalline 2,4,6-trimethyl-1,3:5,7-dibenzylidene-D-perseitol was obtained by the thallous hydroxide and methyl iodide procedure in the following manner. A suspension of 2.0 g. of 1,3:5,7-dibenzylidene-D-perseitol (m. p. 280 ±2°) in 20 ml. of acetone and 40 ml. (4.5 molecular equivalents) of 0.584 *N* thallous hydroxide solution was concentrated *in vacuo* to dryness and further dried by reconcentration with absolute alcohol. The dry residue was refluxed for eighteen hours with 40 ml. of methyl iodide and 10 g. of Drierite, the yellow precipitate was separated by filtration and washed with methyl iodide and the filtrate was evaporated to dryness; it yielded 2.0 g. of a solid melting at 110–130°. This product was dissolved in 20 ml. of acetone and following the addition of 36 ml. (4.0 molecular equivalents) of 0.584 *N* thallous hydroxide the reaction mixture was concentrated as before to a dry solid and refluxed for eighteen hours with 40 ml. of methyl iodide and 10 g. of Drierite; the solids were removed by filtration and the filtrate was concentrated and yielded 1.8 g. of a gummy solid. This product was dissolved in 20 ml. of acetone and the second step repeated as just described. The final filtrate was evaporated and it yielded 1.8 g. of a sirup which was dissolved in 5 parts of warm methanol; as the solution cooled it deposited 0.75 g. of prismatic crystals (m. p. 120–122°) and concentration of the mother liquor gave a further 0.25 g. (m. p. 112–120°) to make the total yield of product 1.0 g. (45%). The compound was recrystallized from 10 parts of methanol and yielded 0.8 g. of pure 2,4,6-trimethyl-1,3:5,7-dibenzylidene-D-perseitol as rosettes of prisms which melted at 121–122° and showed an $[\alpha]^{20}\mathrm{D}$ value −43.5° in chloroform (*c*, 0.62). It is readily soluble in acetone, chloroform, ether and benzene, moderately soluble in methanol and ethanol, and practically insoluble in water. Methylation of the dibenzylidene-D-perseitol (m. p. 153–155°) by this procedure gave a 45% yield of the same trimethyl derivative.

Anal. Calcd. for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02; OCH_3, 21.6. Found: C, 66.91; H, 7.12; OCH_3, 21.7.

2,4,6-Trimethyl-D-perseitol.—(A) A solution of 5.0 g. of sirupy 2,4,6-trimethyl-1,3:5,7-dibenzylidene-D-perseitol in a mixture of 30 ml. of ethanol, 20 ml. of water and 2 ml. of concentrated hydrochloric acid was refluxed for six hours and after neutralization with sodium hydroxide the solution was concentrated *in vacuo* to dryness. The sirupy dark residue was extracted with 50 ml. of ethanol, the solution was warmed on the steam-bath with decolorizing carbon, filtered, and the yellow filtrate was concentrated *in vacuo* to dryness; it yielded 3.0 g. (quantitative) of a dark yellow viscous sirup. The sirup was dissolved in 50 ml. of hot acetone and as the solution cooled fine needles (1.0 g., m. p. 119–121°) formed; they were separated by filtration and the filtrate upon concentration to a small volume and dilution with 50 ml. of ether gave a further 1.0 g. of product (m. p. 114–119°) to make the total yield 2.0 g. (67%). The compound was recrystallized from 20 parts of acetone as small needles which melted at 120–121° and showed $[\alpha]^{20}\mathrm{D}$ values of +11.8° in water (*c*, 1.03) and +14.7° (*c*, 0.84) in ethanol. It is readily soluble in methanol and ethanol, moderately soluble in chloroform and acetone, and nearly insoluble in benzene, hexane, ether and isopentane. (B) A solution of 0.5 g. of 2,4,6-trimethyl-1,3:5,7-dibenzylidene-D-perseitol (m. p. 121–122°) in a mixture of 10 ml. of ethanol, 1.0 ml. of concentrated hydrochloric acid and 9 ml. of water was refluxed for six hours, neutralized with sodium hydroxide and concentrated *in vacuo*. The residue was extracted with 10 ml. of acetone, the filtered extract was concentrated to a volume of 3 ml., seeded and crystallization allowed to progress at 5° for eighteen hours; the yield of needles of 2,4,6-trimethyl-D-perseitol melting at 120–121° and rotating +11.8° in water (*c*, 0.42) was 0.17 g. (54%). The product did not depress the melting point of 2,4,6-trimethyl-D-perseitol prepared from sirupy 2,4,6-trimethyl-1,3:5,7-dibenzylidene-D-perseitol as just described under (A), but it did depress the melting point of 2,4,6-trimethyl-1,3:5,7-dibenzylidene-D-perseitol (m. p. 121–122°).

Anal. Calcd. for $C_{10}H_{22}O_7$: C, 47.23; H, 8.72; OCH_3, 36.6. Found: C, 46.97; H, 8.70; OCH_3, 36.5.

Stability of 2,4,6-Trimethyl-D-perseitol against Oxidation by Sodium Metaperiodate.—To a solution of 0.1031 g. of 2,4,6-trimethyl-D-perseitol in 30 ml. of water 5.0 ml. (5.92 molecular equivalents) of 0.480 *M* aqueous sodium metaperiodate was added and the volume adjusted to 50 ml. with water. The analysis of 5-ml. aliquots at the expiration of one, two, eighteen and forty-two hours showed no consumption of oxidant. This result indicates the absence of a contiguous pair of hydroxyl groups in trimethyl-D-perseitol, which limits its structure to that of 2,4,6-trimethyl-D-perseitol.

1,3:5,7-Dimethylene-D-perseitol and Some of its Derivatives

1,3:5,7-Dimethylene-D-perseitol.—A solution of 20.0 g. of D-perseitol in a mixture of 20 ml. of concentrated hydrochloric acid and 25 ml. of aqueous 37% formaldehyde solution was evaporated at 25° in a crystallizing dish placed in an evacuated desiccator containing small beakers holding concentrated sulfuric acid and pellets of sodium hydroxide. After five days, the damp solid was triturated with 25 ml. of absolute ethanol and the slurry was evaporated to dryness in the evacuated desiccator. The dry solid was transferred to a Büchner funnel with 100 ml. of cold ethanol, washed and dried. The yield of product, which melted at 230–240°, was 16.8 g. (76%). The compound was recrystallized from 15 parts of 50% ethanol and it formed long needles which melted at 251–253° and showed $[\alpha]^{20}\mathrm{D}$ −19.3° in water (*c*, 1.0). It is soluble in hot water and hot aqueous alcohols but nearly insoluble in chloroform, ether, benzene and cold methanol and ethanol.

Anal. Calcd. for $C_9H_{16}O_7$: C, 45.76; H, 6.83. Found: C, 45.79; H, 6.82.

Stability of 1,3:5,7-Dimethylene-D-perseitol against Oxidation by Sodium Metaperiodate.—To a solution of 0.2410 g. of 1,3:5,7-dimethylene-D-perseitol in 30 ml. of water, 7.10 ml. (4.0 molecular equivalents) of 0.575 *M* sodium metaperiodate solution were added and the volume was adjusted to 50 ml. with water. The analysis of 5-ml. aliquots at the expiration of one, two, eighteen, forty-two and one hundred fifteen hours indicated that no oxidant had been consumed.

Dibenzoyl- and Monobenzoyl-1,3:5,7-dimethylene-D-perseitol.—A solution of 1.5 g. of 1,3:5,7-dimethylene-D-perseitol in 37.5 ml. of pyridine was cooled to 0° and 2.7 ml. (3.6 molecular equivalents) of benzoyl chloride was added dropwise. After standing for forty-eight hours at 25° the reaction mixture was poured into 300 ml. of ice-cold water and the crystalline precipitate (2.4 g., m. p. 175–195°) which formed was recrystallized from 50 parts of ethanol and yielded 1.0 g. (36%) of pure dibenzoyl-1,3:5,7-dimethylene-D-perseitol as long lath-like crystals which melted at 212–214° and showed $[\alpha]^{20}\mathrm{D}$ −30.2° in acetone (*c*, 1.04) and −9.3° in chloroform (*c*, 0.86). The compound is soluble in acetone, chloroform, pyridine, benzene and hot ethanol and nearly insoluble in water, cold ethanol, hexane and ether.

Anal. Calcd. for $C_{23}H_{24}O_9$: C, 62.16; H, 5.44; C_6H_5CO, 47.3. Found: C, 62.19; H, 5.49; C_6H_5CO, 47.5.

The aqueous solution from which the 2.4 g. of reaction product had been separated by filtration was extracted with chloroform and the washed and dried extract was concentrated *in vacuo* to dryness. The crystalline residue was recrystallized from 30 parts of ethanol and gave 0.3 g. (21%) of pure monobenzoyl-1,3:5,7-dimethylene-D-perseitol in the form of small needles which melted at 217–219° and showed $[\alpha]^{20}\mathrm{D}$ +74.3° in acetone (*c*, 0.43) and +31.2° in chloroform (*c*, 0.21). The crystals are readily soluble in pyridine and hot ethanol, slightly soluble in acetone and chloroform and nearly insoluble in water, cold ethanol, benzene, hexane and ether.

Anal. Calcd. for $C_{16}H_{20}O_8$: C, 56.46; H, 5.92; C_6H_5CO, 30.9. Found: C, 56.51; H, 5.97; C_6H_5CO, 31.1.

2,4,6-Tribenzoyl-1,3:5,7-dimethylene-D-perseitol.—To a suspension of 1.5 g. of powdered 1,3:5,7-dimethylene-D-perseitol in 30 ml. of ice-cold pyridine, 4.5 ml. (6 molecular equivalents) of benzoyl chloride was added dropwise and the mixture was agitated gently on a shaking machine at 25° for forty-eight hours. The doughy product which precipitated upon pouring the mixture into ice-cold water was crystallized from 40 ml. of hot ethanol and gave two fractions (2.8 g. melting at 161–162° and 0.5 g. melting at 156–159°) of nearly pure tribenzoyldiacetal. The combined crystalline product (3.3 g., 95%) was recrystallized from 15 parts of ethanol and formed prisms which melted at 161–162° and showed $[\alpha]^{20}\text{D}$ +2.6° in acetone (*c*, 0.96) and +14.4° in chloroform (*c*, 1.0). The tribenzoate is readily soluble in acetone, chloroform, pyridine, benzene and ether and nearly insoluble in cold ethanol, water and hexane.

Anal. Calcd. for $C_{30}H_{28}O_{10}$: C, 65.68; H, 5.15; C_6H_5CO, 57.5. Found: C, 65.84; H, 5.22; C_6H_5CO, 57.3.

Ditosyl- and Monotosyl-1,3:5,7-dimethylene-D-perseitol.—Ice-cold solutions of 6.0 g. (3.7 molecular equivalents) of *p*-toluenesulfonyl chloride in 10 ml. of pyridine and 2.0 g. of 1,3:5,7-dimethylene-D-perseitol in 50 ml. of the same solvent were mixed and allowed to stand at 20–25° for two days. The gummy precipitate which formed on pouring the reaction mixture into 300 ml. of ice-cold water gradually crystallized and the crude product (3.0 g., 50%; m. p. 150–160°) was recrystallized from 40 parts of ethanol and yielded 2.5 g. of pure ditosyl-1,3:5,7-dimethylene-D-perseitol in the form of long lath-like crystals which melted at 164–165° and showed $[\alpha]^{20}\text{D}$ −2.5° in chloroform (*c*, 0.9) and −8.7° in acetone (*c*, 1.04). The substance is soluble in pyridine, acetone, benzene and chloroform and nearly insoluble in water, cold ethanol, ether and hexane.

Anal. Calcd. for $C_{23}H_{28}O_{11}S_2$: C, 50.72; H, 5.18; S, 11.77. Found: C, 50.72; H, 5.23; S, 11.69.

The mother liquor from which the 3.0 g. of ditosyl-1,3:5,7-dimethylene-D-perseitol had been separated was extracted with 250 ml. of chloroform and the washed and dried extract was concentrated *in vacuo* to dryness. The crystalline residue was twice recrystallized from 10 parts of alcohol and yielded 0.5 g. of pure monotosyl-1,3:5,7-dimethylene-D-perseitol as elongated six-sided plates which melted at 174–175° (decomposition); a chloroform solution (*c*, 0.22) of the compound failed to show optical activity, but in acetone solution (*c*, 0.88) a rotation $[\alpha]^{20}\text{D}$ +9.2° was observed. The substance is soluble in acetone, pyridine and hot ethanol, slightly soluble in chloroform and nearly insoluble in water, benzene, hexane and ether.

Anal. Calcd. for $C_{16}H_{22}O_9S$: C, 49.22; H, 5.68; S, 8.21. Found: C, 49.40; H, 5.81; S, 8.10.

2,4,6-Tritosyl-1,3:5,7-dimethylene-D-perseitol.—A solution of 2.0 g. of 1,3:5,7-dimethylene-D-perseitol and 10.0 g. (six molecular equivalents) of *p*-toluenesulfonyl chloride in 30 ml. of pyridine was allowed to stand in the dark at 20–25° for eight weeks and then poured into 800 ml. of ice and water. The product (6.2 g., quantitative; m. p. 160–165°) was recrystallized from 80 parts of ethanol and gave 5.1 g. of pure 2,4,6-tritosyl-1,3:5,7-dimethylene-D-perseitol which melted at 172–173° and rotated $[\alpha]^{20}\text{D}$ −4.7° in chloroform (*c*, 0.86) and −5.9° in acetone (*c*, 0.85). The compound is soluble in chloroform, acetone and pyridine and nearly insoluble in water and cold alcohols. The tritosyl derivative did not react with sodium iodide in acetone solution upon heating at 100° for two hours, a result which indicates that tosyl groups are not attached through primary hydroxyl groups.

Anal. Calcd. for $C_{30}H_{34}O_{13}S_3$: C, 51.56; H, 4.90; S, 13.76. Found: C, 51.47; H, 4.91; S, 13.69

2,4,6-Trimethyl-1,3:5,7-dimethylene-D-perseitol by the Methylation of 1,3:5,7-Dimethylene-D-perseitol.—A solution of 4.0 g. of 1,3:5,7-dimethylene-D-perseitol in 110 ml. (3.8 molecular equivalents) of 0.584 *N* aqueous thallous hydroxide[11] was concentrated *in vacuo* to dryness, with the inlet tube carrying a soda lime tube to exclude carbon dioxide, and the residue was dried through concentration *in vacuo* by two evaporations with absolute ethanol. The gray powdery product was refluxed for twenty hours with 10.0 g. of Drierite and 80 ml. of methyl iodide, the solids were separated by filtration and the filtrate was evaporated to dryness; it yielded 3.0 g. of crystalline material melting at 140–170°. This substance was dissolved in 90 ml. of 0.584 *N* thallous hydroxide and the solution concentrated *in vacuo* to dryness as previously described, the crystalline residue was refluxed for twenty-two hours with 10 g. of Drierite and 60 ml. of methyl iodide, the mixture was filtered and the filtrate was evaporated to dryness; it yielded 3.0 g. of product melting at 132–134°. After one more methylation in the same manner there was obtained 2.8 g. of product melting at 138–139°, which was recrystallized from 10 parts of absolute ethanol and yielded 2.1 g. (45%) of pure 2,4,6-trimethyl-1,3:5,7-dimethylene-D-perseitol as needles melting at 140–141° and rotating $[\alpha]^{20}\text{D}$ −6.2° in water (*c*, 0.83). A mixed melting point with the compound prepared by the methylenation of 2,4,6-trimethyl-D-perseitol with aqueous 37% formaldehyde solution and concentrated hydrochloric acid, as described in the following paragraph, showed no depression.

2,4,6-Trimethyl-1,3:5,7-dimethylene-D-perseitol by the Methylenation of 2,4,6-Trimethyl-D-perseitol.—A solution of 1.0 g. of 2,4,6-trimethyl-D-perseitol in a mixture of 2.5 ml. of concentrated hydrochloric acid and 2.5 ml. of aqueous 37% formaldehyde solution was allowed to evaporate to dryness in an evacuated desiccator containing small beakers of concentrated sulfuric acid and pellets of sodium hydroxide; after five days the dry solid (1.0 g., 90%; m. p. 138–142°) which resulted was crystallized from 20 parts of ether and yielded 0.8 g. (70%) of pure 2,4,6-trimethyl-1,3:5,7-dimethylene-D-perseitol melting at 140–141° and rotating $[\alpha]^{20}\text{D}$ −6.0° in water (*c*, 0.81). The compound is readily soluble in chloroform, acetone, benzene and water, sparingly soluble in ether and nearly insoluble in hexane.

Anal. Calcd. for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97; OCH_3, 33.4. Found: C, 51.81; H, 8.00; OCH_3, 33.5.

Acetals of the L- and D,L-Perseitols

1,3:5,7-Dibenzylidene-L-perseitol.—About seven grams of crystalline L-perseitol was prepared by the reduction of D-gala-L-*manno*-heptose. From one gram of it the 1,3:5,7-dibenzylidene-L-perseitol was prepared as has been described in the case of the D-form, using sulfuric acid as the catalyst. The crystals melted at 153–155° and rotated +57.7° in pyridine. They were then recrystallized by refluxing with fifteen parts of pyridine fifteen minutes and adding thirty parts of ethanol to the hot solution; the product then melted at 280 ± 2° and rotated +57.6° in pyridine. Both enantiomorphs thus show the same behavior, namely, a labile form passing on recrystallization to a stable form.

1,3:5,7-Dibenzylidene-D,L-perseitol.—A mixture of equal amounts of the D- and L-enantiomorphs, each of which melted at 280 ± 2°, was dissolved in ten parts of hot pyridine and crystallized by the addition of 25 parts of ethanol. The fine needle-like crystals appear to be a true racemate according to Mr. Keenan's measurements of their indices of refraction (see table) and this conclusion is supported by our observation that they are much less soluble in pyridine than are those of the components. The racemate melts at 271–272°, a lower temperature than the 280° value shown by its components. The same racemate was likewise prepared from equal amounts of the labile forms of the enantiomorphs (m. p. 153–155°) by dissolving them in one thousand parts of 2-methoxyethanol without heating, followed by evaporation of the solvent at 27° by an air current. The crystalline residue melted at 235–237°; one recrystallization of it from hot 2-methoxyethanol raised this value to 267–268°, and a second increased it to 271–272°. Further recrystallization from either 2-methoxyethanol or the pyridine–ethanol mixture caused no change.

1,3:5,7-Dimethylene-L-perseitol.—The substance was prepared essentially as has been described for its enantiomorph. The recrystallized product melted at 252–254° and showed $[\alpha]^{20}\text{D}$ +19.0° in water (*c*, 1.01). Like its enantiomorph it was not oxidized by sodium metaperiodate.

1,3:5,7-Dimethylene-D,L-perseitol.—A solution of equal amounts of the enantiomorphs in fifty parts of hot 80% ethanol deposited fine needle-like crystals which melted at 236–237° and showed no rotation in aqueous solution. The substance is a hemihydrate which becomes anhydrous when heated at 120° *in vacuo* for some hours. The hemihydrate crystals obviously represent a true racemate. The anhydrous material also melts at 236–237°; apparently the water of crystallization leaves the hemihydrate before the substance melts.

Anal. Calcd. for $C_9H_{16}O_7 \cdot {}^1/_2H_2O$: C, 44.08; H, 6.99; H_2O, 3.67. Found: C, 43.90; H, 7.08; H_2O, 3.59.

Calcd. for $C_9H_{16}O_7$ (anhydrous): C, 45.76; H, 6.83. Found: C, 45.91; H, 6.83.

The racemic character of 1,3:5,7-dibenzylidene- and 1,3:5,7-dimethylene-D,L-perseitols was verified by determination of their optical-crystallographic properties by Mr. George L. Keenan. The data for the compounds and their component optically active forms are compiled in Table I.

TABLE I

OPTICAL-CRYSTALLOGRAPHIC PROPERTIES OF THE 1,3:5,7-DIBENZYLIDENE- AND 1,3:5,7-DIMETHYLENE PERSEITOLS

	Dibenzylidene perseitol		Dimethylene perseitol	
	D or L	D,L	D or L	D,L-hemihydrate
$n\alpha$	1.567[a]	1.583[a]	1.515[a]	1.530[a]
$n\beta$	1.615[b]	1.613[b]	1.535[b]	Indeterminate
$n\gamma$	1.625	1.637[b]	1.540[b]	1.530[b]
Elongation	Negative	Negative	Negative	Negative
Extinction	Parallel and inclined	Parallel	Parallel	Parallel and inclined
M. p., °C.	280	271	251	236

[a] Shown lengthwise. [b] Shown crosswise. All the substances crystallize as rods. The refractive indices are for ordinary light at 25° and are ±0.002.

Summary

Proof is presented that dibenzylidene-D-perseitol (dibenzylidene-D-manno-D-*gala*-heptitol) is the 1,3:5,7-dibenzylidene diacetal. Neither it nor the trimethyl-D-perseitol which is obtained by its methylation and hydrolysis is oxidized by sodium periodate and the absence of α-glycol groupings in this related pair of compounds limits the structure of the diacetal to that of 1,3:5,7-dibenzylidene-D-perseitol and that of the derived trimethyl-heptitol to 2,4,6-trimethyl-D-perseitol.

The condensation of D-perseitol with formaldehyde yields a diacetal which must be 1,3:5,7-dimethylene-D-perseitol since its trimethyl derivative is identical with the compound formed by methylenation of 2,4,6-trimethyl-D-perseitol.

The enantiomorphous 1,3:5,7-dibenzylidene- and 1,3:5,7-dimethylene-L-perseitols have been prepared from D-gala-L-*manno*-heptitol and they combine with the D-forms to form true racemate crystals.

BETHESDA, MARYLAND RECEIVED SEPTEMBER 29, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Cleavage of Tetraacetyl-β-D-thioglucosides with Bromine in Acetic Acid[1]

BY WILLIAM A. BONNER

Several years ago it was shown[2] that phenyl tetraacylglucosides were brominated quantitatively when treated with excess bromine in glacial acetic acid. That bromination occurred at the *para* position was shown by hydrolysis of the glucoside and isolation of the brominated aglucone, *p*-bromophenol. In this respect the phenyl glycosides, which are cyclic acetals, resemble true phenyl alkyl ethers such as anisole.

It seemed desirable to extend this reaction to the phenyl polyacylthioglycosides, and to determine whether these undergo similar *para*-bromination. Such was anticipated, since aromatic thioethers are known[3] to undergo nuclear halogenation with readiness. In addition, adducts of bromine to the sulfur atom of the thioglycoside were considered likely, since halogens have been shown[4] to add readily to organic sulfides to form what are presumably halo sulfonium halides.

When phenyl tetraacetyl-β-D-thioglucoside in glacial acetic acid was treated with about thirteen equivalents of bromine and permitted to stand at room temperature for several hours, a white, crystalline material was isolated. On recrystallization pure α-D-glucose pentaacetate was obtained. The crude reaction product was not pure α-D-glucose pentaacetate, however, since its specific rotation (88.5 to 91.7°, depending upon reaction conditions) and its melting point (98–103°) were somewhat below those for the pure substance. The presence of small quantities of the β-anomer may explain these low values, as well as the presence of other impurities. The crude material, however, was substantially α-D-glucose pentaacetate, since this was obtained in reasonable purity on one or two recrystallizations. Based on pentaacetate the yield of crude product varied between 75 and 81%, depending upon reaction conditions.

This striking and unexpected reaction which involves cleavage of the acylated thioglucoside and replacement of the sulfur moiety with acetoxy was found to be quite general with respect to the thioaglucone. Both benzyl tetraacetyl-β-D-thioglucoside and ethyl tetraacetyl-β-D-thioglucoside produced α-D-glucose pentaacetate in comparable

---

[1] Presented before the Division of Sugar Chemistry and Technology of the American Chemical Society, New York, September, 1947.

[2] Hurd and Bonner, THIS JOURNAL, **67**, 1764 (1945).

[3] Bourgeois, *Ber.*, **28**, 2321 (1895); Böeseken and Waterman, *Rec. trav. chim.*, **29**, 321 (1910); Bourgeois and Abraham, *ibid.*, **30**, 418 (1911).

[4] Patein, *Bull. soc. chim.*, **50**, 201 (1888); Fries and Vogt, *Ann.*, **381**, 337 (1911); Chelintzev, *J. Russ. Phys.-Chem. Soc.*, **44**, 1885 (1913).

yields under similar conditions. Thus an aryl, an aralkyl, and an alkyl tetraacetyl-β-D-thioglucoside all showed identical behavior under the influence of bromine in acetic acid.

That bromine alone was responsible for the cleavage was shown by isolation of pure starting material in substantial yield when bromine was omitted from the reaction mixture, or when bromide ion (*i. e.*, lithium bromide) was substituted for bromine. Similarly, both hydrogen bromide and bromoacetic acid, other possible constituents of the reaction mixture, were found incapable of producing cleavage. Experiments designed to elucidate the mechanism of this unexpected cleavage of thioglucosides with bromine are currently in progress.

Under certain conditions bromine was found to have a labilizing effect on the acetyl functions of phenyl tetraacetyl-β-D-thioglucoside. Thus when the cleavage with bromine was attempted in methanol rather than acetic acid, the aqueous layer obtained during processing was dextro-rotatory, while the ether layer yielded only a small quantity of thin oil having a negligible rotation. Apparently bromine in methanol resulted in complete deacetylation. Similarly, when propionic acid was employed as solvent in the reaction, a sirup was isolated from which only minute quantities of indistinct crystalline materials were obtained. It is here probable that bromine engendered a partial replacement of the acetyl functions with propionyl, resulting in a substantially sirupy product. The deacetylating power of bromine in methanol was further demonstrated with α-D-glucose pentaacetate. When this substance was treated with bromine in methanol, permitted to stand several hours, and extracted with ether, optical activity was found in the aqueous layer while the ether layer was inactive. Similarly, when α-D-glucose pentaacetate was treated with bromine in propionic acid a sirup resulted, $[\alpha]^{25}\mathrm{D}$ 51.4°. Since the rotation of this product is fairly close to that of equilibrated sirupy D-glucose pentapropionate,[5] it seems probable that bromine not only caused replacement of acetyl with propionyl, but also brought about anomerization. Although it is indicated that bromine may labilize acetyl groups in acetic acid medium, the medium seems to prevent extensive deacetylation, transacylation or anomerization from occurring. Thus bromine in acetic acid is without action on α-D-glucose pentaacetate. These effects of bromine on acylated carbohydrate derivatives are under more extensive study at the present time.

Experimental Part

Phenyl Tetraacetyl-β-D-thioglucoside and Bromine in Acetic Acid.—Phenyl tetraacetyl-β-D-thioglucoside (1.00 g.) was dissolved in glacial acetic acid (20 ml.) and bromine (1.5 ml., 12.8 equivalents) added. The mixture stood at room temperature for about three hours and was then poured into water (100 ml.). The cloudy red suspension was extracted twice with 60-ml. portions of ether. The ether extract was washed once with water, then with sodium bisulfite solution to remove free bromine, again twice with water, then with saturated sodium bicarbonate solution until gas evolution ceased, and again with water. After drying over anhydrous sodium sulfate and decanting, the solvent was distilled to yield 0.67 g. (75.5%) of a clear glass which crystallized spontaneously. After three recrystallizations from 2-propanol this material melted at 111.5°. It was shown to be α-D-glucose pentaacetate by mixed melting point with an authentic sample (m. p. 112–112.5°), 111–111.5°, and specific rotation $[\alpha]^{25}\mathrm{D}$ 102.8° ($CHCl_3$; *c*, 4.047). The latter value is in agreement with $[\alpha]^{20}\mathrm{D}$ 101.6° reported by Hudson and Dale.[6]

In a second experiment phenyl tetraacetyl-β-D-thioglucoside (1.00 g.) in acetic acid (10 ml.) was treated with bromine (1.5 ml.) and permitted to stand for about twenty-three hours. The reaction mixture was processed essentially as above to yield 0.72 g. (81.3%) of crude, solid product. This crude material showed $[\alpha]^{25}\mathrm{D}$ 88.5° ($CHCl_3$; *c*, 2.535).

In a third experiment the thioglucoside (1.00 g.) in acetic acid (20 ml.) was treated with bromine (1.5 ml.) and allowed to stand for four hours. The crude product, a white solid, weighed 0.68 g. (76.8%). It melted from 98–103° with preliminary softening from 90°, and showed $[\alpha]^{25}\mathrm{D}$ 91.7° ($CHCl_3$; *c*, 1.887).

Benzyl Tetraacetyl-β-D-thioglucoside and Bromine in Acetic Acid.—Benzyl tetraacetyl-β-D-thioglucoside (0.50 g., m. p. 97.5–98°, prepared by the method of Schneider, Sepp and Stiehler[7]) was dissolved in glacial acetic acid (10 ml.), and bromine (0.75 ml.) added. The mixture stood at room temperature for three and one-half hours, was poured into 50 ml. of water, and the product isolated and purified as before. On removal of the ether there resulted 0.48 g. (110%) of thick sirup which crystallized rapidly. After two recrystallizations from a mixture of 2-propanol and water there remained 0.13 g. (30%) of pure α-D-glucose pentaacetate, m. p. 111–111.5°; mixed m. p. with an authentic sample, 110–111°; $[\alpha]^{25}\mathrm{D}$ 102.2° ($CHCl_3$; *c*, 0.920). A second crop (0.05 g.) was obtained from the mother liquors on standing overnight, m. p. 112°.

Ethyl Tetraacetyl-β-D-thioglucoside and Bromine in Acetic Acid.—Ethyl tetraacetyl-β-D-thioglucoside[7] (0.50 g.; m. p. 76.5–77.5°), acetic acid (10 ml.) and bromine (0.88 ml.) were mixed and permitted to stand for four hours. On processing in the usual fashion there resulted 0.46 g. (92%) of crude α-D-glucose pentaacetate. After two recrystallizations from dilute 2-propanol the material melted at 109.5–111°, and showed no melting point depression (110–111°) when mixed with an authentic sample.

Phenyl Tetraacetyl-β-D-thioglucoside and Bromine in Methanol.—Phenyl tetraacetyl-β-D-thioglucoside (1.5 g.) was placed in methanol (30 ml.) in which it was insoluble. On adding bromine (2.2 ml.) the thioglucoside dissolved immediately, and the solution stood for four hours. It was poured into dilute sodium bisulfite solution to decolorize, resulting in a completely clear solution in contrast to the cloudy suspensions previously obtained. The aqueous mixture was extracted twice with ether, and the extract washed as before. Distillation of the solvent resulted in 0.52 g. of a clear, malodorous oil which would not crystallize. This showed a minute rotation, $[\alpha]^{25}\mathrm{D}$ 2.5° ($CHCl_3$; *c*, 4.040), compared with that of the previous crude products. The clear, aqueous layer remaining after the above ether extraction was found to be dextro-rotatory.

Phenyl Tetraacetyl-β-D-thioglucoside and Bromine in Propionic Acid.—The above experiment was duplicated using propionic acid (30 ml.) in place of methanol. There resulted 1.12 g. of amber sirup after customary processing. This product showed qualitative tests for sulfur and bromine. On standing it underwent partial crystallization. A seed was removed, and the remainder dissolved in 2-propanol (8 ml.). The solution was cooled, seeded and placed at 0°. Ten milligrams of solid, m. p. 88–91°, was

---

(5) Bonner, Hurd and Cantor, THIS JOURNAL, **69**, 1816 (1947).

(6) Hudson and Dale, *ibid.*, **37**, 1264 (1915).

(7) Schneider, Sepp and Stiehler, *Ber.*, **51**, 224 (1918).

isolated. The mother liquors were evaporated in an air stream to yield a solid. This was slurried with 2-propanol and filtered, giving a small quantity of crystals, m. p. 147–152°. The filtrate was kept at 0° for several weeks, resulting in *ca.* five milligrams of solid, m. p. 120–140°. No attempt was made to purify or identify these products, a complex mixture apparently having been obtained.

Phenyl Tetraacetyl-β-D-thioglucoside in Acetic Acid.—To be certain that bromine was essential for the cleavage reaction to take place, this constituent was omitted from one reaction mixture. The thioglucoside (1.00 g.) was dissolved in acetic acid (20 ml.) and the solution permitted to stand at room temperature for seventeen hours. The mixture was poured into water and the product isolated exactly as previously described. There resulted 1.01 g. of pure starting material, m. p. 117.5–118°; mixed m. p. 117–117.5°.

Phenyl Tetraacetyl-β-D-thioglucoside and Lithium Bromide in Acetic Acid.—To see if bromide ion was in any way responsible for the cleavage, lithium bromide was employed instead of bromine in one experiment. The thioglucoside (1.00 g.) was dissolved in acetic acid (5 ml.), and lithium bromide (0.59 g., 3 equivalents) was dissolved in acetic acid (4 ml.). The two solutions, cooled to room temperature, were mixed and diluted to 10 ml. Absence of reaction was observed by polarimetric observation, no mutarotation being noted during twenty-four hours. The mixture was poured into water and processed as usual, except that the bisulfite wash was omitted. There was recovered 0.95 g. (95%) of starting material, m. p. 117–117.5°, mixed m. p. 116.5–117.5°.

Phenyl Tetraacetyl-β-D-thioglucoside and Hydrogen Bromide in Acetic Acid.—The thioglucoside (0.61 g.) was dissolved in acetic acid and 32% hydrogen bromide in acetic acid (1.75 g., 5 equivalents of hydrogen bromide) added. The mixture was diluted to 100 ml. and observed polarimetrically. No mutarotation was noted during one hundred and eleven minutes. The mixture was poured into water, extracted with ether, and the product isolated as above. There resulted 0.55 g. (90%) of starting material, m. p. 117–118°, mixed m. p. 117–118°, $[\alpha]^{25}\text{D}$ −17.0° ($CHCl_3$; *c*, 1.587). Thus hydrogen bromide does not enter into the reaction mechanism in any direct manner. It is interesting to note that hydrogen bromide was also completely without action on phenyl tetraacetyl-β-D-glucoside under the same conditions, the starting material being recovered quantitatively.

Phenyl Tetraacetyl-β-D-thioglucoside, Bromoacetic and Acetic Acids.—Bromoacetic acid (1.58 g., 5 equivalents) was dissolved in acetic acid and diluted to 10 ml. Phenyl tetraacetyl-β-D-thioglucoside (1.00 g.) was added and the solution placed in a polarimeter tube. No mutarotation was observed during the course of over two hours. The solution was poured into water and treated as above. There was recovered 0.99 g. (99%) of starting material, m. p. 117–118°; mixed m. p. 117–118°. Thus bromoacetic acid, a constituent which might conceivably arise as a by-product in the cleavage reaction, is in no way responsible for the cleavage.

α-D-Glucose Pentaacetate and Bromine in Methanol.—α-D-Glucose pentaacetate (1.00 g.) was placed in methanol (10 ml.), in which it remained essentially undissolved. Bromine (1.5 ml.) was added to the mixture, causing rapid solution. The solution stood for two hours and was poured into 50 ml. of water. The clear, red solution was decolorized by the addition of sufficient sodium bisulfite, then extracted twice with 30-ml. portions of ether. The aqueous layer was strongly dextro-rotatory (0.34°), while the first ether extract was essentially void of rotation (0.02°), indicating that bromine in methanol had brought about deacetylation of the glucose pentaacetate.

α-D-Glucose Pentaacetate and Bromine in Propionic Acid.—α-D-Glucose pentaacetate (1.00 g.) in propionic acid (20 ml.) was treated with bromine (1.5 ml.) and permitted to stand at room temperature for six hours. The mixture was poured into water (75 ml.), decolorized with sufficient solid sodium bisulfite, extracted with ether, and processed as before. There resulted 1.01 g. of lachrymatory amber sirup as the crude product, $[\alpha]^{25}\text{D}$ 51.4° ($CHCl_3$; *c*, 2.397).

To see if bromine was essential for transacylation, this constituent was omitted from the above mixture. α-D-Glucose pentaacetate (1.00 g.) was dissolved in propionic acid (20 ml.) and the mixture treated as above except that the sodium bisulfite treatment was eliminated. The crude product was a white solid weighing 0.98 g. After one recrystallization from 2-propanol the substance had m. p. 112–112.5° and showed no melting point depression when mixed with starting material.

α-D-Glucose Pentaacetate and Bromine in Acetic Acid.—α-D-Glucose pentaacetate (1.00 g.) was dissolved in acetic acid (20 ml.) and bromine (1.5 ml.) was added. After standing for eighteen hours at room temperature the mixture was poured into water and the product isolated in the usual fashion. The crude product weighed 0.74 g., melted at 110–111.5°, showed no mixed melting point depression (111–112°) with starting material, and had $[\alpha]^{25}\text{D}$ 100.0° ($CHCl_3$; *c*, 4.006).

Summary

On treatment of phenyl, benzyl or ethyl tetraacetyl-β-D-thioglucosides with about thirteen equivalents of bromine in acetic acid, α-D-glucose pentaacetate is formed in good yield. This reaction, involving cleavage of the thiophenyl moiety and replacement with acetoxy, has been shown to be due to bromine alone, and to no other possible constituent of the reaction mixture. In addition, bromine seems capable of labilizing the acetyl functions of several acetylated carbohydrate derivatives, producing deacetylation when methanol is employed as solvent, and transacylation when propionic acid is employed as solvent.

STANFORD UNIVERSITY, CALIFORNIA

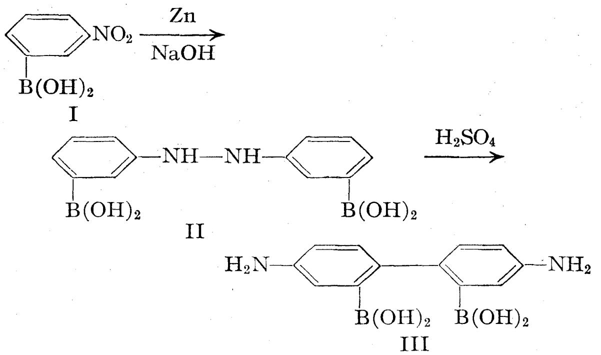
RECEIVED OCTOBER 10, 1947

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

The Synthesis of Benzidine-2,2'-diboronic Acid

BY H. R. SNYDER, CLAY WEAVER[1] AND STANLEY M. PARMERTER[2]

Previous attempts[3] to prepare a biphenyldiboronic acid by the coupling of two molecules of a diazotized aminobenzeneboronic acid in the presence of cuprous hydroxide failed because of the removal of the boronic acid function by the reducing reagent. A synthesis of 4,4'-diaminobiphenyl-2,2'-diboronic acid (III) now has been realized by the application of the benzidine rearrangement to *m*-hydrazobenzeneboronic acid (II).



The alkaline reduction of *m*-nitrobenzeneboronic acid proceeded smoothly and a good yield of the crude hydrazo compound (II) was obtained. Removal of the boronic acid groups by heating the silver salt[4] with water gave azobenzene. Evidently the hydrazine linkage was oxidized to the azo group by the reagent (silver nitrate in the presence of ammonia). Since the reduction product (II) was nearly colorless it could not have contained an azo linkage.

The treatment of the hydrazo compound with acids, under the various conditions which have been employed to effect the benzidine rearrangement, brought about extensive decomposition of the substance. However, when the reaction was effected at temperatures of 50–60° with rather dilute hydrochloric or sulfuric acid (10–20%), the benzidine (III) was formed in sufficient quantity to permit its isolation in yields of 15–20%. The product (III) was amphoteric, and the boron content was very near the theoretical value. The substance (III) gave a good test (diazotization and coupling) for the primary aromatic amino group. When the acetyl derivative of III, prepared by treatment with acetic anhydride in water solution, was subjected to the procedure for the removal of the boronic acid group by hydrolysis of the silver salt diacetylbenzidine was formed. Similarly, treatment of the dibenzal derivative of III with silver nitrate in the presence of ammonia gave the dibenzal derivative of benzidine.

Experimental

***m*-Nitrobenzeneboronic Acid.**—The method of Seaman and Johnson[4] was used on a six-fold scale without detrimental effect upon the yield (65–70%).

***m*-Hydrazobenzeneboronic Acid (II).**—A solution of 15 g. of *m*-nitrobenzeneboronic acid, 20 g. of sodium hydroxide and 15 ml. of alcohol was heated with stirring to gentle reflux. After the solution had refluxed for twenty minutes the heating was discontinued and small portions of zinc were added at such a rate that gentle ebullition was maintained. The first portions of zinc were extremely small, as the initial reaction was quite vigorous. After 23 g. of zinc had been added the color of the solution faded to a light yellow. Near the end of the addition external heating was necessary to keep the solution refluxing. The solid material removed from the hot mixture by filtration under nitrogen was washed with 35 ml. of hot water, and the combined filtrate and washings were cooled and poured slowly with stirring into 18 ml. of cold concentrated hydrochloric acid. The resulting solution was made acid to litmus with 20% acetic acid and allowed to stand in an ice-bath for two hours. The crude *m*-hydrazobenzeneboronic acid was collected on a filter under nitrogen, and ordinarily it was used immediately in subsequent reactions without drying. The weight of the air-dried product corresponded to a yield of 91%.

The *m*-hydrazobenzeneboronic acid could be recrystallized from dilute ethanol. A sample so recrystallized and dried in the air was titrated with 0.1 *N* sodium hydroxide in a dilute ethanol solution with the aid of a *p*H meter. The neutralization equivalent so found was 137 (calcd., 135.9). This sample had no definite melting point; it softened at about 60° and charred at higher temperatures. A sample dried *in vacuo* over phosphorus pentoxide apparently was converted to the anhydride; it did not melt instantly on a Parr melting point bar at temperatures up to 350°, although it charred slowly at temperatures above 250°. This sample was analyzed.

Anal. Calcd. for $C_{12}H_{10}N_2B_2O_2$: N, 11.9. Found: N, 11.5.

Removal of the Boronic Acid Groups.—Application of the procedure of Seaman and Johnson resulted in the formation of a red crystalline solid, m. p. 66–68°, which was identified as azobenzene by a mixed melting point determination.

Benzidine-2,2'-diboronic Acid.—Of a variety of procedures tested in the rearrangement of the hydrazo compound (II) the following[5] gave the best and most consistent results. The crude, moist hydrazo compound from 15 g. of *m*-nitrobenzeneboronic acid was transferred to a flask containing 125 ml. of 10% sulfuric acid through which nitrogen had been bubbled for about an hour to remove dissolved oxygen. Without interruption of the flow of nitrogen the mixture was warmed for three hours in an oil-bath at 60°. The mixture was then filtered and the filtrate was cooled in an ice-bath while it was brought almost to the neutral point by the cautious addition of concentrated ammonium hydroxide. A brown precipitate formed during this process. If too much ammonia was added a white precipitate began to appear; when this occurred dilute sulfuric acid was added to redissolve the white material. The brown precipitate was removed by filtration and the benzidine was precipitated by the addition of ammonium hydroxide to the filtrate.

---

(1) du Pont Post-Doctorate Research Assistant, 1941–1942. Present address: Experimental Station, E. I. du Pont de Nemours and Co., Inc., Wilmington, Delaware.

(2) Present address: The Wm. S. Merrell Co., Cincinnati, Ohio.

(3) Snyder and Weaver, THIS JOURNAL, **70**, 232 (1948).

(4) Seaman and Johnson, *ibid.* **53**, 711 (1931).

(5) The authors are indebted to Dr. Seymour L. Meisel, who carried out this preparation many times, for some of the details recorded here.

For the preparation of the benzidine dihydrochloride the suspension of the benzidine was stored in a refrigerator for two days before it was collected on a filter. The solid was dried to constant weight in a vacuum desiccator and was then extracted with small portions (about 20 ml.) of boiling absolute ethanol until the amount of undissolved solid appeared to undergo no further decrease. The combined ethanol extracts were diluted with twice the volume of anhydrous ether and dry hydrogen chloride was passed into the solution until precipitation of the hydrochloride was complete. The solid was collected and the mother liquor was tested by further dilution with ether; if more solid separated it was combined with the first crop and the second mother liquor was tested in the same way. The total yield of the dihydrochloride so obtained was 3.1 g. (19.3% based on the nitro compound I). The salt had no definite melting point, but decomposed slowly at temperatures above 300°.

Anal. Calcd. for $C_{12}H_{16}O_4B_2N_2Cl_2$: N, 8.15; B, 6.28. Found: N, 8.27; B, 5.85.

For the isolation of the benzidine directly from the rearrangement mixture the crude diamine was filtered immediately after the precipitation with ammonium hydroxide and the filtrate was stored for two days in a stoppered flask. The solid collected in the filtration was extracted with 100 ml. of 30% ethanol and the extract was allowed to cool. Both the dilute ethanol extract and the ammoniacal mother liquor deposited light brown crystals; the two crops were collected and decolorized in 150 ml. of hot 30% ethanol. This solution on cooling deposited 1.6 g. (13%) of the benzidine as short flesh-colored needles melting at 232–234°. The substance was insoluble in water, aqueous ammonia and ether, but soluble in dilute sodium hydroxide dilute acids, ethanol and glacial acetic acid. A sample dried in the air had the composition of a hemihydrate.

Anal. Calcd. for $C_{12}H_{15}O_{4.5}N_2B_2$: C, 51.25; H, 5.38; B, 7.70. Found: C, 51.01; H, 5.64; B, 7.75.

The combustion analyses on samples dried *in vacuo* over phosphorus pentoxide were erratic with respect to carbon and the combustion residues obviously contained carbon; the hydrogen and nitrogen values on such samples indicated that they consisted of the di-anhydride.

Anal. Calcd. for $C_{12}H_{10}O_2N_2B_2$: H, 4.27; N, 11.88. Found: H, 4.45; N, 11.51.

Removal of the Boronic Acid Groups from Derivatives of the Benzidine (III). (a) Diacetylbenzidine.—A solution of 1.36 g. of the diamine in 25 ml. of water containing 0.83 ml. of concentrated hydrochloric acid was treated with 1.16 ml. of acetic anhydride and then warmed to 50°. A solution of 0.82 g. of sodium acetate in 5 ml. of water was added, and the mixture was cooled in an ice-bath. A solid weighing 1.13 g. was collected which was soluble in dilute sodium hydroxide but insoluble in water and acids. A portion of the material was recrystallized from a large volume of 50% ethanol. The analytical data indicated that part of the material had lost boronic acid groups during the reaction.

Anal. Calcd. for $C_{16}H_{18}N_2O_6B_2$: C, 54.0; H, 5.1; B, 6.1. Found: C, 57.4; H, 5.4; B, 4.5.

A sample of about 0.5 g. of the crude acetyl derivative was suspended in 30 ml. of 50% ethanol and treated with 10 ml. of 10% aqueous silver nitrate and 6 drops of concentrated aqueous ammonia. The resulting mixture, which contained a brown precipitate, was refluxed for fifteen minutes and filtered hot. The filtrate deposited a white powder which melted at 329–331°, alone or mixed with authentic diacetylbenzidine.

(b) Dibenzalbenzidine.—To a warm solution of 0.5 g. of the benzidine in 70 ml. of 95% ethanol was added 1 ml. of benzaldehyde. The solution soon began to deposit fine crystals, which were collected after four hours. The yellow product melted at 141–143° and weighed 0.8 g. (97%). The substance could be recrystallized from benzene, but the product so obtained had no definite melting point; the material probably suffered the loss of water from the boronic acid groups during the heating with benzene. About 0.2 g. of the freshly prepared benzal derivative was suspended in 50 ml. of water and treated with six drops of aqueous ammonia; dilute aqueous silver nitrate was added until no further precipitation occurred and the brown solid was separated. The solid was added to 25 ml. of water and the mixture was boiled gently for fifteen minutes. The cooled mixture was filtered and the solid was extracted with 20 ml. of hot benzene. The yellow plates which separated when the benzene solution was cooled melted at 232–234°; the substance did not contain boron, and the melting point was not changed by mixture with authentic dibenzalbenzidine.

Summary

m-Hydrazobenzeneboronic acid can be prepared in good yield by the reduction of *m*-nitrobenzeneboronic acid with zinc in the presence of alkali. Rearrangement of the hydrazo compound by acids leads to complex mixtures, but under certain conditions benzidine-2,2′-diboronic acid is produced and can be isolated in yields of about 20%.

URBANA, ILLINOIS RECEIVED AUGUST 18, 1947

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

The Synthesis of Azo Boronic Acids. II. Dyes from Tetrazotized Benzidine-2,2′-diboronic Acid

BY H. R. SNYDER AND SEYMOUR L. MEISEL[1]

The speculations of Kruger[2] and Zahl and others[3–6] on the possible development of an irradiation therapy based on the nuclear disintegration process (equation 1) occurring when the boron isotope of atomic weight 10 captures a slow neutron have provoked an interest in the synthesis of boron-containing dyes having structures similar to those of Trypan Blue and Evans Blue. Such substances might be expected to concentrate in certain tissues, which might then be irradiated with slow neutrons with the result that the energetic nuclear disintegration would be localized. Recent studies[7] on the localization of derivatives of Trypan Blue and Evans Blue containing radioactive bromine indicate that the relative concentra-

$$ {}_5B^{10} + {}_0N^1_s \longrightarrow {}_3Li^7 + {}_2He^4 \qquad (1)$$

---

[1] Present address: Socony–Vacuum Oil Co., Inc., Paulsboro, N. J.

[2] Kruger, *Proc. Nat. Acad. Sci.*, **26**, 181 (1940).

[3] Zahl, Cooper and Dunning, *ibid.*, **26**, 589 (1940).

[4] Zahl and Cooper, *Science*, **93**, 64 (1941).

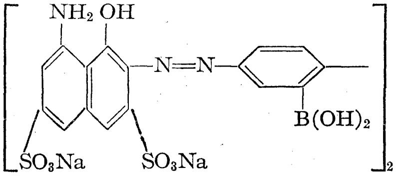
[5] Zahl and Waters, *Proc. Soc. Exper. Biol. Med.*, **48**, 304 (1941).

[6] Zahl and Cooper, *Radiology*, **37**, 673 (1941).

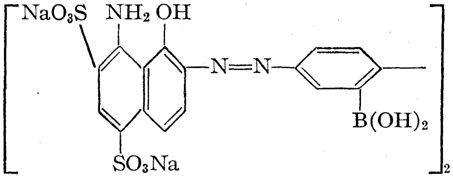
[7] Moore, Tobin and Aub, *J. Clin. Invest.*, **22**, 161 (1943).

tion of the dyes in tumors is by no means as favorable as would be required for therapeutic application. Nevertheless, the possibility remains that a more selective action might be characteristic of the proposed boron-containing dyes, and in any event they should be of value in the study of the general effects of the nuclear disintegration of boron occurring within living tissues.

The dye (I) obtained by coupling benzidine-2,2′-diboronic acid[8] with 1-amino-8-naphthol-3,6-disulfonic acid (H acid) presumably has a structure differing from that of Trypan Blue only in the presence of the two boronic acid groups in the 2 and 2′ positions of the benzidine unit instead of methyl groups in the 3 and 3′ positions. The structure of the dye was not proved, but the linkage of the azo groups at the 7 positions of the 8-naphthol residues may be assumed by analogy to other dyes prepared by coupling with H-acid under comparable conditions.[9] No displacement of boron occurred during the coupling and purification of the product (I). Since the localization of Trypan Blue depends on the fact that it forms colloidal dispersions rather than true aqueous solutions, a qualitative dialysis experiment was carried out with the dye (I); it was found to diffuse only very slowly through a membrane which was readily permeable to phenolphthalein.



I



II

The analog (II) of Evans Blue was prepared by coupling the same benzidine with 1-amino-8-naphthol-2,4-disulfonic acid (Chicago acid). This substance also contained nearly the theoretical amount of boron and it also diffused very slowly through a collodion membrane. Dyes of the expected composition likewise resulted from the coupling of the benzidinediboronic acid with β-naphthol and with acetoacetanilide. Dyes were obtained by coupling of the benzidine with 2-naphthol-3,6-disulfonic acid (R acid), 1-naphthol-4-sulfonic acid (NW acid) and β-naphthylamine, but no satisfactory analytical samples of the products have been obtained.

Dyes of higher boron content and of higher molecular weight should be available by coupling diazotized aminobenzeneboronic acids into the 2 position of I. This possibility is being tested.

Experimental

Tetrazotization of Benzidine-2,2′-diboronic Acid.—A solution of 1 g. of benzidine-2,2′-diboronic acid[8] (or 1.27 g. of the dihydrochloride) in 30 ml. of 3*N* hydrochloric acid was cooled in an ice-bath. About 8 ml. of a solution of 0.52 g. of sodium nitrite in 10 ml. of water was added in small portions with good stirring, and the solution then was tested with starch–iodide paper; if the test was negative further small portions of the nitrite solution were added until a positive test resulted. The mixture was kept cold for one-half hour during which time the positive reaction to starch–iodide was maintained by further additions of small portions of the nitrite solution, if necessary. The excess of nitrous acid then was removed by the addition of very small amounts of the benzidinediboronic acid, and the resulting solution was used immediately in a coupling reaction.

Coupling with H Acid.—The technical H acid was purified as follows: A solution of 100 g. of the technical material in 500 ml. of hot water was filtered, decolorized with 15 g. of charcoal and salted out by the addition of about 70 g. of sodium chloride to the filtrate. The material so obtained was recrystallized from the minimum volume of boiling water, and the purified material was dried in a vacuum oven at 110°.

The cold tetrazonium solution from 1 g. of the benzidinediboronic acid was added over a period of one-half hour to a cold, stirred solution of 2.36 g. of purified H acid and 5 g. of sodium carbonate in 35 ml. of 5% aqueous sodium hydroxide. The resulting mixture was cooled and stirred for two hours, after which time it was warmed to 85° and filtered. The filtrate was stirred at 85° for fifteen minutes and then treated with 35 g. of hydrated sodium acetate, added in five portions. After fifteen minutes the heating bath was removed and the stirred mixture was allowed to come to room temperature. The precipitated dye was collected, dissolved in 50 ml. of hot water and again salted out as before with 30 g. of the hydrated sodium acetate. The product so obtained was extracted ten times with portions of about 15 ml. of boiling ethanol, each extract being removed by filtration. After four to seven extractions the residual dye gave a negative test for sodium acetate.[10] The purified dye weighed 1.5 g. It was a very dark purple powder which did not melt or decompose at temperatures up to 340°. Analytical samples, dried over phosphorus pentoxide at about 95° and at 5 mm. pressure, had the composition of the trihydrate. The boron content was determined by the sodium peroxide fusion method.[11]

Anal. Calcd. for $C_{32}H_{28}O_{21}N_6B_2S_4Na_4$: C, 35.79; H, 2.61; B, 2.02. Found: C, 35.64; H, 2.89; B, 1.88.

For the dialysis test enough of the dye was added to 75 ml. of water to produce an intense purple solution and a few drops of phenolphthalein indicator solution was added. The solution was placed in a collodion bag suspended in 200 ml. of water. After one day the water remained entirely colorless, and portions of it gave the phenolphthalein color when made alkaline. Even after a week the water in the outer compartment had assumed only a very faint color.

Coupling with Chicago Acid.—Technical Chicago acid was purified in the same way as the H acid. In an experiment in which the tetrazotization, coupling and isolation of the product were carried out exactly as described above for the coupling with H acid the yield of the dye II was only 0.6 g. It appeared that the lower yield resulted from lower efficiency in the salting-out process. Other experiments in which ammonium bromide was used for the

---

[8] Snyder, Weaver and Parmerter, THIS JOURNAL, **70**, 773 (1948).

[9] Saunders, "The Aromatic Diazo Compounds," Edward Arnold and Co., London, 1936, p. 108.

[10] Hartwell and Fieser, "Org. Syn.," Coll. Vol. **II**, 1943, p. 145.

[11] Snyder, Kuck and Johnson, THIS JOURNAL, **60**, 105 (1938).

salting-out (with subsequent extraction of the product with methanol for the removal of ammonium bromide) gave about the same yield. The dye II was a very dark purple powder which did not melt or decompose at temperatures up to 340°. It rapidly imparted a purple color to water, but was insoluble in the organic solvents that were tested. Analytical samples, dried at about 95° at 5 mm., had the composition of the trihydrate. In a dialysis experiment it behaved exactly as did I.

Anal. Calcd. for $C_{32}H_{28}O_{21}N_6B_2S_4Na_4$: C, 35.79; H, 2.61; B, 2.02: Found: C, 35.76; H, 2.89; B, 1.77.

Coupling with β-Naphthol.[12]—The tetrazonium solution prepared, as described above, from 0.5 g. of benzidine-2,2′-diboronic acid was added with stirring to a cold solution of 0.54 g. of β-naphthol and 5 g. of sodium carbonate in 18 ml. of 5% aqueous sodium hydroxide. The mixture was stirred in the ice-bath for two hours and then added with stirring to 30 ml. of 5% hydrochloric acid. The mixture was diluted with 25 ml. of ethanol and filtered hot. The red solid was dissolved in the minimum amount of Cellosolve (less than 5 ml.) and the solution was diluted with 5 ml. of ethanol and filtered hot. Water was added to the filtrate until the precipitation of the dye was complete, and the mixture was boiled to coagulate the solid. The solid was collected and dried at 95° at 5 mm. About 0.2 g. of a bright red powder, easily soluble in Cellosolve, less soluble in ethanol and insoluble in water, was obtained; it decomposed at about 240°.

Anal. Calcd. for $C_{32}H_{24}O_6N_4B_2$: C, 66.01; H, 4.13; N, 9.63. Found: C, 65.99; H, 4.21; N, 9.75.

Coupling with Acetoacetanilide.—The coupling procedure was a modification of that described by Linstead and Wang.[13] The tetrazonium solution prepared from 0.64 g. of the benzidine dihydrochloride was added over a period of fifteen minutes to a stirred mixture of 0.64 g. of acetoacetanilide, 1 g. of sodium acetate and 50 ml. of 1% aqueous sodium hydroxide. The resulting mixture was stirred in an ice-bath overnight. The solid was separated by filtration and recrystallized three times from dilute ethanol. The bright yellow solid contained boron. It was insoluble in water or aqueous sodium carbonate, but soluble in 5% aqueous sodium hydroxide. It decomposed sharply at 174–175° to give a black residue which melted at 270–280°.

Anal. Calcd. for $C_{32}H_{30}N_6O_8B_2$: C, 59.29; H, 4.63; N, 12.97. Found: C, 58.87; H, 4.70; N, 12.96.

Summary

Analogs of Trypan Blue and Evans Blue have been prepared by the coupling of tetrazotized benzidine-2,2′-diboronic acid with 1-amino-8-naphthol-3,6-disulfonic acid (H acid) and with 1-amino-naphthol-5,7-disulfonic acid (Chicago acid), respectively. The dyes so obtained have the expected boron contents. Boron–containing dyes also have been prepared by coupling the benzidinediboronic acid with β-naphthol and with acetoacetanilide.

---

[12] The authors are indebted to Dr. Stanley M. Parmerter for the first experiments on this reaction.

[13] Linstead and Wang, *J. Chem. Soc.*, 807 (1937).

URBANA, ILLINOIS RECEIVED AUGUST 18, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

The Preparation of Synthetic Estrogens. I. The Synthesis of Diethylstilbestrol through the Pinacol–Pinacolone Compounds

BY KEIITI SISIDO AND HITOSI NOZAKI

Wessely[1] and others[2] have described synthetic approaches to the estrogenic diethylstilbestrol involving the use of the pinacol–pinacolone and retropinacolone rearrangements. We have carried out further investigations on this approach and have been able to improve several of the steps involved. The synthesis is outlined in the flow sheet.

Model experiments on the reduction of acetophenone and *p*-methoxyacetophenone to the pinacols using the method of Newman[3] gave the pinacols as a stereoisomeric mixture in 73 and 80% yields, respectively. With *p*-methoxypropiophenone (I) the yield of crystalline pinacol (II) was considerably lower, but after rearrangement of the crude pinacol the pinacolone (III) was obtained in 54% yield from the propiophenone (I). After reduction to carbinol (IV) and rearrangement with dilute sulfuric acid, only a small amount of crystalline product was obtained. However, heating the oily mixture with iodine in chloroform[1] effected isomerization and permitted the isolation of the dimethyl ether of diethylstilbestrol (V) in about 14% over-all yield from *p*-methoxypropiophenone (I). By further development of these procedures the yields can probably be improved.

By similar procedures starting with acetophenone we have prepared 2,3-diphenyl-2-butene in 30% over-all yield and 2,3-dianisyl-2-butene from *p*-methoxyacetophenone in 32% over-all yield.

According to a Swedish patent,[4] not accessible to us yet, diethylstilbestrol is said to be obtained from *p*-hydroxypropiophenone in an almost identical way. We have noticed in our model experiments with *p*-hydroxyacetophenone as well as with *p*-acetoxyacetophenone that the existence of free hydroxyl or acetoxyl groups hinders the smooth reaction of the pinacolic reduction.

Experimental[5]

(I) Pinacolic Reduction

2,3-Diphenyl-2,3-butanediol.—To a solution of 30 g. of acetophenone in 300 cc. of absolute alcohol and 200 cc. of dry, thiophene-free benzene were added 12 g. of alu-

---

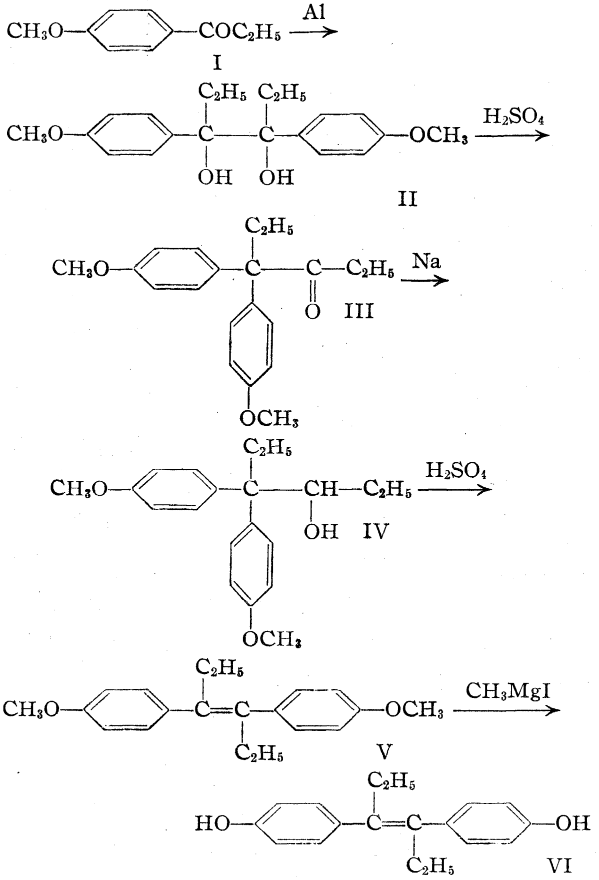
[1] Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic, *Monatsh.*, **73**, 127 (1940).

[2] For a review of these and other syntheses of diethylstilbestrol see Solmssen, *Chem. Rev.*, **37**, 481 (1945).

[3] Newman, THIS JOURNAL, **62**, 1683 (1940).

[4] Adler, Gie and von Euler, Swedish Patent No. 115,816, Feb. 12, 1946; *C. A.*, **41**, 486 (1947).

[5] Microanalyses by Miss Yasuko Meizyô of our Laboratory.



minum foil and 0.5 g. of mercuric chloride. On slight heating, a violent reaction ensued and the contents began to boil. When the reaction had subsided somewhat, the mixture was heated on a water-bath. After six hours of refluxing, the reaction product was poured over crushed ice acidified with hydrochloric acid. The top layer was separated and the bottom one extracted with benzene. The two benzene layers were combined, washed with a sodium chloride solution and dried. When the solvent was distilled off, the residue crystallized on cooling; there was obtained 22 g. of crude pinacol melting at 85–107°, which on recrystallizations from benzene–ligroin melted at 122°.

2,3-Dianisyl-2,3-butanediol.[6]—Forty grams of *p*-methoxyacetophenone[7] was subjected to the pinacolic reduction as above and the crude pinacol, m. p. 145–152°, was obtained with a yield of 32.5 g. Repeated recrystallizations from ethyl acetate gave colorless prisms melting at 159–160°. The same diol prepared by Price and Mueller[6] melted at 168–169°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.19; H, 7.66.

3,4-Dianisyl-3,4-hexanediol[1] (II).—Ten grams of *p*-methoxypropiophenone (I) was reduced in the same manner as mentioned above. As this pinacol is not easily soluble in cold benzene, the reaction product was added with 100 cc. of water and refluxed on a water-bath during an hour with stirring. The benzene layer was separated and the bottom one extracted with hot benzene. The combined benzene solution was washed with warm water and distilled without drying. The residue was crystallized from ligroin, yield 4 g., m. p. 186–190°. On repeated recrystallizations from ethyl acetate, the product formed colorless small prisms, m. p. 192–194°.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H. 7.93. Found: C, 72.31; H, 8.38.

(II) Pinacolone Rearrangement

2,2-Diphenyl-3-butanone.—To a solution of 100 cc. of concentrated sulfuric acid in 100 cc. of water was added 22 g. of 2,3-diphenyl-2,3-butanediol. The mixture was refluxed for one and a half hours under stirring, poured into iced water and extracted with ether. When the extract was distilled under reduced pressure after removing the solvent, there was obtained 13 g. of ketone, m. p. 40°, which value accorded with that of the literature.

When 30 g. of acetophenone was subjected to the pinacolic reduction, and the crude product was immediately, without separating the pinacol, treated with dilute sulfuric acid, 15 g. of the ketone, m. p. 40°, was obtained.

2,2-Dianisyl-3-butanone.[6]—Thirty-two grams of crude 2,3-dianisyl-2,3-butanediol was treated in the same manner as above, and the product was recrystallized from ethyl acetate–petroleum ether; yield was 25 g., m. p. 69–70°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.07; H, 7.09.

3,3-Dianisyl-4-hexanone (III).—From 4 g. of crude crystalline 3,4-dianisyl-3,4-hexanediol 2.3 g. of the ketone in yellowish viscous oil, b. p. 215–225° at 3 mm. was obtained.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.25; H, 7.79.

For the preparation of this ketone, it is rather profitable to treat the crude product of the pinacolic reduction, without separating the crystals of the pinacol. Thus, from 21 g. of *p*-methoxypropiophenone 11.3 g. of the ketonic oil, b. p. 224–228° at 6 mm., was obtained.

Attempts to prepare a crystalline semicarbazone or oxime of this pinacolone were unsuccessful.

(III) Reduction and Retropinacolone Rearrangement

2,3-Diphenyl-2-butene.—A mixture of 50 cc. of xylene and 10 g. of metallic sodium was heated to 140° and 10 g. of crude 2,2-diphenyl-3-butanone was added. Under violent stirring, 110 cc. of absolute alcohol was run in at such a rate that the boiling of the mixture was uniform. To the reaction product isolated in the usual way a mixture of 50 cc. of concentrated sulfuric acid and 50 cc. of water was added. After one and a half hours of heating on a boiling water-bath the content was poured over crushed ice and extracted with ether. When the product was recrystallized from alcohol, there was obtained 5.6 g. of colorless prisms, m. p. 104° in accord with the literature.

2,3-Dianisyl-2-butene.[8]—From 13 g. of 2,2-dianisyl-3-butanone, 6 g. of the product, m. p. 126–128°, was obtained.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.37; H, 7.88.

3,4-Dianisyl-3-hexene (V).—When 10 g. of oily 3,3-dianisyl-4-hexanone (IV) was reduced and the product was dehydrated as above, 1.3 g. of the crude crystals was obtained. The mother liquor was distilled *in vacuo*, and the fraction, boiling at 182–190° at 5 mm., weighing 6.5 g., was treated with 0.7 g. of iodine in 150 cc. of chloroform.[1] When this iodine treatment was repeated, there was obtained in total 2.8 g. of the hexene derivative. Recrystallization from petroleum ether gave colorless plates, m. p. 123–124°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.08; H, 8.01. Found: C, 80.69; H, 7.83.

(IV) Demethylation[9]

2,3-bis-(*p*-Hydroxyphenyl)-2-butene.[8]—To the Grignard reagent from 2 g. of magnesium and 12 g. of methyl

---

[6] Price and Mueller, THIS JOURNAL, **66**, 634 (1944), prepared the same diol by electrolytic reduction.

[7] Noller and Adams, *ibid.*, **46**, 1889 (1924).

[8] Dodds, *et al.*, *Proc. Roy. Soc.* (*London*), **B127**, 140 (1939); **B132**, 83 (1944).

[9] Kuwada and Sasagawa, *J. Pharm. Soc. Japan*, **60**, 27 (1940); U. S. Patent 2,252,696, August 19, 1941. *Cf.* Späth, *Monatsh.*, **35**, 319 (1914).

iodide was added a solution of 2 g. of 2,3-dianisyl-2-butene in 30 cc. of ether, the solvent was removed and the residue heated in an oil-bath to about 170° for forty minutes. Upon working up in the usual way, there was obtained colorless prisms, m. p. 194–196°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.93; H, 6.71. Found: C, 80.25; H, 7.08.

3,4-bis-(*p*-Hydroxyphenyl)-3-hexene (VI).—Demethylation of 2.0 g. of crude 3,4-dianisyl-3-hexene (V) gave 0.8 g. of pure diethylstilbestrol, m. p. 167–169°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.92; H, 7.07.

Summary

1. The Newman method of pinacolic reduction was applied to acetophenone, *p*-methoxyacetophenone and *p*-methoxypropiophenone. There were obtained excellent yields of the corresponding pinacols.

2. 2,3-Diphenyl-2-butene, 2,3-bis-(*p*-hydroxyphenyl)-2-butene and 3,4-bis-(*p*-hydroxyphenyl)-3-hexene were synthesized from these pinacols, improving the previous procedures.

KYÔTO, JAPAN RECEIVED MARCH 24, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

The Preparation of Synthetic Estrogens. II. The Synthesis of Hexestrol and its Homologs

BY KEIITI SISIDO AND HITOSI NOZAKI

One of the most important synthetic routes to hexestrol and related compounds involves the condensation of two molecules of *p*-α-bromopropylanisole (or the chloro derivative) with elimination of halogen. Magnesium, sodium, a Grignard reagent in the presence of cobaltous chloride, and other reagents have been used to effect the condensation.[1] All of these require the use of anhydrous conditions. According to Quelet[2] the α-halogenoalkylanisoles are more stable in the presence of moisture and accordingly a method which would not require the absence of water might have some advantages.

It is of interest that metallic iron powder is capable to act as a dehalogenating agent in the presence of water. Ogata, Turuta and Oda[3] have treated benzyl chloride, benzal chloride as well as benzo trichloride with iron powder in a large amount of hot water and obtained bibenzyl, stilbene and μ,μ′-dichlorostilbene, respectively. Model experiments on this condensation of α-chloroethylbenzene as well as of *p*-(α-chloroethyl)-anisole gave 2,3-diphenylbutane and 2,3-dianisylbutane, respectively, in 5–15% yields. With anethole hydrochloride[4] or hydrobromide the yield of the *meso* form of 3,4-dianisylhexane was 10 or 15%, respectively. It is to be pointed out that the recovered anethole was not subtracted in this calculation, as its purity was not determined. Demethylation of this product by heating with a Grignard reagent[5] gave hexestrol in good yield and in very pure state.

Although the yields realized from the present modification are not always superior to others, this method is believed to possess some merits in the simplicity and in the easy treatment, etc. The possibility of improving the yield by the use of very fine powder of iron or reduced iron in this condensation has been opened for a further research, which is now under way in our Laboratory.

Bretschneider and others[6] have prepared a metamer of hexestrol, 2,3-bis-(*p*-hydroxy-*o*-tolyl)-butane, and discovered that its estrogenic potency is of the same order as that of diethylstilbestrol or hexestrol. We have now prepared the same compound by means of our method from the hydrochloride of *p*-vinyl-*m*-methylanisole synthesized from *m*-cresol methyl ether.[7]

Experimental[8]

2,3-Diphenylbutane.—To a suspension of 12 g. of ordinary iron powder in 140 cc. of water heated at 95–98° was added with stirring 30 g. of α-chlorothylbenzene during ten minutes. The mixture was stirred for an additional three hours at the same temperature. The reaction product was extracted with benzene and the extract was fractionated. At 145–155° and 13 mm. came over 9.3 g. of colorless oil which solidified slowly. Repeated recrystallizations from alcohol yielded 3.6 g. of *meso*-2,3-diphenylbutane, m. p. and mixed m. p. 125.5°.

2,3-Dianisylbutane.—Dry hydrogen chloride was passed into a solution of 10 g. of *p*-vinylanisole containing about 10% of *o*-isomer[2,7] in 45 cc. of ligroin cooled in ice–salt mixture. The reaction solution was washed with ice-cooled water and subjected immediately to the condensation process. To a suspension of 4.2 g. of iron powder in 50 cc. of water the ligroin solution of the chloroethylanisole was added slowly with stirring at 85°. This required about thirty minutes, during which time the ligroin was removed from the vessel through a downward condenser. In the course of this, the ligroin solution contained in the dropping funnel was cooled with several pieces of crushed ice added directly in order to prevent the decomposition of the

---

(1) For a review of these and other syntheses of hexestrol see Solmssen, *Chem. Rev.*, **37**, 481 (1945).

(2) Quelet, *Compt. rend.*, **202**, 956 (1936).

(3) Ogata, Turuta and Oda, *Bull. Inst. Phys. Chem. Research (Tôkyô)*, **21**, 616 (1942) (in Japanese).

(4) Orndorff and Morton, *Am. Chem. J.*, **23**, 194 (1900). *Cf.* the fact that even the uniformity and the structure of the hydrochloride are not certain because of its unstableness.

(5) Kuwada and Sasagawa, *J. Pharm. Soc. Japan*, **60**, 27 (1940). *Cf.* U. S. Patent 2,252,696, August 19, 1941, and Späth, *Monatsh.*, **35**, 319 (1914).

(6) Bretschneider, de Jonge-Bretschneider and Ajtai, *Ber.*, **74** 571 (1941).

(7) Quelet, *Bull. soc. chim.*, **7**, 196 (1940).

(8) Microanalyses by Misses Yasuko Meizyô and Kenko Ogawa of our Laboratory.

chloro compound and to supply the water escaped together with the ligroin. The reaction mixture was heated now under an upward condenser for additional three hours at 95–98° and extracted with benzene. Fractional distillation of the product gave 4.3 g. of semi-solid mass boiling at 185–205° and 10 mm. This was recrystallized from methanol–ligroin and colorless prisms melting at 132.5–133.5° resulted. Mixtures of the product with a known sample of 2,3-dianisylbutane, which we had prepared[9] from 2,3-dianisyl-1,3-butadiene, melted without depression. As 2,3-dianisylbutane described by Dodds, *et al.*,[10] is said to have the m. p. 87–88°, our substance seems to be an isomeric compound, probably of the *meso* form.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.87; H, 8.46.

2,3-bis-(*p*-Methoxy-*o*-tolyl)-butane.—A solution of 10 g. of *p*-vinyl-*m*-methylanisole[7] in 50 cc. of ligroin was saturated with dry hydrogen chloride at -18 to $-10°$ and treated with 5 g. of iron powder in 60 cc. of water as above. After recrystallization from alcohol 1.6 g. or 16% yield of pure colorless plates of the m. p. 142° was obtained.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.91; H, 8.79.

The demethylation of the product with methylmagnesium iodide[5] yielded a free phenolic substance of m. p. 188–189° and the acetylation of the latter compound gave colorless plates of diacetate melting at 164°.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.40. Found: C, 74.67; H, 7.56.

The melting points and other properties of these substances were found to be in accord with those reported by the Hungarian investigators.[6]

3,4-Dianisylhexane.—Twenty-five grams of anethole dissolved in 110 cc. of ligroin was saturated with dry hydrogen chloride. Upon working up the product with 15 g. of iron powder in 150 cc. of water as above, 8 g. of a distillate at 180–210° and 4 mm. was obtained. The first fraction of this vacuum distillation consisted of about 12 g. of anethole which could be employed in the next batch. The product crystallized out from methanol–ligroin and recrystallizations from petroleum ether gave 2.4 g. of colorless plates, m. p. 144°, in accord with the m. p. of the *meso* compound reported in the literature.

When the same procedure was repeated with hydrogen bromide instead of the chloride, the yield of 3.8 g. was obtained.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.12; H, 8.51.

3,4-bis-(*p*-Hydroxyphenyl)-hexane (Hexestrol).—Demethylation of 3,4-dianisylhexane with a Grignard reagent yielded colorless plates, m. p. 186°, which value agreed with that of the literature.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.70; H, 8.32.

On acetylation the diacetate was obtained, m. p. 140–141°.

Acknowledgment.—In preparing these reports I and II we are indebted to the Editorial Board of This Journal for the courtesy of checking the literature references since 1941 (except those of Japan) which we are not able to obtain even now in our city.

Summary

Hexestrol and 2,3-bis-(*p*-hydroxy-*o*-tolyl)-butane were prepared by the condensation of hydrochlorides (or hydrobromide) of anethole and *p*-vinyl-*m*-methylanisole, respectively, by the action of metallic iron powder in a water suspension followed by the demethylation.

Kyôto, Japan Received March 24, 1947

---

[9] Unpublished result.

[10] Dodds, *et al.*, *Proc. Roy. Soc.* (*London*), **B132**, 83 (1944).

[Contribution from Chemical and Physical Research Laboratories, The Firestone Tire and Rubber Co.]

X-Ray Diffraction Study of Some Synthetic Rubbers at Low Temperatures

By E. E. Hanson and G. Halverson

The use of the powerful X-ray diffraction method for the study of high polymers had its inception in 1925 with the experiments of Katz[1] on natural rubber. He observed that the X-ray diffraction pattern of stretched rubber consisted of a broad halo with a superposed set of discrete spots characteristic of crystallites oriented in the direction of stretching. Hauser and Rosbaud[2] observed that the diffraction pattern of frozen unstretched rubber consisted of sharp concentric rings characteristic of a randomly oriented polycrystalline material. From such X-ray data have been determined the unit cell of the rubber crystallite,[3–7] the arrangement and the shape of the molecular segments in the unit cell and the size and shape of the rubber crystallites.[8,9] In addition, the X-ray diffraction method has yielded important information regarding the structures of a host of other polymers,[10] particularly those of the plastics and fibers, most of which give well developed fiber diagrams. Examples of synthetic rubber polymers which crystallize upon stretching are neoprene,[11] polyisobutylene,[12] and thiokol.[13] However, it is unfortunate that the majority of the synthetic rubber polymers give only an amorphous halo and therefore the X-ray diffraction method can give correspondingly little information regarding the structures of these polymers.

---

[1] J. R. Katz, *Naturwissenshaften*, **13**, 37 (1925).

[2] E. A. Hauser and P. Rosbaud, *Kautschuk*, **3**, 17 (1927).

[3] E. A. Hauser and H. Mark, *Kolloid Chem. Beihefte*, **22**, 63 (1926).

[4] H. Mark and G. von Susich, *Kolloid-Z.*, **46**, 11 (1928).

[5] W. Lotmer and V. H. Meyer, *Monatsh.*, **69**, 115 (1936).

[6] E. Sauter, *Z. physik. Chem.*, **B36**, 405 (1937).

[7] A. A. Morss, This Journal, **60**, 237 (1938).

[8] S. D. Gehman and J. E. Field, *J. Applied Phys.*, **15**, 371 (1944).

[9] Review articles covering the field are: S. D. Gehman, *Chem. Rev.*, **26**, 203 (1940); C. W. Bunn, "Advances in Colloid Science," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1946.

[10] M. L. Huggins, *J. Chem. Phys.*, **13**, 37 (1945).

[11] C. J. B. Clews, *Proc. Roy. Soc.* (*London*), **A180**, 100 (1942).

[12] C. S. Fuller, C. J. Frosch and N. R. Pape, This Journal, **62**, 1905 (1940).

[13] J. J. Trillat and R. Tertran, *Compt. rend.*, **219**, 395 (1944); *R. Chem. Tech.*, **19**, 1090 (1946).

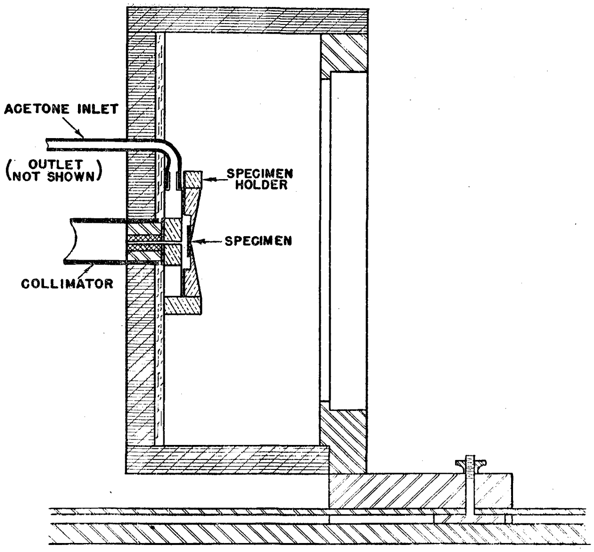


Fig. 1.—Low temperature X-ray camera.

The work to be discussed was an attempt to cause whatever regularity was present in some "non-crystalline" synthetic rubber polymers to show up in the X-ray diffraction experiment. The raw polymers were used because they can be elongated to a greater extent than the vulcanizates and because the cross-linking of molecular chains by vulcanization probably interferes with crystallization. Since the thermal motions of the molecular segments tend to prevent the relatively weak intermolecular forces from forming aggregates, the temperature of the polymer was reduced as much as possible prior to stretching. G. von Susich[14] found that the fibering of natural rubber upon stretching depended upon temperature, the amorphous fraction being favored by raising the temperature. Hauser and Mark[3] suggested freezing stretched natural rubber. In order to prevent relaxation of the elongated specimen during X-ray exposure, the specimen was frozen in an alcohol–Dry Ice bath immediately after stretching and the specimen was maintained at a temperature of −65 to −70° during the X-ray exposure. Essentially the same technique had been used in 1928 by Hock and Barth[15] in their study of polydimethylbutadiene, but their data did not permit calculations of the Bragg spacings of the diffraction lines.

The following steps were used in the manipulation of the specimens. 1. Cool the specimen to a temperature at which it may still be readily elongated. 2. Quickly stretch the sample to as high an elongation as possible. 3. Immediately freeze it at a temperature of −70° in an alcohol–Dry Ice bath, and 4. Obtain the X-ray exposure at a temperature of −65 to −70° in a special camera.

At the temperature of −65°, all of the polymers except emulsion polymerized butadiene were stiff enough to remain in their extended condition without clamping. To determine the elongation of the specimen, the length at −70° was measured, the specimen was allowed to warm up to room temperature, and the length of the relaxed sample was again measured. Conceivably, a small amount of permanent set was present in the relaxed state, and so the percentage of elongation recorded in the present data may be somewhat low.

Apparatus

A General Electric X-ray diffraction unit was used with either a copper target or a molybdenum target tube. The copper radiation was filtered by nickel foil, and the molybdenum radiation was filtered with a commercial zirconium oxide filter.

A sketch of the low temperature camera is shown in Fig. 1.

A box was made from 0.25-inch bakelite plates. One side was clamped firmly to the post supporting the collimating pinhole assembly. The film holder and the other four sides were mounted separately on a post which could be moved along the track. The five sides of the box were constructed to telescope over the sixth side (clamped to collimator assembly). Thus the specimen-to-film distance could be varied at will from 0 to 15 cm. The specimen holder consisted of a copper block with a recess cut away to receive a removable copper disc to which the specimen was clamped. The copper block was constructed with a 0.25-inch square channel, through which chilled acetone was pumped. The acetone circulating and cooling system is shown in Fig. 2. It consists of an automobile fuel pump, which was run continuously, a copper coil immersed in a Dry Ice–acetone-bath, a manually controlled needle valve for rough adjustment of the flow through the tubing by-passing the cooling coil, a second needle valve which was driven by a reversible motor controlled by a Micromax controller–recorder, and in the line a bimetallic spiral thermostat which acted as a limit switch. In this study, the automatic controls were not used because the specimen tempera-

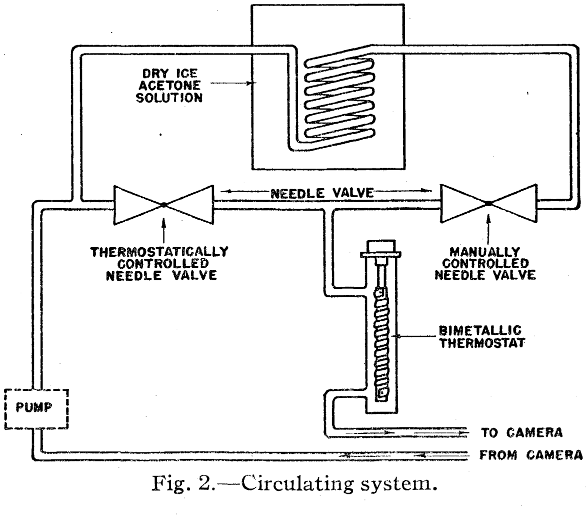


Fig. 2.—Circulating system.

---

(14) G. von Susich, *Naturwissenschaften*, **18**, 915 (1930).

(15) L. Hock and W. Barth, *Z. Physik. Chem.*, **134**, 271 (1928).

ture was kept as low as possible. The specimen temperature was measured with a thermocouple clamped in the copper block close to the path of the X-ray beam.

Results

The following polymers were studied: emulsion and sodium polymerized butadiene, emulsion polymerized 75/25 butadiene–styrene copolymer, emulsion and sodium polymerized isoprene and emulsion polymerized dimethylbutadiene. Morris and Jordon[16] found that a tread-type vulcanizate of GR-S produced weak maxima on the equator of the X-ray diagram. Hock and Barth[15] observed a crystallization of polydimethylbutadiene when the raw polymer was stretched at a low temperature, but their patterns were incomplete and no spacings were given. Evidence for the crystallization of polydimethylbutadiene was also found by Katz and van Campen.[17] They observed that the X-ray pattern of a stretched sample of an especially prepared methyl rubber vulcanizate contained a single pair of equatorial spots (d = 4.3 Å.) and two elongated arcs on the meridian (d = 3.2 and 2.3 A., respectively). No evidence has been found in the literature[18,19] to indicate that any of the other polymers listed above show any ordering in the stretched condition.[20]

Polybutadiene-emulsion Polymerized.—Figure 3 is an X-ray diffraction pattern of emulsion polymerized butadiene elongated 500% at a temperature of −70°. The very intense equatorial arcs occur at a Bragg distance of 4.06 Å. and the second pair of weak equatorial arcs at 2.33 Å. On the meridian two very weak arcs are observed at 2.26 and 1.16 Å., respectively. The two arcs were interpreted as second and fourth order reflections, respectively. The arc at 2.26 Å. could possibly be due to two unresolved spots near the meridianal axis. The limiting values for the spacings of hyperbolic layer lines that can be drawn through the arc are 4.58 and 4.8 Å. The arc at 1.16 Å. lies close to the axis and the corresponding layer line of fourth order gave an identity period of 4.8 Å. which agrees with the largest calculated value derived from the 2.26 Å. arc. Since the planar zig-zag *trans* chain has an identity period of 5.05 Å., this constitutes evidence for the *trans* structure of polybutadiene in accordance with the statements of Meyer[21] and of Mark.[22]

The equatorial spacings are interpreted as the distances between the extended molecules. Now, the equatorial spot corresponding to the larger intermolecular distance is by far the more intense of the two. The degree of this difference is indicated in Figure 4 which is an X-ray pattern taken under similar conditions but with a shorter exposure time and a greater specimen to film distance. The second equatorial arcs and the meridianal arcs would be too weak to be registered by this exposure. Therefore, it seems likely that the extended frozen polymer is composed of an appreciable percentage of amorphous material and a larger percentage of molecules which are divided into two categories of ordering: 1. By far the most numerous of the ordered molecules are lined up in the direction of stretching without forming a three-dimensional lattice. Fuller and Baker[23] refer to this type of ordering as mesomorphic. The very intense equatorial spots are due to scattering from these molecules. 2. The weak equatorial arc at 2.33 Å. and possibly another obscured by the 4.06 Å. intense arc, and the two weak meridianal arcs are due to relatively few crystallites formed of chain segments composed of all 1,4-addition butadiene presumably in the *trans* form.

X-Ray diffraction photographs were also obtained for specimens at zero elongation. At room temperature, the Bragg spacing for the point of maximum intensity of the single amorphous halo was 4.58 Å., which agrees well with Katz[24] value of 4.6 Å. for liquid butadiene. The X-ray diffraction pattern of the unstretched polymer obtained at minus 70° is shown in Fig. 5. Besides the amorphous halo, a sharper ring occurs at a distance of 4.01 Å. which agrees fairly well with the spacing observed for the most intense of the equatorial spots for the stretched specimen. (The ring survived on extraction of the specimen.) It is apparent, therefore, that at the lower temperature there are groupings of parallel molecular segments reminiscent of the smectic state in certain liquids.[21] The amorphous halo has shifted to a lower value, 4.31 Å., as would be expected from the positive coefficient of linear expansion of the polymer.

Polybutadiene—Sodium Polymerized.—A. Saffer and B. L. Johnson[25] using the perbenzoic acid addition method have determined the percentages of 1,4 groups occurring in the polymers referred to in this paper.

They found that the sodium polymer of butadiene contained 40% of 1,4 units as compared with 75% of 1,4 units for the emulsion polymer. Since side groups presumably occur at random along the chain, it is to be expected that the sodium polymer would exhibit much less ordering than the emulsion polymer. That this is true may be seen from Fig. 6 which is the X-ray diagram of the sodium

---

[16] R. E. Morris and C. B. Jordan, *Rubber Age* (*N. Y.*), **55**, 161 (1944).

[17] J. R. Katz and P. van Campen, *Chem. Ztg.*, **51**, 53 (1927).

[18] C. S. Fuller and W. O. Baker, *J. Chem. Ed.*, **20**, 3 (1943).

[19] L. B. Sebrell and A. P. Dinsmore, *R. Chem. Tech.*, **16**, 857 (1941).

[20] L. A. Wood, "Advances in Colloid Science," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1946, p. 57.

[21] K. H. Meyer, "High Polymers. Natural and Synthetic High Polymers," Vol. IV, Interscience Publishers, Inc., New York, N. Y., 1942, p. 183.

[22] H. Mark, "The Chemistry of Large Molecules," Interscience Publishers, Inc., New York, N. Y., 1943, p. 61.

[23] C. S. Fuller and W. O. Baker, *Ann. N. Y. Acad. Sci.*, **44**, 329 (1943).

[24] J. R. Katz, *Trans. Faraday Soc.*, **32**, 77 (1936).

[25] A. Saffer and B. L. Johnson, to be published in *Ind. Eng. Chem.*

polymer elongated 470% at —40°. A slight amount of alignment of molecules is observed from the pair of very weak and very extended equatorial arcs. The equatorial arcs occur at a Bragg spacing of 5.85 Å. as contrasted to the main equatorial spacing of 4.06 Å. for the emulsion polymer. The larger interchain distance for the sodium polymer would be expected from the larger amount of side groups present.

The Bragg spacing of the maximum intensity in the halo obtained from the unstretched polymer at room temperature was 5.92 Å. which is considerably higher than the value of 4.6 Å. given by Katz for the liquid monomer. This discrepancy is presumably due to the larger percentage of side groups present in the polymer.

Butadiene–Styrene Copolymer.—Figure 7 is the X-ray pattern of GR-S elongated 600% at minus 50°. The arc at the equator and the arc on the meridian appear at the same distances as for emulsion polymerized butadiene. The inference is, therefore, that polybutadiene crystallites occur in GR-S. Whether the molecules participating in the formation of these crystallites also contain styrene units outside of the crystallites is a question. No other evidence of regularity was found in the polymer.

It was found that milling the polymer tended to destroy the fiber pattern. A milling time of twelve minutes reduced the X-ray pattern to only the amorphous halo with only a slight enhancement at the equator. This may indicate that essentially pure chains of polybutadiene occur in the copolymer and that the milling process disperses them so thoroughly in the copolymer that they can no longer become associated in ordered aggregates.

Polyisoprene.—An additional factor promoting disorder in the polymer chains has been added in the case of polyisoprene, namely, the possibility of heterogeneous mixtures of head-to-head and head-to-tail additions of the monomer units. There is also the possibility of 3,4 addition. Therefore, it would be expected that these polymers would show less ordering than polybutadiene.

Figure 8 is the X-ray diffraction pattern of emulsion polymerized isoprene stretched 580% at −55°. The only sign of ordering is the weak pair of extended arcs appearing at 4.86 Å.

Figure 9 is the diffraction pattern of the sodium polymer stretched 600% at +10°. Here, too, only a weak equatorial arc appears at 6.53 Å.

The emulsion polymer contains 90% of 1,4 units and the sodium polymer 45% of 1,4 units. The inter-chain distances, therefore, increase with increasing percentages of side groups.

The room temperature X-ray patterns of the unstretched sodium and emulsion polymers consist of halos occurring at 5.95 and at 5.10 Å., respectively. The value given by Katz for the liquid isoprene halo is 4.9 Å. The agreement between the values for the monomer and for the polymer, therefore, is seen to be improved by a higher proportion of 1,4 additions in the polymer.

Polydimethylbutadiene (Emulsion).—Since polydimethylbutadiene is constructed of structurally symmetrical monomer units, the only hindrances to its regularity of structure are the presence of side groups and the possibility of mixtures of *cis* and *trans* forms. The emulsion polymer is known to be composed of about 85% 1,4 addition units. Therefore, it should exhibit a regularity of structure comparable with that of emulsion polymerized butadiene.

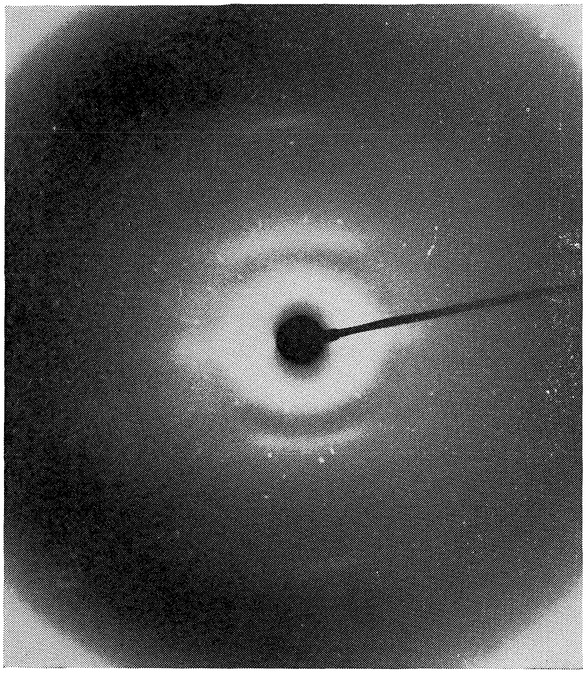
Figure 10 is the X-ray pattern for emulsion polydimethylbutadiene stretched 670% at 0°. A single strong arc is present at 5.3 Å. on the equator and three weak arcs on the meridian at 3.30, 2.24 and 1.17 Å. The 1.17 Å. arc is extremely weak and is not reproducible on a photographic print. Katz and van Campen's[17] values of 2.3 and 3.2 Å. for meridianal arcs correspond quite well with the above values, but their value of 4.3 Å. for the equatorial spot is in disagreement. Our value of 5.3 Å. for the equatorial spot agrees well with their value of 5.4 Å. for the amorphous halo.

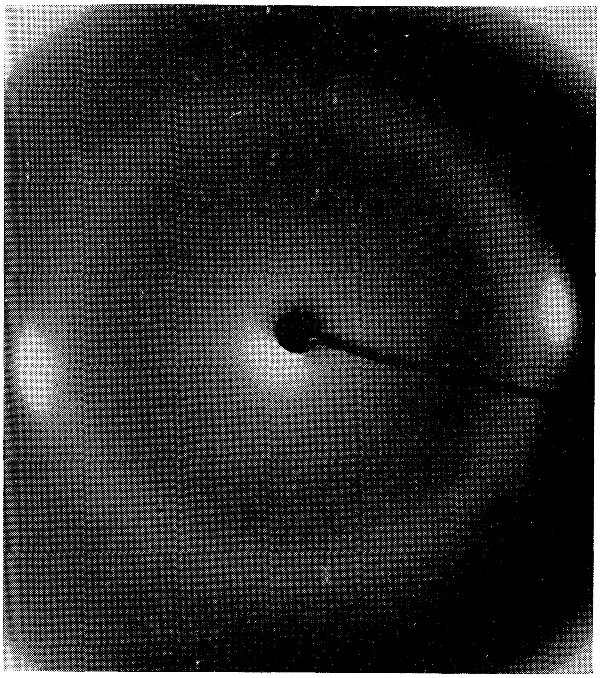
It was found that when the polymer was kept at 0° for one hundred and forty-four hours and elongated 650% the equatorial spot at 5.3 Å. was partially resolved into two spots at 4.8 and 5.8 Å. and a third extremely weak arc appeared on the equator at 3.9 Å. The same pattern could also be obtained after three or more cycles of retraction and elongation at 0° without prolonged storage at this temperature.

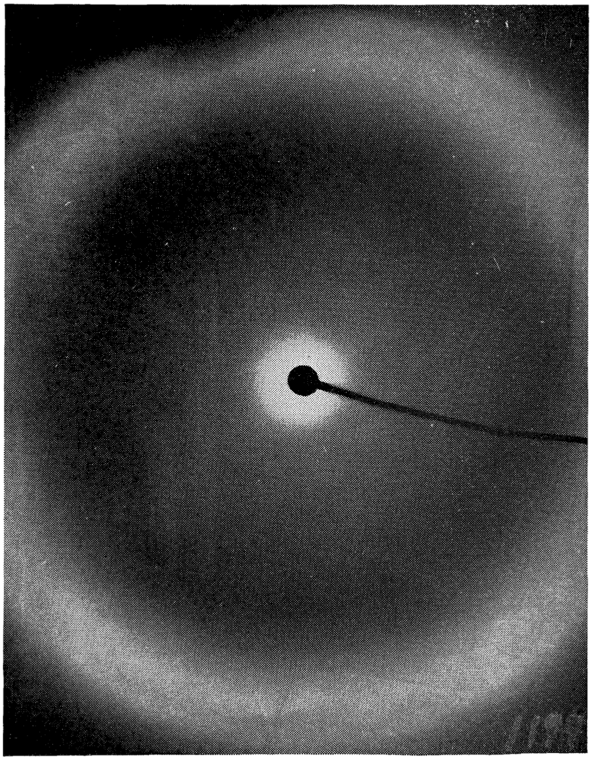
A tentative interpretation may be made of the meridianal arcs in terms of the identity period of the molecule. If the arcs occurring at the Bragg spacings of 3.30, 2.24 and 1.17 Å. are interpreted as reflections of order 2, 3 and 6, respectively, and if the possible layer-line hyperbolae are drawn through the arcs, the possible identity periods are 6.75 to 8.16, 6.72 to 8.26 and 7.38 to 9.0 Å., respectively. Therefore the values which are common to all three arcs lie between 8.16 and 7.38 Å. This would correspond to a *cis* structure for the polymer.

Since the equatorial spots are very intense, we can draw the same conclusions as we did for emulsion polybutadiene. A relatively small number of crystallites of 1,4 addition, polydimethylbutadiene, probably with a *cis* structure, exist together with a relatively large number of molecules containing side groups and which are lined up in the direction of stretch, but exhibit no other characteristics of regularity. In addition there is quite a large amount of the polymer which is amorphous in character.

The maximum in the halo obtained from the unstretched polymer at room temperature corresponds to a Bragg spacing of 5.76 Å. The value given by Katz for the liquid monomer is 5.3 Å.







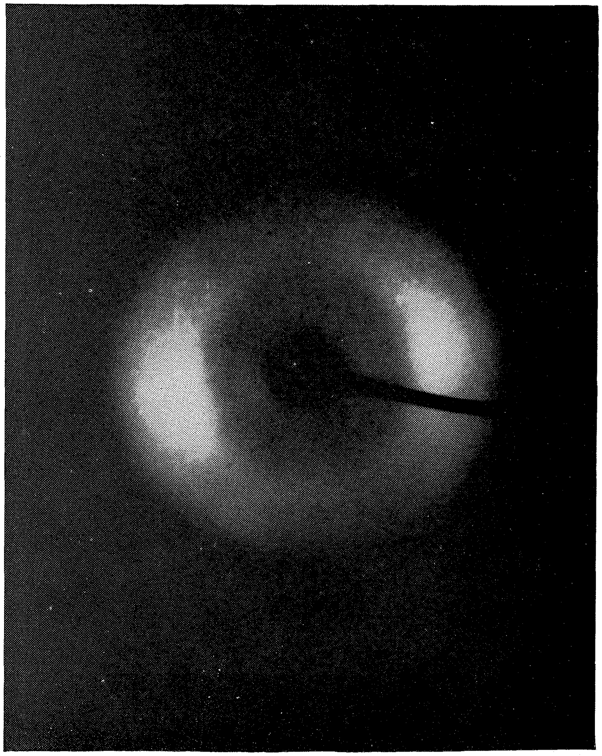
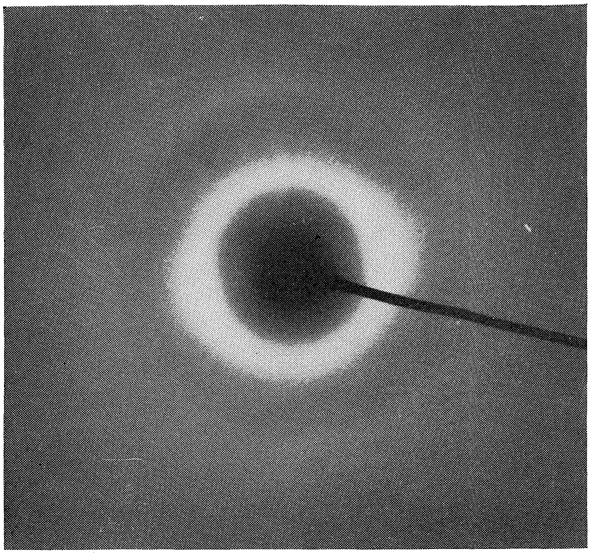
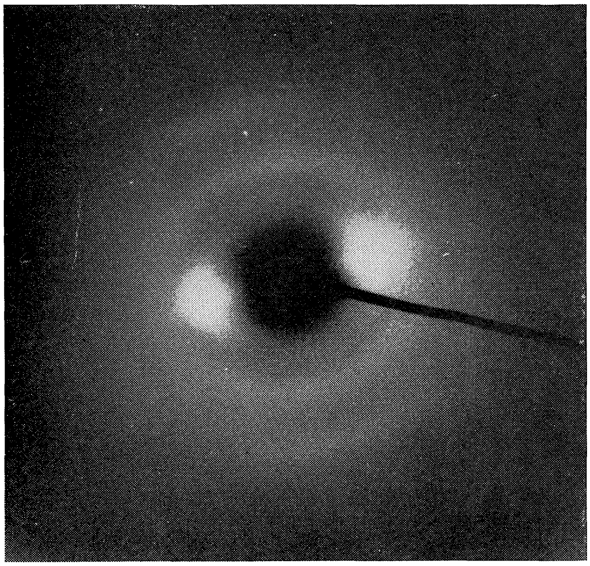


Fig. 3 (*top left*).—Emulsion polybutadiene stretched 500% at −70°. Fig. 4 (*top right*).—Emulsion polybutadiene stretched 600% at −30°. Fig. 5 (*bottom left*).—Emulsion polybutadiene—0% elongation, −70°. Fig. 6 (*bottom right*).—Sodium polybutadiene stretched 470% at −40°.





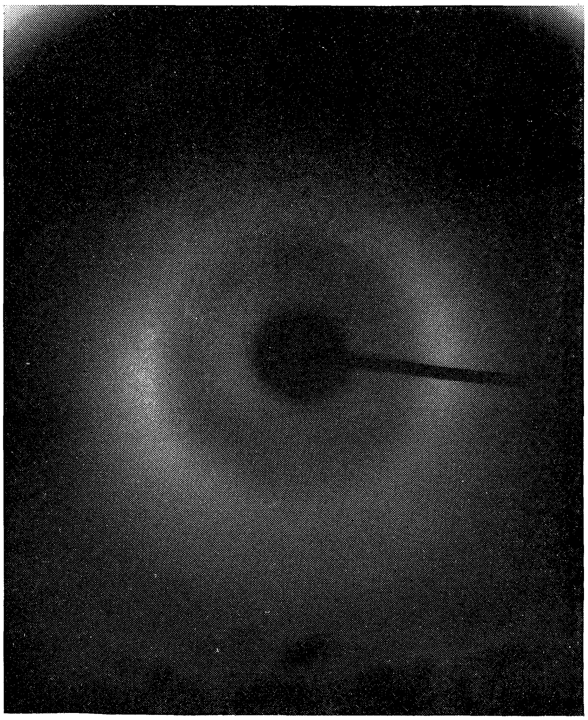


Fig. 7 (*top left*).—GR-S stretched 600% at −50°. Fig. 8 (*top right*).—Emulsion polyisoprene stretched 550% at −55°. Fig. 9 (*bottom right*).—Sodium polyisoprene—600% elongation and 10°. Fig. 10 (*center left*).—Emulsion polydimethylbutadiene—extended 670% at 0.0°. Fig. 11 (*bottom left*).—Emulsion polydimethylbutadiene, elongated 650% at 0°. Stored at 0° for one hundred and forty-four hours.

The difference is probably due to the presence of the side groups in the polymer.

Discussion

The above X-ray diagrams were not necessarily obtained under the most ideal conditions. Long, Singer and Davey[26] have shown that there is a lag in the fibering of rubber after stretching. Since the specimens were elongated by hand, it is not likely that the optimum conditions for fibering prevailed. The effects of temperature and of time will also need to be studied more thoroughly than we could in this preliminary report. However, the results obtained with the technique indicate that it has value in the study of "non-crystalline" high polymers.

The observation was made that the Bragg spacing of the halo obtained from the relaxed specimen at room temperature depended upon the quantity of side groups in the molecules. Similarly, the spacings of the equatorial arc for the stretched specimens increased with increasing percentages of side groups. These values are tabulated in Table I. It may be possible to develop a method for calculating the percentages of side groups present in the polymer from such X-ray data.

TABLE I

CORRELATION OF SIDE GROUPS WITH INTERMOLECULAR SPACING

Polymer	1,4-addition, %	Amorphous halo, Å. Polymer	Amorphous halo, Å. Monomer	Principal equatorial arc, Å.
Emulsion–butadiene	75	4.6	4.6	4.06
Sodium–butadiene	40	5.9		5.85
Emulsion–isoprene	90	5.1	4.9	4.86
Sodium–isoprene	45	6.6		6.53
Emulsion–dimethylbutadiene	85	5.7	5.3	5.30

It is not the purpose of this paper to discuss the correlation of physical properties and structures. However, it was observed that emulsion polybutadiene retained its rubber-like extensibility down to −70°, but that sodium polybutadiene was rigid at −70° and barely extensible at −60°. This constitutes evidence that increasing the side groups (and probably branching) would seem to raise the brittle point temperature. It would seem, from comparisons of the brittle points of rubber (*cis* structure), and balata (*trans* structure), that the *cis* structure should have the better cold properties. However, emulsion polybutadiene with a probable *trans* configuration has the lowest brittle point of all the rubbers.

Acknowledgments.—It is a pleasure to thank the Synthetic Rubber Group, especially Dr. R. L. Bebb, for supplying us with polymers, Dr. M. J. Brock for having the samples extracted, and Drs. B. L. Johnson, A. Saffer, F. W. Stavely and J. W. Liska for discussions of the problem.

Summary

A certain amount of ordering has been found in the "noncrystalline" synthetic rubbers which were studied by the use of the technique of cooling the raw polymer before it is elongated and freezing it immediately after stretching to prevent relaxation. Polybutadiene and polydimethylbutadiene whose monomer units were structurally symmetrical displayed the greatest degree of ordering. The presence of a high percentage of 1,2 units in sodium polymerized butadiene destroyed almost all of the ordering observed in the emulsion polymer. GR-S and emulsion polybutadiene showed the presence of small amounts of crystallites presumably of 1,4 addition polybutadiene, probably the *trans* form. Polydimethylbutadiene showed the presence of crystallites presumably of 1,4 addition in the *cis* form. The intermolecular distance between the extended chains increased with increasing amounts of side groups. The departure of the Bragg angle spacing of the amorphous halo from the corresponding quantity for the liquid monomer increased with increasing amounts of side groups.

AKRON, OHIO RECEIVED MAY 28, 1947

---

[26] J. D. Long, W. E. Singer and W. P. Davey, *Ind. Eng. Chem.*, **26**, 543 (1934).

[Contribution from General Laboratories, United States Rubber Company]

The Quantum Yield of Oxidation of Hevea Rubber and GR-S

By E. J. Hart and M. S. Matheson

I. Introduction

Little previous quantitative work has been reported on the photoöxidation of rubber even though the light aging of rubber products is a serious technological problem. Recently Bateman[1] reported the relative photoöxidation rates of highly purified rubber after fixed oxygen uptake as a function of wave length. The results show a rapid drop in quantum efficiency as the wave length increases above 3000 Å. The considerable amount of qualitative work on the effects of light on rubber, particularly in the presence of air, also show that shorter wave lengths cause more serious oxidation than the longer wave lengths. For example, Raybaud[2] found light below 4000 Å. more effective in deteriorating raw rubber than longer wave lengths, while Yamazaki[3] reports a similar result for vulcanized rubber. According to Asano[4] in the presence of oxygen an insoluble product is formed in raw rubber below 2250 Å. Above this wave length, extending to about 3130 Å., a transparent oxidized rubber resulted.

Quantum yields have been measured for the initial oxidation of rubber following the absorption by the rubber of monochromatic light over the wave length range 2537 to 17,400 Å. Purified Hevea rubber and GR-S (styrene–butadiene copolymer) were investigated.

II. Experimental Details

The quantum yields of oxygen consumption at room temperature (∼25°) were obtained by irradiating thin rubber films with monochromatic light. The oxygen absorbed by the rubber was determined by a differential method and compared with the measured amount of absorbed light.

Apparatus for Ultraviolet and Visible.—The light source was either an Hanovia 85-watt H-3 or 100-watt H-4 mercury arc, operated from a stabilized voltage supply. A fused silica jacket was cemented in place of the original glass envelope of the mercury arc for experiments at 3130 and 2537 Å. It was found that filling the silica jacket with nitrogen prolonged the arc life.

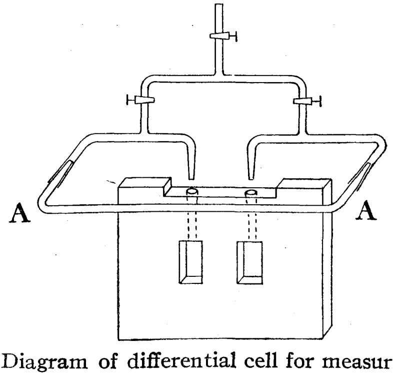


Fig. 1.—Diagram of differential cell for measuring photooxidation rates.

The various mercury lines were isolated by a Gaertner L-234 HT quartz monochromator (F/4 at 2000 Å). However, in one experiment (#15) the light from a portion of an Hanovia SC-2537 tube was focused directly on the rubber film by a quartz lens. This lamp supplies about 90% pure 2537 radiation. The impurity in this light is largely ineffective visible light and so the absorbed intensity was corrected for that fraction of the radiation passed by Pyrex.

The cell of Fig. 1 was placed directly behind the exit slit of the monochromator. This cell consists essentially of an aluminum block with two identical 1 × 2 cm. rectangular holes cut through it. The cavities were closed front and rear with Corning #791 glass windows, sealed with 0.1 mm. polyisobutylene gaskets coated with Apiezon Grease M. The absorption of oxygen by a rubber sample in one side of the cell was followed by the motion of a droplet of Amoil S in a calibrated capillary ($\sim 10^{-3}$ cc./cm.) connecting the two cavities. Barium oxide in each side absorbed any carbon dioxide or water present initially or produced during irradiation.

To measure light intensities an RCA-935 phototube in a Model 510 Electronic Photometer of the Photovolt Corp. was used. Ground quartz screens in front of the photocell diffused the incident light so that uniform response over a 1 × 2 cm. area of the ground quartz was obtained. The Photometer was calibrated against a Gaertner silver-bismuth thermopile L-234 VTBS using the monochromator and H-3 arc. This thermopile had previously been standardized against three National Bureau of Standards lamps. The photometer was corrected for non-linear response by means of an approximate point source and applying the inverse square law as the distance of the photocell from the light source was varied.

To check the photocell calibration, the photocell, H-3 arc and monochromator were used to measure the quantum yield of decomposition in an unstirred uranyl oxalate solution (0.005 M $UO_2C_2O_4$ and 0.025 M $H_2C_2O_4$). We obtained a quantum yield of 0.45 at 3660 Å. while Leighton and Forbes[5] report 0.46 in unstirred solutions of 0.01 M UO_2SO_4 plus 0.05 M $H_2C_2O_4$. According to Forbes and Heidt[6] these two actinometer solutions should give the same quantum yield.

Materials and Preparation of Films.—Deproteinized rubber[7] was prepared by an alkaline hydrolysis method. One liter of triple-creamed Hevea latex (63.3% solids) was diluted with two liters of aqueous 6% sodium hydroxide and heated and stirred eight hours per day at 70°. At night the alkaline latex was allowed to cream and the lower liquid drawn off and replaced with 4% aqueous sodium hydroxide. Ten successive heating and creaming cycles were carried out under oxygen-free nitrogen. The use of carefully purified nitrogen is necessary to avoid oxidation or degradation. After the final creaming, the latex was poured into 60 liters of distilled water and coagulated by adding one liter of 5% acetic acid with continuous stirring. The coagulum was sheeted in a calender between heavy canvas to 0.015″. Acetone extraction under nitrogen for ten days followed by five days of alcohol extraction completed the purification process. The

---

[1] L. Bateman, *Trans. Faraday Soc.*, **42**, 266 (1946).

[2] L. Raybaud, *Caoutchouc & Gutta-Percha*, 5736 (1911).

[3] T. Yamazaki, *J. Soc. Chem. Ind., Japan*, **31**, 66B (1927).

[4] K. Asano, *India Rubber. J.*, **70**, 389 (1925).

[5] W. G. Leighton and G. S. Forbes, This Journal, **52**, 3139 (1930).

[6] G. S. Forbes and L. J. Heidt, *ibid.*, **56**, 2363 (1934).

[7] Adapted from procedure of R. Pummerer and H. Pahl, *Ber.*, **60**, 2152 (1927).

purified rubber of osmotic mol. wt. 500,000–1,000,000 analyzed 0.01% nitrogen and 0.03% ash. The high molecular weight indicates little, if any, degradation occurred during purification. The rubber was stored in an evacuated desiccator containing freshly cut sodium.

The fractionation[8] of 20 g. of deproteinized rubber was carried out on a 2.4% solution of rubber in benzene. To this solution methanol was slowly added with stirring until a cloudy precipitate just appeared at room temperature. The first fraction precipitated at a methanol concentration of 17.25 weight per cent. of total solvent. The solution was heated to 45° to redissolve the precipitate and then the solution flask was placed in a thermostat at 30° overnight. The next morning if a fraction of suitable magnitude had settled in the lower layer, the upper layer was carefully decanted. (Otherwise a small amount of benzene or methanol as necessary was added, the precipitate dissolved by warming and the flask returned to the thermostat.) The lower layer was dried by evacuation in a desiccator and the solid rubber fraction obtained was stored *in vacuo* as described above. Additional methanol was added to the decanted upper layer and the fractionation cycle repeated. Redistilled reagent grade methanol and benzene were used, and except during decantation or solvent addition the rubber solution was kept in the dark under nitrogen. In this way the deproteinized rubber was separated into the five fractions of Table I.

TABLE I

YIELDS OF FRACTIONATED RUBBER

Fraction	Wt. of fraction, g.	
I	2.453	Tough
II	8.365	Medium
III	3.642	Soft
IV	2.048	Soft
V	1.820	Very soft

Fraction II resembled the whole rubber, whereas I was practically insoluble and V was yellow and tacky, possibly containing an oxidized fraction. Fraction V was contained in the solution decanted from IV and probably was degraded during the solvent removal. Solvent was removed from fractions I to IV by pumping in evacuated desiccators, while a stream of commercial nitrogen was used to evaporate solvent from Fraction V.

Films of deproteinized rubber were laid down on glass plates by evaporating 5% *n*-hexane solutions under a slow stream of purified nitrogen. The films were stored *in vacuo* in the presence of sodium until used. Fresh films were prepared every two or three weeks.

Antioxidant-free GR-S (75 parts butadiene–25 parts styrene by weight) was prepared by emulsion polymerization by the Naugatuck Chemical Company, using 0.05 part of hydroquinone as shortstop. The polymer was extracted first with cold acetone and then with cold absolute alcohol under nitrogen. GR-S films were deposited from benzene solution on cellophane covered glass plates, since the films could not be removed without tearing or distortion if they were deposited directly on glass.

Linde tank oxygen passed through Dehydrite and Ascarite was used in all photoöxidation experiments.

Procedure.—A polymer film cut to about 3 × 18 mm. was pressed upon a cell window, which was then attached to the rear of one cell cavity. During handling this 3 × 18 mm. section came in contact only with clean glass. Film thicknesses (0.4 to 2.0 mm.) were calculated from the length, width, weight and density of the film. The cell was evacuated and filled with dry oxygen to one atmosphere pressure. The initial dark rate was generally so small it could be taken as zero. During irradiation the light intensity before and behind the cell was determined. Oxygen consumption was followed during and after irradiation.

Complete details of all photoöxidation experiments appear in Table II.

Infrared Experiments.—A 1000-watt tungsten filament projection lamp was substituted for the mercury arc described above. The monochromator slit widths corresponded to a range of 0.11μ at 1.74μ and of 0.08μ at 1.0μ. For infrared work, the light in front of the cell but not behind it was measured with the calibrated thermopile. At the end of an experiment the rear window was detached and the film transmission determined.

Calculations.—Quantum yields were calculated in the same manner as those for the actinometer, except that a correction was made for the light reflected at the back of the front window of the cell and at the front surface of the rubber film. The refractive index of rubber from L. A. Wood[9] enabled the latter correction to be made.

The oxygen consumption was never followed beyond a pressure decrease of 1–2%; so the pressure was assumed to be constant at 1 atmosphere in converting volumes of absorbed oxygen to molecules absorbed.

Absorption Spectra.—The absorption spectrum of the purified rubber was photographed on a Baird 3 meter grating spectrograph, using a quartz hydrogen discharge tube as a source of continuous radiation. Optical densities were measured with an ARL–Dietert densitometer and the plates were calibrated by varying the exposure with a rotating sector. Solid films of the purified whole rubber were deposited on thin quartz plates by slow evaporation of rubber–benzene solutions. Film thickness was calculated from the weight and area of the rubber. The absorptions of three of the rubber fractions (II, III and IV) were also determined in chloroform solution. The results are shown in Fig. 2 expressed as the molecular extinction coefficient per double bond.

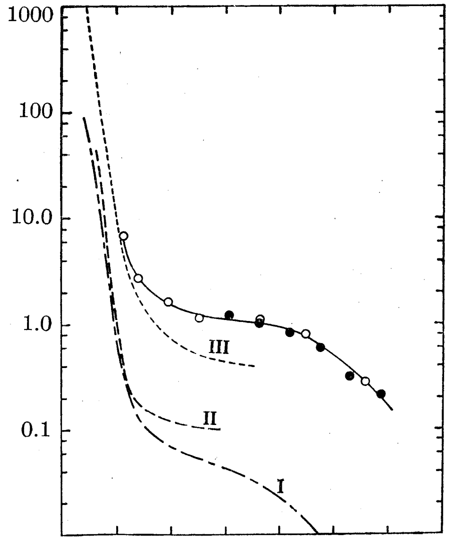


Fig. 2.—The ultraviolet absorption spectra of rubber and related olefins: I, trimethylethylene, ref. 17; II, 2,6-dimethyloctadiene-2,6, ref. 13; III, purified rubber (in cyclohexane + 10% ethyl alcohol) ref. 13; ●, purified rubber fractions II, III and IV (in chloroform)—this paper; ○, purified rubber films—this paper. $K = (1/Cl)\log_{10}(I_0/I)$ = molecular extinction coefficient, where C = moles of $>C=C<$/liter; l = centimeters depth; I_0 = incident light intensity; I = transmitted light intensity.

---

[8] Based on a technique developed by Dr. H. C. Tingey of this Laboratory.

[9] L. A. Wood, *J. Applied Phys.*, **12**, 119 (1941).

TABLE II

PHOTOÖXIDATION OF RUBBER AT ROOM TEMPERATURE AND 760 MM. OXYGEN PRESSURE[a]

Run	Polymer	λ, Å.	Polymer, g.	Thickness polymer, mm.	Light absorbed, %	Quanta absorbed by polymer/sec. × 10^{-13}	Time of exposure, min.	O_2 Absorbed during irrad. % on polymer	Rate of O_2 absorption: Initial, cu. mm./min.	Rate of O_2 absorption: Final, cu. mm./min.	Rate of O_2 absorption: Dark reac. cu. mm./min.	Quantum yields: Initial, $O_2/h\nu$	Quantum yields: Final, $O_2/h\nu$
8	Rubber	4358	0.1231	2.029	22.8	20.15	211	0.0073	(0–211) 0.015	....	(4048–5498) 0.001	(0–211) 0.03	....
9	Rubber	4358	.0733	1.34	14.5	12.23	2589	0.026	(0–181) 0.0046	(1142–2582) 0.0034	....	(0–181) 0.0146	(1142–2582) 0.012
9	Rubber	3660	.0733	1.34	27.8	18.0	212	0.078	(2600–2812) 0.0674	....	....	(2600–2812) 0.153	....
5	Rubber	3660	.0739	1.29	31.7	17.69	221	0.054	(0–221) 0.0662	....	(1274–1629) 0.006	(0–221) 0.153	....
6	Rubber	3660	.0626	1.08	27.5	14.78	191	0.057	(0–191) 0.0712	....	(1173–1413) 0.0047	(0–191) 0.197	....
7	Rubber	3660	.0584	0.964	23.0	12.27	122	0.025	0.049	....	....	(0–122) 0.163	....
7	Rubber	3130	.0584	0.964	63.1	12.99	60	0.066	0.1305	....	....	(130–190) 0.41	....
7	Rubber	3660	.0584	0.964	22.5	11.97	107	0.109	0.077	....	(1270–1723) 0.0047	(197–304) 0.26	....
1	Rubber	3130	.0296	0.45	40.1	7.26	180	0.46	(0–64) 0.1805	(154–178) 0.337	(1511) 0.0216	(0–64) 1.015	(154–178) 1.896
2	Rubber	3130	.0300	0.48	39.6	6.87	178	0.31	(0–60) 0.1141	(172–177) 0.300	(1226) 0.0225	(0–60) 0.68	(172–177) 1.79
4	Rubber	3130	.0414	0.63	49.7	9.12	180	0.21	(0–53) 0.095	(175–180) 0.28	(1184–1420) 0.0208	(0–53) 0.43	(175–180) 1.25
15	Rubber	2537	.0382	0.53	84.8	18.25	62	0.40	(0–11) 0.237	(51–62) 1.147	(1356–1528) 0.043	(0–11) 0.54	(51–62) 2.50
16	Rubber	2537	.0342	0.51	87.2	13.02	75	0.48	(0–12) 0.2365	(66–75) 0.934	(1283–1661) 0.064	(0–12) 0.78	(66–75) 2.81
19	Frac. II	3130	.0473	0.89	67.3	23.5	180	0.37	(0–22) 0.147	(160–179) 0.584	(1364–1765) 0.0668	(0–22) 0.24	(160–179) 1.095
17	Frac. III	3130	.0656	1.23	72.2	24.3	180	0.23	(0–14) 0.148	(167–179) 0.467	(1363–1682) 0.0298	(0–14) 0.23	(167–179) 0.86
18	Frac. V	3130	.0202	0.33	88.9	30.3	181	0.17	(0–19) 0.0922	(160–180) 0.063	$\sim$0	(0–19) 0.12	(160–180) 0.09
20	Rubber	17400	.0778	1.29	32	166.0	270	<0.005	....	....	None in 16 hrs.	<0.001	....
20	Rubber	10000	.0778	1.29	12	45.3	350	<0.003	....	....	....	<0.002	....
21	GR-S	10000	.0855	1.38	24	81	240	<0.005	....	....	....	<0.004	....
11	GR-S	3660	.0483	0.80	70.2	44.8–38.7	1267	0.37	(0–192) 0.0178	(1147–1265) 0.0872	(1280–1572) 0.035	(0–192) 0.0162	(1147–1265) 0.092
13	GR-S	3660	.0462	0.84	71.3	42.9	214	0.019	(0–208) 0.0162	....	....	(0–208) 0.0155	....
13	GR-S	3130	.0462	0.84	90.2	18.8	75	0.040	(220–295) 0.0497	....	(1273–1560) 0.0019	(220–295) 0.108	....
10	GR-S	3130	0.325	0.47	79.5	14.12	287	$\sim$0.11	(90–165) 0.041	(232–283) 0.071	(1265–1362) 0.005	(90–165) 0.119	(232–283) 0.204
12	GR-S	3130	.0515	0.91	91.7	21.28	283	0.094	(0–67) 0.0249	(223–282) 0.1024	(1345–1574) 0.007	(0–67) 0.05	(223–282) 0.197
12												(90–168) 0.119	
14	GR-S	2537	.0271	0.43	98.9	12.32	150	0.19	(0–28) 0.079	(122–149) 0.1017	(1176–1426) 0.0012	(0–28) 0.29	(122–149) 0.31

[a] Figures in parentheses refer to minutes elapsed from start of irradiation.

III. Results

Characteristic oxygen absorption curves as a function of time of irradiation of rubber are given in Fig. 3 for wave lengths 2537, 3130, 3660, and 4358 Å. In every case the intensity of monochromatic light incident on the rubber was kept constant within ±3%. It will be noted that an initial linear absorption occurs at 3130, 3660, and 4358 Å., whereas the absorption at 2537 Å. appears to be sharply autocatalytic from the beginning of irradiation. After about sixty minutes the rate increases autocatalytically at 3130 Å., but the rates remain constant at 3660 and 4358 Å. throughout the periods of observation. As far as the light rates at 2537 and 3130 Å. were followed they continue to increase with time of irradiation.

Fig. 4 in comparison with Fig. 3 shows that in GR-S the initial rates are lower than for rubber at 2537, 3130 and 3660 A. Further, the rates increase with time of irradiation at all these wave lengths, although at 2537 Å. the rate eventually begins to fall off again.

Diffusion of oxygen into the rubber is a factor affecting the rate of oxidation. In rubber at 3130, 3660 and 4358 Å., constant rates of oxygen absorption were apparently attained within a few minutes. However, at 2537 Å. the observed rate increases continually from the onset of irradia-

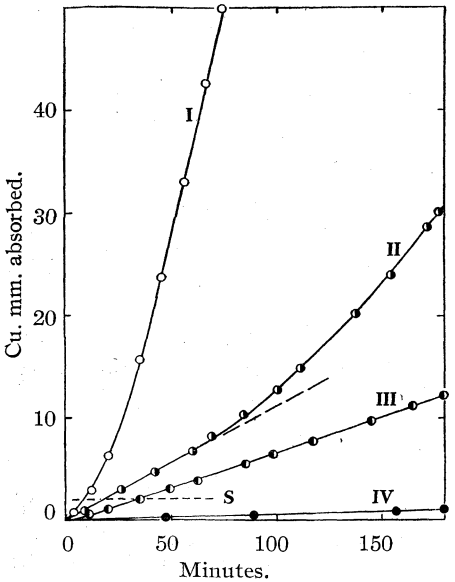


Fig. 3.—Photoöxidation of purified hevea rubber: I, Run 16 at 2537 Å. film 0.51 mm. thick; II, Run 2 at 3130 Å. film 0.48 mm. thick; III, Run 6 at 3660 Å. film 1.08 mm. thick; IV, Run 9 at 4358 Å. film 1.34 mm. thick; *S* = solubility of oxygen at 1 atmosphere pressure in 0.03 cc. of rubber (0.03 cc. = volume of irradiated rubber film 1.0 mm. thick).

tion, and the question arises whether this is due mostly to true autocatalytic effects or to a time lag in attaining a steady state.

No exact calculation has been made of the time lag required for the diffusion of oxygen into the rubber to attain, for example, 90% of a rate of oxygen consumption equal to that initially measured at 2537 Å. However, the following calculations on experiment 16 have been made:

0.0153 cc.	volume of irradiated rubber
0.00107 cc.	oxygen dissolved in irradiated rubber initially
0.000237 cc.	oxygen absorbed per minute according to initial measurement
0.000054 cc.	oxygen would diffuse into rubber per minute if diffusion occurred only through front irradiated area due to a linear concentration gradient down to zero concentration at the rear of the film.

The rate of diffusion and solubility of oxygen are calculated from the data of Barrer.[10] Comparison of the second and third figures shows that in 4.5 minutes as much oxygen flows into the rubber as was originally dissolved in the irradiated volume. This suggests that the rate of diffusion should approach the rate of reaction within a few minutes after irradiation is begun. Thus, the increasing rate may be attributed chiefly to autocatalytic effects and we will assume that at 2537 Å. also the measured rate corresponds closely to the actual rate of reaction at least in the initial stages of irradiation. Since about half the rubber film surface (including edges) which is in contact with oxygen is irradiated, it is apparent that at least half of the measured oxygen inflow must occur through the irradiated area. Comparing half of 0.000237 (the measured O_2 absorption rate) with 0.000054 (rate of O_2 absorption for linear concentration gradient) it appears that there is a high concentration gradient at the irradiated surface and that the gradient decreases in magnitude toward the rear of the sample.

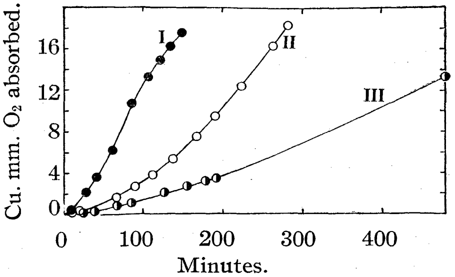


Fig. 4.—Photoöxidation of purified GR-S: I, Run 14 at 2537 Å. film 0.43 mm. thick; II, Run 12 at 3130 Å. film 0.91 mm. thick; III, Run 11 at 3660 Å. film 0.80 mm. thick.

In GR-S the observed rates in the ultraviolet always increased with time. However, since at each wave length the rate of oxygen absorption was considerably less than for rubber, it is likely that the effect of diffusion is less important in the photoöxidation of GR-S.

The quantum yields of oxidation for the measured reaction at various wave lengths of light are summarized in Table III and Fig. 5.

TABLE III

INITIAL AND THREE-HOUR QUANTUM YIELDS FOR DEPROTEINIZED RUBBER AND GR-S

λ (Å.)	Average initial yields		Average three-hour yields	
	Rubber	GR-S	Rubber	GR-S
2537	0.66	0.29	2.65[a]	0.31
3130	.51	.05	1.66	.16
3660	.17	.016	0.17	.016
4358	.02	...	.02	....
10000	..	...	.002[b]	.004[b]
17400	..	...	.001[b]	....

[a] After 1 hour. [b] Upper limits.

From Table III and Fig. 5 the following conclusions can be drawn: (a) All initial quantum yields are of the order of 1.0 or less, (b) initial and three hour quantum yields are lower for GR-S than for rubber, (c) quantum yields for rubber and GR-S decrease with increasing wave length. The initial quantum efficiency drops rapidly above 3660 Å. for rubber, and in the range above 2800 Å. for GR-S, (d) initial efficiencies are lower than the later (three-hour) yields at 2537 and 3130 Å. for both polymers. Figure 4 also shows that there is actually a slight increase at 3660 Å. for GR-S over this time interval, although the given yield is averaged over the first three hours.

Photochemical reactions in rubber not involving

---

[10] R. M. Barrer, *Trans. Faraday Soc.*, **35**, 628 (1939).

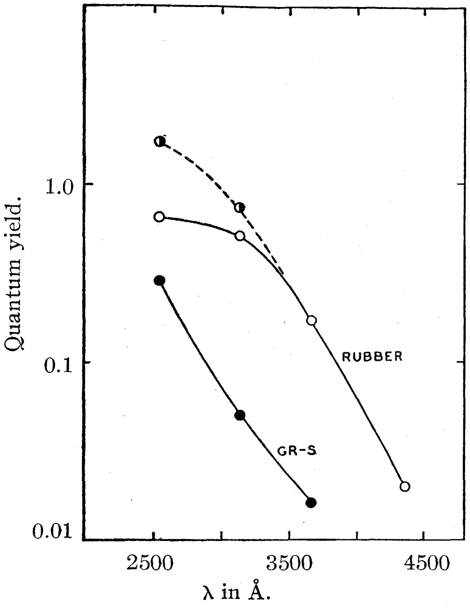


Fig. 5.—Initial quantum yields of photoöxidation as a function of wave length. The dotted line shows our best estimate of the upper limit for the quantum yields if they were measured in extremely thin films to eliminate diffusion effects.

oxygen have been studied by Bateman.[11] He measured the rates of gas formation from thoroughly degassed purified rubber when irradiated *in vacuo* in the wave length range 2300 to 4500 Å. An estimate of 4×10^{-4} was made for the quantum yield of non-condensable gas (mostly hydrogen) formation for the wave band 2300–3650. The largest relative yield reported at 2350–2850 Å. was about 2.5 times this so an upper limit of 10^{-3} may be set for the efficiency of non-condensable gas formation. From a typical experiment cited by Bateman (wave length not given), it can be calculated that the number of crosslinks formed is approximately equal to the molecules of non-condensable gas, while the number of double bonds disappearing may be as much as 100 times as large. Thus, the highest quantum yield of chemical change in rubber is not more than 0.1 in the absence of oxygen. If these calculations are permissible, chemical reactions of the rubber not involving oxygen account only in small part for the low quantum yields of oxidation.

The pale blue fluorescence excited in rubber by 3600 Å. light is visually very much weaker than the fluorescence of biacetyl. Since the strong fluorescence of biacetyl has a quantum yield of only 0.03,[12] it is concluded that fluorescence has a negligible effect in lowering the efficiency of the rubber–oxygen reaction.

The results discussed above on rubber have been obtained on unfractionated deproteinized rubber. In order to test the effects due to possible impurities in the rubber, a study was also made on the photoöxidation of Fractions II, III, and V described above under Experimental Details." The results obtained appear in Table IV.

Table IV

Quantum Yields of Oxidation of Fractions of Deproteinized Rubber at 3130 Å.

Fraction	Quantum yield Initial	Quantum yield 3-hour
II	0.24	1.095
III	.23	0.86
V	.12	0.09
Whole	.51	1.66

Fractions II and III comprise two-thirds of the whole rubber and their quantum yields are substantially the same as for the whole rubber. The somewhat lower values obtained for II and III may be partly due to diffusion effects as thicker films were used for II and III than for the whole rubber. In view of this agreement, it is concluded that the suspended and soluble impurities in the whole rubber do not greatly affect the results. The value of the quantum yield for Fraction V appears to be definitely lower than the values obtained for Fractions II and III. Fraction V shows about ten times the absorption of light as Fractions II and III which in turn are identical with the whole rubber. Fraction V therefore increased considerably in extinction coefficient during the fractionation process. The presence of these new chromophoric groups in the rubber may then be responsible for the lower quantum yield of Fraction V.

In Fig. 2 the extinction coefficient of our rubber appears to be twice that of Bateman and Koch's[13a] at 2537 Å.[13b] If their rubber corresponds to pure polyisoprene, then only half the light in our experiments is absorbed by polyisoprene. If no oxidation results from light absorbed by impurities, then the quantum yield for polyisoprene is double the measured value. If, on the other hand, the light absorbed by impurities causes considerable oxygen reaction, the initial quantum yield of pure polyisoprene may even be lower than found.

The course of the dark reaction following illumination is illustrated in Fig. 6. The dark reaction curve may be divided into three parts: a period of rapid rate decay when light is turned off, a period of apparently constant oxygen absorption, and finally a period when the dark rate begins to show the familiar autocatalysis of olefin oxidation. The initial decay could be due in part to oxidation chains of long life dying away. After irradiation was stopped, the dark rate dropped 60% in experiment 2, 75% in 16, and 50% in 12 in only five minutes and a steady state is achieved in sixty to one-hundred minutes. These results

---

[11] L. Bateman, *I. R. I. Trans.*, **21**, 118 (1945).

[12] G. M. Almy and P. R. Gillette, *J. Chem. Phys.*, **11**, 188 (1943).

[13a] L. Bateman and H. P. Koch, *J. Chem. Soc.*, 600 (1944).

[13b] Farmer, Koch and Sutton[23] give a curve for the absorption of the purified hexaisoprene, squalene, which corresponds very closely to that of our purified rubber in the region 2300–2900 Å.

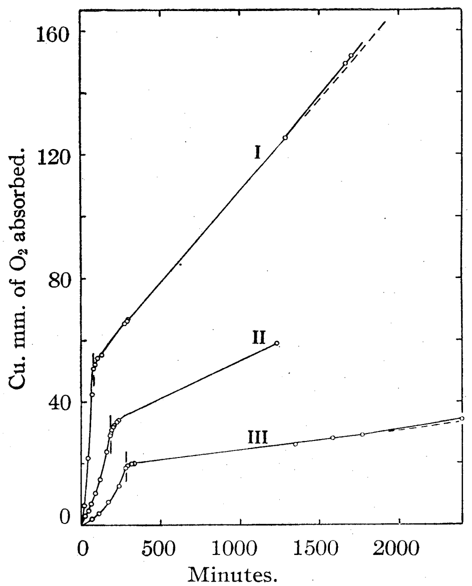


Fig. 6.—Absorption of oxygen by rubber and GR-S during and after irradiation: I, Run 16 rubber at 2537 Å.; II, Run 2 rubber at 3130 Å.; III, Run 12 GR-S at 3130 Å.; vertical lines indicate end of light exposure.

indicate that with the rubber strips used, the major portion of the change in the diffusion rate was achieved in only a few minutes. The steady dark rate after irradiation is 6–8% of the final rate in light, or much too small to account for the oxidation rate increases occurring during irradiation.

The steady dark rate is, as might be expected, approximately proportional to the amount of oxygen absorbed during illumination (Fig. 7). A similar dependence has been found for the dark rate following the chain reaction of later stages of photoöxidation.[1] It has also been found that the thermal rate of autoxidation in ethyl linoleate increases linearly with the extent of oxidation.[14] In Fig. 7, the steady thermal rate is plotted against the per cent. oxygen absorbed by the irradiated portion of the rubber at the end of illumination. This per cent. oxygen is an average value and does not take into account non-uniformity of absorbed light. Oxygen absorbed is greatest at the front surface of the sample, particularly if the extinction coefficient is high. GR-S at 2537 Å. deviates considerably and the reasons for this behavior are discussed later.

IV. Discussion of Results

Before proceeding to a discussion of the significance of these results, it is pertinent to consider the light absorption process. Carr and Walter[15] have shown that in addition to an intense absorption band (*circa* λ = 2000 Å.) unconjugated olefins possess a weak absorption tail extending to longer wave lengths. This long wave length band is shifted to the red by successive alkyl substitutions on the double bond. A simultaneous increase in intensity also occurs. The absorption band at 2000 Å. has been discussed by Mulliken[16] in terms of molecular orbitals, and has been assigned to an N → V transition involving the excitation of an "unsaturation" bonding electron of the double bond to the corresponding antibonding molecular orbital. Since this is a singlet–singlet transition, Snow and Allsopp[17] have suggested that the weak long wave absorption is the analogous singlet–triplet transition, the change in multiplicity thus accounting for the weakness of the absorption.

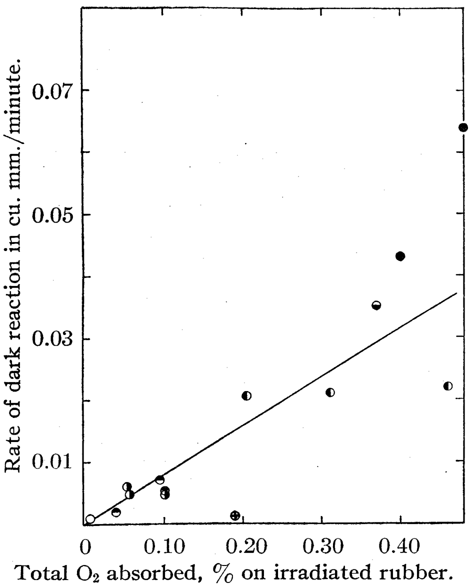


Fig. 7.—Dark reaction rates in rubber and GR-S as a function of the per cent. oxygen absorbed at the end of irradiation:

Rubber	Å.	GR-S
○	4538	
◑	3660	◒
◐	3130	◓
●	2537	⊕

Ultraviolet absorption curves are shown in Fig. 2 for trimethylethylene, 2,6-dimethyl-octadiene-2,6, and purified rubber corresponding, respectively, to one, two, and many isoprene units per molecule. Mulliken explains the red shifts of olefin spectra on alkyl substitution as due to hyperconjugation.[16,18] It is possible that the differences indicated in Fig. 2 between the spectra of mono-, di- and polyolefins are due to impurities, particularly in the case of rubber. If the differences are not due to impurities, these spectra indicate that, in addition to the alkyl substitution effect, there is an enhancement of absorp-

---

(14) J. L. Bolland and G. Gee, *Trans. Faraday Soc.*, **42**, 236 (1946).

(15) E. P. Carr and G. F. Walter, *J. Chem. Phys.*, **4**, 756 (1936).

(16) R. S. Mulliken, *Rev. Mod. Phys.*, **14**, 265 (1942).

(17) C. P. Snow and C. B. Allsopp, *Trans. Faraday Soc.*, **30**, 93 (1934).

(18) R. S. Mulliken, C. A. Rieke and W. G. Brown, THIS JOURNAL, **63**, 41 (1941).

tion in the singlet–triplet region as the number of isoprene units per molecule increases.

All ultraviolet light absorbed in these photooxidation studies is in the long wave length band region. Therefore, we may tentatively conclude that in the photoöxidation of rubber in this spectral region an unsaturation electron of the double bond is lifted by the absorption of a photon to an antibonding level. Further, this electron is not localized but takes part in considerable hyperconjugation especially with the carbon–carbon bond midway between the double bonds.

Consideration of the absorption phenomenon leads to the question of the mechanism of attack by the oxygen molecule. Farmer[19] has shown that for unconjugated olefins photoöxidation leads at room temperature or lower to very high yields of a hydroperoxide on the carbon adjacent to the unchanged double bond. However, as he points out, this product is the result of a chain reaction and does not necessarily indicate that the initial attack occurs on the α-carbon atom. Farmer[20,21] considers the idea that the oxygen molecule in the initial step of the chain adds at the double bond. The radical resulting abstracts the hydrogen from the α-carbon of another olefin unit. However, Farmer, Koch and Sutton[22] in an earlier paper suggest that molecular oxygen may initiate reaction chains by detaching hydrogen atoms from the α-carbon, at least in 1:4-polyenes.

Farmer and Sundralingam[19b] irradiated a 1% rubber solution in cyclohexane at 12° with a mercury arc. The conditions involve high intensity light with the shortest effective wavelength at about 3130 Å. An induction period of less than one hour was reported and the least oxygen uptake recorded was 0.75%. All of our measurements were taken in the induction period of Farmer and Sundralingam's work and no photoöxidation was carried beyond 0.5% oxygen uptake. Thus, the work reported in this paper is concerned with the initiation of photoöxidation in purified rubber.

The initial quantum yield of 1.0 or less suggests that the primary reaction is not a chain process, but involves the addition of molecular oxygen to an isoprene unit to form a relatively stable intermediate. At 3660 and 4358 Å. where oxidation was carried to slight extents, the quantum yield remained constant during the entire period of irradiation and exhibited none of the autocatalytic character associated with the usual peroxidation of rubber. Thus, at these longer wave lengths the lack of chain character is especially apparent. At 3130 Å. the linear rate of oxidation gives way after about an hour to an autocatalytic effect, and at 2537 Å. the rate increases from the onset of irradiation.

The presence of inhibitors as the cause of low quantum yields is ruled out because of the purity of the rubber used. Furthermore, purification of the deproteinized rubber by fractionation did not appreciably change the quantum yield at 3130 Å. An alternative explanation which we favor is that the original stable intermediate, presumably a hydroperoxide, eventually attains such a concentration that a small but definite fraction of the light is absorbed by the hydroperoxide. This absorbed light decomposes the peroxide into radicals which initiate oxidation chains. This hypothesis is in agreement with linear rates at long wave lengths where a lesser extent of oxidation occurred and an increasing rate at shorter wave lengths where higher percentages of oxygen were absorbed. Further, such an effect could be expected to be more important at shorter wave lengths where peroxides absorb more strongly. In this connection, it was found that observed changes in light absorption during irradiation were small (about 1% or less) for all rubber samples except the fractionated rubbers. At 3130, 3660, and 4358 Å. a small decrease was always observed while in runs at 2537 Å. where the autocatalytic effect was most pronounced the light absorption during irradiation increased slightly.

It seems most probable that the oxygen molecule attacks the α carbon–hydrogen in the initial step to form a relatively stable hydroperoxide. If attack occurs at the double bond, a biradical would be formed which would probably initiate oxidation chains leading to high quantum yields, unless an intramolecular stabilizing reaction generally occurred. Farmer[21] suggests such a reaction leading to an allylic hydroperoxide by double bond displacement. With regard to the energetics of the initial reaction, Bolland and Gee[23] state that either double bond or α-methylene attack by oxygen is possible from thermochemical considerations. The possibility of energy transfer from the double bond to the α-methylene group is supported by the following ideas: (1) Heidt[24] has shown in the irradiation of *d*-glycosides that such transfers are possible, (2) the activated electron is not localized but takes part in hyperconjugation with the α-methylene group, and (3) Bateman[13] has shown that solid purified rubber irradiated *in vacuo* yields a gaseous product, mostly hydrogen, and that the reaction is probably due to dissociation of the α-carbon–hydrogen bond. Thus in the absence of oxygen of sufficient concentration, the photon energy occasionally splits off a hydrogen atom, while in the presence of oxygen a more frequent reaction occurs between the activated group and the molecule of oxygen.

---

(19) (a) E. H. Farmer and D. A. Sutton, *J. Chem. Soc.*, 139 (1942); (b) E. H. Farmer and A. Sundralingam, *ibid.*, 125 (1943); (c) 121 (1942).

(20) E. H. Farmer, *I. R. I. Trans.*, **21**, 122 (1945).

(21) E. H. Farmer, *Trans. Faraday Soc.*, **42**, 228 (1946).

(22) E. H. Farmer, H. P. Koch and D. A. Sutton, *J. Chem. Soc.*, 541 (1943).

(23) J. L. Bolland and G. Gee, *Trans. Faraday Soc.*, **42**, 244 (1946).

(24) L. J. Heidt, *J. Franklin Inst.*, **234**, 473 (1942).

The GR-S was prepared with added hydroquinone as a shortstop. Subsequent acetone and alcohol extractions may not have removed all traces of this inhibitor. It is possible that the presence of hydroquinone or of quinone derived therefrom could vitiate some of the conclusions to be drawn. However, at 2537 Å. calculations using the extinction coefficients of ethyl benzene and *p*-benzoquinone show that the absorption of the phenyl groups in GR-S is many orders of magnitude greater than that of the quinone which would be present even if all of the added hydroquinone were converted to benzoquinone. At 3660 and 3130 Å., one can only say that the highest amount possible of benzoquinone accounts for only a very small fraction of the observed absorption.

The low quantum yield of oxidation of GR-S as in rubber indicates that chains do not immediately follow the primary reaction with oxygen. The phenyl group is the effective absorbing group, and it seems likely that the photon energy is not so readily transferred from the benzene nucleus to the adjacent carbon–hydrogen grouping as from the double bond in rubber. Such an effect would explain the lower quantum yields of GR-S as compared with rubber. At all three ultraviolet wave lengths GR-S shows rates increasing with time of absorption which again may be due to photodecomposition of the peroxide first formed. Due to the high extinction coefficient of GR-S, a large proportion of the oxidation will occur near the front surface of the film and near this surface the per cent. oxygen added will be much higher than the average reported in Table II. Thus sufficient peroxides for autocatalysis may be quickly formed. The discrepancy of the dark reaction in GR-S at 2537 Å. in relation to total oxygen absorbed may be due to the formation of an oxygen-impermeable surface film or to the formation of phenolic type inhibitors during oxidation. Larsen, Thorpe and Armfield[25] have shown that alkyl substituted benzenes form inhibitors during thermal oxidation at 110°.

Summary

The initial quantum yields of photoöxidation for purified Hevea rubber have been measured for various mercury arc lines in the wave length region 2537–17,400 Å. All experiments were carried out at room temperature and at an oxygen pressure of one atmosphere. At the outset of irradiation all quantum yields of combined oxygen are less than unity, although the quantum efficiency rises above 1.0 at 2537 and 3130 Å. as photoöxidation proceeds. The low quantum yield suggests that in its initial stages (less than 0.1% oxygen combined on the rubber) photooxidation is not a chain reaction. It is postulated as the first step in rubber photoöxidation that the light activated rubber group reacts with oxygen to give a relatively stable intermediate which does not immediately dissociate to give a free radical reaction chain.

The quantum yields of photoöxidation of purified GR-S were also measured under the same conditions as used for rubber. At each wave length the quantum yield was lower than for rubber, indicating formation of a stable intermediate in the initial reaction also.

[25] R. G. Larsen, R. E. Thorpe and F. A. Armfield, *Ind. Eng. Chem.*, **34**, 183 (1942).

PASSAIC, NEW JERSEY RECEIVED AUGUST 22, 1947

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Studies of Retarders and Inhibitors in the Emulsion Polymerization of Styrene. I. Retarders[1a]

BY I. M. KOLTHOFF AND F. A. BOVEY

Typical retarders of polymerization processes are defined as substances which retard the polymerization throughout the entire reaction period, without giving rise to induction periods. On the other hand, ideal inhibitors are defined as substances which cause a well-defined induction period, after which polymerization starts with its normal rate. There are substances the behavior of which is intermediate between that of compounds in either of these two classes.

Inhibitors and retarders both exert their effect by reacting with free radicals to produce reaction products which are either slow in propagating chains (oxygen is an example of this type of inhibitor) or unreactive so far as further chain propagation is concerned. The rate of reaction of inhibitors with free radicals is much greater than that of retarders. Ideal inhibitors react with such a rate that all the free radicals produced in the system are made inactive. Thus a typical induction period is observed, during which the inhibitor is consumed by reaction with the free radicals.

A typical retarder reacts with free radicals with such a rate that only a fraction of the free radicals produced can initiate normal polymerization. In addition, the growing polymer chains can react with the retarder. Thus a retarder acts as a typical chain-breaker. If this concept is correct, a retarder should reduce the molecular weight of the polymer, although this effect may not be large when effective chain transfer agents are present.

[1a] This investigation was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government's synthetic rubber program.

Also, a fraction of the retarder added to the charge should be consumed during the polymerization and should be found in the polymer.

In the literature the terms "inhibitor" and "retarder" are often used synonymously. If added in large enough quantities, a retarder will virtually prevent the start of polymerization, and if added to a polymerizing mixture will virtually stop further reaction. Such an effect may be easily confused with the occurrence of an induction period. Actually, a large amount of a retarder does not give rise to a typical induction period, but causes the polymerization to be extremely slow at the beginning, and to remain slow throughout the entire reaction period. In this respect, it is of interest that much smaller quantities of an ideal inhibitor than of a typical retarder are required to shortstop a reaction. The shortstopping effect of a small amount of an inhibitor is only temporary, the length of the period of shortstopping increasing in proportion to the quantity of inhibitor initially present.

If the rate of reaction of a substance with free radicals is intermediate between that of an ideal inhibitor and a typical retarder, such a substance will give rise to an extremely small initial rate of polymerization, this rate increasing continually with time as more and more of the substance is consumed. In the presence of such a substance, the initial reaction-time curve approaches that found in the presence of an ideal inhibitor. After an ill-defined induction period, a retarded polymerization is observed, the retardation decreasing as the reaction progresses.

If the reaction product formed by reaction of an inhibitor with free radicals during the induction period acts as a retarder, a well-defined induction period is observed, followed by a retarded polymerization. Thus, such a substance combines the effect of an ideal inhibitor and a typical retarder. Similar behavior might be expected of a compound having functional groups characteristic of both an inhibitor and a retarder (*e. g.*, a nitroquinone).

In Fig. 1 are presented time–conversion curves typical of the effects we have described.

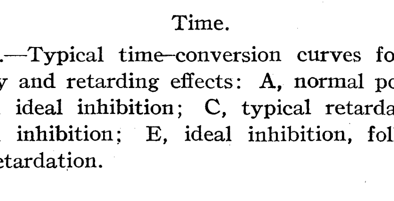


Fig. 1.—Typical time–conversion curves for various inhibitory and retarding effects: A, normal polymerization; B, ideal inhibition; C, typical retardation; D, non-ideal inhibition; E, ideal inhibition, followed by typical retardation.

No kinetic studies of the effect of retarders in emulsion polymerization are to be found in the literature. The present paper deals with the effect of retarders on the emulsion polymerization of styrene. In a subsequent paper, studies on the effect of inhibitors on the emulsion polymerization of styrene will be described.

Quite generally, the interpretation of the action of inhibitors and retarders in emulsion polymerization may be expected to be identical with that found in bulk or solution polymerizations. However, as far as the kinetics is concerned, interesting differences between bulk and solution polymerizations on the one hand and emulsion polymerization on the other may be expected under certain conditions. In emulsion polymerizations, we are dealing with typical heterogeneous systems. In order to act like a retarder, the substance must be at the locus of reaction. Thus, studies with retarders may give some insight into the locus of activation and of propagation. (See the "Discussion" section.)

Experimental Technique

Materials

***m*-Dinitrobenzene.**—A product with a melting point of 88.5–89.5° (lit. 90°) was used in part of this work. In the remainder, a sample recrystallized from ethanol (m. p. 90–91°) was employed.

3,5-Dinitrobenzoic Acid.—A product with a melting point of 201–202° uncor. (lit. 204°) was employed.

1,4-Pentadiene.—The 1,4-pentadiene used was supplied by Prof. C. S. Marvel of the University of Illinois.

Styrene.—Dow styrene with a purity of at least 99.5% was used. This material was distilled *in vacuo* just before use, although it may be safely stored for one or two days at 0 to 10°.

Water.—Conductivity water was used throughout.

Soap Flakes.—Commercial (S. F.) soap flakes (designated as S. F. flakes) supplied by Procter and Gamble were employed. This material is largely composed of the sodium salts of stearic, palmitic, and oleic acids, and contains only very small amounts of soaps of polyunsaturated fatty acids. The same lot of this material was used throughout this work.

Dodecylamine Hydrochloride.—Dodecylamine hydrochloride (designated as DDA·HCl) was prepared by neutralizing a solution of one mole of Armour dodecylamine dissolved in one liter of ethanol with concentrated hydrochloric acid, using methyl red indicator. Five hundred milliliters of ethyl ether was then added, and the hydrochloride was crystallized at about 0°, collected by suction filtration, washed with cold ether, and dried *in vacuo* for twelve hours at 25°.

Potassium Persulfate.—Reagent grade potassium persulfate was twice recrystallized from conductivity water, and the crystals dried *in vacuo* at room temperature.

Polymerization Technique.—The polymerizations were carried out in screw-cap bottles of 130-ml. capacity, sealed with pierced caps containing Buna-N self-sealing gaskets. The bottles were rotated end-over-end at about 35 r. p. m. in a thermostat and were sampled with hypodermic syringes in the same manner as described by Kolthoff and Dale.[1b] The 2-ml. samples thus obtained were expelled into weighed aluminum dishes containing 10.0 ml. of 0.02% aqueous hydroquinone solution, evaporated to dryness, and the residue dried for twenty–twenty-four hours at 80°. Per cent. conversion was calculated as previously described.[1b] The ingredients of the charge were added as described below.

(1b) I. M. Kolthoff and W. J. Dale, This Journal, **69**, 441 (1947).

Polymerization Recipe.—The following recipe, in which the amounts of several of the constituents were varied systematically, was used: styrene, 35.6 g. (39.3 ml. at 25°), designated as 100 parts; water, 65.7 ml., or 185 parts; emulsifier, 1.78 g. or 5 parts, based on the styrene. This quantity of emulsifier is designated as $1 - X$, and other quantities as fractions or multiples thereof. (Thus "$^1/_2 - X$" means 2.5 parts per 100 g. of styrene, or 0.89 g. per bottle.) When recipes containing dodecylamine hydrochloride were employed, the emulsifier was dissolved in water which had been flushed with nitrogen. No special effort was made to remove oxygen completely. Consequently, short and well-defined induction periods were observed, due to residual oxygen. In recipes with fatty-acid soap flakes, a given amount of oxygen causes a considerably larger induction period than in a dodecylamine hydrochloride recipe. To make the induction periods as short as possible, the dry soap flakes were brushed into the bottle while a current of nitrogen was passed into it, in the manner previously described.[1b] In both types of recipe, the styrene and aqueous persulfate solution were flushed with nitrogen while in the bottle. Potassium persulfate: 0.107 g. or 0.3 part, based on styrene. This quantity of persulfate is designated as $1 - X$ and other quantities as fractions or multiples thereof. The potassium persulfate was added as a solution in water. For $1 - X$ persulfate, 15.7 ml. of a 0.68% solution was added to each bottle. Retarders: the concentration of retarding substances is expressed as millimoles per 100 g. of styrene. The *m*-dinitrobenzene and 1,4-pentadiene were added as solutions in styrene. The 3,5-dinitrobenzoic acid was added as a water solution.

Experimental Results

Retardation by *m*-Dinitrobenzene.—Experiments were carried out with concentrations of *m*-dinitrobenzene varying between 0.052 and 0.830 millimole per 100 g. of styrene, employing both the DDA·HCl and soap flakes recipes. The conversion data obtained with the DDA·HCl recipe are plotted in Fig. 2, and the rates of conversion are presented in Table I. The results obtained with the soap flakes recipe are presented in Fig. 3 and Table II.

TABLE I

RATES OF POLYMERIZATION OF STYRENE AT 50° IN 1*X* DDA·HCl, 1*X* PERSULFATE RECIPE, WITH VARYING AMOUNTS OF *m*-DINITROBENZENE, EXPRESSED AS MILLIMOLES PER 100 G. OF STYRENE

Concn. *m*-dinitrobenzene	Rate of poly., % per hr.
0.0	67
.0520	19
.104	13
.208	6.5
.415	3.2
.830	1.8

TABLE II

RATES OF POLYMERIZATION OF STYRENE AT 50° IN 1*X* S. F. FLAKES, 1*X* PERSULFATE RECIPE, WITH VARYING AMOUNTS OF *m*-DINITROBENZENE, EXPRESSED AS MILLIMOLES PER 100 G. OF STYRENE

Concn. *m*-dinitrobenzene	Rate of polym., % per hr.
0.0	65
.0520	27
.104	17
.208	10
.415	6.8
.830	3.5

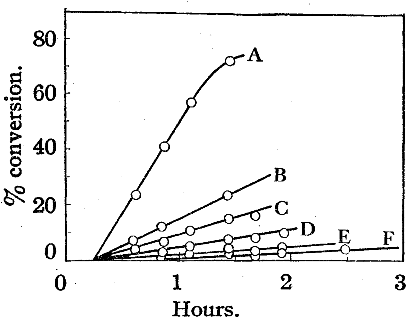


Fig. 2.—Effect of *m*-dinitrobenzene as retarder in emulsion polymerization of styrene: 1*X* dodecylamine hydrochloride, 1*X* persulfate, 50°, concentration of *m*-dinitrobenzene expressed in millimoles per 100 g. of styrene: A, 0.0; B, 0.052; C, 0.104; D, 0.208; E, 0.415; F, 0.830.

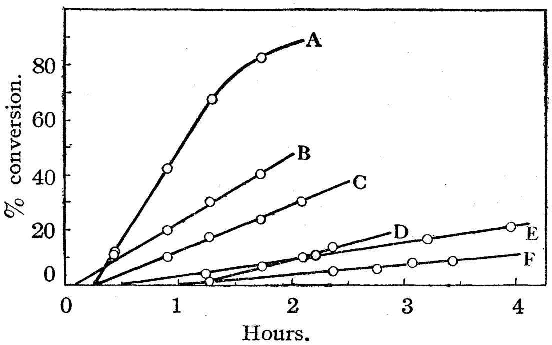


Fig. 3.—Effect of *m*-dinitrobenzene as retarder in emulsion polymerization of styrene: 1*X* S. F. flakes, 1*X* persulfate, 50°, concentration of *m*-dinitrobenzene expressed in millimoles per 100 g. of styrene: A, 0.0; B, 0.0520; C, 0.104; D, 0.208; E, 0.415; F, 0.830.

Since the smallest quantity of *m*-dinitrobenzene employed in the above experiments corresponds to only 0.0087% based on the styrene, it can be seen that *m*-dinitrobenzene is a very effective retarder. Its effectiveness is somewhat greater in the DDA·HCl recipe than in the S.F. flakes recipe. It produces no induction periods in either of the recipes, the small induction periods observed being caused by residual oxygen.

Effect of *m*-Dinitrobenzene on Molecular Weight of Polymer.—If *m*-dinitrobenzene exerts its effect in the soap micelle by terminating the growing polymer chains, the molecular weight of the polymer should be reduced. Accordingly, the experiments in Table II were repeated, the bottles being shortstopped with hydroquinone at times calculated to give approximately equal conversions in all cases. In addition, two more bottles were run, each containing 6.64 millimoles of *m*-dinitrobenzene per 100 g. styrene. These were shortstopped at 20% conversion (26 hr.) and 44% conversion (67.4 hr.). There appears in this case to be a considerable dependence of molecular weight on conversion.

The lattices obtained were coagulated with methanol and the polymer was dried *in vacuo* at 50°.

Intrinsic viscosities of 0.02% solutions in benzene were measured at 30°, using Ostwald pipets. The results obtained are summarized in Table III.

TABLE III

EFFECT OF *m*-DINITROBENZENE ON THE INTRINSIC VISCOSITY OF POLYSTRYENE, MEASURED IN BENZENE AT 30°. 1*X* SOAP FLAKES, 1*X* POTASSIUM PERSULFATE RECIPE AT 50°

Concn. retarder, millimoles per 100 g. of styrene	% conversion when shortstopped	η_i^{30}, in benzene
0	39.7	13.8
.0520	33.1	9.1
.104	36.2	7.0
.208	32.4	6.0
.415	27.9	5.2
6.64	20.0	0.95
6.64	44.0	2.14

Effect of Large Concentrations of *m*-Dinitrobenzene at Varying Concentrations of Persulfate.—Polymerizations have been carried out in the presence of 0.415, 1.660, and 6.64 millimoles of *m*-dinitrobenzene per 100 g. of styrene, using different concentrations of persulfate. Figure 4 gives plots of the logarithm of the concentration of persulfate *versus* the logarithm of the observed rates of polymerization.

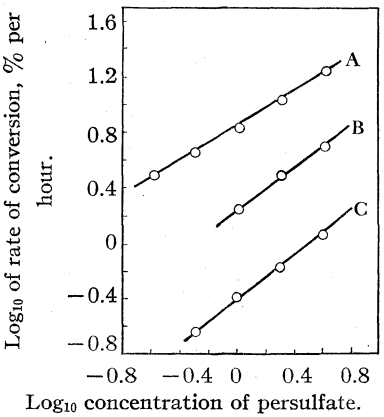


Fig. 4.—Log plots of rate of conversion *vs.* concentration of persulfate at three concentrations of *m*-dinitrobenzene, expressed in millimoles per 100 g. of styrene: A, 0.415; B, 1.66; C, 6.64.

The Disappearance of *m*-Dinitrobenzene during Polymerization.—If a retarder exerts its effect on the polymerization process by reacting with a fraction of the monomer and polymer radicals formed in the system, it appears that the retarder should become incorporated chemically into the polymer, and that the concentration of the free retarder in the reaction mixture should decrease during the polymerization. Experiments have been carried out to measure this decrease. The concentration of unconsumed *m*-dinitrobenzene was determined polarographically.

Curve A in Fig. 5 shows the reduction wave of 0.000880 *M* *m*-dinitrobenzene in 83% ethanol, the solution being 0.1 *N* in hydrochloric acid. It is seen that the reduction wave is composed of two waves, the first diffusion current being very poorly defined and not suitable for analytical purposes. On the other hand, the total diffusion current at potentials between −0.35 and −0.75 volt is well defined, and is suitable for analytical application. Assuming that the diffusion coefficient of *m*-dinitrobenzene is of the same order of magnitude as that of *p*-benzoquinone and benzaldehyde, it is found that the total diffusion current corresponds to a transfer of eight electrons per molecule. Since the height of the first wave is half that of the total wave, it may be concluded that *m*-dinitrobenzene is reduced at the dropping electrode in two steps, each corresponding to the reduction of the nitro group to a hydroxylamino group.

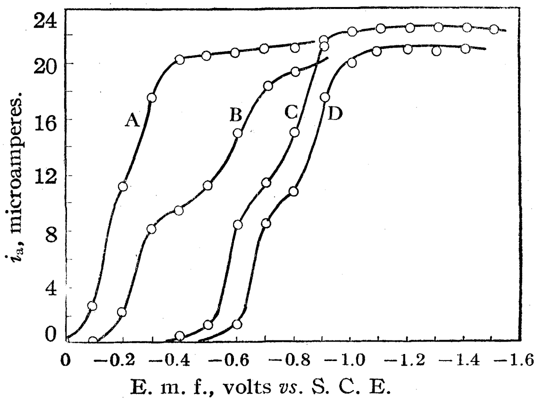


Fig. 5.—Polarographic reduction waves of 0.000880 *M* *m*-dinitrobenzene: A, in 83% ethanol, 0.1 *N* in HCl; B, same as A, but 1.5 ml. of styrene added to 25 ml. of solution in cell; C, in 90% ethanol, 0.1 *N* ammonium chloride plus ammonia, *p*H 8.5; D, same as C, but 1.5 ml. of styrene added to 25 ml. of solution in the cell.

From Curve B, it is seen that the presence of 6% styrene in the solution shifts the *m*-dinitrobenzene wave to more negative potentials, the first diffusion current becoming considerably more pronounced than in the absence of styrene. Unfortunately, the total diffusion current is no longer suitable for analytical purposes because of the appearance of the hydrogen wave.

By increasing the *p*H of the solution, the *m*-dinitrobenzene wave is displaced to more negative potentials. In Curve C is shown the wave of the nitro compound in 90% ethanol, the solution being 0.1 *M* in ammonium chloride, and containing enough ammonia to turn phenol red barely red (*p*H about 8.5). As is seen from Curves C and D the total diffusion current is now easily measurable, even though the presence of styrene shifts the wave to more negative potentials. The lowering of the diffusion current in Curve D is due entirely to dilution with styrene.

In preliminary work, about 20 g. of latex was coagulated in ethanol, and the *m*-dinitrobenzene determined. By adding known amounts of *m*-

dinitrobenzene to a 100% conversion polystyrene latex and coagulating in ethanol, it was found that a considerable amount of the *m*-dinitrobenzene was held in the coagulated polymer. Apparently the *m*-dinitrobenzene is soluble in polystyrene. After further investigation, the following procedure was adopted:

Approximately 25 g. of the latex was weighed into a 100-ml. beaker. In order to reduce the persulfate present, which interferes with the determination of the *m*-dinitrobenzene, 2.5 ml. of 6 *N* HCl and 5.0 ml. of a 5% aqueous solution of hydroxylamine hydrochloride were pipetted in. The contents of the beaker were heated to boiling to complete the reduction and allowed to cool. The polymer had now coagulated. Ammonia (about 3 *N*) was then added until phenol red turned red. The solution was decanted from the polymer through a coarse filter, the filtrate being caught in a 100-ml. volumetric flask. The polymer was washed in the beaker with alcohol and the washings were added to the filtrate. The polymer was extracted with 75 ml. of boiling 22:78 ethanol–benzene for three hours. It was established that by extracting with this solvent mixture, which swells the polymer considerably, 94% of a known quantity of *m*-dinitrobenzene added to a polystyrene latex could be recovered. To remove most of the benzene, the extracting liquid was boiled down on a steam-bath with frequent addition of ethanol. The ethanol solution was then added to the 100-ml. volumetric flask containing the filtrate, and the contents of the flask were diluted to volume with ethanol. This solution was then analyzed polarographically, using the diffusion current at −1.40 volt, and comparing to the current obtained with a known solution of *m*-dinitrobenzene in the same solvent.

This procedure was applied to a recipe containing 1*X* DDA·HCl, 1*X* persulfate, and 0.916 millimole of *m*-dinitrobenzene per 100 g. of styrene. After a reaction time of twenty-four hours, 33.5% conversion was obtained. This is a rate of about 1.4% per hour, or only about 2% of the normal rate in the absence of retarder. A control bottle containing no persulfate but the same quantities of the other ingredients was also run. No conversion occurred in this bottle.

m-Dinitrobenzene was determined after twenty-four hours in both bottles, two samples being taken from the bottle containing persulfate. The results obtained are summarized in Table IV.

TABLE IV

DISAPPEARANCE OF *m*-DINITROBENZENE DURING EMULSION POLYMERIZATION OF STYRENE, 1*X* DDA·HCl, 50°

Expt.	Concn. per sulfate	Conversion in 24 hours	Concn. *m*-dinitrobenzene, millimoles per 100 g. styrene initially present		Rate of *m*-dinitrobenzene disapp., millimoles/hour/liter of aqueous phase
			Initial	Final	
1	1*X*	33.5	0.916	0.609 0.590	0.069 0.073
2	0	0	.916	0.916	0.0

In the last column, the rate of disappearance (assumed to be linear over the twenty-four hour period) of the *m*-dinitrobenzene is expressed as millimoles per hour per liter of aqueous phase, in order to facilitate comparison with the rate of disappearance of *p*-benzoquinone (see "Discussion").

It should be noted that the quantity of *m*-dinitrobenzene that has disappeared, and which we assume to have become chemically bound into the polystyrene molecules, corresponds to a nitrogen content in the polymer of only about 0.026%. While this quantity is determinable by refined methods, the method employed in this investigation appears to be more sensitive and precise, although of course it does not directly indicate the fate of the *m*-dinitrobenzene.

Solubilization of *m*-Dinitrobenzene in Solutions of Emulsifiers.—In connection with the problem of the locus at which a retarder exerts its effect, the solubilization of *m*-dinitrobenzene in 0.14 *M* solutions of dodecylamine hydrochloride and soap flakes (corresponding approximately to "1*X*" in the standard recipe) was measured.

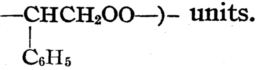
An excess (about 1 g.) of *m*-dinitrobenzene was added to 100 ml. of the emulsifier solution in a screw-cap polymerization bottle. The bottle was rotated for twenty-four hours at 50°, and then a 5.0-ml. sample was removed with a pipet (carrying a glass wool filter on the end), 2.5 ml. of 1 *M* ammonium acetate was added, and the solution diluted to 25 ml. with ethanol. The concentration of *m*-dinitrobenzene was determined polarographically. A blank, using 0.14 *M* ammonium chloride solution instead of DDA·HCl solution, was also run. The results are shown in Table V.

TABLE V

SOLUBILIZATION OF *m*-DINITROBENZENE IN G. PER 100 ML. OF SOLUTION IN 0.14 *M* SOLUTIONS OF DDA·HCl AND S. F. FLAKES

(0.14 *M* NH_4Cl)	0.14 *M* DDA·HCl	0.14 *M* S. F. Flakes
0.147	0.270	0.310
.140	.250	
	.250	

The results indicate conclusively that *m*-dinitrobenzene is solubilized in solutions of the two emulsifiers.

Combined Effect of Oxygen and *m*-Dinitrobenzene.—It has been established[2] that during the induction period caused by oxygen in the emulsion polymerization of styrene, the oxygen is consumed by copolymerizing with the styrene to produce a polymeric styrene peroxide. The rate of this copolymerization is only about 0.1% of that of the normal polymerization in the absence of oxygen. The polymer produced has an average chain length of about 40 styrene peroxide  $-(-\underset{C_6H_5}{\underset{|}{CH}}CH_2OO-)-$ units. It appeared that if this chain process were interrupted by an effective retarder, for example, *m*-dinitrobenzene, the rate of consumption of the oxygen would be decreased, and the induction period caused by a given quantity of oxygen would be prolonged.

An experiment was carried out using 1*X* S. F. flakes, 2*X* $K_2S_2O_8$ and three concentrations of *m*-

---

(2) F. A. Bovey and I. M. Kolthoff, THIS JOURNAL, **69**, 2143, (1947).

dinitrobenzene. In each bottle, 29 ml. of air and 101 ml. of liquid phase were present. The conversion curves obtained are shown in Fig. 6. It can be seen that the induction period caused by oxygen is not affected by the presence of *m*-dinitrobenzene.

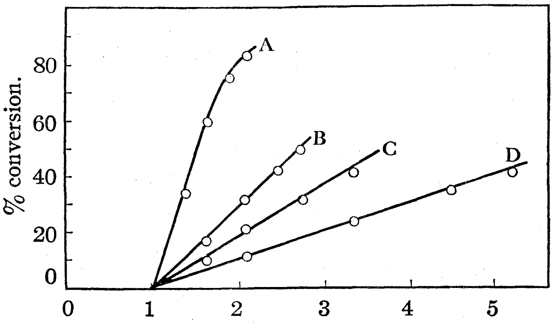


Fig. 6.—Effect of *m*-dinitrobenzene on induction period caused by 29 ml. of air per 101 ml. of charge in 1*X* S. F. flakes, 2*X* persulfate recipe, 50°; concentration of *m*-dinitrobenzene in millimoles per 100 g. of styrene: A, 0.0; B, 0.104; C, 0.208; D, 0.415.

Retardation by 1,4-Pentadiene.—This substance is an example of one type of retarder which may be encountered in commercial practice, since it is believed to occur as an impurity in technical butadiene. In addition, the structure —CH=CHCH$_2$CH=CH— which occurs in this compound also occurs in linoleic and linolenic acids. It is known from investigations carried out in this Laboratory that linoleic acid acts as an effective retarder when present as its sodium soap in commercial soap flakes. Linolenic acid has an even greater retarding effect. It was therefore of interest to compare equal molar quantities of 1,4-pentadiene and of a powerful retarder such as *m*-dinitrobenzene. In Table VI the rates of conversion with varying concentrations of 1,4-pentadiene are presented.

Table VI

Rates of Conversion with Varying Concentrations of 1,4-Pentadiene in Emulsion Polym. of Styrene at 50° 1*X* S. F. Flakes, 1*X* $K_2S_2O_8$

Concn. 1,4-pentadiene, millimoles per 100 g. styrene	Concn. 1,4-pentadiene, parts per 100 g. of styrene	Rate, %/hr.
0	0	78
0.415	0.028	74
0.830	.056	56
1.66	.113	43
3.32	.225	34

It is evident that 1,4-pentadiene is a much less effective retarder than *m*-dinitrobenzene.

3,5-Dinitrobenzoic Acid as Retarder.—If the locus at which a typical retarder, such as *m*-dinitrobenzene, exerts its effect is confined to the soap micelle and polymer particle, it appears that a compound having the structure of a retarder—for example, having two nitro groups in *meta* positions on a benzene ring—would be ineffective if it contained in addition a strongly polar functional group which confined it to the true water phase (*i. e.*, dissolved in water, but not in the micelles or in the polymer particles). Accordingly, 3,5-dinitrobenzoic acid, which has nitro groups meta to each other, was first tried in the alkaline recipe with S. F. flakes in order to compare its effect with that of *m*-dinitrobenzene. The acid is relatively strong ($K = 1.55 \times 10^{-3}$ at 25°), and at a *p*H of about 9, the concentration of free acid is vanishingly small.

In Figure 7 and Table VII are presented data for varying concentrations of 3,5-dinitrobenzoic acid in a 1*X* soap flakes, 1*X* persulfate recipe.

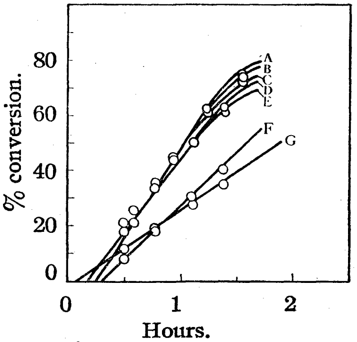


Fig. 7.—Effect of 3,5-dinitrobenzoic acid in emulsion polymerization of styrene: 1*X* S. F. flakes, 1*X* persulfate, 50°; concentration of retarder in millimoles per 100 g. of styrene: A, 0.0; B, 0.0415; C, 0.0830; D, 0.166; E, 0.332; F, 0.663; G, 1.33.

It will be observed that 3,5-dinitrobenzoic acid is very much less effective as a retarder in this recipe than an equal molar quantity of *m*-dinitrobenzene. Although the dinitrobenzoate is a very ineffective retarder, it was anticipated that the free acid would behave in a manner similar to that of *m*-dinitrobenzene, and that the retarding effect of the benzoate would increase with increasing hydrogen ion concentrations in the recipe. This was proved to be true. In Table VII are shown data obtained with a 1*X* DDA·HCl recipe in which the *p*H of the aqueous phase was made 3.3 (measured with the glass electrode) by adding acetic acid to a concentration of 0.3 *M* and sodium acetate to a concentration of about 0.03 *M*. The conversion curves are plotted in Fig. 8.

Table VII

Rates of Conversion with 3,5-Dinitrobenzoic Acid at Various *p*H's Compared to Effect of *m*-Dinitrobenzene at *p*H 9. Concn. Retarder in Millimoles per 100 G. of Styrene

Concn. of retarder → Retarder	*p*H	0	0.104	0.166	0.208	0.332	0.415	0.663	0.830	1.33
m-Dinitrobenzene	9.0	65	17	..	10	..	6.5	..	4	..
3,5-Dinitrobenzoic	9.0	65	..	58	..	58	...	40	..	30
acid	3.3	82	..	42	..	31	...	24	..	18
	1.0	66	..	21	..	11	...	4	..	1

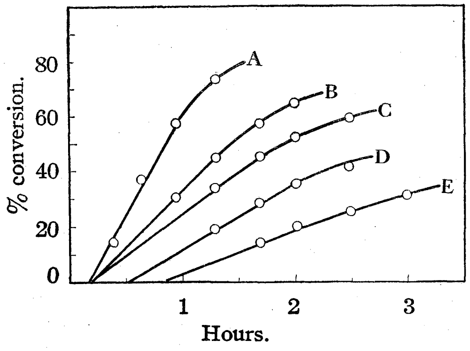


Fig. 8.—Effect of 3,5-dinitrobenzoic acid in emulsion polymerization of styrene: 1*X* S. F. flakes, 1*X* persulfate, sodium acetate–acetic acid buffer, *p*H 3.3, 50°; concentration of retarder in millimoles per 100 g. of styrene: A, 0.0; B, 0.166; C, 0.332; D, 0.663; E, 1.33.

This set of experiments was then carried out using the same recipe, except that instead of the sodium acetate–acetic acid buffer, the aqueous phase was made 0.1 *N* in hydrochloric acid, giving a measured *p*H of 1.0. The rates of conversion obtained under these conditions are also shown in Table VII, and plotted in Fig. 9.

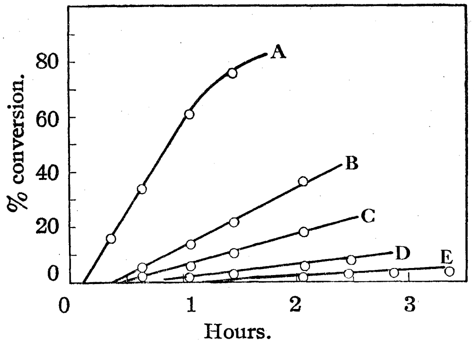


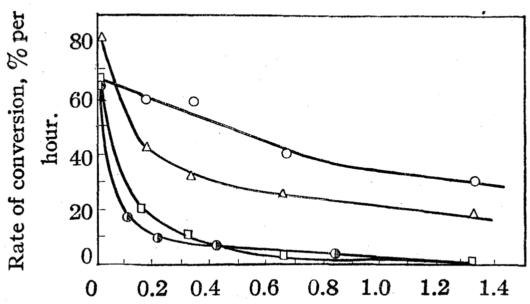
Fig. 9.—Effect of 3,5-dinitrobenzoic acid in emulsion polymerization of styrene: 1*X* dodecylamine hydrochloride, 1*X* persulfate, 0.1 *N* HCl; *p*H 1.0, 50°; concentration of retarder in millimoles per 100 g. of styrene: A, 0.0; B, 0.166; C, 0.332; D, 0.663; E, 1.33.

In Figure 10, the data of Table VII are plotted. It is evident from this plot that 3,5-dinitrobenzoic acid becomes equal in effectiveness to *m*-dinitrobenzene when the hydrogen ion concentration is high enough so that the acid is essentially un-ionized.

TABLE VIII

RATES OF CONVERSION AND INTRINSIC VISCOSITIES OF POLYSTYRENE IN PRESENCE OF 3,5-DINITROBENZOIC ACID; 1*X* $K_2S_2O_8$, 1*X* S. F. FLAKES, 0.03 *M* IN NaOH. CONCN. OF 3,5-DINITROBENZOIC ACID IN MILLIMOLES PER 100 G. OF STYRENE

Concn. of 3,5-dinitrobenzoic acid	Rate, %/hr.	η_i at 25°
0	67	13.2
1.33	46	12.0
2.65	47	12.5



Concentration of retarder, millimoles per 100 g. styrene.

Fig. 10.—Effect of 3,5-dinitrobenzoic acid at varying *p*H compared to effect of *m*-dinitrobenzene at *p*H 9: O, 3,5-dinitrobenzoic acid at *p*H 9.0; Δ, same at *p*H 3.3; □, same at *p*H 1.0; half-shaded circle, *m*-dinitrobenzene (*p*H 9).

Effect of 3,5-Dinitrobenzoate at High *p*H on Molecular Weight of Polymer.—An experiment was carried out with 1*X* $K_2S_2O_8$ and 1*X* S. F. flakes, using 1.33 and 2.65 millimoles of 3,5-dinitrobenzoic acid per 100 g. of styrene. The aqueous phase was made 0.03 *M* in NaOH. The rates of conversion and intrinsic viscosities of the polymers are shown in Table VIII.

It will be observed that, although considerable retardation is produced by these concentrations of 3,5-dinitrobenzoic acid at this high *p*H, the molecular weight of the polymer is practically unaffected.

Discussion

1. From the viewpoint of the locus of reaction, the retarding effects of 3,5-dinitrobenzoate and of 3,5-dinitrobenzoic acid are very instructive. At a *p*H of 10, all of the dinitrobenzoate may be considered to be present in ionic form, and in the "true" aqueous solution (not the soap micelles). As mentioned in previous papers,[1,2] evidence has been obtained in this Laboratory that persulfate exerts its activating effect mainly in the true aqueous phase. Therefore, at a *p*H of 10 the dinitrobenzoate reacts with a fraction of the radicals produced in the aqueous phase. However, it cannot interfere with the chain propagation reaction, which takes place in the soap micelles during the early stages of conversion and in the polymer particles in the later stages of conversion.[3]

On the other hand, at a *p*H of 1, the dinitrobenzoic acid may be considered to be entirely in the un-ionized form and to be in the styrene phase and solubilized with the styrene in the micelles. The retarding effect of the 3,5-dinitrobenzoic acid is now comparable to that of *m*-dinitrobenzene. At a *p*H of 1 these substances have no opportunity to react with the free radicals produced in the true aqueous phase, but act rather as chain-breakers at the locus of propagation.

The above interpretation is substantitated by the results obtained in the measurement of the

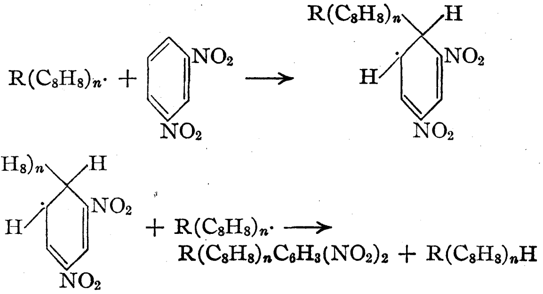
---

(3) W. D. Harkins, *J. Chem. Phys.*, **13**, 381 (1945); THIS JOURNAL, **69**, 1428 (1947).

intrinsic viscosities of the polymers. In the experimental part it has been shown that the polymer formed in the S. F. flakes recipe in the presence of dinitrobenzoate has practically the same intrinsic viscosity, and therefore molecular weight, as the polymer produced in the absence of this mild retarder. On the other hand, the molecular weight of the polymer formed is greatly reduced in the presence of *m*-dinitrobenzene in the same recipe (see Table III). It also has been shown that *m*-dinitrobenzene is solubilized in solutions of the two detergents used in this investigation. Hence this retarder should be present at the locus of the propagation reaction during the early stages of conversion. We also have shown that *m*-dinitrobenzene is soluble in the polystyrene particles. Therefore, it will also be present at the locus of the propagation reaction when the polymer particles become the locus of polymerization.

At higher concentrations of 3,5-dinitrobenzoate, some complex effects have been observed which are being studied further.

2. Following the suggestion of Price,[4] the reaction of the growing polymer chains with *m*-dinitrobenzene may be interpreted as follows



The adduct formed by addition of the radical to the aromatic ring is so much stabilized by resonance as to be unable to react further with monomer, although it can undergo disproportionation with another radical, as indicated.

The following kinetic scheme should be applicable to bulk polymerization and to emulsion polymerization in the presence of retarders. M represents monomer, C catalyst, R· a monomer or polymer radical, r the retarder, and Rr· the stabilized radical formed by addition of retarder to a monomer or polymer radical:

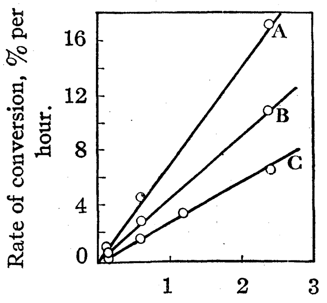


Fig. 11.—Reciprocal of *m*-dinitrobenzene concentration (millimoles per 100 g. styrene) *vs.* rate of polymerization at three concentrations of persulfate: A, 4*X*; B, 2*X*; C, 1*X*.

Initation: $M + C \longrightarrow R\cdot \qquad dR\cdot/dt = K_1(M)(C)$ (1)

Propagation: $R\cdot + M \twoheadrightarrow R\cdot$
$-dM/dt = K_2(M)(R\cdot)$ (2)

Normal termination: $2R\cdot \longrightarrow R_2$
$-dR\cdot/dt = K_3(R\cdot)^2$ (3)

Reaction with Retarder: $R\cdot + r \longrightarrow Rr\cdot$
$-dR\cdot/dt = K_4(R\cdot)(r)$ (4)

$Rr\cdot + R\cdot \longrightarrow Rr + RH$
$-dR\cdot/dt = K_5(R\cdot)(Rr\cdot)$ (5)

Where the concentration of (r) is very large, as with the three largest concentrations of *m*-dinitrobenzene, we may assume as a first approximation that termination of growing polymer chains occurs largely by (4) and (5) and that (3) may be neglected. We then have at the steady state

$$K_4(R\cdot)(r) + K_5(R\cdot)(Rr\cdot) = K_1(M)(C) \qquad (6)$$

$$-dM/dt = K_2(M)(R\cdot) = \frac{K_1K_2(M)^2(C)}{K_4(r) + K_5(Rr\cdot)} \qquad (7)$$

Also

$$K_4(R\cdot)(r) = K_5(R\cdot)(Rr\cdot), \text{ or} \qquad (8)$$
$$K_4(r) = K_5(Rr\cdot)$$

Thus instead of (7) we may write

$$-dM/dt = {}^1/_2\,\frac{K_1K_2(M)^2(C)}{K_4(r)}$$

In the presence of a separate styrene phase we find (M) constant, or

$$-dM/dt = K(C)/(r)$$

It has been well established[5] that in the normal emulsion polymerization of styrene without retarder and with persulfate as catalyst, the following relation holds

$$-dM/dt = K(C)^n$$

in which the value of *n* is 0.5. This relationship has also been repeatedly observed for bulk and solution polymerization with oil-soluble catalysts. From the slopes of the plots (Fig. 4) of the logarithm of the rate of conversion *vs.* the logarithm of the concentration of persulfate, in the presence of large concentrations of *m*-dinitrobenzene, the exponents *n* are found to be

Concn. *m*-dinitrobenzene	*n*
0.0	0.50
0.415	.63
1.660	.76
6.64	.83

As the concentration of retarder is increased the exponent *n* approaches a value of unity as predicted by the above kinetic expression. From the fact that a value of $n = 1$ is not reached, even when the rate of polymerization is less than 1% of the normal rate, it appears that even under these conditions, some normal recombination of polymer radicals (Step 3) occurs, or that the mecha-

---

[4] C. C. Price and D. A. Durham, This Journal, **65**, 757 (1943).

[5] I. M. Kolthoff and W. J. Dale, *ibid.*, **67**, 1672 (1945); C. C. Price and C. E. Adams, *ibid.*, **67**, 1674 (1945).

nism of the normal emulsion polymerization reaction needs revision.

Using the data of Tables II and Fig. 4, it is also possible to test the prediction of expression (8) that at a given persulfate concentration the rate of polymerization should be proportional to the reciprocal of the concentration of retarder at large concentrations of retarder. It is seen from Fig. 11 that this is actually the case at three different persulfate concentrations.

3. Assuming the rate of disappearance of *m*-dinitrobenzene to be constant during polymerization, we find (see Table IV) that this rate is 0.071 millimole per hour per liter of aqueous phase. In a subsequent paper, dealing with the behavior of inhibitors, it will be shown that the rate of disappearance of the ideal inhibitor *p*-benzoquinone is 0.057 millimole per hour per liter of aqueous phase in the same recipe. There is evidence, which is not conclusive, that each molecule of *p*-benzoquinone reacts with two monomer free radicals, but that this substance does not copolymerize with the styrene to any appreciable extent under the conditions of our experiments. Since the rate of disappearance of *m*-dinitrobenzene is about the same as that of *p*-benzoquinone, it is evident that *m*-dinitrobenzene does not copolymerize with styrene, and that the adduct formed by addition of the growing polymer chain to the retarder molecule is incapable of reacting with monomer.

4. From the fact that the induction period caused by oxygen is not affected by the presence of *m*-dinitrobenzene, it is evident that this substance has no retarding effect on the copolymerization of oxygen with styrene. Apparently, *m*-dinitrobenzene cannot compete effectively with oxygen for monomer free radicals, nor with monomer for the peroxide free radicals formed by reaction of monomer radicals with oxygen.

Acknowledgment.—The authors acknowledge the assistance of Miss Julie M. Schott, who performed the experiments in which rates of polymerization were measured.

Summary

An experimental study has been made of the effect of retarders on the emulsion polymerization of styrene with potassium persulfate as catalyst. It is postulated that in the presence of large concentrations of a retarder, such as *m*-dinitrobenzene, the rate of polymerization should be given by

$$-\frac{\mathrm{dM}}{\mathrm{d}t} = K\frac{(\mathrm{C})^n}{(\mathrm{r})} \quad (n = 1)$$

where (C) = concentration of catalyst
(r) = concentration of retarder

The value $n = 1$ has been approached but not attained.

m-Dinitrobenzene is nearly equally effective as a retarder in alkaline and acid recipes. It acts as a chain-breaker and reduces the molecular weight of the polymer formed. From its rate of disappearance, it is concluded that it does not act as a comonomer, but that it reacts with growing polymer chains to produce adduct radicals incapable of further chain propagation.

3,5-Dinitrobenzoate is a very ineffective retarder at a *p*H of 10, but the free acid becomes equal in effectiveness to *m*-dinitrobenzene at a *p*H of 1. The behavior of water-soluble and oil-soluble retarders is explained on the basis of the loci of the activation and propagation reactions.

Minneapolis, Minnesota Received August 1, 1947

[Contribution from the Central Experiment Station, Bureau of Mines]

The Role of Bulk Cobalt Carbide in the Fischer–Tropsch Synthesis[1]

By Sol Weller,[2] L. J. E. Hofer[2] and R. B. Anderson[2]

The Fischer–Tropsch synthesis involves formation of hydrocarbons by the passage of carbon monoxide–hydrogen mixtures over metallic catalysts, usually cobalt or iron, at elevated temperatures. With cobalt catalysts, the equation for the reaction may be written approximately as

$$x\mathrm{CO} + 2x\mathrm{H_2} = (\mathrm{CH_2})_x + x\mathrm{H_2O}$$

The hypothesis that the synthesis proceeds through the intermediate formation of a metal carbide was first suggested by Fischer and Tropsch[3] in 1926. It has been popular ever since in the scientific and the technical literature[4]; patents have even been granted based on the idea that carbiding of catalysts before synthesis is desirable.[5]

The concept of metal carbide as a synthesis intermediate has heretofore been used rather loosely. Distinction has rarely been made between bulk carbide and some sort of "surface" carbide as a possible intermediate. Craxford and Rideal,[4] for example, have done some of the important work on the mechanism of the synthesis and speak of "surface" carbide; they give as evidence for the carbide theory, however, only examples indi-

---

[1] Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. Not copyrighted.

[2] Physical chemist, Research and Development Division, Central Experiment Station, Bureau of Mines, Pittsburgh, Pa.

[3] Fischer and Tropsch, *Brennstoff Chem.*, **7**, 97 (1926).

[4] For example, Craxford and Rideal, *J. Chem. Soc.*, 1604 (1939); Eidus, *Bull. Acad. Sci. URSS*, 447 (1946).

[5] Elian, U. S. Patent 2,369,548; Atwell, U. S. Patent 2,409,235.

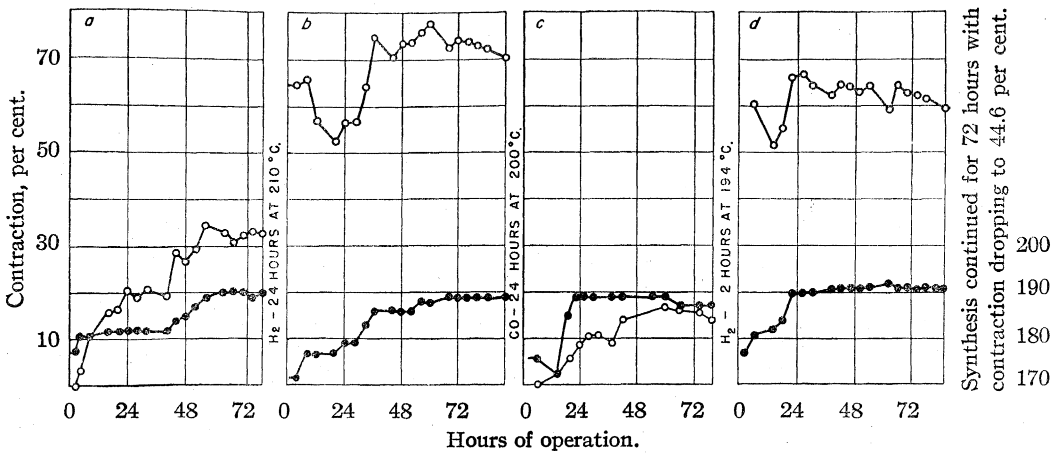


Fig. 1.—Apparent contraction ○ and temperature of operation ● *versus* time for test 73 with cobalt catalyst 108 B at atmospheric pressure. Catalyst was reduced in hydrogen at 360° and carbided with carbon monoxide at 200° for twenty-four hours prior to testing.

cating that bulk carbide accumulates in the catalyst under some conditions. The idea of "surface" carbide is a particularly elusive one, since it is very difficult to distinguish between a "surface" carbide and adsorbed carbon monoxide. The role of "surface" carbide as an intermediate in the synthesis will not be discussed here, but evidence will be presented which demonstrates that bulk carbide, in the case of cobalt catalysts, probably is neither an intermediate in the synthesis nor a catalytically active substrate for the synthesis.

Results and Discussion

Inhibition of Synthesis.—The presence of extensive amounts of carbide in cobalt catalysts severely inhibits the Fischer–Tropsch synthesis. In one experiment, for example, a cobalt–thoria–magnesia–kieselguhr (100:6:12:200) catalyst[6] was reduced with hydrogen at 400°, and carbided with carbon monoxide for twenty hours at 200°; the volume of carbon monoxide reacted was equivalent to 70% conversion of the cobalt to Co_2C. (Treatments of catalysts with hydrogen, carbon monoxide, and synthesis gas were carried out at atmospheric pressure.) Exposure of this carbided sample to circulating synthesis gas resulted in an over-all synthesis rate at 150° of 60–70 $\times 10^{-4}$ g. C/g. Co/hour. After removal of the carbide by hydrogenation at 150–194° and re-exposure of the sample to synthesis gas, a synthesis rate of 250–300 $\times 10^{-4}$ g. C/g. Co/hour was observed—an increase of 400%. The distribution of the synthesis products was about the same in both cases.

In another experiment, a sample of cobalt–thoria–kieselguhr (100:18:100) catalyst[7] was carbided in carbon monoxide at 210° to an extent equivalent to 110% Co_2C.[8] This sample was observed to have no appreciable activity in flowing synthesis gas, while a control sample, similarly reduced initially but not carbided, gave copious yields of oil and water. Partial hydrogenation of the carbided sample at 190°, with removal of 72% of the carbon which had been introduced, restored the activity to about one-half the normal value.

The loss of synthesis activity on carbiding can persist even when synthesis is continued for several days. This behavior is illustrated in Fig. 1. A sample of cobalt–thoria–kieselguhr catalyst[7] was carbided for 24 hours at 200° after initial reduction. On exposure to flowing synthesis gas at 182°, the carbided sample originally showed no catalytic activity, as measured by the fractional decrease in gas volume (contraction) as the gas passed through the converter (Fig. 1a). During operation for one day at 182°, the contraction rose to 20% but did not increase further during another eighteen hours of synthesis. Increasing the temperature to 190° increased the contraction only to 33%, even after a day. Subsequent hydrogenation of this sample at 210° and re-exposure to synthesis gas resulted in a (normal) contraction greater than 70% at 189° (Fig. 1b). Recarbiding the active catalyst for 24 hours at 200° again reduced the activity to the low value observed after the first carbiding (Fig. 1c) and rehydrogenation of the carbided sample again restored the normal activity (Fig. 1d).

This inhibitory effect of precarbiding before synthesis is not explainable as a poisoning due to free carbon deposited during the carbiding, since the effect is completely reversed by hydrogenation at temperatures where free carbon is not affected.[9] It is also known that carbiding of cobalt catalysts

---

(6) Catalyst 89J. Its preparation is described in U. S. Bureau of Mines Technical Paper 709, in press: H. H. Storch, *et al.*, "Synthetic Liquid Fuel Processes. Hydrogenation of Carbon Monoxide," Part I.

(7) Catalyst 108B; see ref. 6.

(8) The excess carbon can be accounted for as a monolayer of chemisorbed carbon monxide.

(9) Bahr and Jessen, *Ber.*, **63**, 2226 (1930); this laboratory, unpublished results.

results in the formation of not more than a monolayer of oxide or chemisorbed carbon monoxide[10]; since this is easily removed by hydrogen at 200° it might be expected to be removed by synthesis gas, and therefore to be not responsible for the inhibition. These experiments show, then, that bulk cobalt carbide is not a catalyst for the synthesis.

Bulk Carbide in Used Catalysts.—A second line of evidence which indicates that bulk cobalt carbide is not important in the synthesis is furnished by X-ray analysis of catalysts that have been used in the synthesis. It has previously been shown[11] that, on low-temperature carburization with carbon monoxide, reduced cobalt catalysts form a carbide, Co_2C, which has a characteristic X-ray diffraction pattern. This fact provides a means of identifying cobalt carbide in the catalyst. It has been observed by X-ray analysis that, if catalyst samples are partly carbided before synthesis and then used in synthesis, carbide is still present in the samples even after several days of synthesis. (In pure hydrogen, the carbide would have been completely removed as methane in several hours.) On the other hand, if the samples are used in the synthesis immediately after reduction (that is, no precarbiding), no carbide is found at the conclusion of the synthesis. In other words, bulk carbide apparently is not built up during steady-state synthesis in quantity sufficient to be detected by X-ray analysis, while carbide already present apparently is not removed at an appreciable rate during steady-state synthesis. Although quantitative determinations of the amount of carbide present under given conditions have yet to be made, the indication is that bulk carbide is neither formed nor destroyed as part of the synthesis process.

Cobalt in Used Catalysts.—The final evidence to be adduced in connection with the role of bulk carbide is also based on X-ray diffraction analysis. Cobalt in catalysts reduced at 400° is present primarily as face centered cubic cobalt.[11,12] There is a transition between face centered cubic cobalt and hexagonal close packed cobalt at about 400°.[13,14] The transition is very sluggish and there is an unusual type of disorder in the hexagonal structure near the transition point.[15] At the temperature of the Fischer–Tropsch synthesis on cobalt–thoria–kieselguhr catalysts (225° and below), the cubic cobalt is thermodynamically unstable with respect to the hexagonal close packed cobalt. Carbiding of the reduced sample containing cubic cobalt, followed by hydrogenation of the carbide so formed, both at 200°, always converts the cobalt to the low-temperature stable, hexagonal close packed form.[11] Now, all samples of cobalt catalysts (not precarbided) which have been examined after use in the synthesis have given a diffraction pattern identical with that of the freshly reduced catalyst. If any appreciable quantity of the cobalt had been through the cycle of carbiding and hydrogenation *at any time* during the synthesis, it would have appeared as close packed hexagonal cobalt rather than cubic.[16] Since this does not occur, it follows that, within the limits of the X-ray method, cobalt was not converted to bulk carbide and subsequently hydrogenated during the synthesis, that is, bulk carbide is not an intermediate in the synthesis.

Summary

Evidence is presented that for cobalt catalysts, bulk cobalt carbide is neither an intermediate in the Fischer–Tropsch synthesis nor a catalytically active substrate for the synthesis:

1. The presence of extensive amounts of carbide in cobalt catalysts severely inhibits the Fischer–Tropsch synthesis.
2. Used catalysts show no carbide by X-ray analysis, but samples carbided before synthesis show carbide to be present after synthesis.
3. The low-temperature unstable cubic cobalt produced by reduction of cobalt catalysts is not converted to hexagonal cobalt during the synthesis, although carbiding and subsequent hydrogenation of a reduced catalyst always results in this conversion.

PITTSBURGH 13, PENNSYLVANIA RECEIVED JULY 2, 1947

---

[10] This laboratory, unpublished results.

[11] Hofer and Peebles, THIS JOURNAL, **69**, 2497 (1947).

[12] The expected 200 line in the powder pattern of the reduced cobalt is almost entirely absent as has been previously mentioned.[11] A detailed discussion of this unusual diffraction pattern will be published. However, the unusual diffraction pattern of the cubic cobalt does not affect the validity of the reasoning concerning the function of bulk carbide in the Fischer–Tropsch reaction.

[13] Hendricks, Jefferson and Shultz, *Z. Krist*, **73**, 376 (1930).

[14] Emmett and Shultz, THIS JOURNAL, **51**, 3249 (1929).

[15] Edwards and Lipson, *J. Inst. Metals*, **69**, 177 (1943).

[16] Because of difficulties inherent in X-ray diffraction analysis this statement is not strictly correct. If, for example, the carbiding-hydrogenation cycle occurs only in the outermost 10–20 atomic layers of cobalt particles, this phase change may not be detected by X-rays. Also X-ray diffraction analysis under any conditions will not detect less than 5% of a minor crystalline constituent so that if less than 5% of cobalt went through this cycle, the change would not be detected.

[Contribution from Chemistry Department, University of British Columbia]

The Dielectric Properties of Solid and Liquid *cis*- and *trans*-Decahydronaphthalene

By Wm. F. Seyer and Gordon M. Barrow[1a]

The measurement of the dielectric constant of *cis*- and *trans*-decahydronaphthalene over a temperature range constitutes another addition to a series of measurements made on these substances. Hydrocarbons have in the pure state a low dielectric constant and have either zero or a very low value for the dipole moment. Hence very slight polarity is to be expected in these bicyclic hydrocarbons and this polarity is possible only when the molecules exhibit some lack of symmetry. One would, therefore, expect the symmetrical *trans* isomer to have no dipole whereas the unsymmetrical *cis* isomer might have a small permanent dipole moment.

In the present investigation it was decided to measure the dielectric constant over a temperature range for both liquid and solid. Any difference in behavior might then throw some light on the spatial structures of these two compounds. The problem of the dielectrics of non-polar substances in solid form has only recently been considered and the theory is therefore limited. Considerable theory has been developed for long-chain ketones which, being polar, show a pronounced change of polarization when they become fixed in a crystal lattice.[1b] Such changes in the dielectric constant of non-polar compounds have been found to be relatively small. Thus Müller noticed that the dielectric constant of a long-chain hydrocarbon increased at the freezing point by 2 to 6% for different experiments.[2] His work, however, was directed toward the measurement of polar compounds and he considered the changes for the hydrocarbon to be negligible. Much experimental work has been done on measuring the dielectric constant change in passing through the melting point region but little in the reverse direction. Recently R. Giullien[3] reported discontinuities in the dielectric constant–temperature relationships near the fusion point.

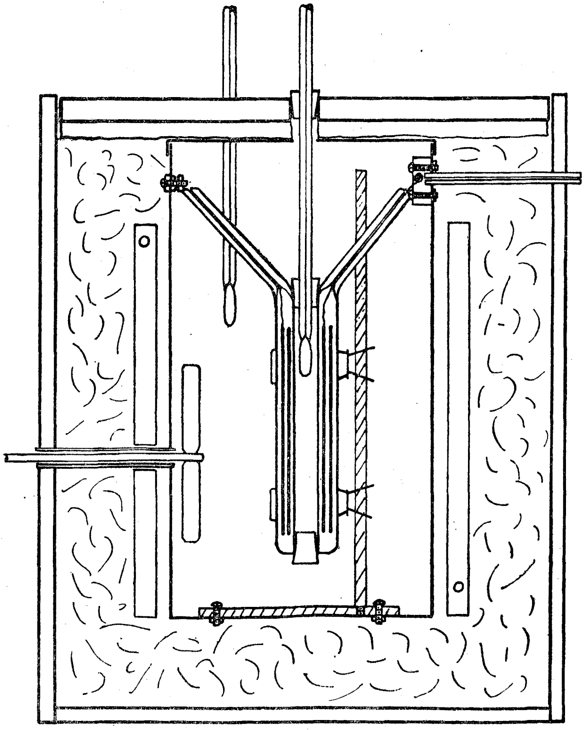


Fig. 1.—Test cell assembly.

The difficulties of measuring the dielectric constants with a cell suitable for both liquid and solid states is at once apparent. The dielectric constant change when the material in the cell crystallizes will depend somewhat upon the rate of crystallization, the type of crystals formed, the viscosity of the material, its latent heat and the temperature at which crystallization starts. All these factors will probably effect the nature of voids between the plates of the condenser. These voids will tend to lower the dielectric constant an indeterminate amount. As a result of these uncertainties it would be extremely difficult to obtain accurate values of the dielectric constant through the transition range from liquid to solid or the reverse. It should be possible, however, to get an indication of the nature of the change transpiring and a comparison of the behavior of the two isomers.

Procedure.—The dielectric constants were measured by using an electrical circuit designed by Alexander[4] and constructed here by Basil A. Dunell.[5] He, using a plate potential of 90 volts, had previously encountered troublesome drifts with the set-up which were, however, completely eliminated in the present case by raising the plate voltage to 160 volts. Also the open stainless steel cell used by him was replaced by one (Fig. 1) similar to that designed by Smyth[6] as evaporation losses were thus eliminated. Instead of three concentric cylinders as in the Smyth cell only two were used with an annular space of 0.09 cm. For shielding, the entire cell was placed in a grounded metal container. The cell held about 40 cc. of the test liquid.

Temperatures between room temperature and −40° were obtained by circulating acetone through the jacket and a copper coil immersed in a Dry Ice–acetone-bath. Temperatures below this and down to −60° were obtained by adding Dry Ice directly to the cell container.

Above room temperature, the temperature was measured by a calibrated mercury thermometer placed in the air-bath. This thermometer could not be placed in the

---

(1a) Holder of the Shell Oil of B. C., Fellowship for 1946–1947.

(1b) H. Fröhlich, *Proc. Roy. Soc.* (*London*), **A185**, 399 (1946).

(2) A. Müller, *Proc. Roy. Soc.* (*London*), **A158**, 403 (1937).

(3) R. Giullien, *J. phys. radium*, [8] **1**, 29 (1940).

(4) F. Alexander, Dielectric Constant Meter, Electronics, 18, #4, p. 116 (1945).

(5) Basil A. Dunell, Master's Thesis, 1946 (holder of the Shell Oil of B. C. Fellowship, 1945–1946).

(6) Smyth and Morgan, This Journal, **50**, 1547 (1928).

center of the cell because the mercury column would carry induced currents to the unshielded center plate. For measuring low temperatures a pentane thermometer was used. This was immersed in a liquid in the center cavity of the cell. Gasoline, being non-polar and having a low freezing point, was used as the liquid. This arrangement gave temperatures which at all times were very close to that of the liquid in the cell itself. With the mercury thermometer arrangement, however, considerable time was required for the liquid in the cell to come to the temperature indicated by the thermometer.

Materials.—The benzene used for calibrating the condenser was recrystallized "Merck thiophene-free benzene." Four crystallizations did not raise the freezing temperature, which remained constant over the entire freezing period. The freezing temperature as measured by a Leeds and Northrup platinum resistance thermometer was 5.38°. The sample was then taken as being pure.

The two isomers of decahydronaphthalene were samples taken from various lots of the material that had been prepared from time to time in this laboratory by methods previously described.[7] The *cis* form had freezing points lying between −43.15° and −43.24°, while that of the *trans* form lay between −30.64° and −30.80°. The cyclohexane was part of a sample specially prepared for spectroscopic work and had a freezing point of 6.5° and a refractive index of 1.4263 for the D line. All the hydrocarbons before use were dried by allowing them to stand for several days over metallic sodium.

Calibration of Cell.—The dielectric constant corresponding to the dial reading of the variable condenser was determined by observing the dial reading for resonance for benzene at a fixed temperature. The cell was filled with benzene and the two condensers (C_1 and C_2) were set so that the dial setting for circuit resonance was at the lower end of the dial for benzene at about 50°. With this setting the dielectric constants of both *cis*- and *trans*-decalin between 0° and 100° were in the dial range. The dial readings for benzene at other temperatures were also observed. From these results and from the known values of the dielectric constant of benzene a calibration curve could be drawn giving the dial readings in terms of the dielectric constant. Since the condenser had been found to vary linearly, the curve could be extrapolated to dial readings between 15 and 85.

The dielectric constants of benzene used in the calibration were taken from the results of Clay, Dekker and Hemelrijh[8] and were extrapolated to higher temperatures on the basis of the linear relation found by previous investigators.

Whenever it became necessary to change the setting of the condenser C_2 in order to measure dielectric constants in a different range, a known dielectric constant in the new range had to be measured and the calibration curve had to be shifted accordingly.

In order to find an unknown dielectric constant it was now only necessary to determine the dial reading for any fixed temperature. The dielectric constant could then be read off the calibration curve.

The maximum variation of the dial reading for successive runs at constant temperature was two dial divisions, corresponding to 0.003 dielectric constant unit. All the results, however, depend upon the benzene calibration and any error in this will produce a proportionate error in all the results. The relationships between the dial readings and the dielectric constants for benzene and those of the two bicyclic compounds were linear. Two methods of measuring the dielectric constants were used, one in which the temperature was kept constant to within 0.1°, and the other in which the temperature was allowed to rise or fall at a steady rate and dial readings were made over small temperature intervals. The values of the dielectric constant at various temperatures for *cis*- and *trans*-decahydronaphthalene were plotted and gave straight lines over the entire temperature range above their fusion points. The equations for these lines by the method of least squares was found to be for the *cis* compound: $\epsilon_{cis} = 2.238 - 0.00103T$ and for the *trans* compound $\epsilon_{trans} = 2.205 - 0.00101T$ where ϵ is the dielectric constant and T the absolute temperature.

Discussion of Results.—Careful attention was directed to the measurements of the dielectric property of the *cis* hydrocarbon in the neighborhood of 50°, since some of the other physical properties of this compound appeared to behave in an irregular manner at this temperature. None were observed in this case although Dunell[5] had observed a pronounced peak in the dielectric constant-temperature curve at this temperature. To test the behavior of this compound still further, a series of readings were made with the temperature slowly rising and falling over a temperature range from 40 to 90° with readings at intervals of 1°. The results when plotted showed decidedly linear relationships.

In measuring the dielectric constant at the liquid–solid transition point several difficulties were encountered. First, these difficulties were due to the fact that the cell and the circuit were designed specifically for the measurement of liquid dielectric constants at and above room temperatures. Since it was difficult to control the temperature in this region readings were taken with the temperature slowly falling or rising and no attempt was made to reach an equilibrium state. Second, the design of the cell made it rather difficult to add a seed crystal; hence, supercooling was another difficulty. Particularly was this so with the *cis*-isomer.

A third difficulty was fluttering and uncertainty due to the large changes in the dielectric constant at the freezing point. As mentioned previously, the circuit was constructed specially for the accurate measurement of small regular dielectric changes. This required a large capacity and a small L/R ratio resulting in considerable instability when abrupt dielectric constant changes were encountered.

Numerous runs for different samples of both the *cis* and *trans* hydrocarbons through the freezing and melting points were made. Typical runs are shown in Fig. 2. The configuration of the *trans*-decalin was remarkedly reproducible, largely perhaps due to the almost complete absence of supercooling. The maximum value of the dielectric constant for eight runs lay between 2.29 and 2.30. Much difficulty was encountered when working with the *cis*-decalin because of supercooling, and here it was always necessary to add a seed crystal to bring about the freezing process. Unlike the *trans*-decalin, only the general behavior and not the exact curves were reproducible.

What is striking in this case is the marked difference in shape of the two areas enclosed by the freezing and melting curves. This is most clearly seen in Fig. 3 where the curves drawn represent averaged values. In the case of *cis*-decalin the dielectric constant of the liquid just above the

---

[7] Seyer and Walker, THIS JOURNAL, **60**, 2125 (1938).

[8] Clay, Dekker and Hemelrijh, *Chem. Abst.*, **38**, 5120 (1946).

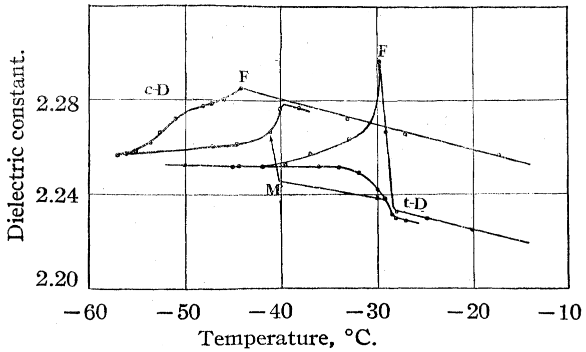


Fig. 2.—Typical run through freezing and melting points: *c*-D, *cis*-decalin; *t*-D, *trans*-decalin; M, melting point; F, freezing points.

freezing point is higher than that of the solid and the shape of the melting point curve is similar to that of many substances already examined, particularly glycerol. It is of course conceivable that if the freezing or melting processes were carried out infinitely slowly the area enclosed by the curves would vanish. In such a case freezing and melting would be a reversible process. It is obvious that the freezing process of the *trans*-decalin is quite different than that of the *cis*-isomer.

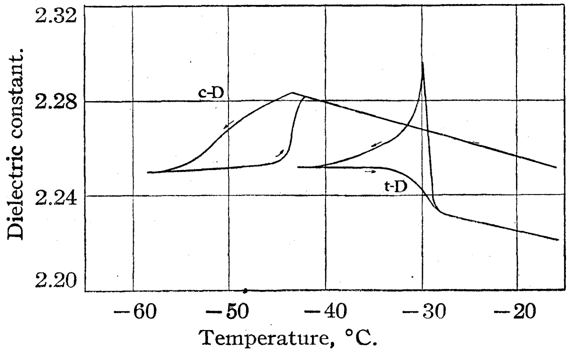


Fig. 3.—Averaged dielectric constant curves through freezing and melting points: *c*-D, *cis*-decalin; *t*-D, *trans*-decalin.

Here the dielectric constant of the liquid just above the freezing point is lower than that of the solid. During the freezing process the dielectric constant not only rises to meet that of the solid but rises considerably above it. Upon melting this path is not followed but the dielectric constant falls slowly to that of the liquid. As mentioned before, if little supercooling was allowed the curves were reproducible with considerable accuracy for the different runs. To investigate this matter further, the hydrocarbon cyclohexane was examined. Recent work on this compound indicates that at room temperatures this substance exists almost entirely in the *trans* state. The behavior of this compound is shown in Fig. 4 and its similarity to that of *trans*-decahydronaphthalene is noteworthy. In the case of cyclohexane the increase in the dielectric constant became so large during the freezing process that the reading was completely off the dial scale. Again, the dielectric constant of the liquid just above the freezing point is lower than that of the solid. Whether or not this sudden augmentation of the dielectric properties during the freezing or solidification process is characteristic of the *trans* state cannot be decided until further observations are made. However, in the case of these two compounds it must be assumed that some deepseated change in the geometrical structure of the molecule must take place, which would involve the loosening of some of the bonds during solidification. Figure 3 shows further that within the limits of experimental error the dielectric constant of solid *cis*- and *trans*-decahydronaphthalene is the same. This would lead one to suspect that the crystal structure of the two solids would be very similar. It would appear that in the *trans* system crystallization and melting are not, at least mechanically speaking, strictly reversible processes. Unlike the case of the *cis* isomer where crystallization and melting are merely the coagulation in an orderly manner and dispersion of the molecules, here some molecular change must precede crystallization.

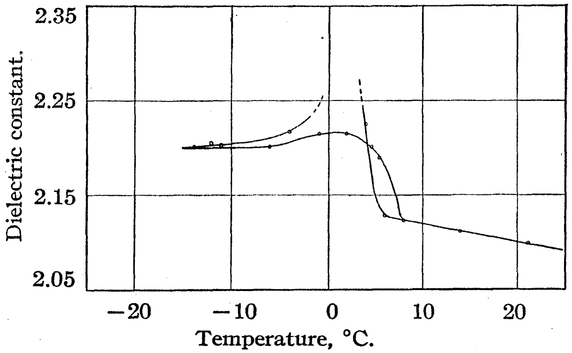


Fig. 4.—Dielectric constant of cyclohexane through freezing and melting points.

The molar polarizations (P) for *cis*- and *trans*-decahydronaphthalene have been calculated for a few temperatures up to 100° and are shown in Table I. The densities were those found previously in this laboratory.[9]

TABLE I

MOLAR POLARIZATION DATA FOR *cis*- AND *trans*-DECALIN

Temp., °C.	Density	Dielectric constant	*P*
	cis-Decalin		
20	0.897	2.219	44.4
50	.874	2.188	44.8
80	.852	2.156	45.1
100	.836	2.136	45.4
	trans-Decalin		
20	0.870	2.184	44.9
50	.848	2.150	45.2
80	.825	2.123	45.6
100	.810	2.103	45.8

---

[9] Seyer and Davenport, THIS JOURNAL, **63**, 2426 (1941).

The slightly larger value of P for the *trans*-isomer than for the *cis*-isomer is to be expected in view of the less compact structure of the former compound. At 20° this difference is close to 0.45. This is small but greater than the limits of error in the measurement of the dielectric constant. The polarizabilities (α) have been calculated in the usual manner and compared with those of benzene in Table II.

TABLE II

COMPARISON OF THE MOLAR POLARIZATIONS AND POLARIZABILITIES FROM RESULTS AT 20°

	P	α_{20}
Benzene	26.71	1.05×10^{-25}
cis-Decalin	44.4	1.75×10^{-25}
trans-Decalin	44.9	1.77×10^{-25}

Again it appears that the polarizability of the *trans*- is slightly greater than that of *cis*-isomer.

A comparison of the dielectric constants and the squares of the refractive index for the D line of sodium is made in Table III for benzene, cyclohexane and the two bicyclic hydrocarbons.

TABLE III

COMPARISON OF THE DIELECTRIC CONSTANT WITH THE SQUARE OF THE REFRACTIVE INDEX

	n_{20}	$(n_{20})^2$	ϵ_{20}	$\epsilon_{20} - n_{20}^2$
Benzene	1.50142	2.254	2.289	0.035
Cyclohexane	1.42635	2.033	2.052	.019
cis-Decalin	1.48113	2.194	2.219	.025
trans-Decalin	1.46968	2.160	2.184	.024

It is seen that even for the simple theory which is not directly applicable to liquids the agreement is quite satisfactory. All results indicate a zero or a very small dipole moment for both isomers.

Summary

1. The dielectric constant of *cis*-decalin has been measured at 3.5 megacycles and 20° and has been found to be 2.219±0.003. The temperature coefficient between the freezing point and 100° is 0.0010 per °C. No anomalous behavior in any of the samples tested was observed between −40 and 100°.

2. Under the same conditions, *trans*-decalin has been found to have the values 2.184±0.003. The temperature coefficient between the freezing point and 100° is also 0.0010 per °C. As in the *cis*-isomer no anomalous behavior was observed.

3. The dielectric constant has been measured through the freezing point and to the solid phase. A marked difference in the behavior of the two isomers was observed. Furthermore, the curves for heating and cooling for both the decahydronaphthalene isomers and cyclohexane are quite different. Both *trans*-decalin and cyclohexane show a pronounced and unexplained maximum at the freezing point.

4. The molar polarizations of *cis*- and *trans*-decalin have been calculated at a number of temperatures and the variation with temperature has been found to be the same as the variation of the polarization of liquid benzene with temperature. Furthermore, the squares of the refractive indices are in close agreement with the dielectric constants.

5. The molar polarization of the *trans*-isomer is slightly larger than that of the *cis*-isomer. This indicates a looser or less compact molecular structure for the *trans*-isomer.

VANCOUVER, B. C., CANADA RECEIVED JULY 11, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Electric Moments of Hydrogen Fluoride, Hydrogen Chloride and Hydrogen Bromide in Several Non-polar Solvents[1]

BY A. J. WEITH, JR.,[1a] MARCUS E. HOBBS AND PAUL M. GROSS

Introduction

The electric moments of hydrogen fluoride, hydrogen chloride and hydrogen bromide in dilute solutions of non-polar solvents are of particular interest since measurements[2] by Fairbrother on some of the hydrogen halides in a limited number of solvents indicated that hydrogen chloride, hydrogen bromide and hydrogen iodide all exhibit a positive solvent effect. Hydrogen fluoride was not measured by Fairbrother; in fact, only recently has a value for the electric moment for this molecule been reported[3] and this was for the gas state. The present measurements were undertaken to establish the magnitude of the solvent effect for these solutes in a more extended series of solvents, to determine the value of the electric moment of hydrogen fluoride in solution and finally to establish the effect of bonding of these acid molecules to acceptor solvent molecules by measuring the electric polarization of the solutes in solutions of dioxane. It was hoped that, because of the relative simplicity of the halides, the data obtained would be useful in future attempts toward elucidation of the origin and mode of action of the solvent effect in electric moment measurements and that some insight might be gained into

---

(1) Part of a Thesis of A. J. Weith, Jr., submitted in partial fulfillment of the requirements of the Ph.D. degree in Chemistry at Duke University, June, 1947.

(1a) Present address: Stamford Research Laboratories, American Cyanamid Company, Stamford, Connecticut.

(2) F. Fairbrother, *Trans. Faraday Soc.*, **30**, 862 (1934).

(3) Hannay and Smyth, THIS JOURNAL, **68**, 171 (1946).

the process occurring when solutes combine with solvents to which proton transfer might occur.

Materials, Apparatus and Procedure

Solvents.—Benzene (Jones and Laughlin reagent grade) which was found to be thiophene free was stored over calcium chloride and then refluxed and finally distilled over sodium through a 2-meter Dufton column. The middle fraction, of essentially one-half the total volume, was collected directly in a transfer flask so the solvent could be transferred directly to the dielectric measuring system. The middle fraction boiling range never exceeded 0.02°. Recovered benzene from previous measurements occasionally was used. It was treated with solid sodium hydroxide to neutralize the acid, totally distilled and finally distilled as above over sodium. No differences in the constants of this benzene and that of a fresh sample were noted.

1,4-Dioxane (Carbide and Carbon Chemical Corp., C. P. Grade) was refluxed over solid sodium hydroxide for several hours, then totally distilled. This product was then refluxed and finally distilled over sodium, the middle fraction being collected directly in the transfer flask. The distillation was carried out only when the sodium showed and retained a bright metallic surface and, in addition, when there was no visible evidence of reaction of the sodium and dioxane. The b. p. range for the middle fraction used was generally 0.06° or less. Recovered solvent from previous measurements was used after being subjected to the same treatment as a fresh sample of dioxane.

n-Heptane (California Chemical Co.) in two-liter portions was shaken repeatedly with about 500 ml. of concentrated sulfuric acid until no further darkening of the sulfuric acid layer was observed. In general four portions of acid were required. The heptane was washed with dilute sodium hydroxide solution and distilled water and finally dried with fused calcium chloride. It was then refluxed and distilled over sodium wire and the middle fraction collected directly in the transfer flask. The middle fraction had a maximum b. p. range of 0.04°. Recovered samples of heptane were used in some runs.

Carbon tetrachloride (Eastman Kodak Co. best quality sulfur free) was purified according to the method suggested by Williams and Krchma.[4] The middle fraction distilled over fused calcium chloride was collected in the transfer flask. The fractions used had a b. p. range not exceeding 0.03°.

The actual boiling points of all samples of solvents were not recorded but samples of the same solvents have, on repeated tests in this laboratory, shown b. p. (cor.) falling within the range indicated: benzene, 80.06 to 80.08°; 1,4-dioxane, 101.25 to 101.45°; *n*-heptane, 98.47 to 98.52°; and carbon tetrachloride, 76.73 to 76.76°.

The average values of the dielectric constant for the solvents at 30.0° based[5] on benzene, $E = 2.263$, are 1,4-dioxane, 2.218; *n*-heptane, 1.906, and carbon tetrachloride, 2.216.

Solutes

Hydrogen flouride (anhydrous) obtained from E. I. du Pont de Nemours and Co., in steel tanks was represented as better than 99% pure. No attempt was made to effect further purification except that slow distillation at room temperatures through a monel metal trap was effected to reduce possible carry-over of liquid from the cylinder. Two cylinders were used during the course of the investigation and the results show no measurable differences. The hydrogen fluoride was distilled directly into the mixing chamber containing the solvent, all operations being carried out so as to exclude moisture.

Hydrogen chloride (anhydrous) was obtained from the Dow Chemical Co. in a steel tank. A typical analysis by them showed 98.2% hydrogen chloride, the chief impurity being nitrogen. This material was allowed to pass at atmospheric pressure through three conventional tube-packed traps maintained a few degrees above the liquefying temperature of the gas with Dry Ice–alcohol mixture. A fourth trap in the same cooling mixture consisted of ten feet of closely coiled 7-mm. o.d. tubing. At no time during the measurements was a visible deposit found in any of the traps.

Hydrogen bromide (anhydrous) obtained from the Dow Chemical Co. in a steel tank was stated to contain no known impurities other than bromine and water. The same trap system and cooling arrangement as for the hydrogen chloride was used on the hydrogen bromide since it was expected that both known impurities would be effectively removed by this method. Repeated measurements with both hydrogen chloride and hydrogen bromide showed no variations other than those that could be accounted for by the normal experimental error in the method used.

Water was used for one measurement in dioxane. It was purified by treatment with potassium permanganate and distilled from a silica still with the middle fraction being collected in a silica receiver.

Apparatus.—The heterodyne beat method of measuring capacity change has been used in this investigation. The oscillator circuits of a modified Hartley type were obtained commercially in the form of a beat frequency Clough–Brengle Audio Oscillator (No. 79-E). The variable oscillator circuit of the Clough–Brengle generator was altered by placing the measuring condenser and the compensating standard precision condenser in parallel with the capacitance in the variable oscillator circuit. With the two condensers at proper capacity, the original capacitance in the variable circuit was then reduced so that the over-all effect was that of the original capacitance. Variations in the capacity of the measuring condenser could then be compensated for and measured by the standard precision condenser, the reference point in all cases being that setting of the standard precision condenser that would give a zero beat frequency between the variable oscillator and the fixed oscillator. The "zero" beat was determined by the electron tube "eye" mounted in the front of the Clough–Brengle Oscillator. The two oscillating circuits in this equipment are very well decoupled so that there was no significant tendency for the two circuits to synchronize as they were tuned to the same frequency. High quality coaxial cable that was relatively insensitive to mechanical movement was used for all connections between the Clough–Brengle and the measuring and precision condensers, single contact microphone connectors being used for the actual connections. The standard precision condenser used was a 500 m.m.f. General Radio Company Precision Condenser, Type 222-B, with 2500 scale divisions. This capacitance was calibrated in arbitrary units which served as the unit for dielectric constant measurements.

It was obviously necessary to carry out all mixing and handling operations as well as the actual measurement in the absence of moisture. This was done by the construction of a completely enclosed measuring system which included a mixing chamber and a measuring condenser (see Figs. 1 and 2). The system was so constructed as to allow concentration and density samples to be withdrawn without contamination of the system. Movement of the solution from one vessel to another was effected by application of gas pressure at the proper point from a well dried (two liquid air traps) nitrogen source. All of the system that came in contact with the solution before or during a measurement was constructed either of monel, silver or nickel. Pure silver was used throughout for all welding. Connections between metal and glass portions were accomplished by means of ground glass–ground metal joints lubricated with graphite and sealed on the outside with De Khotinsky cement.

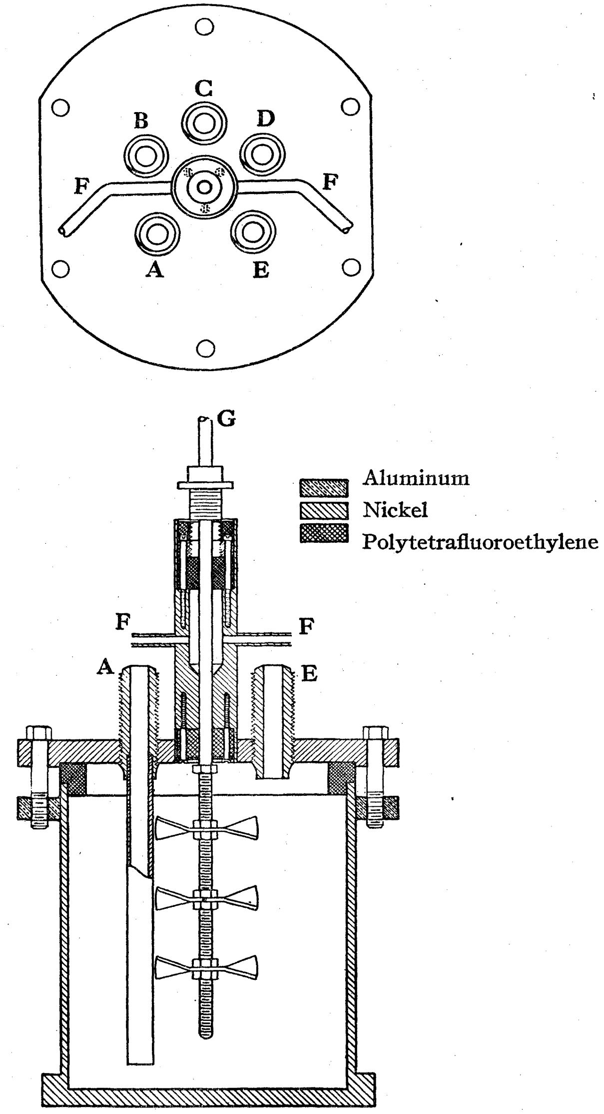
After much difficulty with the insulation problem a sample of polytetrafluoroethylene from the E. I. du Pont Company proved very satisfactory. No apparent deterioration occurred over a period of one and one half years of service.

The measuring condenser cell was constructed (see Fig. 2) of three concentric monel metal cylinders. The two inner cylinders were mounted integral with the top and

---

[4] Williams and Krchma, This Journal, **48**, 1888 (1926).

[5] Hartshorn and Oliver, *Proc. Roy. Soc.* (*London*), **A123**, 684 (1929).



Mixing chamber.

Fig. 1.—Solution mixing chamber: A is the connection to the measuring condenser, B is the inlet tube for nitrogen, C is the inlet tube for the solute gases, D is the exit tube for the mixing chamber vapors, E is the inlet connection for the solvent, F is the inlet and exit tubes for nitrogen which flowed around the stirrer and G is the variable speed stirrer.

the outer one served as a container for the liquid and as support for the top. The top and bottom were formed from nickel plate. The bottom was "sweated" into proper place as determined by an undercut on the inside of the outside pipe. A gas-tight joint was made between the top and the outside pipe by means of compression of a polytetrafluoroethylene gasket. The middle cylinder was connected so that it could be placed either at high or ground potential by means of a switch on the top. This connection was insulated from the top by means of polytetrafluoroethylene. The middle cylinder was rigidly spaced and insulated from the innermost cylinder (which was always at ground potential) by four small pieces of polytetrafluoroethylene, two pieces being placed at each end of the cylinder assembly. The plastic pieces were put into place between the cylinders while the middle cylinder was sprung out of shape. On relieving the pressure on the middle cylinder, the plastic pieces were clamped quite securely between the two cylinders. Where necessary leads through the top were insulated by means of the polytetrafluoroethylene.

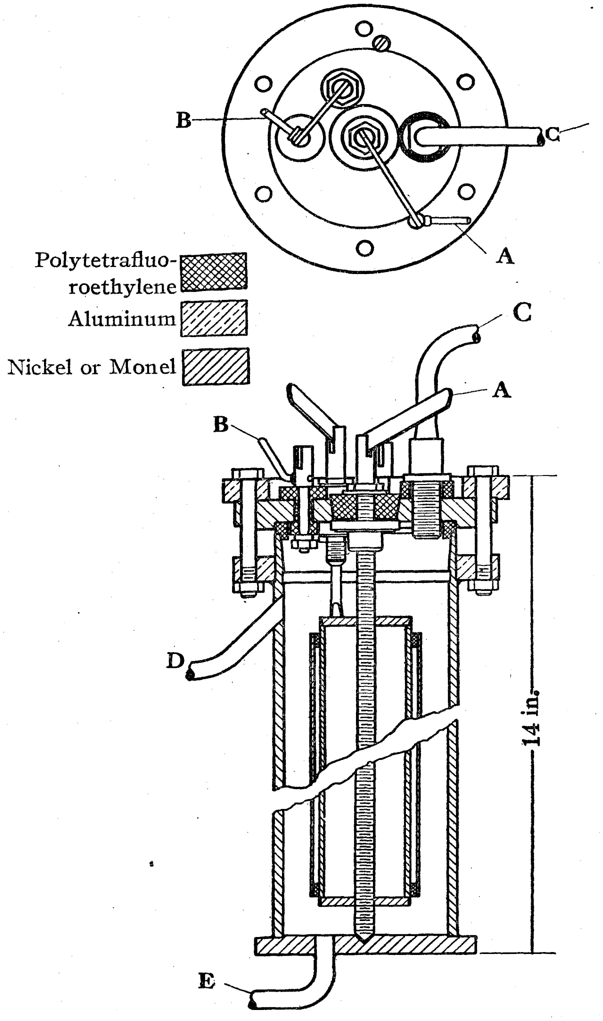


Fig. 2.—Dielectric measuring condenser: A is the ground potential lead, B is the high potential lead, C is the inlet tube for nitrogen, D is the liquid overflow constant level tube, and E is the connection tube to the mixing chamber.

The capacitance change in air when the middle cylinder was switched from ground to high potential was approximately 150 mmf. The condenser was calibrated by the use of air and benzene using Hartshorn and Oliver's value[5] for the dielectric constant of benzene. The liquid capacity of the cell was approximately 800 ml.

The density of the hydrogen fluoride solutions was determined by means of a monel metal pycnometer consisting of a tube equipped with a ground tapered plug at each end. A small hole in one of the ground plugs allowed the liquid to escape and was finally closed off after temperature equilibrium was established with a small tapered monel plug. This method of density determinations would, in general, be far from satisfactory if high precision were required, but in the hydrogen fluoride series the density term contributes less than 1% to the molar polarization so that the accuracy obtained was satisfactory.

The density determinations in the hydrogen chloride and hydrogen bromide series were determined in a conventional[6] glass pycnometer of 100-ml. capacity.

The density of all concentrations for several measurements was determined to test the consistency of the $\Delta d/f_2$ ratio, where f_2 is the solute mole fraction and Δd is the difference in density between the solution and solvent. The results showed that $\Delta d/f_2$ for these systems could be considered constant.[7] Thus, in most cases, only the density of the solvent and one or two of the solutions was determined, the other densities being calculated in turn from these. Several checks of the value of $\Delta d/f$ were made between runs of the same components. All measurements were carried out at 30.0°.

Actual measurements were carried out in the usual manner for solutions except that unusual precautions were taken to see that no air entered the measuring system during the course of a determination. The concentrations of the acids were determined from aliquots delivered directly from the measuring system into excess 0.1 *N* alkali. It was found that in the process of filling and emptying the measuring condenser some small striations of concentration occurred in the case of solvents where the solubility of the solute was low. Therefore, four samples were withdrawn for analysis from various levels of the measuring condenser and the average of these concentrations used as the concentration value in such cases. The average deviation of a series of measurements for such cases was generally less than 2% of the mean value. These uncertainties and other random ones caused the measurements for hydrogen fluoride in carbon tetrachloride and *n*-heptane to spread so much that the values of the electric moment are reported only to the tenths of an electric moment unit for these solvents.

Calculations and Data

The results recorded are the following: P_2 is the molar polarization of the solute calculated from an expanded form[8] of the usual Debye expression; R is the molar refraction; μ_D is the electric moment in debyes calculated from the average (or extrapolated) value of P_2; and μ^* is the external electric moment as calculated for infinite dilution from the Onsager[9] expression for this case, namely

$$(\mu^*)^2 = \frac{E_{12} - E_1}{N_2}\,\frac{3kT}{4\pi} \qquad (1)$$

where N_2 is the number of solute molecules/cc., E_1 is the dielectric constant of the solvent, and E_{12} is the dielectric constant of the solution. N_2 is given more explicitly by

$$N_2 = \frac{f_2 d_{12} N_A}{(1 - f_2)M_1 + f_2 M_2} \qquad (2)$$

The subscript 12 refers to the solution, 1 to the solvent, and 2 to the solute. M is the molecular weight, and N_A is Avogadro's number. The other terms of this expression have their usual meaning. In writing the above expression for $(\mu^*)^2$ the assumption has been made that there is no difference between the square of the refractive index of the solvent, n_1^2, and the dielectric constant of the solvent, E_1.

In the usual case of "so-called" non-polar solvents this assumption would be well taken, but it happens that for dioxane there is a rather large difference (*i. e.*, 0.23 at 30.0°) between the square of the refractive index n_1^2, for sodium light and the dielectric constant. It is recognized that the n_1 of Onsager's expression has reference to the value for the electron and atomic polarizability in a static field but this value is not available and rather than use a dubious extrapolation for n, it was felt that E_1 should be used.[10] μ_0 is the permanent electric moment as calculated from μ^* using the expression

$$\mu_0 = \frac{(2E_1 + n_2^2)}{E_1(n_2^2 + 2)}\,\mu^* \qquad (3)$$

There was some question as to the value of n_2^2 proper to the calculation. It is of course possible to calculate a value of n_2^2 from the molar refraction expression using a value of the density obtained from the density equation for the liquid state. For present purposes this expedient has been followed but it is recognized that the values obtained are truly approximate since the density functions used[11] have been extrapolated considerably beyond their indicated limits of validity.

Results

The results of the measurements at 30.0° are summarized in Table I, and detailed data for the halides are shown graphically in Figs. 3, 4 and 5.

TABLE I

Solute	R_D (cc.)	n_D^2	P_2 (cc.)	μ_D	Solvent	μ^*	μ_0
HF	2.1	1.329	(84)	2.0	CCl_4	2.8	2.2
			(99)	2.2	*n*-C_7H_{16}	2.8	2.3
			76.7	1.91	C_6H_6	2.63	2.04
			114.1	2.34	1–4$C_4H_2O_2$	3.32	2.60
HCl	7.1	1.577	29.8	1.06	CCl_4	1.48	1.12
			36.1	1.19	*n*-C_7H_{16}	1.55	1.23
			38.7	1.25	C_6H_6	1.62	1.22
			98.9	2.12	1–4$C_4H_8O_2$	2.92	2.21
HBr	10.0	1.566	27.8	0.93	CCl_4	1.23	0.93
			31.2	1.02	*n*-C_7H_{16}	1.27	1.00
			33.6	1.08	C_6H_6	1.43	1.08
			176	2.85	1–4$C_4H_2O_2$	4.05	3.07
H_2O	3.7	1.775	78.5	1.89	1–4$C_4H_2O_2$	2.64	1.96

Discussion

The results as summarized in Table I are recapitulated in Table II in terms of the difference between μ_D and the gas values as available in the literature[12]; *viz.* HF = 1.91D, HCl = 1.03D, HBr = 0.78D and H_2O = 1.84D.

TABLE II

	CCl_4	*n*-C_7H_{16}	C_6H_6	1,4-$C_4H_8O_2$
HF	0.1	0.3	0.00	0.43
HCl	.03	.16	.22	1.09
HBr	.15	.24	.30	2.07
H_2O				0.05

---

(6) Connell, Vosburgh and Butler, *J. Chem. Soc.*, 933 (1933).

(7) If one takes $V_{12} = f_1V_1 + f_2V_2$ where V is the molar volume and 1 refers to solvent, 2 to solute and 12 to the solution, it can be readily shown that $\Delta d/f_2$ is given by $M_2(d_2 - d_1)d_1/(M_2d_1 + M_1d_2 (1 - f_2))$ where M is the molecular weight. Since generally $f_2 \ll 1$ it is consistent with the assumption of additive molar volumes that $\Delta d/f_2$ should be independent of f_2 as long as the solutions are sufficiently dilute.

(8) Brooks and Hobbs, THIS JOURNAL, **62**, 2851 (1940).

(9) L. Onsager, *ibid.*, **58**, 1486 (1936).

(10) It may be remarked that dioxane in the gas state [see Schwingel and Greene, *ibid.*, **56**, 653 (1934)] has no permanent moment.

(11) For HF, Simons and Bouknight, *ibid.*, **54**, 129 (1932); for HCl and HBr, "Int. Crit. Tables," Vol. III, p. 22.

(12) C. T. Zahn, *Phys. Rev.*, **24**, 400 (1924), for HCl and HBr; ref. (3) for HF; R. Sanger, *Physik. Z.*, **31**, 306 (1930), for H_2O.

The results in Table II show quite clearly the very significant positive solvent effect for the halides and in the case of dioxane the effect is so large that it may indicate "incipient" ionization.

We may infer that since the acid strength of H_2O is so much lower than the halides its bond moment is only slightly affected by the presumed coördination of the dioxane oxygen and hydrogen of the water. It may be remarked that in general the effects observed appear to be free from serious association effects since the graph of polarization against mole fraction as shown in Figs. 3, 4 and 5 shows trends only in a few cases, and in these the trend is not particularly large.

It should be noted in Table I that the lack of agreement between the μ_D values and corresponding μ_0 is not serious. This is rather important in that the same direction of solvent effect is shown by calculation using either the Debye of Onsager formulation. Furthermore, our data as are shown in Figs. 4 and 5 agree rather well with those of Fairbrother's, and the moment for hydrogen chloride in benzene of 1.25 debyes is to be compared with the value 1.21 debyes found in the same solvent by Mizushima,[13] *et al.*

In considering the results in more detail it appears that, if one excludes the dioxane solutions the observed solvent effects may be explained on the basis of the interaction of a polarizable dipolar molecule with a polarizable solvent. The generalized effect of solvents on the values of electric moments as determined in solution has been considered in some detail by Weigle,[14] Higasi[15] and Frank.[16] For the particular case of some diatomic molecules Fairbrother[17] has given what seems to be a rather specialized treatment which depends on the interaction of the solute in its totally ionic state with the surrounding solvent. From a rather general consideration of the solvent effect as originating from a polarizable solvent and the electric moments induced in it by the dipolar solute molecule the order of the maximum solvent effect to be expected can be shown to be about ±15 to 20% of the electric moment of the polar molecule. The sign of the effect is determined mainly by the geometry of the solute molecule and the location and direction of the electric moment within it.

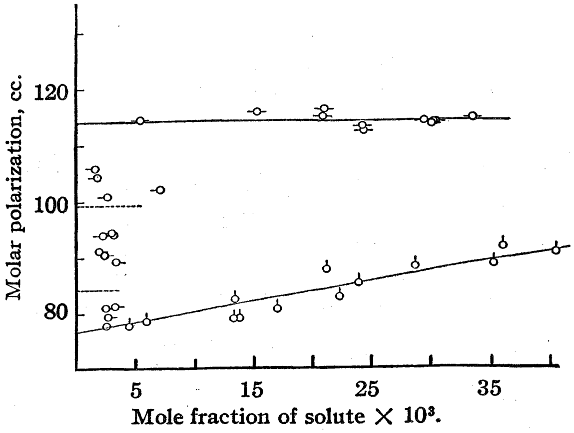


Fig. 3.—Hydrogen fluoride at 30° in: —O—, 1,4-dioxane; ȯ, benzene; -O, *n*-heptane; O-, carbon tetrachloride.

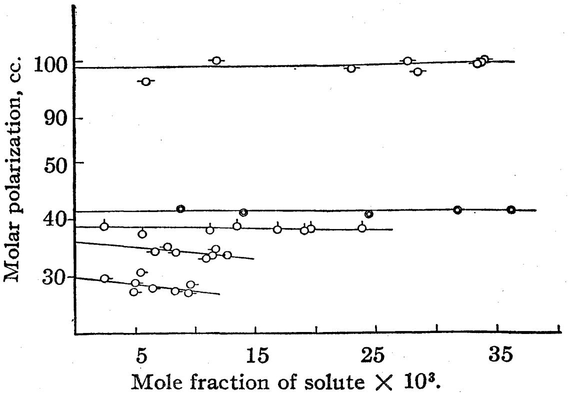


Fig. 4.—Hydrogen chloride in: -O-, 1,4-dioxane at 30°; -O, *n*-heptane at 30°; ȯ, benzene at 30°; O-, carbon tetrachloride at 30°; ◎, benzene (Fairbrother) at 20°.

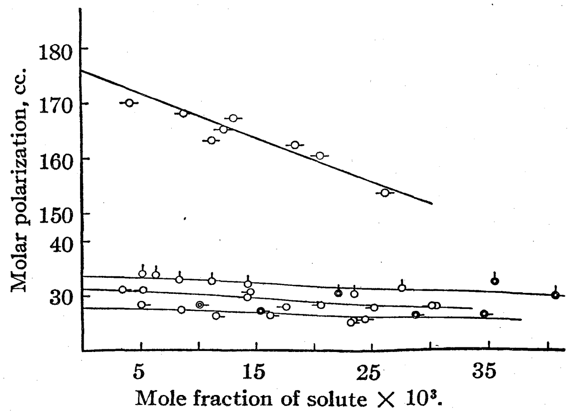


Fig. 5.—Hydrogen bromide in: -O-, 1,4-dioxane at 30°; ȯ, benzene at 30°; -O, *n*-heptane at 30°; O-, carbon tetrachloride at 30°; ◎, benzene (Fairbrother) at 20°; ◎-, carbon tetrachloride (Fairbrother) at 20°.

Review of the data of Table II in the light of this anticipated maximum solvent effect of the order of ±15 to 20% of μ_1 indicates that outside of the dioxane solutions the solvent effects observed can for the most part be accounted for by solute–solvent interactions of the type considered above. Hydrogen bromide in benzene appears to be somewhat high as is hydrogen fluoride in *n*-heptane. Hydrogen fluoride in benzene is anomalously low. As is well known hydrogen fluoride is very prone to associate, and in the case of hydrogen fluoride in *n*-heptane this may explain the apparently high though admittedly uncertain solvent

---

[13] Mizushima, Suenaga and Kozima, *Bull. Chem. Soc. Jap.*, **10**, 167 (1935).

[14] J. Weigle, *Helv. Phys. Acta*, **6**, 681 (1933).

[15] K. Higasi, *Bull. Inst. Phys. Chem. Research* (*Tokyo*), **14**, 146 (1935).

[16] F. C. Frank, *Proc. Roy. Soc.* (*London*), **A152**, 171 (1935).

[17] F. Fairbrother, *Trans. Faraday Soc.*, **33**, 1507 (1937).

effect shown in Table II. In benzene the calculated molar polarization of hydrogen fluoride rises with increasing concentration. This suggests an increasing tendency toward an end to end type association of the hydrogen fluoride as the concentration increases. Buswell,[18] *et al.*, have by means of infrared absorption measurements concluded that dilute solutions (<0.002 mole fraction) of hydrogen fluoride in carbon tetrachloride show very little association of the hydrogen fluoride. Although our data on hydrogen fluoride in carbon tetrachloride are somewhat uncertain it does appear that end to end association in this solvent at the concentration used was not unduly serious. However, in the case of benzene considerably higher concentrations of hydrogen fluoride were reached than was the case with carbon tetrachloride, and if such end to end association did occur at the high concentrations the extrapolation of the polarization curve to the zero concentration axis might well give a value of $P_2{}^\infty$ which was lower than the actual value of the molar polarization of the single molecule of hydrogen fluoride in benzene. With the apparatus and technique used in the measurements values of molar polarization obtained for f_2 values less than 0.005 were for the solutes used too uncertain to warrant detailed investigation of the hydrogen fluoride–benzene system below this value of concentration.

As previously noted the solutions of the halides in dioxane exhibit, as may have been expected, a somewhat different order of solvent effect than was encountered with the other solvents. The oxygen of the ether linkage can presumably bind the hydrogen of the halides by means of a hydrogen bond and because all of these solutes are relatively strong acids in even mildly basic solvents one might expect a sensible change in the apparent ionic character of the solute molecules. Considerable infrared[19] and raman[20] spectroscopic work on these types of solutions has given evidence of a significant change in the hydrogen halide vibration characteristics when the halides form hydrogen bonds with oxygenated or other acceptor type solvents. For the case of the hydroxyl group, rather than the halides, Badger[21] has attempted to show a rather simple relation between the heat of formation of the hydrogen bond and the shift in frequency that occurs in the second harmonic of the OH stretching vibration. Gordy and Martin[22] have shown that for oxygenated solvents the maximum shift of the hydrogen chloride bond occurs in ether type solvents and that, in particular, dioxane causes the hydrogen chloride band that appears at 3.49 μ in benzene solution to shift to 4.05 μ in a 1.1 molar dioxane solution. The presumption is that both hydrogen fluoride and hydrogen bromide would, in dioxane solutions, show similar shifts of major magnitude in their characteristic frequency. To the knowledge of the authors no spectroscopic data is available for these two solutes in dioxane.

Gordy and Stanford[23] have observed a most interesting relation between the magnitude of band shifts for a particular solute in several solvents and the logarithm of the basicity constant[24] of the solvents. It is found that these two quantities are almost linearly related for about twenty observed cases, when the solutes used were D_2O and CH_3OD and the frequency shift observed was for the OD bond in these substances. One might infer that for a given basic solvent and several acids the relative shift for the acids might be in order of the increasing acid strength. In the case of water, hydrogen fluoride, hydrogen chloride and hydrogen bromide the dielectric evidence as will be noted later seems to show some parallelism of apparent shift in electric moment and the acid strength. Spectroscopic data on this series in dioxane is not at present available; therefore, the inference above regarding the frequency shifts cannot be checked.

The fact[22] that hydrogen chloride in dioxane shows absorption bands in a region that can be ascribed to the perturbed hydrogen chloride molecule is good evidence that the solute has not gone over into an ion-pair system in the dioxane. Gemant[25] has recently investigated by potentiometric methods hydrogen chloride in dioxane that was slightly diluted with water (solution of lowest dielectric constant, $E = 2.85$). In this investigation he calculated a dissociation constant, K, of 10^{-14} when $E = 2.85$. There is little reason to suppose that the conductivity or hydrogen ion concentration in these solutions was due to dioxane and hydrogen chloride since it would appear reasonably certain that water would be the ionizing agent as well as dissociating agent in a solution that consisted of a mixture of dioxane and water. The solvation by water of the negative chloride might aid materially in effecting actual dissociation of the hydrogen chloride; in anhydrous dioxane hydrogen chloride solution there would seem to be no reasonable method of achieving solvation effects of sufficient magnitude to energetically favor the existence of dissociated chloride ions in the solution.

The spectroscopic and potentiometric evidence may be taken to at least indicate the absence of serious amounts of ionization or dissociation in the hydrogen–dioxane solutions. This being the case one may tentatively conclude that the large solvent effect calculated for this solution has its origins in an incipient hydronium formation between the HCl and dioxane and that possibly this complex is

---

(18) Buswell, Maycock and Rodebush, *J. Chem. Phys.*, **8**, 362 (1940).

(19) D. Williams, *Phys. Rev.*, **50**, 719 (1936); West and Edwards, *J. Chem. Phys.*, **5**, 15 (1937); Buswell, Rodebush and Roy, THIS JOURNAL, **60**, 2528 (1938); W. Gordy, *J. Chem. Phys.*, **9**, 215 (1941).

(20) West and Arthur, *ibid.*, **5**, 10 (1937).

(21) R. M. Badger, *ibid.*, **8**, 288 (1940).

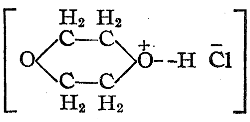
(22) Gordy and Martin, *ibid.*, **7**, 999 (1939).

(23) Gordy and Stanford, *ibid.*, **9**, 204 (1941).

(24) L. P. Hammett, "Physical Organic Chemistry," 1st ed., McGraw-Hill Book Co., New York, N. Y., 1940, p. 222.

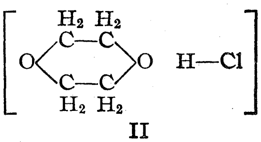
(25) A. Gemant, *J. Chem. Phys.*, **12**, 79 (1944).

stabilized by both ionic and exchange forces. One may imagine exchange forces playing a significant part by considering that such structures as



I

make significant contributions to the ground state of the complex. It is presumed that in this case the most stable contributing structure would be



II

where this bond between the H and Cl is the HCl bond with its usual partial ionic character but in a slightly perturbed state because of the nearness[26] of the ether oxygen with its slightly negative charge. It does not seem unreasonable to suggest that in the case of hydrogen fluoride and dioxane one might expect, because of the great ionic character and bond energy of the HF bond and of the lower acid strength of this molecule, that this complex might partake more of the structure shown as II than that shown by I. Hydrogen bromide in dioxane might be expected to favor structure I even more than does hydrogen chloride. Water on which data was also obtained in dioxane might be expected to favor structure II practically altogether since the acid strength of this substance is very small compared to any of the hydrogen halides. It may be remarked that substances similar to water such as alcohols, weak hydroxy acids, etc., might also favor structure II, and as such one might anticipate only small effects on the apparent electric moment of such substances because of the complex formation. The latter statement is somewhat borne out by measurements made in dioxane on a number of weak organic acids[8,27] and by our data and those of Linton and Maass[28] on water.

In an effort to depict more clearly the relative effects of the complex formation in dioxane solution on the electric moment, data are presented in Table III in the form of calculated ionic character of the respective bonds, it being assumed[29] that the ionic character of the single bonds is given by μ/er where μ is the observed dipole moment in debyes, e is the electronic charge $\times 10^{10}$ *e. s. u.* and r is the internuclear separation in Å. The column under $\Delta\mu/er$ is carried only to the tenths place as the entire procedure of calculation is predicated on the approximation that r stays constant and that the ionicity of the bond is calculable from the measured value of the moment in dioxane solution. This method neglects normal solvent effects and many other recognizable but rather indeterminable compromising effects so that the values under the $\Delta\mu/er$ column should be regarded as indicative of rather than a quantitative measure of the effects involved. In spite of the necessarily approximate methods used, the data of Table III appear to bear out in some detail the arguments advanced in the previous paragraphs. In view of this it seems reasonable to suggest that the electric moment evidence points toward intermediate structures in hydronium formation and that such structures are probably not representable simply by dipole or charge interactions such as is usually considered to be the case for hydrogen bonds. More probably these structures are hybrids which have contributing structures which lie intermediate between true ion pairs and totally separated molecules.

TABLE III

		Gas		Dioxane		
	r	μ	μ/er	μ	μ/er	$\Delta\mu/er$
HF	0.92	1.91	0.43	2.34	0.53	0.1
HCl	1.28	1.03	.17	2.12	.35	.2
HBr	1.42	0.79	.12	2.85	.42	.3
HO(H_2O)	0.96	1.51	.33	1.55	.34	.0

Summary

The electric moments of hydrogen fluoride, hydrogen chloride and hydrogen bromide have been determined in several non-polar solvents. The moment values of the halides each show definite positive solvent effects in agreement with some previous work along these lines. The moment of hydrogen fluoride in solution has been determined for the first time and it may be concluded from the present measurements that the probable value of the electric moment of hydrogen fluoride is between 1.9 and 2.0 debyes. With these data values of the partial ionic character of the hydrogen fluoride bond can be closely approximated. The agreement of the benzene solution value of hydrogen fluoride with the gas value is regarded as coincidence.

The values of the electric moments of hydrogen halides in dioxane solution seem to point toward an incipient ionization of these solutes in this solvent. This concept is considered briefly.

DURHAM, NORTH CAROLINA RECEIVED SEPTEMBER 2, 1947

---

[26] We would suggest a distance less than the sum of the van der Waals radius of the oxygen and chlorine atom.

[27] Wilson and Wenzke, *J. Chem. Phys.*, **2**, 546 (1934).

[28] Linton and Maass, *Can. J. Research*, **7**, 81 (1932).

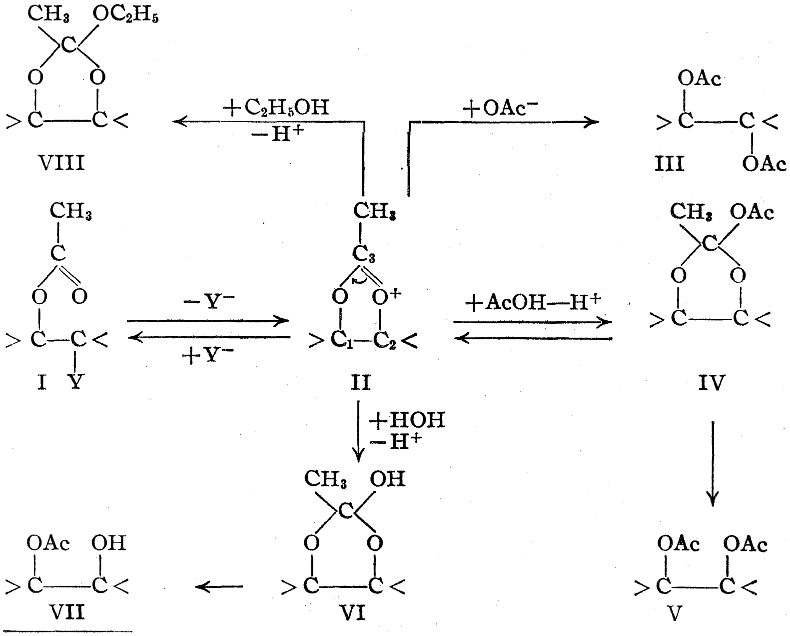
[29] L. Pauling, "The Nature of the Chemical Bond," 1st ed., Cornell University Press, Ithaca, N. Y., 1939, p. 69.

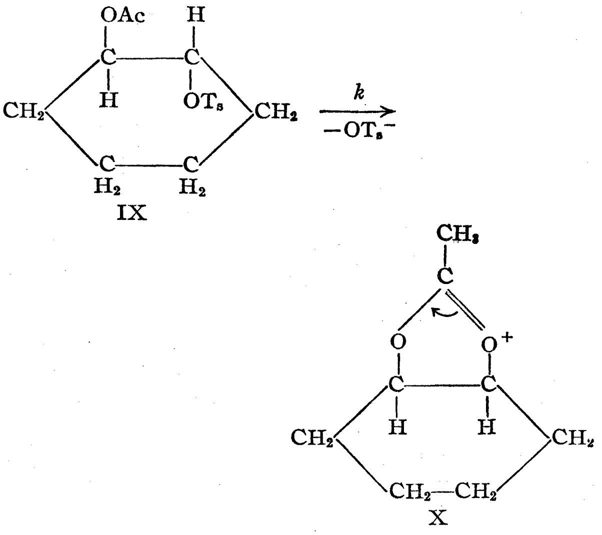
[Contribution from the Chemistry Department of the University of California, Los Angeles]

The Role of Neighboring Groups in Replacement Reactions. X.[1] Kinetics of Solvolysis of trans-2-Acetoxycyclohexyl *p*-Toluenesulfonate[2]

By S. Winstein, Carolyn Hanson and Ernest Grunwald

Of the groups encountered in previous work on the participation of neighboring groups in displacement reactions, the neighboring acetoxy[3–7] group has proved to be, in some respects, the most interesting. Thus, according to our interpretations of the results of previous experiments, the departure or extraction of a group Y such as bromide or toluenesulfonate from a molecule I such as 3-acetoxy-2-bromobutane, *trans*-2-acetoxycyclohexyl bromide or *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate gives rise to the cyclic intermediate II. This intermediate in anhydrous acetic acid containing acetate ion turns up as diacetate III with the familiar over-all steric result of retention of configuration.[3,5,7] In the absence of acetate ion in an acidic solution diacetate V with the inverted configuration is produced probably by way of the orthodiacetate IV. With water, intermediate II is thought to react to give orthomonoacetate VI which isomerizes to monoacetate VII, the over-all steric result being one of inversion.[4,5,7] With alcohol, intermediate II gives the analog of VI, the orthoester[6] VIII.





Since the participating acetoxy group is apt to be one of the most important ones to organic chemists, it seems desirable to understand its behavior as completely as possible. Toward this end we have studied the kinetics of the homogeneous solvolysis of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate IX in acetic acid. This rate work, taken in conjunction with the previous work[3–7] on the nature of the product and the steric results, adds considerable precision to our interpretation of the mechanisms involved and shows up some remaining complications.

The solvolysis of the toluenesulfonate IX (ROT_s) was followed by titration of the toluenesulfonic acid which is seen to be generated according to equation 1.

$$ROSO_2C_6H_4CH_3 + AcOH \longrightarrow ROAc + HOSO_2C_6H_4CH_3 \quad (1)$$

The rates were measured in anhydrous acetic acid solvent, and also in solutions containing one or more of the added materials, water, acetic anhydride, potassium acetate, diphenylguanidine (DPG) and diphenylguanidinium *p*-toluenesulfonate (DPG·HOT_s).

In the presence of added water even in as low a concentration as 0.055 *M*, calculated first-order reaction rate constants were very steady. A typical run is shown in Table I, (ROT_s) representing the molarity of unreacted

---

[1] Paper IX, Winstein and Grunwald, This Journal, **68**, 536 (1946).

[2] Most of the material reported in this paper was presented before the Organic Division at the Cleveland meeting of the American Chemical Society, April, 1944.

[3] Winstein and Buckles, This Journal, **64**, 2780 (1942).

[4] Winstein and Buckles, *ibid.*, **64**, 2787 (1942).

[5] Winstein, Hess and Buckles, *ibid.*, **64**, 2796 (1942).

[6] Winstein and Buckles, *ibid.*, **65**, 613 (1943).

[7] Winstein and Seymour, *ibid.*, **68**, 119 (1946).

ROT$_s$ and k the calculated first-order constant.

Without added water, but in the presence of potassium or diphenylguanidinium acetate, integrated first-order rate constants were quite satisfactory but tended to drop some 8 to 10% by the time the reaction was 70 to 80% complete. In the absence of added water or acetate salt, the kinetics were complicated, the rate constant decreasing markedly at first and then increasing again later in the run.

TABLE I

RATE OF SOLVOLYSIS OF 0.1 *M* *trans*-2-ACETOXYCYCLOHEXYL *p*-TOLUENESULFONATE AT 99.7 ± 0.10° IN AcOH 0.17 *M* IN H_2O

Time, min.	50(ROT$_s$)	$10^4 k$ (sec.$^{-1}$)
0.0	4.255	..
15.0	3.550	2.01
40.0	2.610	2.04
85.0	1.510	2.03
125.0	0.925	2.04
210.0	0.325	2.04
	Mean	2.03

In Table II are collected the data from the runs which yielded satisfactory first-order reaction rate constants. A number of comparisons are possible from this table which show the insensitivity of the rate constant to initial concentration of toluenesulfonate IX. The addition of water or acetate is seen to produce small increases in rate. A linear catalysis by water has been sometimes observed[8] in situations of this kind. In the present case, the catalysis may be linear, but the effect is so small that rigid linearity is obscured by normal experimental variations. The extrapolated rate constant for no added water or salt appears to be approximately 1.90×10^{-4} sec.$^{-1}$, 0.55 *M* water giving an increase in rate of 18%. At a concentration of 0.1 *M* diphenylguanidinium acetate, 0.55 *M* water increases the rate by 15%. For the acetolysis of α-phenylethyl chloride, Steigman and Hammett[8a] found the effect of water to be considerably larger.

TABLE II

SUMMARY OF FIRST-ORDER RATE CONSTANTS FOR ACETOLYSIS OF *trans*-2-ACETOXYCYCLOHEXYL *p*-TOLUENESULFONATE (ROT$_s$) AT 99.7 ± 0.1°

No.	[ROT$_s$]	[H_2O]	[OAc]	Remarks	$10^4 k$ (sec.$^{-1}$)
1	0.100	0.055	....		1.95 ± 0.03
2	.100	.11	....		2.07 ± .03
3	.199	.11	....		2.05 ± .02
4	.100	.17	....		2.03 ± .02
5	.025	.35	....		2.00 ± .02
6	.100	.33	....		2.07 ± .03
7	.100	.33	....	*cis*-diacetate[a]	2.12 ± .03
8	.100	.55	....		2.25 ± .03
9	.028	..	0.0249 KOAc	Ac_2O—0.0459 *M*	1.97 ± .02
10	.030	..	.0293 DPG		2.00 ± .11
11	.050	..	.0488 DPG		2.04 ± .13
12	.100	..	.0671 KOAc	Ac_2O[b]	1.91 ± .07
13	.101	..	.0883 KOAc	Ac_2O[b]	1.92 ± .05
14	.100	..	.0995 KOAc		2.03 ± .06
15	.100	..	.100 DPG		2.09 ± .07
16	.100	.07	.1072 KOAc		2.14 ± .03
17	.100	.11	.0994 DPG		2.25 ± .03
18	.100	.33	.1007 DPG		2.30 ± .05
19	.100	.55	.0996 DPG		2.40 ± .03
20	.101	..	.1425 KOAc	Ac_2O[b]	2.09 ± .03
21	.200	..	.1981 DPG		2.25 ± .06
22	.100	..	.0997 DPG	0.0997 *M* DPG·HOT$_s$	2.16 ± .11
23	.100	.33		74.90°	0.148 ± .003
24	.100	.33		74.90°	0.152 ± .002
25[c]	.040	..	.0847 KOAc	75.04°	0.0995 ± .0019

[a] 0.10 *M* in *cis*-1,2-diacetoxycyclohexane. [b] Excess acetic anhydride. M. p. of solvent 16.32°. [c] Anhydrous ethanol as solvent.

The increase in rate due to addition of 0.1 *M* diphenylguanidine to the normal anhydrous solvent amounts to about 10%. The rates with potassium acetate in the presence of a slight excess of acetic anhydride in the solvent are in general a few per cent. lower, in part, at least, due to the removal of the residual trace of water from the glacial acetic acid.

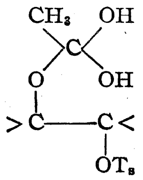
Following the previous interpretations,[3-7] the first order reaction rate constants in Table II represent the rate constant k of formation of the cyclic intermediate X (or II) and toluenesulfonate

---

(8) (a) Steigman and Hammett, THIS JOURNAL, **59**, 2536 (1937); (b) Farinacci and Hammett, *ibid.*, **59**, 2542 (1937).

ion from toluenesulfonate IX. The effects of water and acetate salt are then solvent and salt effects.

The small magnitude of the effect of water on the rate constant for solvolysis of the acetate-tosylate IX makes it very clear that water, which in the presence of acetate ion diverts the product to monoacetate VII and the steric result to inversion of configuration, does not accomplish these results in the rate-determining stage of the solvolysis. Were its action in the rate-determining step, then, judging by its efficiency, the reaction involving water when appreciable water concentrations are used would be much faster than the residual one. Thus, the presence of water would give rise to a large rate increase, unless, by some chance, toluenesulfonate IX and water combine quite completely to give a compound which is only moderately reactive. Conceivable examples of such compounds are a hydrogen-bond complex or the addition compound[4,5] XI (which may be criticized on other grounds).



XI

Actually, such compound formation would be reflected in abnormally small depressions of the freezing point of acetic acid by mixtures of toluenesulfonate IX and water. Pertinent freezing point measurements, summarized in Table III, speak against compound formation.

TABLE III

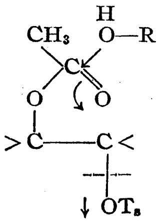
FREEZING POINTS OF ACETIC ACID SOLUTIONS OF WATER AND *trans*-2-ACETOXYCYCLOHEXYL *p*-TOLUENESULFONATE

(ROT_s), *M*	0.00	0.00	0.00	0.20	0.50	0.20
(H_2O), *M*	.00	.30	0.50	0.00	0.00	0.30
F. p. lowering, °C.	.00	.97	1.69	0.57	1.32	1.72

It can be seen that the depression of the freezing-point for the solution containing both the acetate-tosylate and water is even greater than the sum of the depressions for the appropriate concentrations of each solute alone, although this difference is not much greater than the experimental error. Thus no compound formation is indicated at the freezing point and is expected to be even less probable at the higher temperatures used in the rate experiments.

In the case of alcoholysis of the toluenesulfonate IX (which gives rise to orthoacetate VIII) again it is clear that no unique role is to be ascribed to the alcohol in the rate-determining step. The first-order rate constant for alcoholysis at 75° was steady and amounted to about two-thirds (Table II) of the value in glacial acetic acid. This is in line with the near equality of acetic acid and ethanol as solvents for solvolysis of halides.[9]

It becomes possible therefore to rule out for the present case such mechanisms as the one symbolized by XII which postulate a concerted attack by a water or alcohol molecule and simultaneous departure of the toluenesulfonate ion. This latter type of mechanism has been envisioned by Isbell[10] for orthoester formation from acetohalogen sugars. Similar mechanisms involving acetate ion instead of water are ruled out also by the data.



XII

The data for several runs with no added water or acetate salt (which gave the decreasing and then increasing first-order reaction rate constants) are summarized in Table IV. The first column lists *a*, the initial concentration of toluenesulfonate IX, and the second column indicates the concentration of added diphenylguanidinium *p*-toluenesulfonate (DPG·HOT_s) when it was used. From a plot of ln $(a - x)$ against time, *t*, *x* being the concentration of generated toluenesulfonic acid, fairly accurate values of the slope, d ln $(a - x)/dt$,

TABLE IV

SUMMARY OF DATA ON ACETOLYSIS OF *trans*-2-ACETOXYCYCLOHEXYL *p*-TOLUENESULFONATE IN ACETIC ACID CONTAINING 0.0459 *M* ACETIC ANHYDRIDE AT 99.7°

a	Solute	*x* at min.	Min. 10^4 *k* (sec.$^{-1}$)	10^4 k_0 (sec.$^{-1}$)
0.028		0.008	0.98	
.05		.008	.87	1.91 ± 0.29
.10		.012	.61	
.032	0.027 *M* DPG·HOT_s	.009	.84	2.3

TABLE V

INSTANTANEOUS FIRST-ORDER RATE CONSTANTS FOR ACETOLYSIS OF 0.02766 *M* *trans*-2-ACETOXYCYCLOHEXYL *p*-TOLUENESULFONATE AT 99.7° IN ACETIC ACID 0.0459 *M* IN ACETIC ANHYDRIDE

Time, min.	10^3 *x*	10^4 *k* (sec.$^{-1}$)
0.00	0.00	2.02
2.15	0.67	1.81
14.15	3.15	1.14
22.15	4.45	1.10
30.15	5.64	1.08
51.57	8.32	0.95
77.90	11.18	1.03

---

[9] *E. g.*, for methylvinylcarbinyl chloride see Roberts, Young and Winstein, *ibid.*, **64**, 2157 (1942), and Young and Andrews, *ibid.*, **66**, 421 (1944).

[10] Isbell, "Annual Review of Biochemistry," Annual Reviews, Inc., Stanford Univ. Press, Stanford Univ. P. O., Calif., 1940, p. 65.

called k, could be measured at various points with the aid of a tangent meter. In Table V are shown the k values thus determined for one run. In the third and fourth columns of Table IV are listed the values of x and k at the minima. The last column gives the extrapolated initial value of k, k_0. It is seen that, within the accuracy of this kind of a procedure, the initial rate constants, k_0, were roughly those expected. The minimum rate constant, one-third to one-half the initial value, occurred at a value of x of about 0.01 M.

It is very clear that the complex behavior of the rate constant is due to generated toluenesulfonic acid. Toluenesulfonate ion by itself did not give a lowered rate by virtue of any ability to compete successfully with solvent or acetate ion for the intermediate X (or II). Thus the initial rate constant with added diphenylguanidinium *p*-toluenesulfonate (Table IV) was normal. Also, the substitution of DPG·HOTs for half of the diphenylguanidine in runs 21 and 22, Table II, gave essentially no rate lowering. On the other hand, runs with two moles of ester per mole of diphenylguanidine gave a quite normal rate constant initially which held up fairly well until the solution became acidic when it decreased very markedly and then increased again.

This phase of the subject has not been more completely investigated and requires more knowledge of the chemistry of orthoester intermediates. The indications from the rate work and the earlier work are that toluenesulfonate ion in acid acetic acid solution in the absence of water is able to divert some intermediate back to *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate IX (or I). The back reaction may involve orthodiacetate IV (which may not proceed to *cis*-diacetate V rapidly enough and thus accumulate), a proton and toluenesulfonate ion, perhaps by way of the cation X (or II) in equilibrium with orthodiacetate IV. In the presence of water no such complication is possible because of the very successful competition of water with acetic acid for coördination to carbon atom C_3 of the intermediate II, producing orthomonoacetate VI and subsequently monoacetate VII.

Experimental

Anhydrous Acetic Acid.—The water content of General Chemical Company reagent grade glacial acetic acid, m. p. 16.2° or higher, was estimated from its m. p., assuming water to be the impurity. Enough pure acetic anhydride was added to react with the water and the mixture was held under reflux for four hours. Distillation yielded, as a main fraction, acid, m. p. 16.55°. Virtually the same m. p. was obtained when the acid was dried with triacetyl borate.[11]

Solvent with excess acetic anhydride was prepared by refluxing 250 ml. of dry acid with 2.0 ml. pure acetic anhydride for three hours (m. p. 16.32°). For some of the runs, another solvent, 0.0459 M in acetic anhydride, was used.[12]

Diphenylguanidinium *p*-Toluenesulfonate.—To 150 ml. of dry ether was added 4.3 g. (0.0226 mole) of *p*-toluenesulfonic acid monohydrate. A small aqueous phase appeared which was separated and extracted with 50 ml. of ether. The combined ether solutions were slowly added with shaking to a solution of 4.9 g. (0.0232 mole) of diphenylguanidine in 150 ml. of dry ether. The mixture was kept in a refrigerator several hours. Then the crystals were filtered off, washed with cold ether and dried to yield 7.8 g. (0.0204 mole), 91% of material; m. p., after recrystallization from chloroform–benzene, 171.9–172.4°.

Anal.[13] Calcd. for $C_{20}H_{21}O_3N_3S$: C, 62.64; H, 5.52. Found: C, 62.61; H, 5.75.

***trans*-2-Acetoxycyclohexyl *p*-Toluenesulfonate.**—This material, m. p. 78°, was prepared as described previously.[5]

Titrations in Glacial Acetic Acid.—Approximately 0.05 N or 0.10 N perchloric acid in glacial acetic acid, prepared from 60% aqueous acid of known titer against aqueous standard sodium hydroxide, was used as standard acid. As standard base was employed either Eastman Kodak Co. diphenylguanidine, m. p. 147–148°, or standard sodium acetate prepared from pure sodium carbonate. As indicator was used either crystal violet[8a,14] or, in the later stage of the work, a brom phenol blue indicator solution.[12]

Procedure for Rate Measurements.—The reagents were weighed out and made up to volume in the proper acetic acid solvent at 20–23°, water being added from a graduated pipet in some cases. Concentrations are all given at room temperature. Approximately 6–7-ml. portions were sealed in tubes and immersed either in the vapor over boiling water in a 100° thermostat or an ordinary thermostat at 74.90 ± 0.05°. The exact temperature in the 100° thermostat was obtained from the barometric reading, but was always 99.70 ± 0.10. Time was counted from immersion of the tube to its removal and quenching in ice-water. After being cooled a tube was allowed to come to room temperature, then it was opened and a 5-ml. aliquot was pipetted out for titration with standard acid or base from a 5-ml. microburet. Time was called zero for the first tube after attainment of temperature, initial concentrations being adjusted from the titration data on this tube. In the experiments with added acetate ion titration of an unheated tube was used to check on the initial acetate ion concentration.

In the dry acetic acid solvent in the absence of acetate ion, the tubes tended to darken toward the end of a run. This made it impossible to obtain an infinity titre. With acetate ion present, titration after seventeen hours at 100° showed 99.9% of the theoretical consumption of base. Another series of experiments showed 99.6% after ten hours at 110°.

Titration of toluenesulfonic acid and diphenylguanidine solutions in glacial acetic acid showed that the former maintained its titre within 0.5% after two and one-half hours at 100°, and the latter within 0.4% after four hours at 100°.

Diphenylguanidinium *p*-toluenesulfonate, which was added in some of the rate runs, was shown not to liberate any detectable acid on heating two hours in acetic acid containing 0.0459 M acetic anhydride either in neutral solution or in solution 0.016 M in perchloric acid.

For the alcoholysis of the toluenesulfonate in absolute ethanol, the reaction was followed by titration of 5 ml. aliquot portions with 0.05 N standard aqueous base to the brom thymol blue end-point.

The potassium acetate used as a solute in some of the runs was carefully dried reagent-grade material.

Summary

The kinetics of acetolysis of *trans*-2-acetoxycycylohexyl *p*-toluenesulfonate are closely first-order in the presence of small concentrations of water or acetate ion. The evidence is that the

---

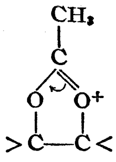
[11] Eichelberger and La Mer, THIS JOURNAL, **55**, 3633 (1933).

[12] Winstein, Grunwald and Ingraham, *ibid.*, **70**, 821 (1948).

[13] Analysis by Mr. Jack Ralls.

[14] Nadeau and Branchen, THIS JOURNAL, **57**, 1363 (1935).

rate-determining step in the solvolysis is the formation of the ion II.



II

Water and acetate ion, which control the nature of the product and the steric result, do not exercise this control in the rate-determining step.

Similarly, for alcoholysis of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate, II appears to be the intermediate, orthoester formation being accomplished at a later step than the rate-determining one.

The rate constants for acetolysis of the toluenesulfonate in acetic acid not containing water or acetate ion decrease seriously as acid develops and then increase again. The best interpretation of the downward drift is that *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate is regenerated by the action of acid and toluenesulfonate ion on an intermediate such as orthodiacetate.

LOS ANGELES, CALIFORNIA RECEIVED APRIL 3, 1947

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

The Role of Neighboring Groups in Replacement Reactions. XI. Some Reactivities Involving Neighboring Groups[1]

BY S. WINSTEIN, E. GRUNWALD, R. E. BUCKLES AND C. HANSON

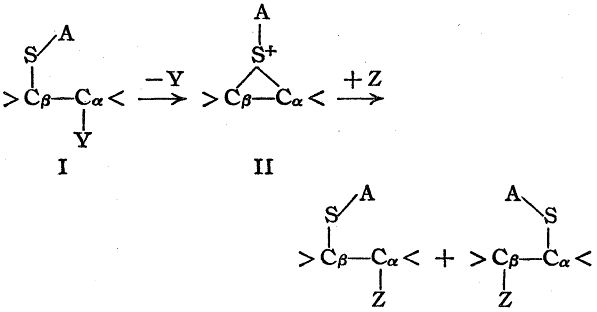
Participation of neighboring groups in displacement reactions has long been known with such groups as O^- (from OH) and NH_2, prior ring closure[2] to isolatable oxide or imine occurring on attempted displacement of halide in a halohydrin or aminohalide. In these cases the groups are those which also take part in known bimolecular displacements[3] symbolized in equations 1 and 2.

$$RO^- + R'X \longrightarrow ROR' + X^- \qquad (1)$$

$$RNH_2 + R'X \longrightarrow (RNH_2R')^+ + X^- \qquad (2)$$

While the so-called classical groups, O^-, NR_2 and SR have been mentioned in preceding articles of this series,[4] the main stress[5] has been on participation in nucleophilic displacement reactions by such neighboring groups as OAc, Br and OCH_3, which are not known to participate in external displacements. Actually there is no sharp division between the latter groups and the more classical ones.

Participation by a neighboring group S-A is symbolized[4a] below, Y and Z indicating the leaving and entering groups, respectively.



We have previously indicated there are questions of intimate mechanism with respect to both the closing and opening of the ring in II.[4a] Rate measurements are helpful in this connection, and in the present article and subsequent ones are reported reactivity measurements in some unimolecular-type[6] nucleophilic displacement reactions.

As is brought out in this paper and articles XII and XIII in the series, the rate measurements yield important formation concerning the nature of the rate-determining ionization step. Using a common set of symbols for all three papers, the ionization step may be[4a] either **A**, a one-stage ring closure to the cyclic intermediate II with Walden inversion (W.I.) at C_α or **B**, an ionization to the substituted carbonium ion III.[3,4a,7]

Two different criteria for distinguishing between the two rate-determining steps A and B have been employed in the work described in this paper. First, the effect on the rate of the disposition of the neighboring group *cis* or *trans* to the departing

---

[1] Most of the material contained in this paper was reported before the Organic Division of the American Chemical Society at the Cleveland and Atlantic City meetings, April, 1944, and April, 1946.

[2] (a) Smith and Nilsson, *J. prakt. Chem.*, **162**, 63 (1943); (b) Braun and Weissbach, *Ber.*, **63**, 3052 (1930); (c) Freundlich and Salomon, *Z. physik. Chem.*, **A166**, 161 (1933).

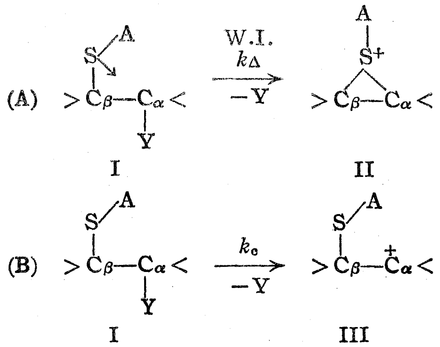
[3] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapters V and VI.

[4] (a) Winstein and Buckles, THIS JOURNAL, **64**, 2780 (1942); (b) Winstein and Buckles, *ibid.*, **64**, 2787 (1942); (c) Winstein, *ibid.*, **64**, 2791 (1942); (d) Winstein, *ibid.*, **64**, 2792 (1942); (e) Winstein, Hess and Buckles, *ibid.*, **64**, 2796 (1942); (f) Winstein and Buckles, *ibid.*, **65**, 613 (1943); (g) Winstein and Henderson, *ibid.*, **65**, 2196 (1943); (h) Winstein and Seymour, *ibid.*, **68**, 119 (1946); (i) Winstein, Hanson and Grunwald, *ibid.*, **70**, 812 (1948).

[5] Very recently a number of cases of participation by NR_2 and SR have been noted, *e. g.*: (a) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188 (1947); (b) Gilman and Philips, *Science*, **103**, 409 (1946); (c) Golumbic, Stahmann and Bergmann, *J. Org. Chem.* **11**, 550 (1946); (d) Fuson, Price and Burness, *ibid.*, **11**, 475 (1946).

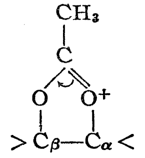
[6] This term is used to indicate nucleophilic displacement reactions which do not involve in the rate-determining step a nucleophilic attack on carbon by an external reagent. The term *S_N1* type was used previously[4] but this expression is best reserved for step **B**.

[7] (a) Bateman, Church, Hughes, Ingold and Taher, *J. Chem. Soc.*, **979** (1940); (b) Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).



group has been investigated. Second, rates of substitution involving various neighboring halogens are reported, and the influence of a change in the halogen atom on the reactivity is observed.

In order to appraise the influence of the geometric position of the neighboring group on the substitution rate, the reactivities of cyclohexyl chloride and the *cis*- and *trans*-2-acetoxycyclohexyl chlorides toward silver acetate in glacial acetic acid have been compared. After a reaction period of thirty-two hours in acetic acid at 100–110°, cyclohexyl chloride was converted partly to cyclohexyl acetate and largely to cyclohexene. Under the same conditions, *trans*-2-acetoxycyclohexyl chloride reacted only incompletely in dry and slightly aqueous acetic acid to give 40–50% yields of materials of steric configurations identical with those reported before[4a,b] for the acetoxybromide and interpreted on the basis of the cyclic intermediate IV.


IV

Under the same conditions, *cis*-2-acetoxycyclohexyl chloride proved so unreactive that only unreacted starting material was recovered. Similarly only unreacted starting material was recovered when a reaction temperature some 20° higher was employed.

A more quantitative evaluation of the effect of a *cis*- and *trans*-acetoxy group is derived from the rates of first-order acetolysis of the cyclohexyl *p*-toluenesulfonates. The rate of acetolysis of trans-2-acetoxycyclohexyl *p*-toluenesulfonate is reported in a preceding paper,[4i] and we now add for comparison the rates for the cyclohexyl and *cis*-2-acetoxycyclohexyl esters.

In Tables I and II are given typical data obtained in the determination of the first-order rate constants k of acetolysis of the cyclohexyl and the *cis*-2-acetoxycyclohexyl esters. In Table III are collected first-order rate constants for the three compounds in anhydrous acetic acid with and without added 0.1 M diphenylguanidinium acetate. It is evident from the data in Table III that the specific rates remain quite unchanged, allowing for salt effects, upon the addition of 0.1 M acetate salt, indicating that the reactions are of the unimolecular type. On the basis of these data, the relative reactivities in anhydrous acetic acid at 99.7° are in the following sequence: unsubstituted, 1.00 > *trans*-2-OAc, 0.30 ≫ *cis*-2-OAc, 4.5 × 10^{-4}.

TABLE I

ACETOLYSIS OF CYCLOHEXYL *p*-TOLUENESULFONATE (ROTs) IN ACETIC ACID AT 74.9°

Time, min.	ROTs, M	$10^5\,k$, sec.$^{-1}$
0	0.0896	..
11	.0876	..
31	.0834	4.13
71	.0755	4.16
171	.0586	4.18
371	.0336	4.44
581	.0192	4.44
		Mean 4.27 ± 0.14

TABLE II

ACETOLYSIS OF *cis*-2-ACETOXYCYCLOHEXYL *p*-TOLUENESULFONATE (ROTs) IN ACETIC ACID AT 99.7°

Time, min.	ROTs, M	$10^7\,k$, sec.$^{-1}$
0	0.09689	..
50	.09665	..
630	.09563	3.05
1620	.09412	2.82
2565	.09252	2.89
		Mean 2.92 ± 0.09

TABLE III

RATE CONSTANTS OF ACETOLYSIS OF *p*-TOLUENESULFONATES IN ACETIC ACID

p-Toluenesulfonate	Other solute	Temp., °C.	k (sec.$^{-1}$)
Cyclohexyl	....	74.9	$(4.27 \pm 0.14) \times 10^{-5}$
	0.095 M DPG[a]	74.9	$(6.13 \pm 0.06) \times 10^{-5}$
	....	99.7	$(6.42 \pm 0.13) \times 10^{-4}$
	0.100 M DPG[a]	99.7	$(8.7 \pm 0.2) \times 10^{-4}$
trans-2-Acetoxy-	....	99.7	1.9×10^{-4}
cyclohexyl[4i]	0.100 M DPG[a]	99.7	2.1×10^{-4}
cis-2-Acetoxy-	....	99.7	$(2.92 \pm 0.09) \times 10^{-7}$
cyclohexyl	0.108 M DPG[a]	99.7	$(5.3 \pm 0.7) \times 10^{-7}$
	....	131	$(8.0 \pm 0.3) \times 10^{-6}$

[a] Diphenylguanidinium acetate.

The relatively high reactivity of the *trans*-isomer, and the striking difference in reactivity between the *cis*- and *trans*-isomers are not readily explained on the basis of the carbonium ion mechanism B alone. It is clear from the available data on inductive effects, such as Branch and Calvin's inductive constants,[8] that the acetoxy group is strongly electron-removing. As a result, the reaction by way of a carbonium ion intermediate is expected to be considerably slower in the presence of a neighboring acetoxy group as is actually the case only with the *cis*-material. In order to correlate the observed reactivities, it is suggested

---

[8] Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, Chapter VI.

that the reaction of the *trans*-2-acetoxycyclohexyl ester proceeds by way of the one-stage ring-closure mechanism **A** which apparently involves a more favorable free-energy of activation than the carbonium ion mechanism **B**. On the other hand, the acetolysis of the *cis*-ester proceeds very probably by way of a carbonium ion mechanism because in the *cis*-position the neighboring acetoxy group cannot form a cyclic intermediate with inversion of configuration at C_α without essentially prohibitive strain.

Whereas the *cis*-2-acetoxycyclohexyl chloride was too inert to the action of silver acetate to allow isolation of the product, the acetolysis of *cis*-2-acetoxycyclohexyl *p*-toluenesulfonate proceeded rapidly enough so the stereochemistry of the displacement could be examined. The *cis*-toluenesulfonate yielded after a twenty-four hour reflux period in a potassium acetate solution in anhydrous acetic acid a diacetate which, on direct saponification and subsequent sublimation, gave rise to quite pure *trans*-glycol. Thus the steric result with the *cis*-compound is very predominant inversion of configuration in contrast to the very predominant retention of configuration in contrast to the very predominant retention of configuration observed[4e] under the same conditions with the *trans*-compound. Thus we have here another example of the tendency for production of *trans*-product from *cis*- and *trans*-2-substituted materials.[4a] The analogous action of an acetoxy group in the reactions of acetohalogen sugars with silver acetate has already been discussed.[4a]

The comparison of the effects of the various neighboring halogen atoms was based on semi-quantitative measurements of the rate of reaction of some alcohols with hydrobromic or hydrochloric acid. The reactions were followed by observing the rate of growth of the halide layer from a solution of the proper alcohol in the hydrobromic or hydrochloric acid and estimating the time for half-reaction. One set of reactivities deals with 2-butanol and the related bromohydrin and chlorohydrin, while another set is available for cyclohexanol and the related halohydrins. The pertinent data are summarized in Table IV. The rates of the unsubstituted and β-bromo and β-chloro-substituted alcohols were conveniently compared in fuming hydrobromic acid. The reactivity in the presence of neighboring iodine was so high that the less active concentrated hydrochloric and 48% hydrobromic acids were employed as reagents. Even though the half-life of cyclohexanol in 48% hydrobromic acid was 500 times that in the fuming acid, *trans*-2-iodocyclohexanol reacted so fast in the former solvent that the solution was cloudy before solution of the solid iodohydrin was complete. It is evident from the data in Table IV that a neighboring *trans*-iodine atom raises the reactivity of cyclohexanol almost to that of *t*-butyl alcohol.

TABLE IV

REACTIVITY OF VARIOUS ALCOHOLS TOWARD HALOGEN ACIDS

Compound	Solvent	Half-life *ca.* 20°	Rel. rate
Cyclohexanol	Fuming HBr	20 min.	1.0
Cyclohexanol	48% HBr	7 days	1.0
Cyclohexanol	Concd. HCl	12 days	1.0
trans-2-Chlorocyclohexanol	Fuming HBr	85 days	1.6×10^{-4}
trans-2-Bromocyclohexanol	Fuming HBr	4 hr.	0.08
trans-2-Iodocyclohexanol	48% HBr	*ca.* 15 min.	700
trans-2-Iodocyclohexanol	Concd. HCl	*ca.* 15 min.	1200
2-Butanol	Fuming HBr	75 min.	1.0
2-Butanol	48% HBr	76 hr.	...
threo-3-Bromo-2-butanol	Fuming HBr	3 hr.	0.4
Mixed 3-chloro-2-butanols	Fuming HBr	No halide layer in 25 days	3×10^{-4a}
t-Butyl alcohol	Concd. HCl	45 sec.	...

[a] Conservative estimate.

Again, the reactivities in Table IV are not compatible with the carbonium ion mechanism **B** alone. In the case of a rate-determining formation of a carbonium ion, the rates in the presence of a β-halogen atom are expected to be considerably slower than those of the unsubstituted alcohol due to the strong electron-removal by halogen which clearly opposes the formation of a positive charge on carbon. Moreover, from such physical evidence as ionization constants of aliphatic acids[8] and dipole moments of alkyl halides,[9] it would be reasonable to expect the retardation of the unimolecular rate to be not very far from equal for the various halogen atoms. The predicted rate sequence is therefore: unsubstituted $\gg$ I $\approx$ Br $\approx$ Cl. It is clear that the observed rates are not even in qualitative accord with this sequence, a neighboring iodine atom increasing reactivity by three powers of ten and a neighboring chlorine atom decreasing it by four powers of ten. In order to correlate the high reactivities in the presence of neighboring bromine and iodine, we suggest that we are here dealing with the one-stage mechanism of ring-formation, **A**. The sequence I $\gg$ Br is reasonable because iodine is generally a better nucleophilic agent than bromine. The data do not permit a definite decision regarding the substitution mechanism in the presence of neighboring chlorine although the sluggishness of the substitution suggests a carbonium ion intermediate, III. More evidence on this point is presented in succeeding papers.

It has been assumed in the preceding discussion that the reactions of the cyclohexanols and 2-butanols with halogen acids proceed by way of a unimolecular-type mechanism. This assumption is reasonable for the cyclohexanols since the alternate substitution process, bimolecular attack on carbon, has been shown to proceed only very slowly in the cyclohexyl system.[10] Moreover, the

---

(9) Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 123.

(10) *E. g.*, Bartlett and Rosen, THIS JOURNAL, **64**, 543 (1942).

stereochemistry of the replacement process in the presence of neighboring bromine[4d] rules out the possibility of considerable bimolecular reaction with inversion of configuration in the reaction of the bromohydrins. On the other hand, the reaction of 2-butanol may well proceed to a considerable extent by way of the bimolecular process C.

$$\text{(C)}\quad Br^- + ROH_2^+ \longrightarrow Br - R + OH_2$$

This fact is indicated by the rather high survival of optical activity together with the change in sign of rotation in the transformation.[11] In the analogous case of 2-octanol, we can estimate from the observed optical rotation data and data in the literature[11] a 57% survival of activity with predominant inversion in the reaction with fuming hydrobromic acid. As is clear from experiments described in the experimental section, racemization is of some importance during these transformations, so inversion would be even more prominent after proper correction.

Another indication that the reaction of 2-butanol may be largely bimolecular in type is the contrast in the reaction rates of cyclohexanol and 2-butanol in various halogen acids. While the reactivity of cyclohexanol is reduced to 1/500 by a change in reagent from fuming hydrobromic to 48% hydrobromic acid, the reactivity of 2-butanol is lowered only by a factor of 50. Moreover, while the rates of cyclohexanol in 48% hydrobromic and concentrated hydrochloric acid are quite comparable, solution of optically active 2-butanol in concentrated hydrochloric acid gives rise to no appreciable reaction and no change in optical activity after elapsed times comparable to the half-life in 48% hydrobromic acid. On the basis of these data it is probable that the relative rate of *threo*-3-bromo-2-butanol in a unimolecular-type displacement may well be above the figure 0.4 listed in Table IV.

Experimental

***cis*-2-Chlorocyclohexanol.**—This material was prepared by the method of Bartlett.[12] Careful distillation of the material after destruction of the *trans*-isomer with base yielded a solid product, b. p. 92.5–93.0° (27 mm.), m. p. 31.5°.

***cis*-1-Acetoxy-2-chlorocyclohexane.**—Acetylation of 20 g. of *cis*-chlorohydrin by the procedure used with the *trans*-bromohydrin[4a] gave rise to an 87% yield of acetate, b. p. 98.3–99.0° (12 mm.) n^{25}_D 1.4654.

Anal.[13,14] Calcd. for $C_8H_{13}O_2Cl$: C, 54.39; H, 7.42; Cl, 20.07. Found: C, 53.83; H, 7.41; Cl, 19.64.

***trans*-1-Acetoxy-2-chlorocyclohexane.**—*trans*-Chlorohydrin, prepared by the method of Coleman and Johnstone,[15] was acetylated by the procedure used with the *trans*-bromohydrin[4a] to yield material, b. p. 98.0–98.5° (12 mm.), n^{25}_D 1.4630.

Treatment of Cyclohexyl Halides with Silver Acetate.—Cyclohexyl chloride and the *cis*- and *trans*-2-acetoxycyclohexyl chlorides were treated with silver acetate in glacial acetic acid in the manner used previously with the analogous bromides.[4a,b] A bath temperature of 100–110° and a reaction time of thirty-two hours were employed.

From 17.7 grams (0.10 mole) of the *trans*-2-acetoxycyclohexyl chloride, using anhydrous acetic acid, was obtained on distillation at 12 mm.: 5.5 g., b. p. 98.5–100.0°, n^{25}_D 1.4609; 4.0 g., b. p. 100.0–117.4°; and 4.0 g., b. p. 117.4–118.8°, n^{25}_D 1.4482; the residue being 0.5 g. The saponification analysis procedure[4a] with the diacetate fraction (high-boiling) gave rise to a glycol, m. p. up to 95° (98–102° on mixing with *trans*-glycol), 103–103.5° after recrystallization from carbon tetrachloride.

Similarly from the treatment in acetic acid with an equivalent amount of water was obtained at 12 mm.: 5.5 g., b. p. 97.5–100.0°, n^{25}_D 1.4600; 4.0 g., b. p. 100.0–112.5°; 4.0 g., b. p. 112.5–115.0°, n^{25}_D 1.4568; residue 0.5 g. The high boiling fraction yielded largely *cis* glycol, m. p. up to 85° (m. p. lowered on mixing with *trans*-glycol), 97.0–97.5° after recrystallization from carbon tetrachloride.

Analogous treatment under anhydrous conditions of 17.7 g. (0.10 mole) of the *cis*-2-acetoxycyclohexyl chloride gave rise at 12 mm. to a 1.5 g. forerun up to 98.5°, 11.5 g., b. p. 98.5–100.0°, n^{25}_D 1.4651, and a 2 g. tarry residue from which diacetate could not be distilled. A similar run with a stoichiometric amount of water yielded at 12 mm. 2 g. of forerun, 11.5 g., b. p. 98.5–100.0°, n^{25}_D 1.4654, and a 0.5 g. residue. A run with xylene, b. p. 136–141°, as a solvent at the reflux temperature gave at 12 mm. 15 g., b. p. 97.5–100.5°, n^{25}_D 1.4674, and a 0.5 g. residue.

Treatment of 11.9 g. (0.10 mole) of cyclohexyl chloride, filtration, dilution with water and extraction with ether gave an ether extract of the product. This was washed with carbonate solution and dried over anhydrous potassium carbonate. Distillation gave rise to 2.5 g. (30%) of cyclohexene, b. p. 82°, and 2.1 g. (15%) of cyclohexyl acetate, b. p. 95–99° (67 mm.).

***cis*-2-Acetoxycyclohexanol.**—To a mixture of 59 g. (0.51 mole) of *cis*-1,2-cyclohexanediol (m. p. 98°), 51 g. (0.50 mole) of acetic anhydride and 10 ml. of ether was added 10 drops of concentrated sulfuric acid. Ten more drops of acid were added after a time. After the mixture had returned to room temperature it was shaken with calcium carbonate to neutralize the acid. Then it was filtered and distilled. From the distillate, 4 g. of solid glycol were filtered out. The remaining 62 g. of product, b. p. 114–115° (12 mm.) n^{25}_D 1.4618, saponification equivalent weight 149, 92 mole per cent. monoacetate, 8 mole per cent. diacetate, represented an 84% yield allowing for recovered glycol.

***cis*-2-Acetoxycyclohexyl *p*-Toluenesulfonate.**—This material was prepared analogously to the *trans*-isomer[4e,16] by treatment of the *cis*-1,2-cyclohexanediol monoacetate–diacetate mixture with *p*-toluenesulfonyl chloride in pyridine. Stirring the reaction mixture with water which was later acidified with sulfuric acid gave rise to an oil which was taken up in ligroin. Drying of the ligroin solution over anhydrous potassium carbonate and storage in the refrigerator gave rise to a 67% yield (on a 40 g. batch) of crude crystalline product, m. p. 76–77° after one recrystallization from aqueous methanol and 77–78° after another recrystallization.

Anal. Calcd. for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45. Found: C, 57.65; H, 6.53.

Cyclohexyl *p*-Toluenesulfonate.—This material was prepared in 46% yield by the general method of Gough, Hunter and Kenyon.[17] After recrystallization from petroleum ether the m. p. was 43.5–44.0° (reported[18] 44–45°).

Rate Measurements.—The procedure for the acetolysis measurements in anhydrous acetic acid was the same as

---

[11] (a) Pickard and Kenyon, *J. Chem. Soc.*, 45 (1911); (b) Hughes, Ingold and Masterman, *ibid.*, 1196 (1937); (c) Cowdrey, Hughes, Ingold, Masterman and Scott, *ibid.*, 1252 (1937).

[12] Bartlett, THIS JOURNAL, **57**, 224 (1935).

[13] C, H analyses by Mr. Fukushima.

[14] Chlorine analysis by courtesy of Dr. Haagen-Smit of the California Institute of Technology.

[15] Coleman and Johnstone, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, N. Y., 1932, p. 151.

[16] Criegee and Stanger, *Ber.*, **69B**, 2753 (1936).

[17] Gough, Hunter and Kenyon, *J. Chem. Soc.*, 2052 (1926).

[18] Hückel, Neunhoeffer, Gercke and Frank, *Ann.*, **477**, 99 (1929).

described previously.[4i] Refluxing chlorobenzene was used as a thermostat liquid at 131°. The *cis*-2-acetoxycyclohexyl *p*-toluenesulfonate reacted very slowly and was followed to 5–6% reaction at 99.7 ± 0.10° and to 20% reaction at 131°. In the case of cyclohexyl *p*-toluenesulfonate the reaction was followed to 70–80% reaction.

Acetolysis of *cis*-2-Acetoxycyclohexyl *p*-Toluenesulfonate.—A 1.5 g. portion of *cis*-2-acetoxycyclohexyl *p*-toluenesulfonate was held under reflux twenty-four hours in 6 ml. of acetic acid containing a trace of acetic anhydride and a slight excess of potassium acetate. The neutralization of the reaction mixture, extraction of the ester product with ether, drying of the ether solution and evaporation of the ether yielded the ester product. Saponification of the ester, treatment of the reaction mixture with carbon dioxide, evaporation and then sublimation gave rise to 0.11 g. (20%) of glycol, m. p. 90–92°, 101–102.5° after recrystallization from carbon tetrachloride (103–104° on mixing with authentic *trans*-glycol). A blank saponification of *cis*-2-acetoxycyclohexyl *p*-toluenesulfonate followed by sublimation did not give glycol.

The yield of glycol (20%) was quite normal if one allows for the fact that, interpolating with the aid of the available rate constants in Table III, it is estimated that the extent of acetolysis of *cis*-2-acetoxycyclohexyl *p*-toluenesulfonate in twenty-four hours at *ca.* 120° is 35%.

***trans*-2-Iodocyclohexanol.**—To 100 ml. of 46% reagent-grade hydriodic acid (density 1.50) cooled in a salt–ice-bath was slowly added with effective stirring 49.2 g. (0.50 mole) of cyclohexene oxide. After approximately three fourths of the oxide had been added, solid precipitated. Stirring was continued for fifteen minutes after the addition of oxide was complete. Then the iodohydrin was filtered off and air-dried. The crude product obtained in nearly quantitative yield was dissolved in ether. The iodine color was discharged by the addition with vigorous shaking of small portions of solid sodium bisulfite. The ether solution was decanted and dried over anhydrous potassium carbonate. The ether was then removed at room temperature with the aid of the water pump, and 100 ml. of petroleum ether was added. Cooling gave crystalline product which was recrystallized from petroleum ether to yield 75 g. (66%) of air-dried material, m. p. 39–40°. Another recrystallization gave material, m. p. 39.9–40.4° (reported[19] m. p. 41.5–42.0°), which was slower to develop color on standing. The equivalent weight of the iodohydrin on treatment with base[12] was 226.3 (calculated 226.1).

Treatment of Alcohols and Halohydrins with Fuming Hydrobromic Acid.—This was usually carried out as previously described,[20] the reaction mixture being sealed at 0° and allowed to warm up to and remain at room temperature. The preparation of the samples of *threo*-3-bromo-2-butanol,[20] *trans*-2-bromocyclohexanol,[4a,d] and the mixed 3-chloro-2-butanols[21] needs no further description.

From the treatment of cyclohexanol, isolation of the product after 2 days gave rise to a 75% yield of cyclohexyl bromide, b. p. 69.5–69.8° (31 mm.), $n^{25}\mathrm{D}$ 1.4932.

From the treatment of a 17.5 ml. volume of partially resolved 2-butanol, b. p. 98.5–99.0° (745 mm.), $\alpha^{22.5}\mathrm{D}$ (1 dcm.) 1.20° was obtained after two days 24 g. of crude, 19.0 g. of distilled bromide, b. p. 89–91°, $n^{21.5}\mathrm{D}$ 1.4365, $\alpha^{23}\mathrm{D}$ (1 dcm.) −2.32°.

The bromide layer from the treatment of a 22.13 g. quantity of 2-butanol, prepared by mixing 11.15 g. of active 2-butanol, b. p. 99.0–99.3° (754 mm.), $\alpha^{24}\mathrm{D}$ (1 dcm.) 4.93°, with 10.98 g. *dl*-2-butanol, b. p. 98.8–99.0° (745 mm.), was removed three times so that three nearly equal portions of halide were obtained. The fractions, 12.4 g. 12.9 g. and 12.5 g., totaled 37.8 g. (92%) before distillation. Distillation of the portions gave materials boiling at 90.2–90.3° (750 mm.), $\alpha^{20}\mathrm{D}$ (1 dcm.) for the fractions, −5.33°, −5.12°, −4.45°, average −4.97°.

Partially active 2-bromobutane, $\alpha^{24}\mathrm{D}$ (1 dcm.), −5.03°, b. p. 90.3° (746 mm.), was sealed with fuming aqueous hydrobromic acid saturated at 0°. The mixture was kept on a shaker for seven hours and then left overnight. Isolation yielded bromide, b. p. 90.3° (746 mm.), $\alpha^{25}\mathrm{D}$ (1 dcm.) −4.26°.

Octanol-2 (14.5 g.), $\alpha^{22.5}\mathrm{D}$ (1 dcm.) −6.20°, was treated with fuming hydrobromic acid prepared from 100 g. of the 48% material. The octanol did not dissolve but with occasional shaking the reaction proceeded with shrinkage of the upper layer. This shrinkage appeared complete in about four hours. After two days the bromide was isolated to yield 19.5 g. crude, 15.5 g. of pure material, b. p. 77.8–78.5° (17 mm.), $n^{22}\mathrm{D}$ 1.4508, $\alpha^{23}\mathrm{D}$ (1 dcm.) 16.31°.

A solution of 7.75 g. of *trans*-2-chlorocyclohexanol in 54 g. of 48% hydrobromic acid was saturated with hydrogen bromide at 0°, sealed, shaken and observed at room temperature. The estimated weights of separated dihalide after 12, 17, 26, 40 and 102 days were 0.08, 0.3, 1.0, 1.6 and 5.8 g., respectively. After 139 days, the oil layer was removed with the aid of 15 ml. of petroleum ether, the extract was washed with carbonate solution and dried over magnesium sulfate. Distillation through a small Vigreux column yielded 4.0 g. of a colorless material, b. p. 66–69° (3.5–4.5 mm.), $n^{22.6}\mathrm{D}$ 1.5321, d_4^{23} 1.602. The equivalent weight on halogen analysis[22] of this material was 108.8. Analysis for chlorohydrin by treatment of a methanol solution with excess standard base and back-titration to the brom thymol blue end-point after four minutes showed only 0.3% chlorohydrin. The equivalent weight indicates the material was a 50–50 by weight mixture of cyclohexene bromochloride and dibromide, some exchange of bromide for chloride taking place in the reagent or product during the lengthy reaction period.

Treatment of Alcohols and Halohydrins with Concentrated Hydrochloric Acid or 48% Hydrobromic Acid.—The concentration of the cyclohexanols in each of the reagents was approximately 1 *M*.

Upon mixing 0.01 mole of *trans*-2-iodocyclohexanol with 10 ml. of concentrated hydrochloric acid or 48% hydrobromic acid at 0° the iodohydrin partly or largely dissolves and rapidly forms the insoluble liquid dihalide which wets and dissolves the remainder of the solid iodohydrin. The volume of the oily layer amounts to about 70% of the final volume after a period of about ten minutes with either halogen acid. The oily layer proved to be a mixture of dihalide and iodohydrin.

A 0.100 mole quantity of iodohydrin was shaken twenty-five minutes with 100 ml. of ice-cold concentrated hydrochloric acid. Then 25 ml. of carbon tetrachloride was added and the organic layer was separated, washed, dried and distilled at reduced pressure. There was obtained 20.5 g. (*ca.* 85%) of an iodochloride fraction b. p. 73–74° 2 mm.), $n^{24}\mathrm{D}$ 1.5674. Stephanov analysis[22] for halogen gave an equivalent weight of 154.3, corresponding to 55% by weight iodochloride.

A 10 ml. volume of *dl*-2-butanol was dissolved in 50 ml. of 48% hydrobromic acid at room temperature. The approximate volume of oil layer was 1.5 ml. after twenty-one hours, 6.0 ml. after six days and 7.5 ml. after twelve days.

Approximately 2 ml. of active 2-butanol, $\alpha^{24}\mathrm{D}$ (1 dcm.) 4.93°, was dissolved in approximately an equal volume of concentrated hydrochloric acid. The $\alpha\mathrm{D}$ (1 dcm.) remained at 2.21 ± 0.01° for twenty-three hours at the end of which time the solution was very slightly turbid. The reading after seventy-one hours was 2.17°.

Summary

In connection with participation of neighboring groups in nucleophilic displacements of the unimolecular type, rate measurements lead to an understanding of the rate-determining ionization step. This may be either a direct formation of the

---

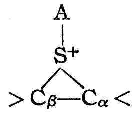
[19] Brunel, *Ann. chem.*, [8] **6**, 221 (1905).

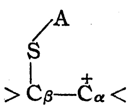
[20] Winstein and Lucas, THIS JOURNAL, **61**, 1576, 1581 (1939).

[21] Wilson and Lucas, *ibid.*, **58**, 2396 (1936).

[22] Kamm, "Qualitative Organic Analysis," John Wiley and Sons, New York, N. Y., 1942, p. 200.

cycle II or the preliminary formation of ion III.


II


III

Rates of acetolysis of cyclohexyl *p*-toluenesulfonates give the sequence: unsubstituted, 1.00 $>$ *trans*-2-OAc, 0.30 $\gg$ *cis*-2-OAc, 4.5×10^{-4}. Rates of reaction of the corresponding chlorides with silver acetate are qualitatively similar. Reactivities of 2-butanols and cyclohexanols toward hydrohalogen acids show that a neighboring *trans*-bromine atom gives a rate comparable to that of the unsubstituted material. A *trans*-iodine atom increases and a *trans*-chlorine atom decreases reactivity by factors of approximately 10^3 and 10^4, respectively.

These results are taken to indicate that with the *trans*-OAc, Br and I groups, the ionization is directly to II. On the other hand, with *trans*-Cl and *cis*-OAc, ionization is probably to III.

The product of acetolysis of *cis*-2-acetoxycyclohexyl *p*-toluenesulfonate is very predominantly *trans*.

LOS ANGELES 24, CALIF.

RECEIVED APRIL 3, 1947

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

The Role of Neighboring Groups in Replacement Reactions. XII. Rates of Acetolysis of 2-Substituted Cyclohexyl Benzenesulfonates[1]

BY S. WINSTEIN, ERNEST GRUNWALD AND L. L. INGRAHAM

In the present article are reported further rate measurements which give information on solvolysis rates involving a substantial series of neighboring groups in a cyclohexyl system. The reaction rate measured was that of acetolysis of a series of 2-substituted cyclohexyl *p*-bromobenzenesulfonates or *p*-toluenesulfonates symbolized by formulas VI and VII. These rate measurements serve to establish relative rates in the presence of various neighboring groups in a reaction of one charge-type and lend themselves better to a quantitative discussion than some reported in the previous paper.[2]

Results

Materials for Acetolysis.—For the most part, the materials for rate measurements (Table I) were prepared by conventional methods from the proper alcohol or glycol IV or V. The assignment of configuration (*trans* or *cis;* IV, VI *vs.* V, VII) to the various materials has been illustrated sufficiently in previous work[3] and is clear from the methods of preparation described in the experimental section.

The *trans*-2-iodocyclohexyl *p*-toluenesulfonate IX is very reactive and unstable and was difficult to obtain. All attempts at preparation by conventional methods from the cyclohexene iodohydrin IV (S-A = I) failed. A successful synthesis was achieved using the reaction of cyclohexene with silver *p*-toluenesulfonate and iodine in absolute ether. Under the special conditions used for this latter reaction (*e. g.*, absence of pyridine; no reactive solvent necessary in working up the reaction mixture) the product IX survived well enough to be isolated in reasonable yield. The reaction is formulated as proceeding through the iodonium ion VIII which reacts, in the absence of any better nucleophilic agent, with toluenesulfonate ion to yield *trans*-product IX. The material IX, thus prepared, gave a fair carbon–hydrogen analysis (Table I; this was not on the best sample). Also equivalent weight values which averaged within 1.5% of theory were obtained from: (a) titration of the iodine liberated on treatment with potassium iodide; (b) hydrolysis in aqueous acetone to iodohydrin followed by measurement of the quantity of alkali necessary to neutralize the acid and convert the iodohydrin to oxide; (c) the "infinity" titer in the actual acetolysis rate measurements.

TABLE I

2-SUBSTITUTED CYCLOHEXYL *p*-BROMOBENZENESULFONATES

Substituent	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
None	48.1–48.6	45.15	45.13	4.73	4.80
trans-OAc	97.4–97.9	44.57	44.69	4.54	4.66
trans-Br	91.9–92.3	36.20	36.16	3.54	3.54
trans-OCH_3	65.6–66.0	44.71	44.84	4.91	4.92
trans-Cl	77.9–78.3	40.75	40.63	3.99	3.89
cis-OAc	118.4–118.8	44.57	44.44	4.54	4.49
cis-$OSO_2C_6H_4Br$	128.7–129.2	39.00	38.91	3.27	3.52
trans-$OSO_2C_6H_4Br$	123.3–123.7	39.00	39.05	3.27	3.32
trans-OH	106.9–108.8	42.99	42.83	4.51	4.56
trans-I[a]	51–52	41.06	40.69	4.51	4.70

[a] *p*-Toluenesulfonate.

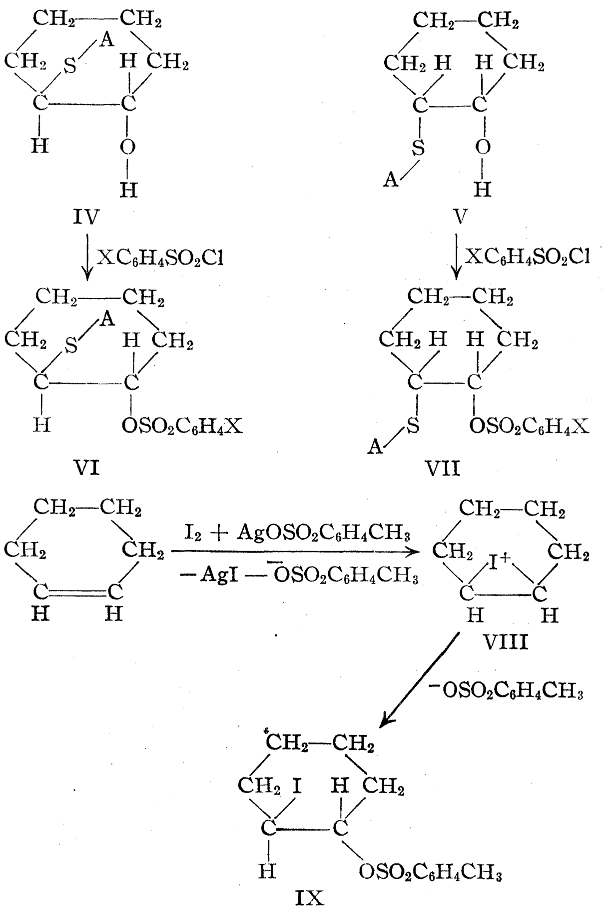
Solvolysis Rates.—The solvolysis rates were measured in glacial acetic acid containing a

---

[1] Most of the material in this paper was presented before the Organic Division at the Atlantic City meeting of the American Chemical Society, April, 1946.

[2] Winstein, Grunwald, Buckles and Hanson, THIS JOURNAL, **70**, 816 (1948).

[3] (a) Winstein and Buckles, *ibid.*, **64**, 2780 (1942); (b) Winstein and Buckles, *ibid.*, **64**, 2787 (1942); (c) Winstein, *ibid.*, **64**, 2792 (1942); (d) Winstein, Hess and Buckles, *ibid.*, **64**, 2796 (1942); (e) Winstein and Henderson, *ibid.*, **65**, 2196 (1943).



slight excess of acetic anhydride, and also in some cases in two other stock solvents, one containing 0.025 M potassium acetate, and one 0.36 M in water. The reactions were followed by titrating at intervals for the arylsulfonic acid liberated during the acetolysis. The observed kinetics were nicely first-order in almost all cases, and the precision of the measurements was usually 2% or better except when the rate constants were below 10^{-7} sec.$^{-1}$. In the latter case, the reactions were so slow that initial rates were measured (to *ca.* 15% completion), and the precision attained was about 5%. In the case of the di-*p*-bromobenzenesulfonates, rate constants were evaluated on the assumption that two moles of acid are generated per mole of ester destroyed. With the β-halocyclohexyl esters, no serious difficulty was encountered due to displacement of the halogen atom. Thus, in the case of the iodine compound, the acid titer after 23 half-lives was only 0.7% greater than after 9 half-lives, while with the bromine analog the acid titer after ten half-lives was only 4–8% high. Table II lists the data for a run with *trans*-2-methoxycyclohexyl *p*-bromobenzenesulfonate, while a run with the unreactive di-*p*-bromobenzenesulfonate of *trans*-1,2-cyclohexanediol is illustrated in Table III. It is seen that in the two runs, which are typical of our measurements, a first-order rate constant $k = (1/t)\ \ln\ [a/(a - x)]$, where a is the initial concentration of ester and x is the concentration of sulfonic acid at time t, is satisfactorily constant. The slight upward drift during the runs, which was observed fairly consistently, is probably real and attributable to the salt effect of the liberated acid. In only three cases were the drifts in k outside of experimental error. The acetolysis rate of cyclohexyl *p*-bromobenzenesulfonate in dry acetic acid and in acetic acid 0.36 M in water increased during a kinetic run, and a typical set of data is presented in Table IV. A calculated first-order rate constant k decreased during the acetolysis of *trans*-2-acetoxycyclohexyl *p*-bromobenzenesulfonate in dry acetic acid, in qualitative agreement with the behaviour of the *p*-toluenesulfonate described previously,[4] and a typical set of kinetic data is given in Table V. It is seen that the drifts in either case are small. Initial rate constants were

Table II

Acetolysis of *trans*-2-Methoxycyclohexyl *p*-Bromobenzenesulfonate in Acetic Acid (Solvent III) at 74.99°

Time, hours	$ROSO_2R'$ 10^3 M	10^6 k (sec.$^{-1}$)
0.000	63.15	..
1.850	59.49	8.99
4.033	55.42	8.99
5.492	52.96	8.90
7.400	49.79	8.92
8.63	47.60	9.10
12.87	41.40	9.12
		Mean 9.00 ± 0.07

Table III

Acetolysis of Di-*p*-bromobenzenesulfonate of *trans*-1,2-Cyclohexanediol in AcOH (Solvent I) at 74.95°, a = 0.05046 M

Time, hours	10^3 x	100 x/a	10^8 k (sec.$^{-1}$)
144.9	0.43	0.43	0.82
318.9	1.02	1.01	.88
476.2	1.47	1.46	.86
644.3	2.07	2.05	.89
954	3.24	3.21	.95
1386	4.51	4.47	.92
1896	6.22	6.16	.93

Table IV

Acetolysis of Cyclohexyl *p*-Bromobenzenesulfonate in Acetic Acid (Solvent I) at 34.95°

Time, hours	$ROSO_2R'$ 10^3 M	10^7 k (sec.$^{-1}$)
0.00	57.45	7.52[a]
19.05	54.54	7.59
41.12	51.28	7.67
67.10	47.69	7.71
91.57	44.30	7.88
136.8	38.80	7.97

[a] Extrapolated to x = 0.00 mM.

---

(4) Winstein, Hanson, and Grunwald, This Journal, **70**, 812 (1948).

TABLE V

ACETOLYSIS OF *trans*-2-ACETOXYCYCLOHEXYL *p*-BROMOBENZENESULFONATE IN ACETIC ACID (SOLVENT I) AT 74.91°

Time, hours	$ROSO_2R'$ 10^3 *M*	$10^5 k$ (sec.$^{-1}$)
...	47.71	2.96[a]
0.000	45.25	..
1.475	38.95	2.82
2.483	35.17	2.82
3.533	32.01	2.72
4.650	29.07	2.64
6.700	24.24	2.59

[a] Extrapolated to $x = 0.00$ mM.

estimated in these cases with satisfactory precision from a plot of *k vs.* extent of reaction by extrapolation to zero reaction. On the other hand the acetolysis of *cis*-2-acetoxycyclohexyl *p*-bromobenzenesulfonate in acetic acid 0.36 *M* in water was greatly catalysed by the liberated acid, and a precise estimate of the initial rate constant could not be obtained. The details of the observed kinetics are described in the experimental part.

Table VI contains a summary of the observed rate-constants and of the quantities of activation derivable from them. $\Delta\tilde{H}^{\ddagger}$ and $\Delta\tilde{S}^{\ddagger}$ symbolize the enthalpy and entropy of activation, and are calculated with the aid of equation 1.[5]

$$k = \frac{kT}{h} e^{-\Delta\tilde{H}^{\ddagger}/RT} e^{\Delta\tilde{S}^{\ddagger}/R} \qquad (1)$$

We estimate in general probable errors within 0.5 kcal. for $\Delta\tilde{H}^{\ddagger}$, and within 2 e. u. for $\Delta\tilde{S}^{\ddagger}$. The specific rates listed in the Table are averages of the observed values, except in the three cases discussed in the preceding paragraph where extrapolated initial rate-constants are given.

TABLE VI

RATE CONSTANTS OF ACETOLYSIS OF 2-SUBSTITUTED CYCLOHEXYL *p*-BROMOBENZENESULFONATES

2-Substituent	Solvent[a]	Temp., °C.	*k* (sec.$^{-1}$)	k/k_H	$\Delta\tilde{H}^{\ddagger}$ (kcal.)	$\Delta\tilde{S}^{\ddagger}$ (e. u.)
H	I	34.95	7.52×10^{-7}			
	I	74.90	12.4×10^{-5}	1.00	26.6	−0.3
	II	74.95	15.0×10^{-5}			
	III	34.95	9.68×10^{-7}			
	III	74.90	17.3×10^{-5}		27.0	+1.5
trans-OAc	I	74.95	2.97×10^{-5}	0.240		
	I[b]	74.95	3.99×10^{-5}			
	II	74.95	3.75×10^{-5}			
	III	74.91	4.07×10^{-5}			
	III	99.52	5.23×10^{-4}		26.0	−4.2
trans-Br	I	74.95	1.25×10^{-5}	0.101		
	II	74.95	1.36×10^{-5}			
	III	74.95	1.57×10^{-5}			
	III	99.53	2.53×10^{-4}		28.4	+0.8
trans-OCH_3	I	74.95	7.04×10^{-6}	0.057		
	II	74.95	7.86×10^{-6}			
	III	74.99	9.04×10^{-6}			
	III	99.53	1.31×10^{-4}		27.3	−3.4
trans-Cl	I	74.95	5.64×10^{-8}	4.6×10^{-4}		
	I	99.72	1.43×10^{-6}		33.0	+2.7
cis-OAc	I	74.95	4.7×10^{-8}	3.8×10^{-4}		
	I	99.60	9.7×10^{-7}		30.9	−3.5
	II	74.95	5.9×10^{-8}			
	III	74.95	*ca.* 5.6×10^{-8}			
	III[c]	74.95	11.1×10^{-8}			
cis-$OSO_2C_6H_4Br$	I	74.95	9.5×10^{-8}	7.7×10^{-5}		
trans-$OSO_2C_6H_4Br$	I	74.95	8.5×10^{-8}	6.9×10^{-5}		
H[d]	III	34.66	2.61×10^{-7}		27.0	−1.1
	III	75.00	4.9×10^{-5}			
	III[e]	23.60	4.84×10^{-8}	1.00		
trans-I[d]	III	23.60	5.64×10^{-5}	1170[f]		
	III	34.92	2.26×10^{-4}		21.7	−4.9

[a] Solvents: I, acetic acid, 0.0459 *M* in acetic anhydride; II, acetic acid, 0.0088 *M* in acetic anhydride, 0.025 *M* in potassium acetate; III, acetic acid, 0.36 *M* in water, m. p. 15.37°. [b] 0.0247 *M* sodium perchlorate. [c] 0.0351 *M* potassium acetate. [d] *p*-Toluenesulfonate. [e] Calculated from the data at higher temperatures. [f] Previously[6] estimated at 1800 using *k* for cyclohexyl *p*-toluenesulfonate at 75° and a previous value of 27.8 kcal. for $\Delta\tilde{H}^{\ddagger}$.

---

(5) Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., New York, N. Y., 1941, p. 14.

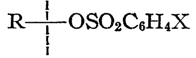
(6) Winstein and Grunwald, *ibid.*, **68**, 536 (1946).

Table VI gives an impression of the effects of solvent changes on the first-order acetolysis rate-constants. The change to the slightly aqueous solvent from the one containing a small amount of acetic anhydride raises the rate, as is to be expected,[7] by 26–39% in the case of the *trans*-Br, *trans*-OCH_3, *trans*-OAc, and unsubstituted compounds. For these compounds as well as for the *cis*-OAc compound, the change from the solvent containing 0.0459 *M* acetic anhydride to one 0.0088 *M* in acetic anhydride and 0.025 *M* in potassium acetate gives rise to increases in rate-constant of a similar magnitude. A portion of this effect is due to the decrease in acetic anhydride concentration.

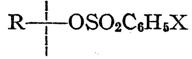
Discussion

Nature of the Acetolysis.—Although the extent of the bimolecular and unimolecular reactions in alcoholysis and hydrolysis of secondary halides is still a matter of doubt,[8] our measured *k* values must be those for unimolecular ionization of the sulfonate group. Bimolecular reactions of cyclohexyl compounds, at least of halides,[9] are very slow. Moreover acetic acid is a poor nucleophilic agent and would be expected to coöperate only poorly in bimolecular displacement and elimination reactions which require an attack on carbon or hydrogen coincident with the departure of the sulfonate ion. Addition of acetate ion which would participate more readily in such bimolecular reactions, gives rise to no serious increase in observed rates.

It is assumed that the mode of cleavage of the sulfonate is the usual carbon–oxygen one (X) even in the slowest cases. Actually, there is evidence


$R-\!\!\mid\!\!-OSO_2C_6H_4X$

X

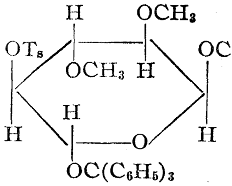

$R-\!\!\mid\!\!-OSO_2C_6H_5X$

XI

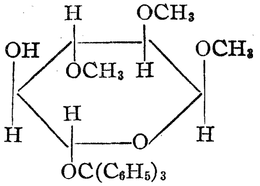
of long standing that sulfur–oxygen cleavage (XI) occurs in certain cases. Thus, in the case of phenyl *p*-toluenesulfonate, Lapworth[10a] reported and discussed the reaction with sodium ethylate, the rate-determining step of which must be a displacement on sulfur of phenolate ion by ethylate ion according to equation 2.

$$C_6H_5OSO_2C_6H_4CH_3 + C_2H_5O^- \longrightarrow C_6H_5O^- + C_2H_5OSO_2C_6H_4CH_3 \quad (2)$$

Lapworth's explanation was later supported by Phillips.[10b] This type of displacement must be responsible for some of the difficult displacements without inversion of a toluenesulfonate group from carbohydrate toluenesulfonates. An example of such a case is the hydrolysis without inversion of 4-*p*-tosyl-6-trityl-2,3-dimethyl-*α*-methylglucoside XII to XIII with the aid of sodium methoxide in benzene.[11]



XII



XIII

In dry acetic acid as a solvent, the sulfur–oxygen mode of cleavage of the sulfonate ester could depend only on an attack on sulfur by acetic acid to displace alkoxide ion or some type of ionization of the sulfur–oxygen bond, processes which would seem to be at least as favorable with phenyl esters as in our cases. Accordingly, the acetolysis of phenyl *p*-bromobenzenesulfonate was followed, no detectable reaction being observed in glacial acetic acid at 75° in three months. The rate constant was accordingly below 5×10^{-11} sec.$^{-1}$, the latter value representing an upper figure for the rate that could possibly be assigned to this other mode of cleavage of the sulfonate esters.

k/k_H Values.—The relative rates of acetolysis of the cyclohexyl benzenesulfonates are given in Table VI in the column headed k/k_H, k_H signifying the rate of acetolysis of the unsubstituted cyclohexyl ester. The effects of neighboring *trans*-halogen atoms are seen to be very similar in the present reaction to those observed previously[2] for the reaction of halohydrins with hydrohalogen acids. Again an iodine atom is rate-enhancing by a factor of *ca.* 10^3, while a chlorine atom is rate-retarding by *ca.* 10^4. The rate sequence for the halogens is $I \gg H \approx Br \gg Cl$ instead of $H \gg I \backsimeq Br \backsimeq Cl$ which would be expected for the carbonium ion mechanism **B**. Again the qualitative conclusion is that with neighboring iodine and bromine the ionization is very largely by mechanism **A**.

The contrast in behavior of the *cis*- and *trans*-di-*p*-bromobenzenesulfonates and the *cis*- and *trans*-2-acetoxycyclohexyl esters is striking. The two di-*p*-bromobenzenesulfonates react at nearly equal rates, k/k_H being less than 10^{-4}. On the other hand, as observed with the corresponding toluenesulfonates,[2] the *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate is very much more reactive than the *cis*-isomer, the factor between them being nearly 10^3. The data suggest that with the *trans*-2-OAc group, ionization is by step **A**, while with *cis*-2-OAc group, it is probably by step B. For the di-*p*-bromobenzenesulfonates with the very poorly nucleophilic neighboring *p*-bromobenzenesulfoxy group, a possible explanation of the equality in rates for *cis*- and *trans*-isomers is that ionization is by the carbonium ion mechanism B in both cases. The slow rate is consistent with the powerful electron-removing effect which can be expected from a benzenesulfoxy group. Also, the near equality in rates is not surprising in the mobile cyclohexane system although it would perhaps not be anticipated in a more rigid system.

---

[7] Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).

[8] Dostrovsky, Hughes and Ingold, *J. Chem. Soc.*, 173 (1946).

[9] Bartlett and Rosen, THIS JOURNAL, **64**, 543 (1942).

[10] (a) Ferns and Lapworth, *J. Chem. Soc.*, **101**, 273 (1912); (b) Phillips, *ibid.*, **123**, 44 (1923).

[11] Oldham and Robertson, *ibid.*, 685 (1935).

k_Δ/k_c Values.—A more quantitative discussion based on the relative reactivities k/k_H begins with the recognition that the measured rate constants k must represent the sums of k_Δ and k_c, where k_Δ is the specific rate constant for the ionization **A** to yield the cyclic intermediate II, and k_c is the specific rate constant for ionization **B** to yield the open carbonium ion III. Thus the relative reactivities are given by equation 3. If k_c/k_H can be estimated, it becomes possible to estimate the relative

$$k/k_H = k_c/k_H + k_\Delta/k_H \qquad (3)$$

values of k_Δ and k_c, in other words the relative importance of steps **A** and **B**. The ratio of k_Δ to k_c is given by equation 4.

$$k_\Delta/k_c = [(k/k_H)/(k_c/k_H)] - 1 \qquad (4)$$

Judging by the behavior of the *cis*- and *trans*-di-*p*-bromobenzenesulfonates, it becomes possible to estimate k_c/k_H for the *trans*-2-acetoxycyclohexyl *p*-bromobenzenesulfonate as the figure observed for k/k_H with the *cis*-isomer. This estimate of k_c/k_H is listed in Table VII, together with the derived value of k_Δ/k_c equal to 2.33×10^3. The values of k/k_H in Table VII have been corrected to the uniform temperature 25°, and the other figures in the table refer to this temperature.

To estimate k_c/k_H for some of the other neighboring groups we have used an approach which has been used before in interpreting the effect of substituents on the strength of carboxylic acids and the rates of saponification of esters. This approach accounts for the effect of the substituent on electrostatic grounds. Kirkwood and Westheimer[12] have made important improvements in the method especially with regard to the calculation of an effective dielectric constant, $\mathbf{D_E}$, and Westheimer and co-workers[12] have made quite successful applications to the interpretation of both equilibria and rates.

The procedure is to calculate the extra work W involved in the generation of the C–O dipole of moment M_1, due to the partly ionized bromobenzenesulfoxy group in the transition state, against the dipole, moment M_2, due to the neighboring group. The interaction energy W (in kcal./mole) of two dipoles is given[13] by equation 5, where r is the length of the vector joining the centers of the dipoles, and ϵ, θ, and θ' are angles between M_1 and M_2, M_1 and r, and M_2 and r, respectively.

$$W = 1.439 \times 10^{13}\, M_1 M_2 \mathbf{D_E}^{-1} r^{-3}\, (\cos \epsilon - 3 \cos \theta \cos \theta') \qquad (5)$$

The assumed model for the transition state was simplified to involve a coplanar *trans* arrangement of the dipoles M_1 and M_2 and tetrahedral bond angles for carbon. The assumed value of M_1 was 4.6 D, one half of the moment, 9.2 D, calculated for complete ionization at the assumed[14] transition state distance of 1.93 Å. All other interatomic distances were derived from the covalent bond radii given by Pauling.[15] The point-dipoles were taken as situated at the midpoints of the respective bonds. The neighboring group dipole moment, M_2, was taken as 1.87 D for C–Cl, 1.78 D for C–Br, and 1.59 D for C–I.[12,16] A composite moment of 0.85 D was taken for the C–OCH$_3$ dipole, with the center of the dipole 0.72 Å. from the β-carbon atom.

For dipole–dipole interaction the effective dielectric constant $\mathbf{D_E}$ is close to the internal dielectric constant $\mathbf{D_i}$ as Westheimer has pointed out to us in private communications. For $\mathbf{D_i}$ Kirkwood and Westheimer have consistently used the value of 2.00. We have treated $\mathbf{D_E}$ as a disposable parameter, choosing a value which gives a calculated k_c/k_H equal to k/k_H in the case of chlorine. In the case of neighboring chlorine, the data previously[2] and now presented, and evidence included and discussed in the following article[17] indicate that the original ionization step is very predominantly by path **B** and thus that $k = k_c$. The relation between W and k_c/k_H is given by equation 6. The value of $\mathbf{D_E}$ determined in this way was

$$\ln (k_c/k_H) = W/RT \qquad (6)$$

1.23, a value which is quite reasonable, considering that we are requiring this adjusted value for $\mathbf{D_E}$ to compensate for the arbitrary choice of the other parameters. Values for $\mathbf{D_E}$ as low as 1.00[18] have sometimes been used in situations of this sort. On the whole, it is clear that the calculation along electrostatic lines accounts fairly quantitatively for the magnitude of the reduction in solvolysis rate due to a neighboring *trans*-chlorine atom.

Using the value 1.23 for $\mathbf{D_E}$, equations 5 and 6 have been applied to neighboring Br, I and OCH$_3$, the values of W and k_c/k_H being summarized in Table VII. The derived values of k_Δ/k_c are listed also. Although the treatment is admittedly crude and we comment in the following article[17] on a further complication, the values of k_Δ/k_c for neighboring bromine and iodine indicate, just as for *trans*-OAc, the very large predominance of ionization by process **A**, the fraction of this being k_Δ/k or $k_\Delta/(k_\Delta + k_c)$.

On the other hand, the case of *trans*-OCH$_3$ is in the nature of a borderline one, k_Δ/k_c being estimated at 4.3. From the nature of the treatment, when k_Δ/k_c is small as it is here, no accuracy can be claimed for the fraction of ionization proceeding by process **A**. For this case k_Δ and k_c are more comparable in magnitude and further work[17] will be required to more accurately estimate k_Δ/k.

---

[12] (a) Kirkwood and Westheimer, *J. Chem. Physics*, **6**, 506, 513 (1938); (b) Westheimer, THIS JOURNAL, **62**, 1892 (1940); (c) Westheimer and Shookhoff, *ibid.*, **61**, 555 (1939).

[13] Smythe, "Static and Dynamic Electricity," McGraw-Hill Book Co., Inc., New York, N. Y., 1939, p. 7.

[14] The normal C–O distance[15] was increased by 0.50 Ångstrom; see Baughan and Polanyi, *Trans. Faraday Soc.*, **37**, 648 (1941).

[15] Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1944, p. 164.

[16] Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 123.

[17] Winstein and Grunwald, THIS JOURNAL, **70**, 812 (1948).

[18] *E. g.* Ri and Eyring, *J. Chem. Phyics.*, **8**, 433 (1940).

TABLE VII

ACETOLYSIS RATES IN THE PRESENCE OF VARIOUS NEIGHBORING GROUPS

Neighboring group	k/k_H (25°)	W (Eq. 5) kcal./mole	k_c/k_H 25° (Eq. 6)	k_Δ/k_c 25° (Eq. 4)	L kcal./mole 25°
trans-Cl	0.94×10^{-4}	(5.50)	(0.94×10^{-4})	...	..
trans-Br	7.18×10^{-2}	5.09	1.87×10^{-4}	383	3.53
trans-I	1120	4.33	6.7×10^{-4}	1.7×10^{6}	8.49
trans-OCH_3	5.28×10^{-2}	2.73	1.00×10^{-2}	4.3	0.86
trans-OAc	0.305	..	1.31×10^{-4}	2.33×10^{3}	4.60

Driving Force Due to Participation.—It is useful to introduce a variable L which will be termed the driving force due to the participation of the neighboring group in the rate-determining process. The variable L is defined by equation 7, and the values for some of the neighboring groups are included in

$$L = RT \ln (k_\Delta/k_c) \qquad (7)$$

Table VII. These run from 0.86 kcal./mole in the case of *trans*-OCH_3 to 8.49 kcal./mole for *trans*-I, supplying a quantitative measure for the so-called driving force of neighboring groups.

The driving force L may be discussed in terms of the relative stabilities of the two envisaged cationic intermediates II and III. It is a necessary condition for the existence of a positive driving force due to participation of the neighboring group that the conversion of carbonium ion III to three-membered ring II be attended by a decrease in free energy. The observed driving-force represents that fraction of this decrease in free energy which is already applicable to the transition-states.

It is interesting to consider the relative contributions of enthalpy and entropy terms to the free energy effects associated with the various rate ratios discussed. Inspection of Table VI indicates that variations in k/k_H are due mainly to changes in $\Delta\tilde{H}^{\ddagger}$. Thus, the relative enthalpies of activation, $\Delta\tilde{H}^{\ddagger} - \Delta\tilde{H}^{\ddagger}_H$, vary from -5.3 to $+6.4$ kcal./mole corresponding to a rate-factor of *ca.* 10^8, while the relative entropies of activation, $\Delta\tilde{S}^{\ddagger} - \Delta\tilde{S}^{\ddagger}_H$ vary from -5.7 to $+3.0$ e. u., corresponding to a rate-factor of *ca.* 10^2. This indicates the greater importance, in general, of energy over entropy effects in consideration of k_c/k_H and k_Δ/k_c values. Although the differences in the entropies of activation are relatively small, the observed trend in $\Delta\tilde{S}^{\ddagger}$ for the halogens, with *trans*-I having the lowest value because it is involved in the most constrained transition-state configuration, is consistent with the general interpretations advanced.

Experimental

Carbinols and Glycols.—*trans*-1,2-Cyclohexanediol,[3c] m. p. 103°, *trans*-2-bromocyclohexanol,[3a,c] b. p. 72° (3 mm.), *trans*-2-methoxycyclohexanol,[3e] b. p. 68.9–70.2° (8 mm.), and *trans*-2-iodocyclohexanol,[2] m. p. 39–40° were prepared from cyclohexene oxide[3c] as previously described. *cis*-1,2-Cyclohexanediol, prepared by Criegee's method,[3d,19] was converted to the monoacetate, b. p. 112–114° (12 mm.) in the usual manner.[2]

trans-**2-Chlorocyclohexanol.**—This material, b. p. 78.7–79.8° (14 mm.), was prepared in 65% yield by reaction of 0.3 mole of cyclohexene oxide with 40 ml. of concentrated hydrochloric acid similarly to the preparation of the analogous bromohydrin.[3c]

Preparation of *p*-Bromobenzenesulfonates (Table I).—The equivalent amount of *p*-bromobenzenesulfonyl chloride was added in one portion to a solution, cooled to 0°, of 0.1 mole of carbinol or glycol in 100 ml. of anhydrous pyridine. The reaction mixture was shaken and left in the cold room, usually overnight. Then it was poured with vigorous stirring into 200 ml. of ice-cold 6 N hydrochloric acid. The product, either oily or crystalline, was taken up in carbon tetrachloride. The carbon tetrachloride solution was dried over potassium carbonate and placed in an evaporating dish. After evaporation of the solvent at room temperature, the residue was usually crystalline. In the case of *trans*-2-hydroxycyclohexyl *p*-bromobenzenesulfonate, the product was not soluble in carbon tetrachloride so it was directly filtered and dried. The materials were recrystallized from Skellysolve B (petroleum ether, b. p. 60–70°) or ethyl acetate–Skellysolve B. Methanol was sometimes used with the less reactive materials. Yields of products obtained were in the range of 45–89% except in the case of the di-*p*-bromobenzenesulfonates of *cis*- and *trans*-1,2-cyclohexanediol, where they were much lower.

Phenyl *p*-bromobenzenesulfonate, m. p. 116.6–117.1° (reported[20] 115.5°) was prepared by the above general procedure.

The cyclohexyl and *trans*-2-hydroxycyclohexyl *p*-bromobenzenesulfonates were the least stable of the bromobenzenesulfonates prepared and could not be kept long. The latter material showed an equivalent weight of 331.5 (calculated 335.2) on treatment for several minutes with methanolic base and back titration with acid as in the case of *trans*-2-chlorocyclohexanol.[21]

The treatment of *trans*-1,2-cyclohexanediol with 2 equivalents of *p*-bromobenzenesulfonyl chloride gave rise to a product contaminated with monoester which was destroyed with methanolic base before purification of the desired di-ester. In the case of the *cis*-1,2-cyclohexanediol, treatment with one equivalent of acid chloride gave rise to di-*p*-bromobenzenesulfonate as the isolated product just as in the case of the toluenesulfonate.[19]

trans-**2-Acetoxycyclohexyl *p*-Bromobenzenesulfonate.**—To a solution of 5 drops of concentrated sulfuric acid in 50 ml. of acetic anhydride cooled in an ice-bath was added 0.1 mole of *trans*-2-hydroxycyclohexyl *p*-bromobenzenesulfonate in approximately 8 portions and with vigorous shaking. There were added 5 drops more of sulfuric acid during the addition and 5 drops at the end. The mixture was shaken for one hour at room temperature, then treated with 300 ml. of water. The crude product obtained in nearly quantitative yield gave material, m. p. 97.4–97.9°, in 70–80% yield on recrystallization from ethyl acetate-Skellysolve B.

trans-**2-Iodocyclohexyl *p*-Toluenesulfonate.**—A mixture of 5 ml. of cyclohexene, 20 ml. of absolute ether, 5.8 g.

---

[19] Criegee and Stanger, *Ber.*, **69B**, 2753 (1936).

[20] Sekera, THIS JOURNAL, **55**, 421 (1933).

[21] Bartlett, *ibid.*, **57**, 224 (1935).

(0.021 mole) of silver toluenesulfonate[22] and 5.08 g. (0.020 mole) of resublimed iodine was shaken in a glass-stoppered flask for thirty minutes with occasional cooling in tap water. The silver iodide was removed on a filter and washed with two 10-ml. portions of a wash liquid containing 2 parts of absolute ether to 1 part of dry Skellysolve B. To the filtrate and washings was added dry Skellysolve B until no more precipitation of toluenesulfonic acid occurred. The mixture was filtered rapidly and the filtrate was cooled to Dry Ice temperature. An oil was obtained which crystallized as the mixture warmed up with shaking. Renewed cooling to Dry Ice temperature produced a crop of white crystals. Rapid filtration and washing with dry Skellysolve B with precautions against access of moisture gave rise to material, m. p. 51–52°, in yields of 20–50%. The material was quite unstable and a batch was prepared and used immediately for equivalent weight determinations and rate-runs.

A mixture of 2.0 g. of potassium iodide, 20 ml. of absolute acetone and 0.1376 g. of the iodocyclohexyl *p*-toluenesulfonate was left for two hours at room temperature. After acidification, 14.12 ml. of 0.0499 *N* thiosulfate was required for titration: equivalent weight 195.3, calcd. 190.1. A sample of the iodohydrin *p*-toluenesulfonate weighing 0.3570 g. was held in 100 ml. of 80% aqueous acetone at 35° for twenty-two hours. There was then added 39.15 ml. of 0.05063 *N* sodium hydroxide and the solution was left ten minutes. Back titration to the brom thymol blue end-point required 1.39 ml. of 0.0962 *N* acid. From these data the equivalent weight is 193.1, calcd. 190.1. From the rate runs, the iodocyclohexyl *p*-toluenesulfonate appeared to contain 1–2% by weight of toluenesulfonic acid.

The attempted preparation of the toluenesulfonate and also the bromobenzenesulfonate from cyclohexene iodohydrin by the ordinary method gave rise to an oil, from which was recovered a small amount of crude cyclohexene iodohydrin, m. p. 37°. An attempted preparation of the bromobenzenesulfonate in absolute ether using 1.2 molecular proportions of pyridine was unsuccessful with cyclohexene iodohydrin as well as with cyclohexanol. Reaction times of three to eighteen hours at 0° were employed, good recoveries of bromobenzenesulfonyl chloride being obtained.

Titrations.—Analyses were performed with approximately 0.05 *N* standard perchloric acid and/or sodium acetate in glacial acetic acid. The standard perchloric acid in acetic acid was prepared from 70% aqueous acid which was compared with Bureau of Standards potassium acid phthalate. The sodium acetate reagent was obtained by dissolving reagent grade sodium carbonate in glacial acetic acid and making the solution up to volume. Titrations were carried out with 5 ml. micro-burets.

The indicator which we empirically found to be advantageous was brom phenol blue (supplied by Paragon Testing Laboratories, Orange, New Jersey), used in the form of a saturated acetic acid solution (*ca.* 0.1%). The indicator is colorless in acidic acetic acid solution, dim yellow in neutral solution and brilliant yellow in basic solution, the strongest color change occurring at an acetate ion concentration approximately 10^{-6} to 10^{-5} *M*. It is most convenient to approach the end-point from the acid side, the accuracy being good with either perchloric, bromobenzenesulfonic or toluenesulfonic acid. Several checks on the titration procedure were carried out.

The standard sodium acetate and perchloric acid were many times compared. A complete summary of data obtained in a six months working period showed that the normality of perchloric acid based on the sodium acetate normality and the acid–base ratio agreed with the normality based on the weight of the standard perchloric acid within 0.0 ± 0.15%.

A slightly impure sample of cyclohexyl *p*-bromobenzenesulfonate was solvolyzed in methanol–water and also in acetic acid. The aqueous solution was titrated with base to the methyl orange end-point, the acetic acid solution with sodium acetate to the brom phenol blue end-point. The equivalent weight of the bromobenzenesulfonate was 324.0 in acetic acid, 324.4 in water–methanol.

A sample of *p*-toluenesulfonic acid monohydrate was titrated in aqueous solution to the phenolphthalein end-point, the equivalent weight being 192.4 ± 0.4. In acetic acid solution, the equivalent weight proved to be 191.7 ± 0.5.

For the titration of 5 ml. quantities of both toluenesulfonic and perchloric acids, variation in the concentration of acid from 0.05 *N* to 0.001 *N* gave rise to no systematic error in the volume of sodium acetate solution required. The precision of titration remained within the larger of the two errors, ±0.5% or ±0.004 ml.

Solvents. (Table VI).—The stock solvents were prepared from J. T. Baker reagent glacial acetic acid, pure acetic anhydride, and dried reagent grade potassium acetate. Concentrations of acetic anhydride were determined by Kilpi's anthranilic acid method.[23]

Rate Measurements.—Solutions, 0.03 to 0.05 *M*, of the compounds to be solvolyzed were made up at room temperature in a volumetric flask from a weighed portion of the material. In case of insufficient solubility at room temperature, solutions were made up gravimetrically. About 6-ml. portions of the solutions were sealed in ampoules and immersed in a suitable thermostat. At suitable times reaction was interrupted by removing an ampoule and immersing it in ice. The ampoule was then brought to room temperature and opened, a 5-ml. aliquot being removed for analysis. The time of the first analysis was called "zero time."

On complete acetolysis, the equivalent weight of cyclohexyl *p*-bromobenzenesulfonate was 320.8 (calcd. 319.2), of *trans*-2-acetoxycyclohexyl *p*-bromobenzenesulfonate 378.5 (calc. 377.3), and of *trans*-2-iodocyclohexyl *p*-toluene sulfonate 380.1 ± 4.0 (calc. 380.2).

With the *cis*-2-acetoxycyclohexyl *p*-bromobenzenesulfonate, the rate constant in solvent III at 75° climbed rapidly an effect which disappeared on addition of potassium acetate to the solvent. A plot of x against t gave, with the aid of a tangent meter, a rough estimate of the initial rate constant and a more accurate estimate of the instantaneous rate constant $k' = [(\mathrm{d}x/\mathrm{d}t)/(a-x)]$.

The variation of k' with x is given quite accurately by equation 8

$$10^3 k' = 27.76\, x^{1/2} - 0.23 \qquad (8)$$

obtained from the data by the method of least squares. This equation is based on the assumption of some preliminary rate-determining reaction of the acetoxybromobenzenesulfonate which is hydrogen ion-catalyzed, toluenesulfonic acid being treated simply as a weak acid. The experimental data as well as the values of k' calculated from equation 8 are summarized below.

$10^3 x$	$10^3 k'$ obsd.	calcd.
1.12	0.73	0.70
2.18	1.05	1.07
3.61	1.42	1.44
5.39	1.74	1.81
7.56	2.25	2.18
9.62	2.56	2.49
11.70	2.71	2.77

Summary

A series of 2-substituted cyclohexyl *p*-bromobenzenesulfonates and a toluenesulfonate have been prepared. A study of the acetolysis of these esters has given the relative rates of ionization of the alkyl–oxygen bond. These relative rates of solvolysis, k/k_H at 25° are in the sequence: *trans*-

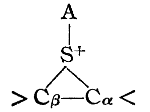
---

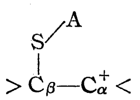
[22] Claesson and Wallin, *Ber.*, **12**, 1851 (1879).

[23] Kilpi, *Suomen Kemistilehti*, **13B**, 19 (1940); *C. A.*, **35**, 2445 (1941).

I, 1120; *trans*-OAc, 0.305; *trans*-Br, 7.18×10^{-2}; *trans*-OCH_3, 5.28×10^{-2}; *cis*-OAc, 1.31×10^{-4}; *trans*-Cl, 0.94×10^{-4}; *cis*-$OSO_2C_6H_4Br$, 1.6×10^{-5}; *trans*-$OSO_2C_6H_4Br$, 1.4×10^{-5}. Variations in rate are largely due to variations in $\Delta H^{\ddagger}$.

The rate-determining ionization step appears to be largely a direct formation of the cycle II (rate constant k_Δ) in the case of neighboring *trans*-I, Br, and OAc and predominantly the formation of carbonium ion III (rate constant k_c) with neighboring *trans*-Cl and $OSO_2C_6H_4Br$ and *cis*-OAc and $OSO_2C_6H_4Br$.


II


III

Using k/k_H for neighboring Cl to determine an effective dielectric constant, the interaction energy between the C_β-SA and C_α-O dipoles in the transition state for formation of III has been calculated for neighboring I, Br and OCH_3. Thus estimates of k_c/k_H have been obtained and corresponding values of k_Δ/k_c have been calculated from the relation $k_\Delta/k_c = [(k/k_H)/(k_c/k_H)] - 1$.

The driving force L due to the *trans*-neighboring groups, defined as $RT \ln (k_\Delta/k_c)$, has the following values in kcal./mole at 25°: I, 8.49; OAc, 4.60; Br, 3.53; OCH_3, 0.86.

LOS ANGELES 24, CALIF. RECEIVED APRIL 3, 1947

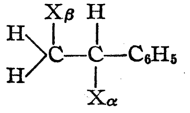
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

The Role of Neighboring Groups in Replacement Reactions. XIII.[1] General Theory of Neighboring Groups and Reactivity

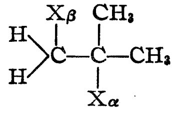
BY S. WINSTEIN AND ERNEST GRUNWALD

In the previous[2,3] rate work involving effects of neighboring groups, C_α and C_β were both secondary in the molecules (I)[2] whose ionization rates were measured. In considering further structural variations, it must be expected that the relative energies of the closed and open forms of the ionic intermediate,[2] II and III, respectively, will change with *alpha* and *beta* substitution. Thus there will be a change in L, the driving force,[3] which reflects that portion of the free energy difference between II and III which already appears in the transition states for ionization of I. In this paper, with the aid of relative reactivities here reported and others from the literature, we attempt to generalize the theory to cover the whole range of possible structures for the *alpha* and *beta* carbon atoms. Also, the discussion will logically lead to a consideration of the nucleophilic closure of small rings of the classical sort, most attention being given the ethylene oxide ring.

Rate Comparisons.—A group of the rate constants to be considered deals with solvolysis in alcohol or aqueous alcohol of some of the styrene dihalides IV and isobutylene dihalides V.


$H_2C(X_\beta)-CH(X_\alpha)-C_6H_5$

IV


$H_2C(X_\beta)-C(CH_3)(X_\alpha)-CH_3$

V

Although there were some difficulties in the determination of the desired solvolysis rates, it was possible to obtain rate constants reliably enough for the purpose. The rates were in some cases so slow that the measurements were complicated by reaction of hydrogen bromide, produced by solvolysis of a dibromide, with the ethanol solvent. This difficulty was met by determination of the initial rate of solvolysis. With olefin iodochlorides, the solvolysis was accompanied by a slight amount of iodine production but analyses for iodine showed this was not extensive enough to be very serious.

The first-order rate constants determined as described in a later section are summarized in Table I. It seems clear from our procedure in obtaining initial rate constants and from the chemistry of the materials IV and V and analogous ones that the rate constants relate to the solvolysis of the first and most reactive halogen atom, labelled *alpha* in IV and V. Thus styrene iodochloride is reported[4] to react with water to give iodohydrin and with silver nitrate to yield first its chlorine atom and next its iodine atom. Similarly, isobutylene iodochloride gives the β-iodo-*t*-butyl methyl ether[5] on refluxing with methanol. Analogous to the styrene derivatives are such materials as indene dibromide[6a] VI and 1-phenyl-1,2-dibromopropane[6b] VII.

The rate constants for solvolysis are interpreted as rates of unimolecular[7] solvolysis.[8] In

---

[1] Much of the material in this paper was presented before the Organic Division at the Atlantic City meeting of the American Chemical Society, April, 1946.

[2] Winstein, Grunwald, Buckles and Hanson, THIS JOURNAL, **70**, 816 (1948).

[3] Winstein, Grunwald and Ingraham, *ibid.*, **70**, 821 (1948).

[4] Ingle, *J. Soc. Chem. Ind.*, **21**, 587 (1902).

[5] Istomin, *J. Russ. Phys.-Chem. Ges.*, **36**, 1199 (1904); *Chem. Centr.*, **76**, I, 429 (1905).

[6] (a) Porter and Suter, THIS JOURNAL, **57**, 2022 (1935); (b) Spaeth and Koller, *Ber.*, **58**, 1269 (1925).

[7] (a) Bateman, Church, Hughes, Ingold and Taher, *J. Chem. Soc.*, 979 (1940); (b) Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).

[8] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapters V and VI.

TABLE I

RATE CONSTANTS FOR THE SOLVOLYSIS OF STYRENE AND ISOBUTYLENE DIHALIDES

Halide	Solvent	Temp., °C.	k (sec.$^{-1}$)	k/k_H
$BrCH_2CHBrC_6H_5$	C_2H_5OH	54.95	1.90×10^{-7}	0.99×10^{-3}
$BrCH_2CHBrC_6H_5$	C_2H_5OH, 0.1369 M $NaClO_4$	54.95	2.85×10^{-7}	
$ICH_2CHClC_6H_5$	C_2H_5OH	69.95	4.9×10^{-5}	1.3
$BrCH_2CBr(CH_3)_2$	80% C_2H_5OH	25.10	5.8×10^{-8}	1.60×10^{-4}
$ICH_2CCl(CH_3)_2$	80% C_2H_5OH	25.00	4.44×10^{-6}	0.486
$ICH_2CCl(CH_3)_2$	80% C_2H_5OH	35.00	15.0×10^{-6}	
$CH_3CCl(CH_3)_2$	48.61 wt. % dioxane	34.86	6.30×10^{-4}	
$ICH_2CCl(CH_3)_2$	48.61 wt. % dioxane	34.86	1.45×10^{-4}	
$CH_3CHClCH{=}CH_2$	H_2O	27.2	1.06×10^{-3}	

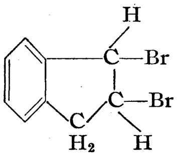
TABLE II

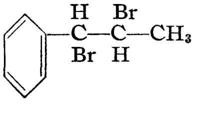
COMPARISON OF SOME SOLVOLYSIS RATES

Compound		Solvent	Temp., °C.	k_A/k_B	Ref.
A	B				
$CH_3CH_2CCl(CH_3)_2$	$CH_3CCl(CH_3)_2$	80% ethanol	25.0	1.67	14
$(CH_3)_2CHCCl(CH_3)_2$	$CH_3CCl(CH_3)_2$	80% ethanol	25.0	0.92	14
$(CH_3)_3CCCl(CH_3)_2$	$CH_3CCl(CH_3)_2$	80% ethanol	25	1.19	14
$CH_3CHBrCBr(CH_3)_2$	$BrCH_2CBr(CH_3)_2$	2:3 dioxane–water	45	17.5	15
$(CH_3)_2CBrCBr(CH_3)_2$[a]	$CH_3CBr(CH_3)_2$	Ethanol, 50.1 mole % water	18.5	3.25×10^{-2}	16
$(CH_3)_2CClCCl(CH_3)_2$[a,b]	$CH_3CCl(CH_3)_2$[c]	80% ethanol	100.0	5.8×10^{-4}	13, 17
$ClCH_2CCl(CH_3)_2$	$CH_3CCl(CH_3)_2$[c]	80% ethanol	79.0	3.3×10^{-4}	13, 18
$ClCH_2CCl(CH_3)(C_2H_5)$	$CH_3CCl(CH_3)_2$[c]	80% ethanol	79.0	6.1×10^{-4}	13, 18
$HOCH_2CCl(CH_3)_2$	$CH_3CCl(CH_3)_2$[d]	H_2O	18.0	6.5×10^{-3}	19, 20
$CH_3CH(OH)CCl(CH_3)_2$	$CH_3CCl(CH_3)_2$[d]	H_2O	18.0	3.4×10^{-3}	19, 20
$(CH_3)_2C(OH)CCl(CH_3)_2$	$CH_3CCl(CH_3)_2$[d]	H_2O	18.0	6.0×10^{-3}	19, 20
$HOCH_2CHClCH{=}CH_2$[e]	$CH_3CHClCH{=}CH_2$[f]	H_2O	18.0	7.3×10^{-3}	21, Table I

[a] Specific rate constant multiplied by a statistical factor of $^1/_2$. [b] Specific rate constant calculated from the data of Tischchenko[17] on the assumption that the solvolysis of the dichloride is slow compared to that of the daughter monochloride. [c] Extrapolated from data[13] at lower temperatures. [d] The specific rate in 5% acetone–95% water reported by Swain[20] was used. $E\ddagger$ was taken as 22.9 kcal./mole.[13] [e] Extrapolated from data[21] at higher temperatures. [f] $E\ddagger$ was taken as 23.5 kcal./mole.

the case of the very slow reactions (*e. g.*, in the case of styrene dibromide), there is the possibility that at least part of the solvolysis is bimolecular involving solvent. In this sense the values are upper limits. For styrene dibromide, the effect of added salt (sodium perchlorate) on the rate of alcoholysis was observed. This was quite high and to be anticipated[7] for a unimolecular solvolysis, much higher than for the alcoholysis (S_N2) of ethyl bromide as we report elsewhere.[9]


VI


VII

Comparison of the rate constants in Table I with the corresponding values k_H for α-phenylethyl bromide,[10] α-phenylethyl chloride,[11] *t*-butyl bromide[12] and *t*-butyl chloride[13] gives the relative rates k/k_H listed in the last column of Table I. Further pertinent rate comparisons are available from the literature and these are summarized in Table II.

The rate comparisons so far reported in Tables I and II and those for the cyclohexyl and 2-butyl systems reported in the two preceding papers[2,3] have been converted to values of k/k_H at 25° which are given in Table III for neighboring I, Br, Cl, OH or OCH_3 groups. Ratios have been calculated to 25° either with the help of activation energies when available, or otherwise, on the assumption that a rate difference between two similar substances is due to a difference in activation energy. For the cases on which information is available,[3] this is a fair approximation for the rough and small corrections being made. From Table II it is clear that the rate of solvolysis of $RCCl(CH_3)_2$ is very constant to variations in R from CH_3 to $(CH_3)_3C$. In deriving the values of k/k_H for Table III, the value of k for $CH_3CCl(CH_3)_2$ was used for k_H for materials of the type $RCCl(CH_3)_2$ and k for $CH_3CBr(CH_3)_2$ was used for k_H for materials of the type $RCBr(CH_3)_2$. The body of Table III is based on data with systems of the charge type actually represented by formulas I, II and III, that is, the departing group is $XC_6H_4SO_3^-$ or halide ion. The footnotes give the data in which the departing group is OH_2. In the Table, the nature of C_β and C_α is indicated by P,

---

(9) Grunwald and Winstein, THIS JOURNAL, **69**, 2051 (1947).

(10) Hughes, Ingold, Masterman and McNulty, *J. Chem. Soc.*, 899 (1940).

(11) Hughes, Ingold and Scott, *ibid.*, 1201 (1937).

(12) Cooper and Hughes, *ibid.*, 1183 (1937).

(13) Hughes, *ibid.*, 255 (1935).

TABLE III

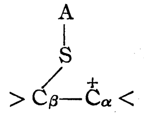
SUMMARY OF VALUES FOR k/k_H AND k_Δ/k_c

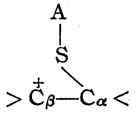
Neighboring group C_β	C_α	I k/k_H obs. 25°	I k_Δ/k_c	I k_Δ/k_c calcd. Eq. 9	Br k/k_H obs. 25°	Br k_Δ/k_c	Br k_Δ/k_c calcd. Eq. 9	Cl k/k_H obs. 25°	OH or OCH_3 k/k_H obs. 25°	OH or OCH_3 k_Δ/k_c	OH or OCH_3 k_Δ/k_c calcd. Eq. 9
P	**T**	0.486	7.2×10^2	1.1×10^3	1.6×10^{-4}	1.1	1.0	0.78×10^{-4}[d]	7.3×10^{-3}[a]	...	$4.5 \times 10^{-}$
S	**T**			2.3×10^4	3.4×10^{-3}[c]	44	21	....	3.8×10^{-3}[a]	...	$9.3 \times 10^{-}$
T	**T**			4.7×10^5	3.5×10^{-2}	4.7×10^2	4.3×10^2	0.85×10^{-4}	6.7×10^{-3}[a]	...	1.9
P	allyl			....			....	....	8.2×10^{-3}[a]	...	...
P	CHC_6H_5	1.3	1.9×10^3	....	4.9×10^{-4}	6.5	....	....			...
P	**S**			5.2×10^4			47	....			0.21
S	**S**[e]	1120	1.7×10^6	1.1×10^6	7.2×10^{-2}	3.9×10^2	9.5×10^2	0.94×10^{-4}	5.3×10^{-2}[b]	4.3	4.3
T	**S**			2.2×10^7			2.0×10^4				91
P	**P**			2.4×10^6			2.1×10^3				9.9
S	**P**			4.9×10^7			4.4×10^4				2.0×10^2
T	**P**			1.0×10^9			9.0×10^5				4.0×10^3

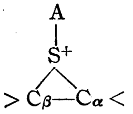
[a] Neighboring OH. [b] Neighboring OCH_3. [c] Calculated from the data of Suter and Zook in 2:3 dioxane–water[15] and the value of k/k_H for isobutylene dibromide in 80% ethanol. [d] The reported value refers to isobutylene dichloride. k/k_H for 2-methyl-1,2-dichlorobutane, 1.4×10^{-4}. [e] The corresponding values of k/k_H from reactions of cyclohexanols and 2-butanols with hydrobromic or hydrochloric acid are: cyclohexanols, *trans*-I, 1200 $\gg$ *trans*-Br, 0.08 $\gg$ *trans*-Cl, 1.6×10^{-4}; 2-butanols, *trans*-Br, 0.4.

S and T for *primary, secondary* or *tertiary*, respectively, or more specifically for the α-phenylalkyl or α-allyl types.

Qualitative Theory of the Effect of *alpha* and *beta* Substitution.—To understand the general reactivity situation it is necessary to refer to intermediates II and III. It is possible to predict the effect of *alpha* and *beta* substitution on the relative energies of II and III and therefore on the relative free energies of the corresponding transition states for the ionization of I. Intermediate II receives contributions[22] from such structures as VIII–X. Now the effect of *alpha* methyl or phenyl in stabilizing the carbonium ion III by hyperconjugation[23] or ordinary resonance is well understood.[7] The same substitution will also favor the contribution of structure VIII to intermediate II so that there will be less bond character between the neighboring group and C_α in II. This will decrease any superiority of II over III and decrease k_Δ relative to k_c. Thus, *alpha* methyl or phenyl groups will lower the driving force due to a neighboring group.


VIII


IX


X

The stability of structure IX and therefore its contribution to the stabilization of the hybrid intermediate II will depend on the structure of C_β, being greatest for *tertiary* and least for *primary*. Thus *beta* methyl groups will increase k_Δ relative to k_c and the driving force L will increase as C_β varies from *primary* to *tertiary*.

The same conclusions are reached in another way. There has long been a feeling that the transition in C–C bond type from ethylene to cyclopentane is gradual. Thus certain features of the ethylenic linkage remain in the cyclopropane ring. For example, there is spectroscopic evidence[24] of conjugation of the carbonyl group with a cyclopropane ring. Also, the dipole moment of cyclopropyl chloride[25] is intermediate between vinyl chloride and ethyl chloride. Another characteristic feature of the ethylenic linkage, stabilization by alkyl substitution, is expected to be retained in three-membered rings including the heterocyclic ring compounds of the type II.

On the basis that methyl substitution on a three-membered ring should give rise to what amounts to hyperconjugation energy,[23] it is clear that either an *alpha* or a *beta* methyl group will stabilize intermediate II and increase k_Δ. In the case of a *beta* methyl group this will result in a greater driving force L. In the case of an *alpha* methyl group, the hyperconjugative stabilization of an open carbonium ion III is expected to be greater than that of II, and k_c will increase more than k_Δ. The driving force L will consequently decrease even though the rate increases.

In discussing the effect of *alpha* substitution on k_Δ, we are in effect discussing the effect of substitution on an internal variety of a bimolecular displacement. Thus we are dealing with a phase of the general question of the factors involved in understanding concerted nucleophilic displacements on carbon. There have been some recent discussions[26,27] of some of these factors and we hope to contribute elsewhere on this general ques-

---

(14) H. C. Brown, abstract of paper presented before the Organic Division at the Atlantic City meeting of the American Chemical Society, April, 1946.

(15) Suter and Zook, THIS JOURNAL, **66**, 738 (1944).

(16) Petrenko-Kritschenko, *Ber.*, **61**, 852 (1928).

(17) D. V. Tischenko, *J. Gen. Chem.* (*U. S. S. R.*), **9**, 1380 (1939).

(18) Brown, Kharasch and Chao, THIS JOURNAL, **62**, 3435 (1940).

(19) Lennart Smith, *Z. physik. Chem.*, **156A**, 135 (1933).

(20) Swain, THIS JOURNAL, **68**, 658 (1946).

(21) Kadesch, *ibid.*, **68**, 46 (1946).

(22) Winstein and Lucas, *ibid.*, **61**, 1576 (1939).

(23) Mulliken, Rieke and Brown, *ibid.*, **63**, 41 (1941).

(24) (a) Carr and Burt, *ibid.*, **40**, 1590 (1918); (b) Klotz, *ibid.*, **66**, 88 (1944).

(25) Rogers and Roberts, *ibid.*, **68**, 843 (1946).

(26) Dostrovsky, Hughes and Ingold, *J. Chem. Soc.*, 173 (1946).

(27) (a) Evans, *Nature*, **157**, 438 (1946); (b) Hughes and Ingold, *ibid.*, **158**, 94 (1946).

tion. In discussing k_Δ we have focused attention on only those considerations which are most important in the present connection. Some of these considerations are helpful in the general case, although the aspect of the stabilization of a small ring is unique with the present problem.

Neighboring Cl and OH. Structure and k_c/k_H.—Inspection of Table III reveals very constant values of k/k_H for neighboring chlorine and hydroxyl groups. For neighboring chlorine, the values however near 0.86×10^{-4}. This is very near the value of 0.94×10^{-4} calculated for k_c/k_H by the simplified electrostatic treatment previously[3] described. In this treatment one calculates, after some geometrical assumptions, the extra work involved in the generation of the transition state dipole due to the effect of the neighboring group dipole.

For neighboring hydroxyl the values of k/k_H hover near 6.5×10^{-3} while 1.07×10^{-2} is estimated (Table IV) as the value of k_c/k_H from the electrostatic treatment ($D_E = 1.23$) for a *trans*-chlorohydrin. As explained previously,[3] when k is of the order of magnitude expected for k_c, it is not possible to make any good estimate of the extent of operation of mechanism **A**. It is possible to conclude that k_c is at least comparable to k_Δ. Judging by the lack of any large effects of *beta* methyl groups, this last conclusion follows even when C_β is *tertiary* for neighboring hydroxyl with C_α *tertiary* and for neighboring chlorine with C_α *secondary* or *tertiary*. This kind of diagnosis on the basis of effects of *beta* substitution should prove to be very helpful.

TABLE IV

DEPENDENCE OF CALCULATED RELATIVE RATE k_c/k_H ON DEPARTING GROUP

N. group	Departing group	W^a (cal./mole)	k_c/k_H
trans-Br	$\bar{O}SO_2C_6H_4Br$	5090	1.87×10^{-4}
trans-Br	Br^-	5630	0.75×10^{-4}
trans-Br	Cl^-	5500	0.94×10^{-4}
trans-OH	Cl^-	2640	1.07×10^{-2}
trans-OH	$\bar{O}SO_2C_6H_4Br$	2510	1.45×10^{-2}

[a] D_E assumed equal to 2.23. Dipole moments and distances selected as in a previous paper.[3]

The constancy in the values of k/k_H (not far from k_c/k_H) for neighboring chlorine and hydroxyl is instructive in another way. It indicates how insensitive are the values of k_c/k_H to change in solvent, structure of C_α and C_β, and the nature of the departing group. This insensitivity is, to a considerable degree, expected on the basis of the electrostatic model previously[3] used in estimating k_c/k_H. As pointed out previously,[3] the effective dielectric constant D_E is very close to the internal one for dipole–dipole interactions. Thus the effects of change in external solvent and change in structure on D_E are very slight. Because of the geometry of the situation the effect of change in the departing group is also slight and this is shown in Table IV. In this Table, the calculated extra work W (see previous paper[3]) of ionization in the presence of neighboring groups Br or OH is summarized for departing Cl^-, Br^- or $BrC_6H_4SO_3^-$.

Actually, the value of k/k_H (essentially k_c/k_H) in the case of neighboring chlorine for the chlorohydrin–hydrobromic acid reaction is very nearly equal to the others, so it remains to be seen how gross may the changes in reaction type be with maintenance of essentially constant values of k_c/k_H.

Neighboring Br and I. Comparison with Qualitative Theory.—Turning to neighboring bromine and iodine in Table III, the values of k/k_H are far from constant as they would be if k were always substantially equal to k_c. For neighboring bromine k/k_H varies all the way from 1.6×10^{-4} to 7.2×10^{-2}. The calculated[3] values of k_c/k_H (Table IV) are 0.75×10^{-4} for departing Br^- and 1.87×10^{-4} for departing $\bar{O}SO_2C_6H_4Br$. Values of k_Δ/k_c are listed in Table III ranging from borderline values such as 1.1 to the value of 4.7×10^2.

For neighboring iodine the values of k/k_H vary over a thousandfold from 0.486 to the value 1120 reported previously[3] in the cyclohexyl system. Even the low value is much larger than the value of 6.7×10^{-4} anticipated for k_c/k_H from the electrostatic approach.[3] The corresponding values of k_Δ/k_c are given in Table III and are quite high (7.2×10^2 to 1.7×10^6).

For neighboring iodine there is further evidence that at least a substantial part of the rate-determining ionization is by mechanism **A**. First, for solvolysis of isobutylene iodochloride in 80% alcohol, $\Delta H^{\ddagger}$ is 21.8 kcal./mole and $\Delta S^{\ddagger}$ is -9.8 e. u./mole compared to values of 22.5 and -6.3, respectively, for *t*-butyl chloride.[13] The differences are in the same direction as in the case of the secondary system[3] previously reported, and smaller. Second, the change from a 48.61% aqueous dioxane solvent to 80% ethanol at 35° increases the solvolysis rate of *t*-butyl chloride by a factor of 19.7 and that of isobutylene iodochloride by a factor half as large, namely, 9.70. The lower sensitivity to solvent change for the latter compound is consistent with mechanism **A** by analogy with solvent effects in intermolecular cases. Thus the rate of bimolecular reaction of alkyl halides with neutral solvent has been shown to be less sensitive to a change to a more ionizing solvent than the rate of unimolecular solvolysis.[7]

The dependence of k/k_H on solvent in the presence of neighboring iodine indicates that k_Δ/k_H and thus k_Δ/k_c and L are not quite constant in different solvents. However, the drift with solvent is not extensive, judging by the case of iodine quoted above.

The values of k/k_H for neighboring bromine and iodine derived from the rough rates[2] of reaction of halohydrins with hydrohalogen acids (Table III) agree fairly well—as in the case of neighboring chlorine—with those derived from solvolysis rates of sulfonates. Thus values of k_Δ/k_c must also agree fairly well.

It is clear that the preceding theoretical considerations regarding the effect of *alpha* and *beta* substitution account qualitatively for the trends in k_Δ/k_c observed in Table III. *alpha*-Substitution definitely decreases k_Δ/k_c. For example the change from $\mathbf{S}_\beta\mathbf{S}_\alpha$ to $\mathbf{S}_\beta\mathbf{T}_\alpha$ with neighboring bromine changes k_Δ/k_c from 3.9×10^2 to 44. On the other hand *beta* substitution increases k_Δ/k_c. For example the change from $\mathbf{P}_\beta\mathbf{T}_\alpha$ to $\mathbf{S}_\beta\mathbf{T}_\alpha$ to $\mathbf{T}_\beta\mathbf{T}_\alpha$ with neighboring Br changes k_Δ/k_c from 1.1 to 44 to 4.7×10^2, respectively.

In classifying the systems as $\mathbf{S}_\beta\mathbf{S}_\alpha$, etc., we class methyl and other alkyl groups (as in cyclohexyl) together. Actually, closer inspection will probably show up significant differences. For example, the indications are that k_Δ/k_c is larger for 2-butyl[2] than for cyclohexyl (Table III).

With neighboring bromine and iodine, k_Δ/k_c is somewhat larger with the α-phenylethyl than the *t*-butyl halides. Even this detail is predicted by the qualitative considerations advanced. Judging that *alpha* substitution favors k_c more than k_Δ, and deducing that two methyl groups are slightly more than equivalent to a phenyl group from the slightly greater solvolysis rates of *t*-butyl[12,13] over α-phenylethyl halides,[10,11] one predicts the greater k_Δ/k_c for the α-phenylethyl type.

The striking variation of k/k_H with structure constitutes the most convincing single argument for the operation of both mechanisms **A** and **B** in ionization. We considered an alternative interpretation in which mechanism **B** was the sole one, the open carbonium ion always being formed in the rate-determining step. In this interpretation, deviations of k/k_H from the calculated values of k_c/k_H would be due to polarization of the neighboring group. The effect of *alpha* methyl or phenyl groups would be to diffuse the positive charge of C_α by hyperconjugation or resonance and thus decrease the polarization of the neighboring group and the corresponding gain in stability of the transition state. To explain the effect of *beta* methyl groups one could conceivably call on a steric effect such as is envisioned by Brown[28] and termed B-strain. Due to the postulated strain due to the alkyl groups on C_β, the relief afforded in spreading the $C–C_\beta–C$ angles could favor closer approach of the neighboring group to C_α with resultant increase in its polarization.

Examination of such an interpretation reveals some difficulties. First, a steric effect of *beta* methyl groups of the kind postulated appears to be too small in other phenomena to be of sufficient importance here. For example, in solvolysis of halides, steric strain might be expected to be rate-enhancing. In practice, rates of solvolysis[14] of $R_1R_2R_3CCl$ from $(CH_3)_3CCl$ to $(C_2H_5)_2CClCH(CH_3)_2$ are within a factor of 3. If strain were already serious with methyl groups, serious increases in rate would accompany change to the more substituted structures. Furthermore, the k/k_H values with a neighboring group such as Br drop too rapidly to practically the calculated value of k_c/k_H with addition of methyl to C_α and removal from C_β. Finally, such an interpretation does not predict the contrast between Cl on the one hand and Br and I on the other. With Cl, k/k_H is not sensitive to structure while with Br and I it is. However, estimates of the stabilization due to a dipole[29] at the center of the halogen atom induced by half a unit positive charge on C_α show that the effect is comparable in magnitude with all three halogens. Besides, the magnitude of the effect is far from sufficient to account for the large value of k/k_H with iodine. Even on the exaggerated basis of a half-charged C_α atom (not a transition state $C_\alpha–Y$ dipole), using usual distances and angles and halogen polarizabilities derived from atomic refractions one obtains values of the polarization energy in kcal./mole of: Cl, 1.8; Br, 2.3; I, 2.9. Distortion of the $C_\alpha–C_\beta–S$ angle (in I or III) from tetrahedral to 90°, for example, increases these values by only approximately 75 per cent., hardly enough to compensate for the work of bond-bending.

Thus on the basis of data so far available the interpretation on the basis of mechanisms **A** and **B** seems preferable. However, it is clear that the previous calculation of k_c/k_H based on neighboring Cl neglecting polarization and treating the effective dielectric constant $\mathbf{D_E}$ as an adjustable parameter actually is made on the simplifying assumption that polarization effects of the type mentioned in the transition state for formation of III are of comparable importance throughout. Thus there is still another reason[3] for lack of accuracy in k_c/k_H.

Closure of Other Small Rings.—The same theoretical considerations used above in discussing structure and reactivity are useful in interpreting the closure of classical small rings such as epoxide, imine and episulfide rings. In the case of epoxide ring closure, especially, there are available instructive data from the work of Smith[19] on the second-order rate constants k_2 for

TABLE V

RATE CONSTANTS FOR REACTION OF CHLOROHYDRINS WITH SODIUM HYDROXIDE

Compound	k_2 (18°) min.$^{-1}$	pK_A	k sec.$^{-1}$
$HOCH_2CH_2Cl$	0.31	16.9	5
$CH_3CH(OH)CH_2Cl$	6.5	17.0	1.3×10^2
$HOCH_2CHClCH_3$	1.7	17.0	34
$(CH_3)_2C(OH)CH_2Cl$	78	17.2	2.5×10^3
$HOCH_2CCl(CH_3)_2$	77	17.0	1.5×10^3
$(CH_3)_2C(OH)CHClCH_3$	424	17.2	1.3×10^4
$CH_3CH(OH)CCl(CH_3)_2$	633	17.1	1.6×10^4
$(CH_3)_2C(OH)CCl(CH_3)_2$	3600	17.3	1.4×10^5

---

(28) (a) Brown, Bartholomay and Taylor, THIS JOURNAL, **66**, 435 (1944); (b) Brown, *Science*, **103**, 385 (1946).

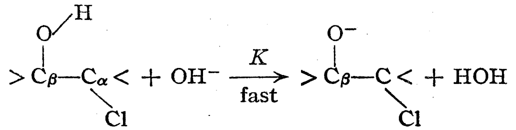
(29) Debye, "Polar Molecules," Dover Publications, New York, N. Y., 1945, p. 18.

reaction with sodium hydroxide of the series of methyl substituted ethylene chlorohydrins. These rate constants are listed in Table V.

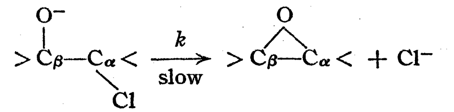
The mechanism we have suggested previously for the epoxide ring closure[22] involves the unimolecular conversion (specific rate constant k) of the chloroalcoholate ion to oxide (equations 4 and 5). The unimolecular rate constant k is given as a function of the measured second-order constant k_2 by equation 6, where K_A is the acidity constant of the chlorohydrin and K_W is the ion-product of

$$k_2 = kK = kK_A/K_W \qquad (6)$$

water. In order to estimate k, rough pK_A values for the chlorohydrins were calculated by the method of Branch and Calvin,[30a] using their inductive constants for Cl and CH_3 and a pK_A of 18.0 for ethanol.[30b] These estimated pK_A values are shown in Table V together with the derived values for k. The order of magnitude (5 to 10^5 sec.$^{-1}$) of the specific rate of conversion of chloroalcoholate ion to oxide is very large.



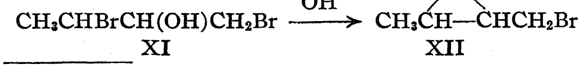
$$>\overset{\overset{H}{\diagup}O}{C_\beta}-\underset{\diagdown Cl}{C_\alpha}< + OH^- \xrightarrow[\text{fast}]{K} >\overset{O^-}{C_\beta}-\underset{\diagdown Cl}{C}< + HOH \qquad (4)$$



$$>\overset{O^-}{C_\beta}-\underset{\diagdown Cl}{C_\alpha}< \xrightarrow[\text{slow}]{k} >\overset{O}{\overbrace{C_\beta-C_\alpha}}< + Cl^- \qquad (5)$$

Primary and secondary halides ionize at rates no greater than 10^{-8} and 10^{-4} times, respectively, those of the corresponding tertiary halides.[7,26] Thus, from Smith's values[19] for the rate of hydrolysis of the tertiary halohydrins, values of the order of 5×10^{-13} and 5×10^{-9} sec.$^{-1}$, respectively, become upper limits for k_c of primary and secondary halohydrins. These estimates are exceeded by the values for k in Table V by factors of 10^{13} to 5×10^{15} in the case of the primary halohydrins and 7×10^9 to 3×10^{12} in the case of the secondary halohydrins. These factors are too large to ascribe to a simple electrostatic effect of the O^- charge, the ring closure being very predominantly a concerted one ($k = k_\Delta$).

The expected rate-enhancing effect of methyl substitution on either carbon atom of the halohydrin system is observed. While the primary propylene chlorohydrin is more reactive than the secondary, the latter is more reactive than ethylene chlorohydrin. The beneficial effect of alkyl substitution on oxide ring closure is further illustrated by the reported formation[31] of the most substituted oxide XII from the halohydrin XI which carries competing primary and secondary bromine atoms.



$$\underset{\text{XI}}{CH_3CHBrCH(OH)CH_2Br} \xrightarrow{OH^-} \underset{\text{XII}}{CH_3\overset{O}{\overbrace{CH-CH}}CH_2Br}$$

Other classical small ring closures show the rate-enhancing effect of an *alpha* methyl group. Thus in the case of ethylene imine formation in water at 25° relative reactivities[32] are $CH_3CHClCH_2NH_2$,4 > $CH_2ClCH_2NH_2$,1. On the other hand, for the closure of a 5-membered imine ring an *alpha* methyl group gives the unfavorable effect characteristic of external type bimolecular displacements.[32] The rate-enhancing effect of an *alpha* methyl group on β-lactone formation[33] is shown by the relative rates in water at 70°: $CH_3CHClCH_2CO_2^-$, 5 > $ClCH_2CH_2CO_2^-$, 1.

Inspection of the k values for the tertiary halohydrins in Table V reveals effects of methyl substitution which are formally correct for k_Δ. Actually, a calculation by the method of Kirkwood and Westheimer[34] of the extra electrostatic energy W due to the interaction of the negative charge on the O^- oxygen atom with the transition state C_α-Cl dipole (moment 5.42 D) gives values of k/k_{OH} (where k_{OH} is k_c for neutral halohydrin and k is from Table V) of the observed order of magnitude (Table VI). However, the factor of 10^2 introduced by two *beta* methyl groups is hard to account for electrostatically since the effective dielectric constant D_E is low and relatively constant. This gives calculated values of k/k_{OH} relatively constant to *beta* methyl substitution. On this account, the values of k of at least the *beta*-methyl substituted tertiary halohydrins are believed substantially equal to k_Δ.

TABLE VI

ELECTROSTATIC CALCULATION OF EFFECT W OF NEGATIVE CHARGE IN CHLOROALCOHOLATE ION

Compound	D_E[a]	W,[b] kcal./mole	k/k_{OH}, 18° C. calcd.	observed
$HOCH_2CCl(CH_3)_2$	2.70	10.85	1.4×10^8	2.3×10^7
$CH_3CH(OH)CCl(CH_3)_2$	2.60	11.28	2.9×10^8	4.7×10^8
$(CH_3)_2C(OH)CCl(CH_3)_2$	2.51	11.68	5.9×10^8	2.3×10^9

[a] Effective dielectric constant calculated from Kirkwood and Westheimer's equation 11 for a spherical molecule.[34a] Molecular radii calculated from Kopp's atomic volumes quoted by Leermakers and Weissberger.[35] Internal dielectric constant 2.00, external dielectric constant 78. [b] $W = (eM \cos \theta)/r^2D_E$. Symbols have usual meaning. Previous[3] conventions regarding tetrahedral bonds, bond distances, *trans*-arrangement of C–Cl and C–O^- bonds employed here. Transition-state C–Cl distance of 2.26 Å.

Semi-Quantitative Theory of the Effect of *alpha* and *beta* Substitution.—It is possible to extend the qualitative considerations with regard to *alpha* and *beta* methyl substitution to a semi-quantitative treatment for L and thus k_Δ/k_c, k/k_c and k/k_H. For any one neighboring group, leaving group and solvent, one can approximate

---

(30) (a) Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, Chapter VI; (b) McEwen, THIS JOURNAL, **58**, 1124 (1936).

(31) Petrov, *J. Gen. Chem.* (*U. S. S. R.*), **11**, 713 (1941).

(32) Freundlich and Salomon, *Z. physik. Chem.*, **166**, 161 (1933).

(33) Simpson, THIS JOURNAL, **40**, 674 (1918).

(34) (a) Kirkwood and Westheimer, *J. Chem. Phys.*, **6**, 506 (1938); (b) Westheimer, THIS JOURNAL, **62**, 1892 (1940); (c) Westheimer and Shookhoff, *ibid.*, **61**, 555 (1939).

(35) Leermakers and Weissberger in Gilman, "Organic Chemistry," Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 1743.

$\Delta F_c^{\ddagger}$, the free-energy of activation for mechanism **B**, by equation 7. L_c represents the free-

$$\Delta F_c^{\ddagger} = L_c - C_\alpha N_\alpha \qquad (7)$$

energy of activation for step **B** of the *beta*-substituted ethyl compound, N_α the number of *alpha* methyl groups, and C_α is a parameter that would have the value of *ca.* 5.5 kcal./mole from a tentative factor of *ca.* 10^4 per alpha methyl group in solvolysis rates.[7,26] Equation 7 assumes relative insensitivity to *beta* methyl groups of rates of ionization to open carbonium ions III. For solvolysis of $R_3CCCl(CH_3)_2$, Table II shows the lack of effect of *beta* methyl groups.

In approximating $\Delta F_\Delta^{\ddagger}$, the free-energy of activation of step **A**, equation 8 is used. L_Δ rep-

$$\Delta F_\Delta^{\ddagger} = L_\Delta - d_\alpha N_\alpha - d_\beta N_\beta \qquad (8)$$

resents the free-energy of activation for step **A** of the *beta*-substituted ethyl compound, N_β the number of β-methyl groups, and d_α and d_β are parameters. Equation 8 is based on the assumption that the stabilization by *alpha* and *beta* methyl groups of the transition-state leading to intermediate II is proportional to the number of *alpha* and *beta* methyl groups.

From equations 7 and 8, the variation of the driving force L with structure is readily derived. In principle d_α and d_β in equation 8 may vary with structure and neighboring group, depending on the extent of carbonium ion character of C_α. However, one single equation 9 fits the available experimental data quite well. In equation 9, L_0 is

$$L = 1.365 \log (k_\Delta / k_c) = L_0 - 2.27\ N_\alpha + 1.79\ N_\beta \quad (9)$$

$(L_c - L_\Delta)$ and is fairly insensitive to the nature of the solvent and leaving group. It varies mainly with the nature of the neighboring group and is termed the standard driving force of the neighboring group.

The values of L_0 for neighboring I, Br and OCH_3 are listed in Table VII. The value for OCH_3 stems from the one borderline value of k_Δ/k_c obtained in the cyclohexyl system.[3] In Table III, alongside the experimental values of k_Δ/k_c are given the values calculated from equation 9. It is clear that the crude energy treatment represented by equation 9 fits the data satisfactorily. Also listed in Table III are values of k_Δ/k_c calculated from equation 9 for structures where no direct determinations were possible.

According to equations 7, 8 and 9, d_β = 1.79 kcal. and $C_\alpha - d_\alpha$ = 2.27 kcal. Thus the hyperconjugative stabilization per methyl group in the transition-states is *ca.* 5.5 kcal. at C_α for step **B**, and *ca.* 3.2 kcal. at C_α and 1.8 kcal. at C_β for step **A**. The latter figure speaks for a stabilization energy per methyl group in the three-membered charged heterocyclic rings II in excess of the 2.5 kcal. hyperconjugation energy per methyl[23] in olefins. The sequence $C_\alpha > d_\alpha > d_\beta$ is reasonable because it is also the sequence of decreasing carbonium ion character of the corresponding carbon atoms.

The rates of oxide closure (k in Table V) afford a test of the validity of an equation of the type 8 over the entire range of structure of C_α and C_β. Equation 10 with the values of 1.45 for d_α and 1.67 for d_β fits the data in Table V with a mean de-

$$1.332 \log k = 0.94 + 1.45\ N_\alpha + 1.67\ N_\beta \qquad (10)$$

viation of 0.17 in log k.

Driving Force and Nucleophilic Character of Neighboring Groups.—Returning to the L_0 values in Table VII, we notice that we are in effect focusing attention on the relative abilities of the neighboring groups in nucleophilic attack on the adjacent carbon atom. Even for external substitutions, efficiency in nucleophilic attack on carbon is not well understood. In considering the activity of various nucleophilic agents, basicity is a fair guide as long as one remains with one attacking atom (*e. g.*, O in OH, CH_3COO, etc.). However, when one varies the nature of the attacking atom (*e. g.*, O, S), polarizability seems to be an important aspect. For internal substitution the problem is even more complicated because of such factors as strain. The values of L_0 for the neighboring groups represent one measure of nucleophilic character. To the values of L_0 derived from equation 9 and listed in Table VII are added rough minimum estimates of the driving force L for the neighboring groups SCH_2CH_2OH, NH_2 and O^- in the β-substituted ethyl chlorides in water at 25°. The estimated values of k/k_H for these compounds are also listed in Table VII, representing an alternative measure of nucleophilic character of the neighboring groups.

TABLE VII

VALUES OF STANDARD DRIVING FORCE L_0 AND k/k_H FOR VARIOUS NEIGHBORING GROUPS IN β-SUBSTITUTED ETHYL COMPOUNDS

Neighboring group	L_0	k/k_H
SCH_2CH_2OH	$13^{a,b}$	10^7
I	8.71	1.6×10^3
NH_2	$8^{a,c}$	10^4
O^-	$6^{a,d}$	10^{10}
Br	4.55	0.39
OH, OCH_3	1.34	0.1

[a] k_H for C_2H_5Cl in water at 25° estimated at 10^{-8} times value[20] for t-C_4H_9Cl or 3×10^{-10} sec.$^{-1}$ (upper limit). [b] k_c/k_H estimated at 10^{-2}. k_Δ from data of Bartlett and Swain.[36] [c] k_c/k_H estimated at 10^{-1}. k_Δ from Freundlich and Salomon.[32] [d] k_c/k_H estimated at 10^6. k_Δ from Table V.

Neighboring Groups in Primary Systems.—In considering the whole range of structure of compound I with a neighboring group, we expect the greatest driving forces L or highest values of k_Δ/k_c when C_α is primary as shown in Table III. Actually, it is only with some of the classical type neighboring groups such as O^-, NR_2 and SR that

---

(36) Bartlett and Swain, Report No. 4683, Division 9, N.D.R.C., O.S.R.D.

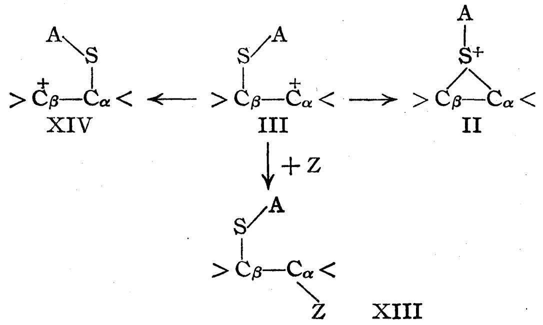
we have known rates which definitely indicate high values of k_Δ/k_c for primary compounds. With other neighboring groups such as Br, OCH_3, etc., we are in the process of collecting data on further structures, some with C_α primary. Because of the care which must be exercised in seeking unimolecular mechanisms with primary compounds, there is little of significance in the literature on these latter cases. Thus, for example, Bennett and Reynolds[37] found the reaction of ethylene chlorohydrin with hydrogen bromide in phenol proceeded at a rate negligible compared to that of ethanol. If the unimolecular type interpretation of Bennett and Reynolds were correct, the effect of the chlorine atom would be of direct interest here. However, it is very probable that the mechanism is bimolecular[9,26] ($R\overset{+}{O}H_2 + Br^-$) at least with ethanol.

Also of interest is the reaction of ethylene dihalides with silver salts. Ethylene dibromide has been reported[38] to react with alcoholic silver nitrate faster than ethyl bromide. However, Petrenko-Krichenko and Opotsky[39] report quantitative work to the contrary, and we have confirmed their findings by comparison of the relative rates of precipitate formation on treatment of pure samples of ethyl and ethylene bromides with alcoholic silver nitrate. From the data of Petrenko-Krichenko and Opotsky[39] on the reaction of halides with silver nitrate, it is clear that ethylene chloride is quite inert relative to ethyl chloride, ethylene bromide is roughly one-tenth as reactive as ethyl bromide and ethylene iodide is fully as reactive as ethyl iodide. While the effects of the neighboring Cl, Br, and I atoms are at least in the right order for participation, the reaction of halides with silver nitrate is too much complicated[40,41] by such things as higher order reactions and adsorption effects to justify any certain deductions and comparisons with values of k_Δ/k_c in Table III at the present time.

Rates, Stereochemistry and Products.—To control steric results of nucleophilic displacement reactions it is often necessary to assess the relative tendencies for bimolecular displacement with inversion or unimolecular type displacement which can lead to various steric results of which, perhaps, the most interesting is retention of configuration in the presence of a suitable neighboring group. For this purpose, a knowledge of the rates in reactions of the unimolecular type (as well as the bimolecular type) of the substituted compounds is essential, and toward this end the rate work so far reported is already useful.

Correlating the present work on rates of unimolecular solvolyses with the previous[42] work on the stereochemistry and products of such reactions, it becomes clear that most of the previous work has dealt with cases in which the rate-determining reaction step was the type **A**. Inversion of configuration in this step, followed by a second inversion in the conversion of cycle II to product, accounts for the clean-cut retentions of configuration.

For the situations where the rate work indicates the ionization is at least partly by mechanism **B**, there is little information on products and stereochemistry. In this sense, the rate work has helped to select crucial cases for stereochemical scrutiny. It is clear from the work of Lucas and Gould[43] that a neighboring chlorine atom gives rise to retention of configuration in the reaction of the 2-butene chlorohydrins with thionyl chloride. The conditions here are, of course, remote from those in the rate measurements. Also, it is evident that in the reactions of stilbene derivatives[42d] with silver acetate in acetic acid, a β-acetoxy group participates in the displacement reaction for at least one of the diastereomeric acetoxychlorides, whereas, apparently, a neighboring chlorine atom fails to participate in at least one of the diastereomeric dichlorides. In the cases where the rate-determining step is **B**, the rate constants refer to the rate of formation of open carbonium ion III and do not yield information on the reaction paths III follows. The ion III may close to II, it may coördinate with reagent or solvent Z to give product XIII, or it may rearrange either to new ion XIV or in other ways, to mention some of the possibilities. Also, the stereochemical results may be controlled by restriction of rotation around the C_β–C_α bond. Further chemical work is being carried on in these directions.



Experimental

Styrene Dibromide.[44]—This compound was prepared by addition of bromine to styrene. Recrystallization from alcohol gave material, m. p. 72.3–72.5°, reported variously[45] from 72° to 74–75°.

---

[37] Bennett and Reynolds, *J. Chem. Soc.*, 131 (1935).

[38] Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 43.

[39] Petrenko-Krichenko and Opotsky, *Ber.*, **59**, 2131 (1926).

[40] Roberts, Young and Winstein, THIS JOURNAL, **64**, 2157 (1942).

[41] Dostrovsky and Hughes, *J. Chem. Soc.*, 169 (1946).

[42] (a) Winstein, Hess and Buckles, THIS JOURNAL, **64**, 2796 (1942); (b) Winstein and Buckles, *ibid.*, **65**, 613 (1943); (c) Winstein and Henderson, *ibid.*, **65**, 2196 (1943); (d) Winstein and Seymour, *ibid.*, **68**, 119 (1946).

[43] Lucas and Gould, *ibid.*, **63**, 2541 (1941).

[44] We are indebted to Mr. Bruce Garner for the preparation of some of this material and for preliminary work on its alcoholysis.

[45] (a) V. Braun and Moldanke, *Ber.*, **54**, 619 (1921); (b) Read and Reid, *J. Chem. Soc.*, 1488 (1928).

Styrene Iodochloride.—To a mixture of 13.6 g. (0.050 mole) of mercuric chloride, 10.4 g. (0.10 mole) of freshly distilled styrene and 200 ml. of absolute ether in a 1-liter round-bottom flask equipped with a reflux condenser, a mercury-sealed stirrer, and protected with a calcium chloride tube, was added with stirring 25.4 g. (0.10 mole) of iodine. Stirring was continued for one hour and then, because of illness, the reaction mixture was allowed to stand approximately a month.

The ethereal solution was decanted from the mercuric iodide and concentrated to a volume of 60 ml. with the aid of a water pump. The concentrated solution was washed rapidly with aqueous potassium iodide, then aqueous sodium bisulfite, finally water, and dried over potassium carbonate. Removal of the ether at reduced pressure and recrystallization of the residue from petroleum ether yielded 12.5 g. (47%) of product, m. p. 40.6° unimproved by further recrystallization. Ingle[4] reported m. p. 46° for the product of addition of iodine monochloride to styrene, but repetition of this preparation yielded material, m. p. 40°. After treatment of 0.1907 g. of material, m. p. 40.6°, in a stoppered Erlenmeyer flask overnight with a solution of 2 g. of sodium iodide in 25 ml. of absolute acetone, titration with thiosulfate required 28.49 ml. of 0.0499 *N* solution. Equivalent weight: 134.1 (calculated 133.3).

Isobutylene Dibromide.—Redistilled Eastman Kodak Co. material, b. p. 76.4–76.8° (74 mm.), $n^{19}\text{D}$ 1.5095 (reported[46] b. p. 147–148° (742 mm.), $n^{17}\text{D}$ 1.5103) was used for rate measurements.

Isobutylene Iodochloride.—Approximately a 20% excess of liquid isobutylene was distilled into a well-stirred mixture of 81.6 g. (0.300 mole) of mercuric chloride, 152 g. (0.600 mole) of iodine and 400 ml. of ether in a flask equipped with a dry-ice condenser and a mercury-sealed stirrer, and protected with a calcium chloride tube. Stirring was continued for one hour and then the mixture was left overnight. The ethereal solution was decanted, concentrated at reduced pressure and then washed rapidly with aqueous potassium iodide, aqueous sodium bisulfite and then water. It was dried over magnesium sulfate, then over potassium carbonate. The ether was removed at reduced pressure and the residue was distilled at 22.5 mm. through an 18″ glass spiral column to yield 88.3 g. (67%) of product, b. p. 55.5–56.2°, $n^{23}\text{D}$ 1.5237, $d^{23}{}_4$ 1.727, *MR*D 38.69 (calc. 38.34), equivalent weight for iodine chloride elimination as in the case of styrene iodochloride 109.4 (calc. 109.2). Istomin[5] reported $d^{15}{}_4$ 1.7502 for the product of addition of iodine chloride to isobutylene.

Solvents.—The absolute alcohol solvent contained less than 0.02% water by the paraffin oil test of Robertson.[47] Four volumes of alcohol were diluted with one volume of conductivity water at 25° to prepare 80% alcohol.

Aqueous dioxane was prepared by addition of 946 g. of conductivity water to 1000 g. of dioxane, b. p. 100.0° (747 mm.), purified according to the directions of Fieser.[48]

Rate Measurements.—The rates at 55° and 70°, and the rate of solvolysis of isobutylene dibromide at 25°, were measured by the sealed ampoule technique. The other measurements were carried out more conveniently by removing at intervals aliquots of the thermostated reaction mixture from a thin-walled glass-stoppered Erlenmeyer flask. Titrations were carried out on 5-ml. aliquots with 0.05 *N* sodium hydroxide from a 5-ml. microburet to the brom thymol blue end-point. Since in the partly aqueous solvents some halohydrin is produced during the solvolysis, a slightly acid green end-point color was used consistently, and titrations were performed rapidly with vigorous shaking in the cold, essentially by the method of Suter and Zook.[17] In all measurements except those in aqueous dioxane, aqueous base was found satisfactory. In the latter case, 0.05 *N* base in "50%" dioxane was used. The titrations were usually reproducible to within ±0.010 ml. of base, except in the earlier work on the dibromides where the probable titration error was *ca.* ±0.020 ml. of base.

In the case of the iodochlorides the concentration of halogen was estimated at intervals by rapid titration with 0.05 *N* aqueous thiosulfate. The amount of halogen was less than 1.5 and 7–12 mole % of the acid produced in the case of the isobutylene and styrene derivatives, respectively.

An approximate estimate of the specific rate of α-methylallyl chloride was obtained by a procedure similar to that used by Peters and Walker.[49] One to three drops of halide, b. p. 64.5–64.8° (752 mm.), $n^{20}\text{D}$ 1.4159, were added to 100 ml. of water containing two drops of brom thymol blue indicator and a known amount of sodium hydroxide. The time, *t*, until the indicator changed color was measured with a stop-watch, and the concentration of acid after at least ten periods of half-change was determined by titration. From these data, a first-order rate constant can be calculated.

Details on Rate Constants.—First-order rate constants, *k*, where $k = (1/t) \ln [a - x)]$, *a* being initial concentration in moles/liter of the organic halide, *t* the elapsed time, and *x* the concentration of generated acid or consumed base, were calculated.

In Table VIII are given data on a typical run on the alcoholysis of styrene dibromide. The first-order rate-constants are seen to drop during a run due to reaction of the liberated hydrogen bromide with the ethanol solvent.[9] The decrease in *k* is linear with time, and equation 11, obtained by the method of least squares, fits the data of this

$$k = 6.83 \times 10^{-4} - 0.0127 \times 10^{-4}\,t \qquad (11)$$

and a duplicate run with a mean deviation of 2.3%. Thus the empirical extrapolation gives an initial rate constant of 6.83×10^{-4} hr.$^{-1}$ or 1.90×10^{-7} sec.$^{-1}$. With added 0.1369 *M* sodium perchlorate there was no systematic decrease in the calculated first-order constants until the elapsed time was more than 122 hours. This was probably mainly due to the much lower rate of reaction of the generated hydrogen bromide with ethanol solvent[9] at this high ionic strength.

TABLE VIII

DATA FOR ETHANOLYSIS OF 0.1183 *M* STYRENE DIBROMIDE AT 54.95°

t, hours	*x* in ml. 0.0459 *N* NaOH per 9.96-ml. aliquot	$10^4 k$ (hr.$^{-1}$)
22.5	0.382	6.66
49.5	0.750	5.92
72.7	1.068	5.84
116.1	1.54	5.33
142.6	1.80	5.11
172.5	1.93	4.53
214.4	2.19	4.16
236.7	2.22	3.82

In the case of ethanolysis of *ca.* 0.10 *M* styrene iodochloride at 69.95°, first-order rate constants showed a tendency to climb, probably at least partly due to the greater effect of rising ionic strength than that of reaction of hydrogen chloride with solvent. This is illustrated in Table IX. Extrapolation to zero acid production for two such runs gave initial rate constants of 4.6×10^{-5} sec.$^{-1}$ and 5.2×10^{-5} sec.$^{-1}$.

For the determination of solvolysis constants in the aqueous ethanol or dioxane solvents, it was not necessary to extrapolate. The first-order rate constants were steady with a mean deviation of less than 3% to the following extents of reaction: 0.065 *M* isobutylene dibromide in 80% ethanol, *ca.* 10%; 0.085 *M* isobutylene iodochloride in 80% ethanol, *ca.* 13%; 0.033 *M* isobutylene iodochloride in the aqueous dioxane, *ca.* 20%; 0.007 *M* and 0.015 *M*

---

(46) Dojarenko, *Ber.*, **59**, 2946 (1926).

(47) Robertson, "Laboratory Practice of Organic Chemistry," The Macmillan Co., New York, N. Y., 1937, p. 161.

(48) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1941, p. 368.

(49) Peters and Walker, *Biochem. J.*, **17**, 260 (1923).

TABLE IX

DATA FOR ETHANOLYSIS OF 0.1075 *M* STYRENE IODOCHLORIDE AT 69.95°

t, sec.	$10^3 x$	$10^5 k$ (sec.$^{-1}$)
0	1.00	..
180	2.10	5.78
540	4.71	6.56
720	6.20	6.96
900	7.73	7.25
1260	10.96	7.80

t-butyl chloride, b. p. 50.2° (752 mm.), in the aqueous dioxane, 80%. For *t*-butyl chloride the rate constants were $6.14 \pm 0.11 \times 10^{-4}$ sec.$^{-1}$ at the lower concentration, $6.43 \pm 0.11 \times 10^{-4}$ sec.$^{-1}$ at the higher concentration, and $6.30 \pm 0.15 \times 10^{-4}$ sec.$^{-1}$ for the mean of both runs.

In Table X are given the data on the crude estimate of the rate constant for hydrolysis of α-methylallyl chloride in water at 27.2°.

TABLE X

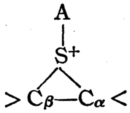
DATA ON HYDROLYSIS OF α-METHYLALLYL CHLORIDE AT 27.2°

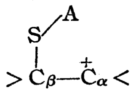
$10^3 a$	$10^3 x$ (NaOH)	*t* (sec.)	$10^3 k$ (sec.$^{-1}$)
0.632	0.252	624	0.82
1.053	.135	107	1.28
2.637	.240	86	1.11
3.48	.249	73	1.02
		Mean	1.06 ± 0.14

Summary

The rates of solvolysis (k) of styrene dibromide, styrene iodochloride, isobutylene dibromide and isobutylene iodochloride have been determined for comparison with reported rates (k_H) of the corresponding α-phenylethyl and *t*-butyl halides. The rates of solvolysis are also reported for *t*-butyl chloride in 48.61 wt. per cent. aqueous dioxane at 34.86° and for α-methylallyl chloride in water at 27.2°. The relative reactivities, k/k_H, here reported, together with others either previously reported or derived from rate data in the literature, cover the range of structure for both the *alpha* and *beta* carbon atoms (C_α and C_β) which may be *primary* (**P**), *secondary* (**S**), or *tertiary* (**T**)

With neighboring Cl in $\mathbf{S}_\beta\mathbf{S}_\alpha$, $\mathbf{P}_\beta\mathbf{T}_\alpha$, and $\mathbf{T}_\beta\mathbf{T}_\alpha$ systems and with neighboring OH in $\mathbf{P}_\beta\mathbf{T}_\alpha$, $\mathbf{S}_\beta\mathbf{T}_\alpha$, $\mathbf{T}_\beta\mathbf{T}_\alpha$ systems and in $HOCH_2CHClCH{=}CH_2$ values of k/k_H are quite constant. In these cases, the rate-determining ionization is predominantly the formation of the carbonium ion III (rate constant k_c) rather than the direct formation of cycle II (rate constant k_Δ) so that k/k_H is essentially k_c/k_H. The observed insensitivity of k_c/k_H to changes in structure, solvent and departing group is rather expected from the electrostatic treatment previously used in discussing the effect of neighboring groups.


II


III

For neighboring Br and I, k/k_H varies widely with structure. The values of k_Δ/k_c, obtained with the aid of estimates of k_c/k_H from the electrostatic treatment, range for I from 7.2×10^2 in the $\mathbf{P}_\beta\mathbf{T}_\alpha$ system to 1.7×10^6 in the $\mathbf{S}_\beta\mathbf{S}_\alpha$ system and for Br from 1.1 in the $\mathbf{P}_\beta\mathbf{T}_\alpha$ system to 4.7×10^2 in the $\mathbf{T}_\beta\mathbf{T}_\alpha$ system. These trends are exactly those predicted by a qualitative theory which recognizes that *alpha* substitution stabilizes II and, to a greater extent, III, and that *beta* substitution stabilizes II. Thus *beta* substitution increases k_Δ and k_Δ/k_c while *alpha* substitution increases both k_Δ and k_c and decreases k_Δ/k_c.

The qualitative theory explains the trends observed in rates of closure of the ethylene oxide ring from variously substituted ethylene chlorohydrins. Similarly, it is in accord with the favorable effect of *alpha* methyl substitution for closure of the ethylene imine and the β-lactone rings.

For neighboring Br, I and OCH_3 the data on the variation of the driving force L, defined as $RT \ln (k_\Delta/k_c)$, with the numbers, N_α and N_β, of *alpha* and *beta* methyl groups have been fit by the relation

$$L = L_0 - 2.27\ N_\alpha + 1.79\ N_\beta$$

L_0, the driving force in the $\mathbf{P}_\beta\mathbf{P}_\alpha$ system, is tabulated for I, Br, OCH_3, O^-, NH_2 and SCH_2CH_2OH neighboring groups.

LOS ANGELES 24, CALIF.

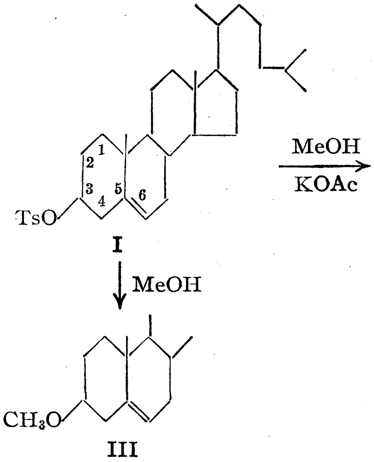
RECEIVED APRIL 3, 1947

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

The Role of Neighboring Groups in Replacement Reactions. XIV. The 5,6-Double Bond in Cholesteryl *p*-Toluenesulfonate as a Neighboring Group

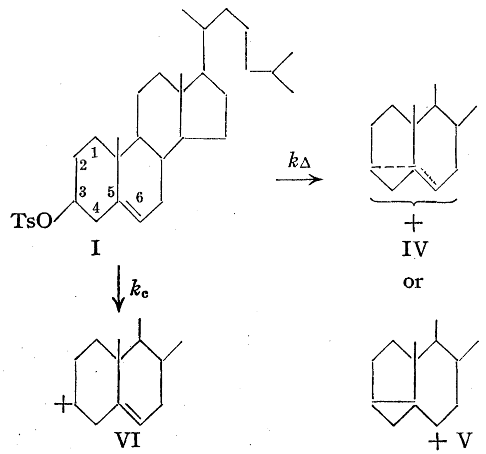
BY S. WINSTEIN AND ROWLAND ADAMS

Shoppee[1] has very recently pointed out the tendency toward a steric result of retention of configuration in nucleophilic displacements at C_3 in Δ^5-cholestene derivatives and similar systems. Also he has drawn an analogy which we also have been using between this phenomenon and our work, presented in previous papers of this series, on participation of such neighboring groups as bromine in nucleophilic displacement processes. We are prompted to report the results of a study of the kinetics of acetolysis of cholesteryl *p*-toluenesulfonate I which we carried out some time ago as part of an investigation which was unavoidably interrupted.



It is known[2] that cholesteryl *p*-toluenesulfonate I on treatment with potassium acetate in methanol gives rise to a material which is best represented as the *i*-ether[3] II. In the absence of potassium acetate in the methanol, normal ether III is produced. By the action of potassium acetate in acetic anhydride, I is converted to *i*-acetate.[3c,d] Cholesteryl chloride, similarly to the toluenesulfonate, also[4] gives rise to *i*-ether. The *i*-ethers are relatively unstable, for example being converted to normal acetate on treatment with potassium acetate in glacial acetic acid.[3a,b] From the properties of the *i*-ethers it is apparent that the action of the potassium acetate in the methanol where *i*-ether is formed from I is merely to buffer the solution so that high acidity is not developed.

The *i*-sterol rearrangement (I → II) represents a case of participation in a nucleophilic displacement reaction by a properly situated ethylenic linkage, a suitable example of which we had been seeking for study when we began the present investigation. The most likely general mechanism for this rearrangement would seem to involve either the hybrid carbonium ion IV or the rearranged carbonium ion V. The intermediate (IV or V) then reacts with nucleophilic agents more rapidly at C_6 than C_3.



With regard to the formation of the intermediate IV or V, the alternatives (with no regard for stereochemistry) are a direct formation by ionization of I or prior formation of unrearranged carbonium ion VI, which then is converted to intermediate V (as though an energy barrier existed between V and VI). The specific reaction rate constants for the two modes of rate-determining ionization are symbolized by k_Δ and k_c, the symbols used previously[5] for other neighboring groups.

The kinetics of acetolysis of cholesteryl *p*-toluenesulfonate I support the general mechanism outlined and point to the direct ionization to intermediate IV or V (rate constant k_Δ). The acetolysis of I in glacial acetic acid proved to be very cleanly first-order, the first-order rate constants k at 35.00 and 50.00° being summarized in Table I.

The catalytic effect of water and sodium acetate on the acetolysis is quite marked. However, these effects are definitely solvent and ionic

---

[1] Shoppee, *J. Chem. Soc.*, 1147 (1946); journal received March 3, 1947.

[2] Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).

[3] (a) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 907 (1936); (b) Beynon, Heilbron and Spring, *ibid.*, 406 (1937); (c) Wallis, Fernholz and Gephardt, THIS JOURNAL, **59**, 137 (1937); (d) Ford and Wallis, *ibid.*, **59**, 1415 (1937); (e) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 1459 (1937); (f) Ford, Chakravorty and Wallis, THIS JOURNAL, **60**, 413 (1938); (g) Heilbron, Hodges and Spring, *J. Chem. Soc.*, 759 (1938); (h) Ladenburg, Chakravorty and Wallis, THIS JOURNAL, **61**, 3483 (1939).

[4] Wagner-Jauregg and Werner, *Z. physiol. Chem.*, **213**, 119 (1932).

[5] (a) Winstein, Grunwald and Ingraham, THIS JOURNAL, **70**, 821 (1948); (b) Winstein and Grunwald, *ibid.*, **70**, 828 (1948).

TABLE I

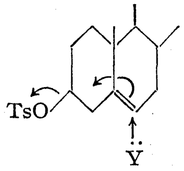
RATE CONSTANTS OF ACETOLYSIS k OF *ca.* 0.01 M CHOLESTERYL p-TOLUENESULFONATE IN GLACIAL ACETIC ACID

Other solute	Temp., °C.	$10^3 k$, min.$^{-1}$
....	50.00	7.9[a]
0.50 M H_2O	50.00	12.2
.0100 M KOAc	50.00	19.8
.0100 M NaOAc	50.00	20.0
.0200 M NaOAc	50.00	20.0
.0100 M $LiClO_4$	50.00	24.1
....	35.00	1.19[a]
....	50.00	0.111[b]

[a] $\Delta H^{\ddagger} = 24.4$ kcal./mole. [b] Cyclohexyl p-toluenesulfonate.

strength effects. Thus the effect of sodium acetate is not even as large as that of lithium perchlorate. Also raising the concentration of sodium acetate from 0.01 to 0.02 M gives no further increase in rate, which is not too surprising for ionic strength effects[6] in a solvent of as low a dielectric constant as that of acetic acid (*ca.* 6).

The fact that acetic acid is such a poor nucleophilic agent, that the rate is still nicely first order on addition of sodium acetate and that the effect of sodium acetate (the same at 0.01 and 0.02 M) is less even than that of lithium perchlorate indicates that the acetolysis represents a reaction of the unimolecular type and that concerted mechanisms of the type shown in VII are not important here.



VII

The rate of acetolysis of cholesteryl p-toluenesulfonate I is seen to be some 10^2 (depending on ionic strength) times as large as that for cyclohexyl p-toluenesulfonate[7] also determined at 50.00° for comparison (Table I). The latter compound represents at least one good choice of a model substance for comparison in order to estimate k_c. Now reactivities of ring compounds are not yet clearly understood so that other comparisons are desirable. Actually, there are other indications of enhanced reactivity due to the 5,6-ethylenic linkage. Thus, Stoll[8] compared cholesteryl p-toluenesulfonate I with cholestanyl and ergostanyl p-toluenesulfonates in ethanol (no added ethoxide) at 78° and from his first-order rate constants one calculates factors of the order of 40 in favor of the cholesteryl ester. In the solvent ethanol we had felt there was more reason to suspect mechanisms of the type VII. However, the rate constant of acetolysis of cholesteryl p-toluenesulfonate I extrapolated to 78° is 0.176 min.$^{-1}$, a value nearly equal to Stoll's value of 0.18–0.19 min.$^{-1}$ in ethanol. Since ethanol and glacial acetic acid give comparable[9] solvolysis rates in unimolecular solvolyses, the indications are against mechanism VII in alcohol also. Further, in the case of chlorides, rather than toluenesulfonates, there are qualitative indications of greater reactivity of the Δ^5-compounds and Shoppee[1] refers to these.

The evidence then is that the 5,6-ethylenic linkage exerts a driving force[5] in favor of ionization of I, the main ionization being directly to intermediate IV or V (rate constant k_Δ). Thus a pair of electrons in an ethylenic linkage may play a role analogous to that of neighboring groups discussed in previous articles. There are further indications of the ionization by the k_Δ process. Thus the $\Delta H^{\ddagger}$ of activation for cholesteryl p-toluenesulfonate is less than that for the cyclohexyl ester[5a] by some 2.6 kcal./mole. This kind of a decrease with an increase in rate effected by a neighboring group has been noticed before.[5]

Also, the acetolysis of cholesteryl p-toluenesulfonate is much more sensitive to addition of water and salts than is the case with the cyclohexyl esters. While further comparison with medium effects in the case of higher molecular weight saturated esters such as cholestanyl are needed, one is led to compare the present situation with the one prevailing in the case of solvolysis of alkyl halides studied by Hughes, Ingold and co-workers.[6] In the latter case, the increase in rate by salt climbs as one proceeds from t-butyl to benzhydryl, separation of charge in the transition state being larger in the latter example. It is possible that the cyclohexyl-cholesteryl trend is analogous, the transition state for ionization of cholesteryl p-toluenesulfonate having positive charge both on C_3 and C_6.

Just as a pair of electrons of the 5,6 double bond in I imparts reactivity in ionization at C_3, the pair of electrons in the 3-membered rings of i-compounds such as II apparently imparts high reactivity at C_6. One very likely mechanism for the reverse i-sterol rearrangement of type II to type I, which we are also investigating, involves ionization followed by competitive reactions at C_3 and C_6. On this basis, judging by the high reactivity of i-compounds[3], V is not the intermediate. If these suppositions prove to be correct, the mesomeric ion IV would be the common intermediate for forward and reverse rearrangements, no energy barrier existing between the limiting resonance structures V and VI.

The over-all steric result of the conversion of cholesteryl p-toluenesulfonate I or chloride to an i-compound (type II) and back to a normal compound is clearly quite clean-cut retention of configuration. Thus, i-ether II gives cholesteryl

---

(6) Bateman, Church, Hughes, Ingold and Taher, *J. Chem. Soc.*, 979 (1940).

(7) Winstein, Grunwald, Buckles and Hanson, THIS JOURNAL, **70**, 816 (1948).

(8) Stoll, *Z. physiol. Chem.*, **246**, 6 (1937).

(9) Winstein, Hanson and Grunwald, THIS JOURNAL, **70**, 812 (1940).

chloride[3a,b] on treatment with hydrogen chloride in acetic acid and also is easily converted to cholesteryl acetate.[3a,b] This steric result is analogous to that involving other neighboring groups and is expected from the mechanism outlined for the formation of the *i*-compound and a reverse rearrangement which requires nucleophilic attack on C_3 to completely sever the C_3–C_5 bond.

Over-all retention of configuration with Δ^5-materials is very general and Shoppee[1] has summarized[10] the displacement reactions at C_3 in which 3-OH is converted to 3-Cl and 3-Cl to 3-OCOR. However, in these cases there is still need for further scrutiny to determine whether *i*-product is not the first predominant one, which quickly is rearranged to normal product.

Experimental

Materials.—Cholesteryl *p*-toluenesulfonate, m. p. 132–133°, was prepared in the usual manner.[3c] This material generated 98.5% of the theoretical amount of acid in acetolysis.

Lithium perchlorate trihydrate was prepared by treatment of Merck reagent grade lithium carbonate with perchloric acid. The reaction mixture, *p*H 4.5, was filtered, concentrated to a small volume and then allowed to cool slowly. The deposited crystals were pressed dry and dried in an oven at 140° for four hours. The hot liquid product was allowed to cool with stirring to yield a white crystalline solid, m. p. 93–94.5°.

The acetic acid solvent was prepared from Grasselli reagent grade acid and pure acetic anhydride, the residual concentration[5a] of the latter being 1×10^{-3} *M*.

Rate Measurements.—The titration procedures were those used previously.[5a] In case lithium perchlorate or sodium acetate (sodium carbonate was used) was added to the solvent, water was destroyed by treatment with the proper amount of acetic anhydride.

In the case of cyclohexyl *p*-toluenesulfonate,[7] m. p. 44–45°, sealed ampoules were used, concentrations being approximately 0.03 *M*. With the cholesteryl *p*-toluenesulfonate, concentrations approximately 0.01 *M* were used due to low solubility and low rate of solution. The toluenesulfonate was added to the solvent already at bath temperature and the mixture was shaken violently in a glass-stoppered flask until solution of the toluenesulfonate was nearly complete. Then the mixture was filtered rapidly into a volumetric flask already in the bath. In this way a homogeneous solution of the toluenesulfonate at bath temperature could be achieved in approximately five minutes. The initial concentration of the material was determined by titration of a sample of the reaction mixture after ten half-life periods.

Rates were followed to approximately 70% completion, the mean deviation of the individual first-order constants in one run being within 3% even for the rapid cases.

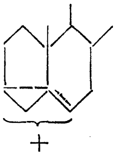
It is a pleasure to acknowledge helpful discussions with Drs. Byron Riegel of Northwestern University and Sam Siegel of the Illinois Institute of Technology.

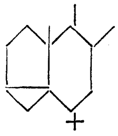
Summary

A study of the acetolysis of cholesteryl *p*-toluenesulfonate has shown that the first-order rate constant is *ca.* 10^2 (because of a corresponding decrease in $\Delta H^{\ddagger}$) times that for the cyclohexyl ester. Also the rate is quite sensitive to the addition of water, sodium or potassium acetate, or lithium perchlorate to the acetic acid solvent.

The poor nucleophilic character of acetic acid, the fact that the salt effect of sodium acetate in acetolysis is no greater than that of lithium perchlorate, and the near identity of acetolysis and alcoholysis rates of cholesteryl *p*-toluenesulfonate speak against a mechanism for the isosterol rearrangement involving nucleophilic attack at C_6 in the rate-determining step. Thus the isosterol rearrangement represents a case of participation by a pair of electrons of the 5,6-ethylenic linkage in a unimolecular type displacement reaction at C_3.

The relatively high rates of acetolysis and alcoholysis of cholesteryl *p*-toluenesulfonate and other qualitative indications of high reactivity of Δ^5-materials show that the double bond furnishes a substantial driving force. This speaks for the direct formation of intermediate IV or V in the ionization of the C_3-derivatives. It is highly possible that the reversed isosterol rearrangement (*i*-compounds to normal ones) normally proceeds through the same intermediate. On this basis, the high reactivity of *i*-compounds speaks for a driving force due to the pair of electrons in the 3-membered ring and thus intermediate IV is indicated.


IV


V

The over-all steric result of the conversion to an *i*-compound and back to a normal compound is analogous to the retention of configuration observed with other neighboring groups.

LOS ANGELES 24, CALIF. RECEIVED APRIL 3, 1947

---

[10] Bergmann [*Helv. Chim. Acta*, **20**, 590 (1937)] previously had remarked on such anomalous steric results and ascribed them vaguely to the unsaturated linkage.

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

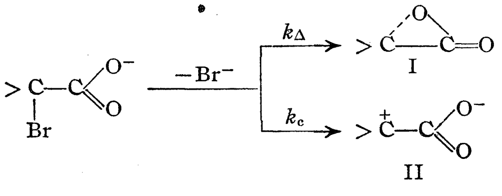
The Role of Neighboring Groups in Replacement Reactions. XV. Rates and Medium Effects in the Alcoholysis and Hydrolysis of α-Bromopropionate Ion. The Carboxylate Ion Group

BY ERNEST GRUNWALD AND S. WINSTEIN

Of the neighboring groups which participate in unimolecular type[1] nucleophilic displacements, one of the more important in organic chemistry is the α-carboxylate ion group. The recognition of retention of configuration as a possible over-all steric result of unimolecular reactions of materials of the type of α-bromopropionate ion has gone far toward clearing up a long-existing confusion attending the stereochemistry of displacement reactions of compounds containing various forms of the α-carboxyl group.[2]

Hughes and Ingold[2a] explained the effect of the carboxylate ion group as due to the presence of the negatively charged group in an alkyl cation, thus stabilizing the ion in a pyramidal configuration. We have since shown that the phenomenon of participation of neighboring groups such as OAc, Br, etc., in unimolecular displacement reactions is a general phenomenon, neutral groups being able to bring about retention of configuration. The action of the CO_2^- group is but one illustration of this general phenomenon, a charge being in principle unnecessary.

As in the case of other groups,[1,3] actual rates and other kinetic features of the unimolecular displacement reactions of α-halocarboxylate ions are of interest for the possible information afforded regarding the intimate mechanism of formation and the nature of the intermediate I, which has been termed an α-lactone[4] or a zwitterion.[2a] In principle, the rate determining ionization of the α-carboxylate ion may produce I directly with inversion of configuration (rate constant k_Δ) or it may yield first the more open zwitterion II (rate constant k_c). The first of these descriptions has been used previously.[4]



In connection with neutral neighboring groups, we have previously made some use of the variation of rate with changes in the solvolyzing medium (solvent or salt effects). The case of the CO_2^- group is one where salt effects might prove to be particularly helpful. For the intermolecular analogs of processes with the rate constants k_Δ and k_c, S_N2 and S_N1 type reactions of alkyl halides with a carboxylate ion, the sign of medium effects can be anticipated on the basis of the general theory[5] of solvent effects with which Hughes, Ingold and co-workers have had considerable success. For the S_N2 reaction, there is subdivision of charge in the transition state so that addition of inert salt or change to a more ionizing solvent will lead to a decrease in rate. In the S_N1 reaction, there is generation of charge in the transition state so the effect of solvent change will be opposite in sign. By analogy, k_c will increase with addition of inert salt or change to a more ionizing solvent. On the other hand, if there is enough involvement of the CO_2^- group with the carbon atom undergoing substitution in the transition state, k_Δ will decrease with such solvent change.

The most recent pertinent work on the solvolysis of α-bromopropionate ion is that of Cowdrey, Hughes and Ingold[6] and Chadwick and Pacsu.[7] With regard to salt effects, Cowdrey, Hughes and Ingold[6] report a large decrease in the first order rate on addition of 0.5 *M* sodium bromide in methanol solution. This they expect on the basis that "the rate-controlling stage is an ionization, in the transition state of which the anionic charge becomes divided between the carboxylate group and the bromine atom." This kind of salt effect would indicate that ionization occurs essentially by the process labelled k_Δ. On the other hand, in water Chadwick and Pacsu[7] report slight increases in first order rate with increase in ionic strength.

In this article are reported the results of a reinvestigation of the alcoholysis and hydrolysis of α-bromopropionate ion, special attention being given to salt effects.

In solvolysis, for example methanolysis, of α-bromopropionate ion, two reactions are prominent, the second order reaction with methoxide ion

$$CH_3O^- + CH_3CHBrCO_2^- \xrightarrow{k_2} CH_3CH(OCH_3)CO_2^- + Br^-$$

and the first order reaction by way of the so-called α-lactone or zwitterion III

---

[1] Winstein, Grunwald, Buckles and Hanson, THIS JOURNAL, **70**, 816 (1948).

[2] (a) Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1252 (1937); (b) Hughes, *Trans. Faraday Soc.*, **34**, 202 (1938); (c) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 175.

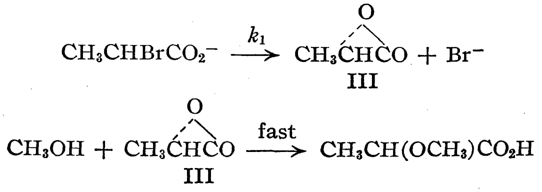
[3] (a) Winstein, Grunwald and Ingraham, THIS JOURNAL, **70**, 821 (1948); (b) Winstein and Grunwald, *ibid.*, **70**, 828 (1948); (c) Winstein and Adams, *ibid.*, **70**, 838 (1948).

[4] (a) Winstein and Lucas, *ibid.*, **61**, 1576 (1939); (b) Winstein, *ibid.*, **61**, 1635 (1939).

[5] (a) Hughes and Ingold, *J. Chem. Soc.*, 244 (1935); (b) Bateman, Church, Hughes, Ingold and Taher, *ibid.*, 979 (1940); (c) Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).

[6] Cowdrey, Hughes and Ingold, *J. Chem. Soc.*, 1208 (1937).

[7] Chadwick and Pacsu, THIS JOURNAL, **65**, 392 (1943).



$$\mathrm{CH_3CHBrCO_2^-} \xrightarrow{k_1} \mathrm{CH_3\overset{O}{CHCO}} + \mathrm{Br^-}$$

III

$$\mathrm{CH_3OH} + \mathrm{CH_3\overset{O}{CHCO}} \xrightarrow{\text{fast}} \mathrm{CH_3CH(OCH_3)CO_2H}$$

III

either reaction path predominating, depending on conditions. At high concentrations of methoxide ion, κ_2, an apparent second-order reaction rate constant, is fairly constant, and at low concentrations of methoxide ion, κ_1, an apparent first-order reaction rate constant, is also quite constant. If one is interested in the first-order reaction rate constant in the low concentration region, a correction still needs to be made for the second-order contribution. Furthermore, if at low methoxide ion concentration the ionic strength is increased, κ_1 increases markedly, but so much of this is due to the increase in the second-order contribution that a careful analysis is necessary to decide whether increase in ionic strength increases or decreases κ_1.

Kinetic Part

For convenience the symbols we employ are summarized below:

t = time in seconds.
α_0 = concn. in moles/l. of α-bromopropionate ion at zero time.
α = concn. in moles/l. of α-bromopropionate ion at time t.
β_0 = concn. in moles/l. of methoxide or hydroxide ion at zero time.
β = concn. in moles/l. of methoxide or hydroxide ion at time t.
x = concn. in moles/l. of bromide ion from solvolyses at time t.
$\kappa_2 = \frac{1}{t(\alpha_0 - \beta_0)} \ln\left(\frac{\beta_0(\alpha_0 - x)}{\alpha_0(\beta_0 - x)}\right)$
$\kappa_1 = \frac{1}{t} \ln\left(\frac{\alpha_0}{\alpha_0 - x}\right)$
k_2 = specific reaction rate constant for the second-order reaction.
k_1 = specific reaction rate constant for the first-order reaction.
k' = depressed first order rate constant in presence of bromide ion.
μ = ionic strength in moles/l. at 64.04 ± 0.04°.
$\phi = x \Big/ \left(\frac{k_1}{k_2} + \beta_0\right)$
k_{Br} = specific reaction rate constant for reaction of intermediate with bromide ion.
k_s = specific reaction rate constant for reaction of intermediate with solvent (methanol or water).

Equation 1 is the differential equation applicable in the present case, both k_1 and k_2 being functions of ionic strength.

$$\mathrm{d}x/\mathrm{d}t = k_1\alpha + k_2\alpha\beta = k_1(\alpha_0 - x) + k_2(\alpha_0 - x)(\beta_0 - x) \quad (1)$$

Values of k_2 at various ionic strengths necessary in evaluating k_1 were derived as follows. A series of experiments with α_0 at *ca.* 0.03 M and β_0 at 0.25 M to 1.0 M (Table I) gave κ_2 values which were constant within experimental error in each run. Average values in each run, $\bar{\kappa}_2$, were corrected for first-order contribution according to equation 2 which chooses

$$k_2 = \bar{\kappa}_2 - k_1/(\beta_0 - \alpha_0/3) \quad (2)$$

$(\beta_0 - {}^1/_3\alpha_0)$ as a good working mean between β_0 and $\beta_0 - \alpha_0$, the extreme values to be considered here. Since $\beta_0 >> \alpha_0$ in these runs, the accuracy in this empirical procedure is good. In this correction, k_1 is at first an estimate based on data from largely first-order solvolyses. These first values of k_2 which were always within 4% of the final values enable one to obtain better values of k_1 (see below) and second approximations (which are sufficient) become possible for k_2. The data for the largely second-order runs in both methanol and water are summarized in Table I. In this table, as well as in all subsequent ones, rate-constants and concentrations have been corrected for solvent expansion.

The plot of log k_2 against $\mu^{1/2}$ gives a good straight line. Equation 3, obtained by least squares, fits runs 1 through 5 with a

$$\log k_2 = -4.568 + 1.308\mu^{1/2} \quad (3)$$

mean deviation of 0.006 in log k_2. For the runs 6 and 7 in water as a solvent one can write[8] equation 4

$$\log k_2 = -3.681 + 0.343\mu^{1/2} \quad (4)$$

The values of k_1 at different ionic strengths were based on runs with low methoxide or hydroxide ion concentrations, sodium perchlorate (or nitrate) being added. The solution of equation 1 is equation 5

$$\frac{1}{t}\left\{\ln\left[\frac{k_1 + k_2(\beta_0 - x)}{k_1 + k_2\beta_0}\right]\left(\frac{\alpha_0}{\alpha_0 - x}\right)\right\} = k_1 + k_2(\beta_0 - \alpha_0) \quad (5)$$

with which some investigators[7,9] have worked directly, although this is admittedly laborious. We found it much more convenient to evaluate an apparent first-order constant κ_1 and then, using ϕ as previously defined, equation 6 follows. The expansion of $-\ln(1 - \phi)$ in

TABLE I

SECOND ORDER RATE CONSTANTS FOR SOLVOLYSIS OF α-BROMOPROPIONATE ION AT 64.04°

Run	Solvent	μ	$10^4\bar{\kappa}_2$ (sec.$^{-1}$ M^{-1})	10^4k_2 (sec.$^{-1}$ M^{-1})
1	CH_3OH	1.019	6.18 ± 0.16	5.57
2	CH_3OH	0.930	5.60 ± .07	4.94
3	CH_3OH	.745	4.35 ± .05	3.51
4	CH_3OH	.462	3.48 ± .01	2.12
5	CH_3OH	.370	3.44 ± .07	1.69
6	HOH	1.024	6.11 ± .08	4.63
7	HOH	0.504	6.48 ± .05	3.65

---

(8) The slopes for the variation of log k_2 with $\mu^{1/2}$ in these concentration ranges are roughly one-third the limiting Debye–Hückel–Brönsted values of $1.826 \times 10^6\ [2/(\epsilon T)^{3/2}]$. These limiting values are 4.58 for methanol and 1.118 for water at 64.04° (T = 337.2) using values for dielectric constants, ϵ, of 25.52 for methanol and 65.30 for water [Akerlof, THIS JOURNAL, **54**, 4125 (1932)].

(9) Meisenheimer and Beutter, *Ann.*, **508**, 58 (1933).

TABLE II

FIRST ORDER REACTION RATE CONSTANTS FOR SOLVOLYSIS OF α-BROMOPROPIONATE ION AT 64.04°

Run	Solvent	μ	α_0	β_0	Other salts, M	$10^5\bar{k}_1$ (sec.$^{-1}$) Ag$^+$	H$^+$	$10^5\bar{k}_1$ (sec.$^{-1}$) av.
8	CH_3OH	0.991	0.03	0.03	0.944 $NaClO_4$	5.84 ± 0.05	5.83 ± 0.16	5.84
9	CH_3OH	.546	.03	.03	.486 $NaClO_4$	5.65 ± .05	5.65 ± .14	5.65
10	CH_3OH	.539	.03	.03	.482 $NaClO_4$	5.73 ± .05	5.69 ± .08	5.71
11	CH_3OH	.300	.03	.03	.239 $NaClO_4$	5.76 ± .11	5.76 ± .07	5.76
12	CH_3OH	.0749	.03	.0460	....	5.17 ± .01	5.15 ± .02	5.16
13	CH_3OH	.0589	.03	.03	....	5.06 ± .10	4.97 ± .07	5.02
14	CH_3OH	.0410	.02	.02	....	5.19 ± .03	....	5.19
15	CH_3OH	.941	.03	.03	.883 NaBr	....	1.48 ± .06	1.48
16	CH_3OH	.917	.03	.03	.855 NaBr	....	1.72 ± .04	1.72
17	CH_3OH	.475	.03	.03	.415 NaBr	....	2.66 ± .06	2.66
18	CH_3OH	.304	.03	.03	.240 NaBr	....	3.43 ± .09	3.43
19	HOH	1.053	.03	.03	.992 $NaNO_3$	13.25 ± .25	....	13.25
20	HOH	0.933	.03	.03	.878 $NaClO_4$	13.25 ± .10	13.25 ± .10	13.25
21	HOH	.564	.03	.03	.502 $NaNO_3$	12.90 ± .20	....	12.90
22	HOH	.496	.03	.03	.434 $NaClO_4$	13.10 ± .15	12.95 ± .20	13.05
23	HOH	.0804	.03	.05	....	12.55 ± .20	12.45 ± .05	12.50
24	HOH	.0638	.03	.03	....	12.45 ± .05	12.55 ± .05	12.50
25	HOH	1.040	.03	.03	.976 NaBr	....	7.48 ± .15	7.48
26	HOH	0.540	.03	.03	.476 NaBr	....	9.54 ± .32	9.54

$$\kappa_1 - k_1 = k_2(\beta_0 - \alpha_0) - \frac{1}{t}\ln(1 - \phi) \qquad (6)$$

$$\kappa_1 - k_1 = k_2(\beta_0 - \alpha_0) + \frac{1}{t}\left(\phi + \frac{\phi^2}{2} + \frac{\phi^3}{3} + \ldots\right) \qquad (7)$$

a series gives rise to equation 7 which is a convenient working equation since ϕ turns out to be of the order of 0.05, so that ϕ^3 is usually negligible and ϕ^2 and ϕ^3 can be obtained with the slide rule.

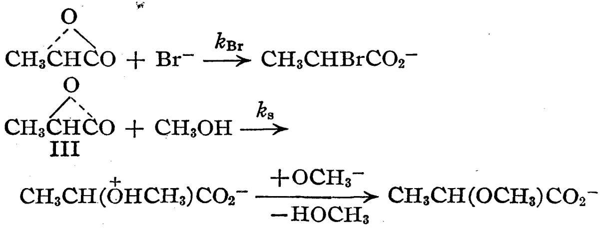
In the rate runs summarized in Table II a value of κ_1 was evaluated for each analytical point. Using κ_1, the known values of x, β_0 and α_0, the value of k_2 for the given ionic strength calculated from equation 3 or 4, and guessing a reasonable value for k_1, the right-hand side of equation 7 was easily evaluated and thus a first value for k_1 at any one analytical point was obtained. A second approximation (usually sufficient) was obtained by substituting this first approximation for k_1 into the right-hand side of equation 7. The values for k_1 at the different analytical points were averaged to give the values shown in Table II. In some cases separate rate constants are listed based on titration for both base and bromide ion and these are averaged for the final values.

Discussion

Inspection of Table II shows, in agreement with the report of Chadwick and Pacsu, that the first order reaction rate constant k_1 for solvolysis rises with ionic strength when sodium perchlorate is the added salt both in water and methanol. In water approximately a 6% increase is produced by a change in ionic strength from 0.06 to 1 M while the analogous figure is 17% in methanol. In water, Chadwick and Pacsu[7] recorded increases of 12 and 5% at 49.2° and 59.7°, respectively, on the addition of 0.95 M sodium nitrate to 0.2 N sodium bicarbonate solutions of the α-bromopropionate (*ca.* 0.04 M).

The observation of Cowdrey, Hughes and Ingold[6] with regard to the direction of the salt effect in methanol was due to the choice of the added salt, sodium bromide. The bromide ion competes very well for the intermediate III. This represents a type effect on which Hughes, Ingold and coworkers[5b] have since done considerable work but which they had not yet discovered at the time of the earlier work. In connection with the hydrolysis of bromomalonate ion Hughes and Taher[10] have reported a similar action of sodium bromide and mention the possibility that some of the effect is a "mass-law" effect.

The effect of bromide ion on the rate constant is very marked and may be treated according to the scheme



which depicts a competition between bromide ion and solvent molecules for the intermediate III, and neglects the competition by methoxide or hydroxide ion. According to this scheme, the first order rate constant k' evaluated by use of equation 7 (putting k' in place of k_1) is given by equation 8. This predicts, as is actually observed, that k' will be satisfactorily constant if the bromide concentration is essentially constant. The latter condition is fulfilled if the initial bromide concentration

$$k' = k_1 \frac{1}{1 + (k_{Br}/k_s)(Br^-)} \qquad (8)$$

---

[10] Hughes and Taher, *J. Chem. Soc.*, 956 (1940).

is large compared to that produced in the reaction. Comparison of the rate constant k' in the presence of sodium bromide with the rate constant k_1 at the corresponding ionic strength in the runs with sodium perchlorate allows one to estimate the ratio k_{Br}/k_S. These are shown in Table III, the values being close to constant at 2.9 in methanol and 0.76 in water.

The value of k_{Br}/k_S would not be expected to be absolutely independent of ionic strength. Actually our values show a slight downward drift with decrease in ionic strength but this is too slight to be sure it is not accidental, especially since we would have expected a reverse trend.

The success of equation 8 indicates that the rate constant for reaction of intermediate III with methoxide ion or hydroxide ion cannot be much greater than k_{Br}. In the course of a run, the methoxide or hydroxide ion concentration decreases markedly and, were these ions competing for intermediate III, bromide ion would show an increasing ability to compete for III and give a decreasing reaction rate constant as the reaction progresses. Instead, solutions containing high bromide ion and low base concentration produce acid in a good first-order fashion after allowance is made for second-order reaction with methoxide ion. The relative inactivity of the base ion for attack on the intermediate recalls the inactivity of hydroxide ion in the case of ethylene oxides.[11]

TABLE III

RELATIVE RATES OF REACTION OF INTERMEDIATE III WITH BROMIDE ION AND SOLVENT

Solvent	μ	(Br^-)	10^6k_1 (sec.$^{-1}$)	$10^5k'$ (sec.$^{-1}$)	k_{Br}/k_S	k_{Br}/k_S av.
CH_3OH	1	0.893	5.84	1.48	3.30	2.86 ± 0.22
CH_3OH	1	.865	5.84	1.72	2.77	
CH_3OH	0.5	.425	5.68	2.66	2.67	
CH_3OH	0.3	.250	5.76	3.43	2.72	
HOH	1	.986	13.25	7.48	0.78	0.76
HOH	0.5	.486	13.00	9.54	0.75	

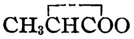
Judging by the data obtained following the reactions for both bromide ion and base, either perchlorate ion shows negligible reaction with intermediate III or any ester product is unstable. Nitrate ion does react slightly with III (see experimental).

The information on k_{Br}/k_S adds information of a type which needs to be greatly expanded before the general phenomenon of participation is fully understood. These values for k_{Br}/k_S are listed in Table IV along with some related ones from similar situations. The value for the intermediate from bromomalonate ion is a rough one calculated from the data of Hughes and Taher.[10] The value for the intermediate from phenylbromoacetate ion is calculated from the data of Bulcraig and Dawson.[12] These workers report rate constants of hydrolysis of the 0.025 M neutral salt of 0.0238 (0.975 M $NaNO_3$) and 0.0250 (0.975 M $NaClO_4$) for an average of 0.0244, whereas the rate constant is 0.0184 for 0.975 M NaBr. The value for the stilbene bromonium ion is given by Bartlett and Tarbell[13] and the value for ethylene oxide is from the data of Bronsted, Kilpatrick and Kilpatrick.[11] More needs to be known regarding temperature coefficients of these values and, sometimes, effects of ionic strength before the figures are properly comparable.

The small positive salt effect in the unimolecular solvolysis of α-bromopropionate ion indicates generation of charge in the transition state for the rate-determining ionization of the bromide ion. Corresponding to the salt effect is the effect of solvent change, the solvolysis rate in water at 64° being approximately twice that in methanol. Thus the sign of the medium effects does not enable one to choose unambiguously between the two modes (rate constants k_Δ or k_c) of the rate-determining ionization. The intermediate III has very high ionic character[5b,14] to the new carbon–oxygen bond. Thus, even if it is produced in one stage (k_Δ), the transition state could have increased charge over the reagent α-bromopropionate ion. This possibility gains support from the observation that the effect of neutral salts and of solvent change in the case of β-lactone formation, which more surely proceeds by a concerted ring closure (k_Δ) in the examples available, is the same in sign as for α-bromopropionate ion. This is shown in Table V. On the other hand for the closure of the larger 6-membered ring from $CH_3CHBrCONHCH_2CO_2^-$ Chadwick and Pacsu[7] observed a salt effect of the sign anticipated for the intermolecular example.

TABLE IV

COMPETITION FOR INTERMEDIATES

Compound	T, °C.	Solvent	k_{Br}/k_S
 CH_3CHCOO	64	MeOH	2.9
 CH_3CHCOO	64	HOH	0.76
 $\overset{-}{O}_2CCHCOO$	100	HOH	2.7
 C_6H_5CHCOO	25	HOH	0.33
 $C_6H_5CH\overset{+}{Br}CHC_6H_5$	0	MeOH	1.21
 $H_2C\overset{+}{O}HCH_2$	20	HOH	37

In the case of the other neighboring groups it was useful to compare the unimolecular rate constant k with k_H, the rate constant of the unsubstituted material[3]. Estimated values of k_c/k_H made it possible to derive estimates of k_Δ/k_c. In the present case k_H is the specific rate of $CH_3CHBrCH_3$ if O_2^- is considered the neighboring group. With the charged neighboring group, the choice of solvent for the comparison k/k_H is difficult because a change to a more ionizing solvent affects the al-

---

[11] Bronsted, Kilpatrick and Kilpatrick, THIS JOURNAL, **51**, 428 (1929).

[12] Bulcraig and Dawson, *J. Chem. Soc.*, **80** (1943).

[13] Bartlett and Tarbell, THIS JOURNAL, **58**, 466 (1936).

[14] Winstein and Henderson, *ibid.*, **65**, 2196 (1943).

kyl halide so much more than the α-halocarboxylate ion. Also k_c/k_H is hard to estimate since it may be considered to involve a large rate retardation due to two oxygen atoms which are ordinarily electron-attracting and the very large rate enhancement due to the negative charge of the O_2^- group.

TABLE V

RATES OF UNIMOLECULAR TYPE SOLVOLYSIS OF SOME BROMIDES

Compound	Solvent	Temp., °C.	k_1 (sec.$^{-1}$)	Ref.
$CO_2^-CHBrCH_2CO_2^-$	H_2O^a	25.8	4.65×10^{-5}	15
$CO_2^-CHBrCH_2CO_2^-$	H_2O, 0.9 M KNO_3^a	25.8	6.34×10^{-5}	15
$CO_2^-CHBrCH_2CO_2^-$	MeOH	25.8	4.06×10^{-5}	16
$CH_3CHBrCH_2CO_2^-$	H_2O^b	45.0	4.5×10^{-4}	17
$CH_3CHBrCH_2CO_2^-$	$MeOH^c$	45.0	1.03×10^{-4}	16
$(CH_3)_2CBrCO_2^-$	H_2O^d	44.3	2.13×10^{-3}	18
$(CH_3)_2CBrCO_2^-$	MeOH	44.3	2.6×10^{-4}	16
$(CH_3)_2CBrCH_3$	$MeOH^e$	44.3	3.3×10^{-4}	
$CH_3CHBrCO_2^-$	MeOH	64.0	5.12×10^{-6}	Table II
$CH_3CHBrCH_3$	$MeOH^e$	64.0	5×10^{-8}	

[a] Interpolated between data at 25.00° and 37.39°. [b] Extrapolated from data at 25.0° and 38.0°. [c] At 0.2 M ionic strength, κ_1 has the following values[16]: $\beta = 0.129$ M, $10^4\ \kappa_1 = 2.70$; $\beta = 0.085$ M, $10^4\ \kappa_1 = 2.13$. Using $\kappa_1 = k_1 + k_2\beta$, $k_1 = 1.03 \times 10^{-4}$ sec.$^{-1}$; $k_2 = 1.30 \times 10^{-3}$ sec.$^{-1}$ M^{-1}. [d] Values of $10^4\ k_1$ (sec.$^{-1}$) at 25.0° and 35.0° are 1.21 ± 0.04 and 5.59 ± 0.08, respectively. These values were calculated from the data given by Simpson[18] on the hydrolysis of sodium α-bromoisobutyrate in initially neutral solution, assuming that the ratio of ionization constants of the α-bromo and α-hydroxy acid is 8.0 and using the equations developed by Bulcraig and Dawson.[12] Values of k_1 were satisfactorily constant up to 90% reaction at 25° and 70% reaction at 35°. [e] k_1 for *t*-butyl bromide at 25.0° is estimated at 3.53×10^{-5} sec.$^{-1}$ on the basis of solvolysis rates in alcohol-water mixtures[19] by a method to be published soon.[20] Taking $E^{\ddagger}$ as 22.0 kcal.,[19] k_1 is 3.3×10^{-4} sec.$^{-1}$ at 44.3° and 2.6×10^{-3} sec.$^{-1}$ at 64.0°. The ratio of specific rates of isopropyl and *t*-butyl bromide is tentatively taken[20] as 2×10^{-5}.

However, it is instructive to choose one solvent throughout and to contrast k/k_H for the α-bromopropionate ion with that for the α-bromoisobutyrate ion, $(CH_3)_2CBrCO_2^-$. Table V lists the necessary first order rate constants in methanol. It is seen that k/k_H for $CH_3CHBrCO_2^-$ is of the order of 10^2 or 10^3 while for $(CH_3)_2CBrCO_2^-$ it is 0.8. In the latter case, the carboxylate ion group is inferior to a methyl group. The data are consistent with a substantial driving force,[3a] $RT \ln (k_\Delta/k_c)$, due to the O_2^- group in α-bromopropionate ion and at least a much smaller one in the case of the more highly α-substituted α-bromoisobutyrate ion. This decrease in the driving force of a neighboring group with α-methyl substitution has been observed previously.[3a,b]

Consistent with a lowered interaction between the carboxylate ion group and the α-carbon atom in the transition state for ionization of α-bromoisobutyrate ion is the greater effect of solvent change than for α-bromopropionate ion. From the rate constants in Table V it is seen that the factor between water and methanol for α-bromoisobutyrate ion is approximately 8 whereas it is 2.4 for α-bromopropionate ion.

The extent of the superiority of the CO_2^- group over the CO_2R group for participation in unimolecular type displacement reactions is of some interest but not easy to judge. While k_c is high for the CO_2^- group and any positive driving force makes unimolecular reactions even easier to attain, k_c is very low in the case of the CO_2R group. Thus in the latter case even if k_Δ/k_c were appreciable, unimolecular reactions would be hard to attain. In the case of the reaction of ethyl α-bromopropionate with silver oxide in alcohol, one explanation[14] but, as pointed out, not necessarily the unique one, was that the reaction is unimolecular in type but that the carbethoxy group does not participate. It is probable that the reaction is not unimolecular in type and thus no information is afforded regarding participation of the carbethoxy group.

Experimental

Solvents.—Commercial synthetic methanol, dried by the method of Bjerrum and Zechmeister,[21] and containing less than 0.08% water from the miscibility temperature with cyclohexane,[22] was used in this work. Conductivity water was used as solvent in the aqueous runs.

α-Bromopropionic Acid.—Eastman Kodak Co. material was redistilled at reduced pressure. The samples used in the course of the work were: I, b. p. 99.0° (13 mm.), $n^{21.5}D$ 1.4747, equivalent wt. 152.8 ± 0.6 (calcd. 153.0), m. p. 24.2°; II, b. p. 98.5–98.8° (13.5 mm.), $n^{24}D$ 1.4737, equivalent wt. 152.8 ± 0.6, m. p. 25.3°.

Inorganic Salts.—Sodium nitrate and bromide were Baker and Adamson reagent grade or C. P. materials dried at 120° before use. Sodium perchlorate was prepared halide-free by careful neutralization of J. T. Baker C. P. 70% perchloric acid with C. P. sodium carbonate to the methyl orange endpoint. Concentration of the solution gave crystalline material which was washed with a little ether, and dried to constant weight over sulfuric acid *in vacuo*.

Rate Measurements.—Reaction mixtures were prepared by mixing weighed amounts of α-bromopropionic acid and added salts and measured volumes of aqueous sodium hydroxide or methanolic sodium methoxide (prepared by dissolving sodium in the absolute methanol) in a volumetric flask, the volume being made up at room temperature. As quickly as possible the initial titre of base was determined by titration of an aliquot with standard acid. Aliquot portions (20 ml.) of the reaction mixture were sealed off in tubes and placed in a thermostat at 64.04 ± 0.04° for suitable intervals. On removal from the thermostat, the tubes were chilled in ice and the contents were analyzed for base by adding an excess of standard halide-free nitric acid and back-titrating with standard halide-free base to the phenolphthalein endpoint. The neutral solution was analyzed for bromide ion by titration with standard silver nitrate with eosin or, sometimes, dichlorofluorescein as indicator. Control experiments showed that both titrations were reliable within ordinary experimental error. "Zero" time was called

---

(15) Long and Olson, *J. Phys. Chem.*, **41**, 267 (1937).

(16) Madsen, *Z. physik. Chem.*, **92**, 98 (1918).

(17) (a) Johansson, *Ber.*, **48**, 1262 (1915); (b) Olson and Miller, THIS JOURNAL, **60**, 2687 (1938).

(18) Simpson, *ibid.*, **40**, 674 (1918).

(19) (a) Cooper and Hughes, *J. Chem. Soc.*, 1183 (1937); (b) Bateman, Cooper, Hughes and Ingold, *ibid.*, 925 (1940).

(20) Winstein and Grunwald, unpublished work.

(21) Bjerrum and Zechmeister, *Ber.*, **56**, 894 (1923).

(22) Jones and Amstell, *J. Chem. Soc.*, 1316 (1930).

the time of removal of the first tube after attainment of temperature.

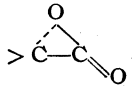
The "infinite" titer of bromide ion agreed well with the expected as indicated by the equivalent weights of the α-bromopropionic acid samples. The "infinite" titer of base was usually unreliable by a few per cent., probably due to reaction of the glass. Soft glass tubes were used in the experiments with methanolic solutions, and Pyrex tubes were employed for the aqueous runs.

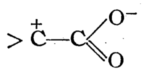
In the runs with high base concentration, the reaction was followed chiefly by titration for bromide ion. With the low base concentrations, titration was carried out for both base and bromide ion except where bromide ion was added in large amounts initially. When added sodium perchlorate the rate constants based on the two titrations agreed closely (Table II). With added sodium nitrate, the rate constants from bromide titration were steady but those based on base titration were lower and drifted downward. In run 21 with 0.5 *M* added sodium nitrate, the base consumed during a run averaged 98.8 ± 0.7% of the bromide ion produced, while the analogous figure was 96.6 ± 1.5% for run 19 with *M* added sodium nitrate.

Summary

The hydrolysis and methanolysis of sodium α-bromopropionate in the presence of sodium hydroxide or methoxide was investigated in solutions of varying ionic strength at 64.04°. A kinetic analysis reveals that both the bimolecular and unimolecular specific reaction rate constants, k_2 and k_1, respectively, increase with ionic strength.

The variation of k_1 with change in solvent and ionic strength is discussed in terms of a rate-determining ionization either to the zwitterion II (specific rate k_c), or the α-lactone I (specific rate k_Δ). An unambiguous decision regarding the reaction mechanism is not possible from the salt and solvent effects alone.


I


II

However, the sign of these effects and related evidence, particularly the high reactivity of α-bromopropionate ion compared to isopropyl bromide and the contrast with α-bromoisobutyrate ion, are consistent with the rate-determining ionization symbolized by k_Δ.

The ratio of rate constants for reaction of the intermediate in the solvolysis of α-bromopropionate ion with bromide ion and solvent, k_{Br}/k_S, derived from measurements in solutions containing high bromide ion concentrations, is 2.9 in methanol and 0.76 in water.

LOS ANGELES 24, CALIFORNIA RECEIVED JUNE 11, 1947

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

The Correlation of Solvolysis Rates

BY ERNEST GRUNWALD AND S. WINSTEIN

One of the important mechanisms (**A**) for solvolysis[1,2] of alkyl halides involves more than one stage and is at present best formulated as involving a rate-determining ionization (equation 1) to a cationic intermediate. The rate constant k_1

$$RX \xrightarrow{k_1} R^+ + X^- \qquad (1)$$

depends on the so-called ionizing power of the solvent, and it is possible from such rates to arrange solvents in a relative order. For example substitution of the unimolecular type[3] proceeds slightly more rapidly in acetic acid than in absolute ethanol.[4] The rate is increased by addition of water to alcohol or partly aqueous acetone or dioxane.[1,2] Further, substitution is about as rapid in formic acid as in 50% aqueous ethanol.[5]

The question arises whether it is possible to assign to each solvent a definite number **Y** which is a quantitative measure of its ionizing power in determining k_1. In this article is reported a scheme for correlating unimolecular solvolysis rates with the aid of such a set of **Y** values and a simple functional relationship between k_1 and **Y**. Also, the theoretical implications of the method are discussed.

In addition to the solvolysis mechanism **A** there occurs solvolysis in neutral and acidic solvents by a process or processes (**B**, rate constant k_x) for which the nucleophilic character as well as the ionizing power of the solvent is important. The best understood concerted process is the so-called bimolecular substitution in which a solvent molecule plays a role such as that of a pyridine molecule in the Menshutkin reaction. One of the important problems for the proper understanding of such subjects as reactivity, stereochemistry of displacements and rearrangements[1b] is that of sorting out the fractions of solvolysis proceeding by mechanisms A and B.

The scheme for correlating solvolysis rates allows one to make deductions regarding the rate by process **A** and therefore the fraction of solvolysis by mechanism **A.** This application of the method is being actively pursued and the procedure is illustrated in the present article for isopropyl *p*-bromobenzenesulfonate.

A Quantitative Measure of Ionizing Power. The Y Function.—The specific solvolysis rates *k* for a number of halides which, the accumulation

---

[1] (a) Hughes, *Trans. Far. Soc.*, **37**, 611 (1941); (b) Dostrovsky, Hughes and Ingold, *J. Chem. Soc.*, 173 (1946).

[2] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 166 ff.

[3] Winstein, Grunwald, Buckles and Hanson, THIS JOURNAL, **70**, 816 (1948).

[4] Winstein, Hanson, and Grunwald, *ibid.*, **70**, 812 (1948).

[5] Dostrovsky and Hughes, *J. Chem. Soc.*, 166, 171 (1946).

TABLE I

SOLVOLYSIS RATES OF SOME HALIDES AND Y VALUES FOR SOLVENTS

Compound	Temp., °C.	Solvent	$E^{\ddagger}$, kcal.	k(sec.$^{-1}$)	Ref.	Y
$(CH_3)_3CCl$	25.0	Absolute EtOH	25.97	9.70×10^{-8}	Table II	−1.974
		90% EtOH, N_{H_2O} = 0.262		1.73×10^{-6}	6	−0.727
		80% EtOH, N_{H_2O} = 0.448	23.06	9.24×10^{-6}	6	0.000
		70% EtOH, N_{H_2O} = 0.582		4.07×10^{-5}	6	0.644
		60% EtOH, N_{H_2O} = 0.684		1.27×10^{-4}	6	1.139
		50% EtOH, N_{H_2O} = 0.765	22.92	3.67×10^{-4}	6	1.604
		40% EtOH, N_{H_2O} = 0.829		1.29×10^{-3}	6	2.151
		80% $(CH_3)_2CO$	22.6	1.94×10^{-6}	6	
		5% $(CH_3)_2CO$, N_{H_2O} = 0.987		2.57×10^{-2}	7	3.449
		48.61 wt. % H_2O in dioxane	22.8	1.81×10^{-4}	8, 11b	1.292
		H_2O-MeOH, N_{H_2O} = 0.000	25.0	8.20×10^{-7}	8, Table II	−1.052
		H_2O-MeOH, N_{H_2O} = 0.070		1.75×10^{-6}	8	−0.722
		H_2O-MeOH, N_{H_2O} = 0.175		4.33×10^{-6}	8	−0.329
		H_2O-MeOH, N_{H_2O} = 0.230		7.14×10^{-6}	8	−0.112
		H_2O-MeOH, N_{H_2O} = 0.282		1.13×10^{-5}	8	0.088
		H_2O-MeOH, N_{H_2O} = 0.346		2.12×10^{-5}	8	0.361
		H_2O-MeOH, N_{H_2O} = 0.432		5.28×10^{-5}	8	0.757
		H_2O-MeOH, N_{H_2O} = 0.497		9.75×10^{-5}	8	1.023
		H_2O^e		3.3×10^{-2}		3.56
		$HCOOH^b$	22.9^a	1.1×10^{-3}	9a	2.08
		AcOH, 0.025 *M* KOAc	26.43	2.13×10^{-7}	Table II	−1.633
		AcOH-Ac_2O, N_{AcOH} = 0.042 0.017 *M* KOAc	26.4^a	4.77×10^{-9}	Table II	−3.287
$(CH_3)_3CBr$	25.0	EtOH	23.0^a	5.69×10^{-6}	10c	
		90% EtOH		7.14×10^{-5}	10a	
		80% EtOH	22.8	3.63×10^{-4}	10a	
		76.5% EtOH, N_{H_2O} = 0.501	22.5^a	5.22×10^{-4}	10d	
		60% EtOH	21.7	3.76×10^{-3}	10a	
		95% $(CH_3)_2CO$, N_{H_2O} = 0.178	22.7	2.10×10^{-6}	10b	-2.402^c
		90% $(CH_3)_2CO$, N_{H_2O} = 0.313	20.8	1.27×10^{-5}	10e	-1.549^c
		80% $(CH_3)_2CO$, N_{H_2O} = 0.506	20.8^a	1.10×10^{-4}	10a	-0.527^c
		70% $(CH_3)_2CO$, N_{H_2O} = 0.637		5.15×10^{-4}	10e	0.205^c
$CH_3CHClCH{=}CH_2$	25.0	EtOH	23.5^a	8.8×10^{-9}	11a	
		50% EtOH		1.14×10^{-5}	11a	
		H_2O	23.5^a	8.1×10^{-4}	11b	
$(CH_3)_3CCH_2Br$	95.0	70% EtOH		1.54×10^{-7}	5	
		50% EtOH	29.0	9.20×10^{-7}	5	
		HCOOH		1.53×10^{-6}	5	
$(C_6H_5)_2CHCl$	25.0	EtOH		5.30×10^{-5}	10f	
		90% EtOH		4.90×10^{-4}	12b	
		80% EtOH		1.72×10^{-3}	12b	
		90% $(CH_3)_2CO$	19.6	4.60×10^{-6}	10e	-3.377^d
		80% $(CH_3)_2CO$	21.0	7.24×10^{-5}	10e	-1.797^d
		70% $(CH_3)_2CO$		3.20×10^{-4}	10e	-0.945^d
$C_6H_5CHClCH_3$	50.0	EtOH	21.9^a	5.85×10^{-7}	13	
		80% EtOH	21.4	1.64×10^{-4}	12^a	
		MeOH	21.7^a	7.06×10^{-6}	13	
		80% $(CH_3)_2CO$	21.8^a	1.44×10^{-6}	13	
		60% $(CH_3)_2CO$	21.5^a	4.19×10^{-5}	13	
		AcOH, 0.2 *M* KOAc		3.9×10^{-6}	14	

[a] Value used by the authors. [b] Rate constants have been reported[9a] at 15.0° ranging from 2.0×10^{-4} to 3.9×10^{-4} sec.$^{-1}$. An average value was used. Rate measurements in formic acid are complicated by decomposition of the solvent[9b,c] into carbon monoxide and water. [c] From *t*-butyl bromide. [d] From benzhydryl chloride. [e] Obtained by extrapolation from the plot of log k^{BuCl} *vs.* N_{H_2O} using the data[6,7] in aqueous acetone.

---

(6) Hughes, *J. Chem. Soc.*, 255 (1935).

(7) Swain and Ross, THIS JOURNAL, **68**, 658 (1946).

(8) Olson and Halford, *ibid.*, **59**, 2644 (1937).

(9) (a) Bateman and Hughes, *J. Chem. Soc.*, 935 (1940); (b) Bateman and Hughes, *ibid.*, 940 (1940); (c) Weissberger and Proskauer, "Organic Solvents," Clarendon Press, Oxford, 1935, p. 145.

(10) (a) Bateman, Cooper, Hughes and Ingold, *J. Chem. Soc.*, 925 (1940); (b) Cooper and Hughes, *ibid.*, 1183 (1937); (c) Hughes, Ingold, Masterman and McNulty, *ibid.*, 899 (1940); (d) Petrenko-

TABLE II

FIRST-ORDER SOLVOLYSIS RATE CONSTANTS AT 70.0°. FOR *t*-BUTYL CHLORIDE AND PINACOLYL AND ISOPROPYL *p*-BROMOBENZENESULFONATES

Compound	Solvent	(RX) $10^3 M$	(KOAc) $10^3 M$	k, sec.$^{-1}$
$(CH_3)_3CCl$	AcOH-97.5% Ac_2O	40.3	19.07	$(1.620 \pm 0.048) \times 10^{-6}$
	$N_{AcOH} = 0.042$	42.3	15.67	$(1.625 \pm 0.048) \times 10^{-6}$
	AcOH-0.1% Ac_2O	12.04	24.63	$(7.12 \pm 0.12) \times 10^{-5}$
		19.25	24.54	$(7.45 \pm 0.10) \times 10^{-5}$
		19.60[a]	24.89	$(8.78 \pm 0.17) \times 10^{-7}$
		18.43[a]	24.91	$(8.91 \pm 0.20) \times 10^{-7}$
	EtOH	52.16	60.2	$(3.19 \pm 0.03) \times 10^{-5}$
		37.25	35.0	$(3.12 \pm 0.03) \times 10^{-5}$
		52.16[b]	60.2	$(3.82 \pm 0.07) \times 10^{-7}$
		37.25[b]	35.0	$(3.69 \pm 0.07) \times 10^{-7}$
	MeOH	19.21	58.5	$(2.07 \pm 0.07) \times 10^{-4}$
		37.40	58.5	$(2.10 \pm 0.03) \times 10^{-4}$
	80% EtOH[c]			1.51×10^{-3}
$(CH_3)_3CCH(OSO_2C_6H_4Br)CH_3$	AcOH-97.5% Ac_2O	33.46	19.91	$(11.49 \pm 0.15) \times 10^{-6}$
	$N_{AcOH} = 0.042$	19.40	8.99	11.66×10^{-6}
	AcOH-80.3% Ac_2O	24.71	...	$(7.89 \pm 0.11) \times 10^{-5}$
	$N_{AcOH} = 0.294$			
	AcOH-0.1% Ac_2O	22.61	..	$(2.734 \pm 0.026) \times 10^{-4}$
		34.29	...	$(2.742 \pm 0.033) \times 10^{-4}$
		27.60	24.87	$(2.811 \pm 0.022) \times 10^{-4}$
	EtOH	16.55	...	$(7.02 \pm 0.10) \times 10^{-5}$
		12.37	...	$(7.01 \pm 0.13) \times 10^{-5}$
		7.16	...	$(7.09 \pm 0.09) \times 10^{-5}$
	MeOH	19.82	...	$(3.19 \pm 0.06) \times 10^{-4}$
		12.05	...	$(3.15 \pm 0.05) \times 10^{-4}$
		5.87	...	$(3.29 \pm 0.05) \times 10^{-4}$
	80% EtOH	9.94	...	$(1.369 \pm 0.018) \times 10^{-3}$
		12.84	...	$(1.386 \pm 0.017) \times 10^{-3}$
$(CH_3)_2CHOSO_2C_6H_4Br$	AcOH-97.5% Ac_2O	30.65	...	1.30×10^{-6}
	$N_{AcOH} = 0.042$	36.72	22.28[d]	1.50×10^{-6}
		21.81	10.25[d]	1.46×10^{-6}
	AcOH-80.3% Ac_2O	28.33	...	$(8.48 \pm 0.11) \times 10^{-6}$
	$N_{AcOH} = 0.294$			
	AcOH-0.1% Ac_2O	42.66	...	$(6.98 \pm 0.08) \times 10^{-5}$
		26.72	...	$(6.90 \pm 0.05) \times 10^{-5}$
		24.10	25.03	$(7.41 \pm 0.07) \times 10^{-5}$
	EtOH	23.16	...	$(2.64 \pm 0.04) \times 10^{-4}$
	MeOH	23.31	...	$(7.34 \pm 0.08) \times 10^{-4}$
		18.15	...	$(7.28 \pm 0.16) \times 10^{-4}$
	80% EtOH	11.35	...	1.73×10^{-3}
		11.93	...	1.67×10^{-3}

[a] Data at 34.85°; $E^{\pm} = 26.43$ kcal./mole. [b] Data at 34.43°; $E^{\pm} = 25.97$ kcal./mole. [c] From data of Hughes.[6] [d] $k_2 = 3.61 \times 10^{-4}$ sec.$^{-1}$ M^{-1}.

of evidence indicates, react by the unimolecular-type mechanism **A**, are summarized in Table I together with the values of the corresponding Arrhenius activation energies, $E^{\pm}$, wherever available. The solvolysis rates for any one compound have been corrected to one temperature with the aid of available values of $E^{\pm}$ or else on the basis of reasonable estimates of $E^{\pm}$. The values of $E^{\pm}$ for any one compound are fairly insensitive to solvent change and all values of $E^{\pm}$ hover near 22 kcal (Table I). It is therefore possible to estimate $E^{\pm}$ with sufficient accuracy since the corrections made are small. Even an error of 2.0 kcal. in $E^{\pm}$ would cause an error of no more than 0.079 in log k for a 20° correction.

Supplementing the data in Table I are the solvolysis rates k we have measured for *t*-butyl chloride and α-methylneopentyl *p*-bromobenzenesulfonate, $(CH_3)_3CCH(OSO_2C_6H_4Br)CH_3$, in a num-

---

Kritschenko, *Ber.*, **61**, 852 (1928); (e) Bateman, Church, Hughes, Ingold and Taher, *J. Chem. Soc.*, 979 (1940); (f) Hughes, Ingold and Taher, *ibid.*, 949 (1940).

(11) (a) Young and Andrews, THIS JOURNAL, **66**, 421 (1944); (b) Winstein and Grunwald, *ibid.*, **70**, 828 (1948).

(12) (a) Ward, *J. Chem. Soc.*, 445 (1927); (b) Ward, *ibid.*, 2285 (1927).

(13) Hughes, Ingold and Scott, *ibid.*, 1201 (1937).

(14) Steigman and Hammett, THIS JOURNAL, **59**, 2536 (1937).

ber of solvents. These measurements are summarized in Table II.

Inspection reveals a simple quantitative relationship among the various solvolysis rate constants. Thus, when the values of log k for any one compound in a number of solvents are plotted against log k of some other compound in the same solvents a straight line is obtained. This linear relationship is illustrated for a number of compounds in Fig. 1.

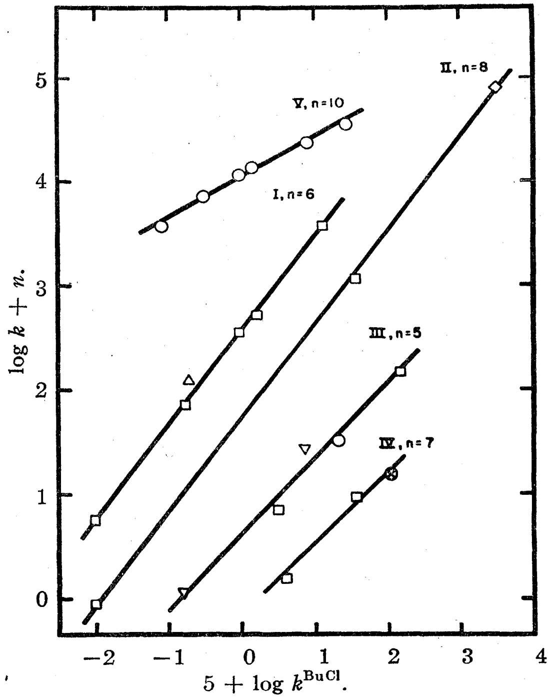


Fig. 1.—Plots of log k *vs.* log k^{BuCl}: I, *t*-butyl bromide 25.0°; II, α-methylallyl chloride, 25.0°; III, α-methylneopentyl *p*-bromobenzenesulfonate, 70.0°; IV and V, neopentyl bromide, 95.0°, and *n*-butyl bromide, 59.4°, both *vs.* *t*-butyl chloride, 25.0°; solvents: ◇, H_2O; □, EtOH–H_2O; ○, MeOH–H_2O; ▽, AcOH–Ac_2O; △, acetone–H_2O; ⊗, HCOOH.

The linear plots illustrated in Fig. 1 indicate that log k^{BuCl} (BuCl = *t*-butyl chloride) satisfies the requirements for a useful quantitative measure of ionizing power of a given solvent. However, log k^{BuCl} varies with temperature and is usually a negative entity of an inconvenient order of magnitude. It is convenient to define **Y** by equation 2, where k^{BuCl} and k_0^{BuCl} are the rate constants of

$$\mathrm{Y} = \log k^{\mathrm{BuCl}} - \log k_0^{\mathrm{BuCl}} \qquad (2)$$

t-butyl chloride at 25.0° in the given solvent and in "80%" ethanol, respectively. By virtue of this definition, **Y** is zero in "80%" ethanol, a solvent often employed and of intermediate reactivity, and **Y** varies from *ca.* +4 to −3 for the most common solvolyzing media. Although 25.0° is chosen as the reference temperature for computing values of **Y** it is clear from the near constancy of $E^{\ddagger}_{\mathrm{BuCl}}$ in various solvents that any other reference temperature would give an almost identical set of **Y** values.

The linear relationships illustrated in Fig. 1 combined with the defining equation 2 for **Y** lead to equation 3 for the variation of solvolysis rate constant k with solvent for these compounds. In

$$\log k = m\mathrm{Y} + \log k_0 \qquad (3)$$

this equation, m and log k_0 are parameters, although physically k_0 is the solvolysis rate constant in "80%" ethanol. Equation 3 is the basis of the quantitative scheme for correlating solvolysis rates.

In Table I are summarized values of **Y** for an extensive series of solvents. **Y** values for all solvents except the acetone–water mixtures were calculated from the available data for *t*-butyl chloride at 25.0° (Tables I, II). In order to obtain **Y** values in the latter solvent mixtures the parameters m and log k_0 were evaluated for *t*-butyl bromide and benzhydryl chloride from data at 25.0° in ethanol–water mixtures, and **Y** was calculated for various acetone–water mixtures with the aid of equation 3, using the available values of log k for these compounds. Two different sets of **Y** are obtained in this way, of which one (from *t*-butyl bromide) is used for aliphatic compounds while the other (from benzhydryl chloride) is used with α-phenylethyl chloride. Acetone–water mixtures were the only solvents where it was found necessary to use two different sets of **Y** in order to correlate all rates of unimolecular-type solvolysis scrutinized by the authors to date.

The functional relationship between **Y** and the composition of mixed solvents is apparently not

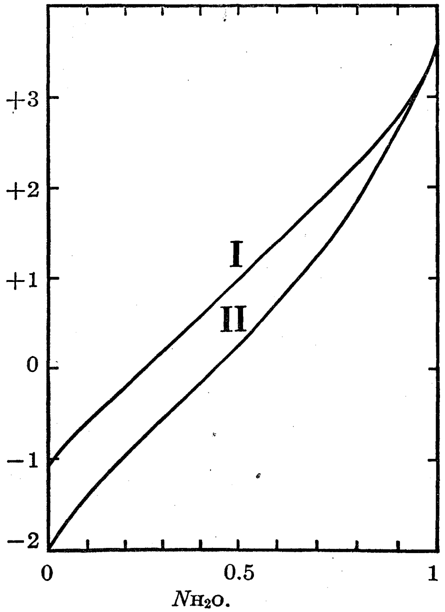


Fig. 2.—Plot of **Y** *vs.* mole fraction of water (N_{H_2O}) for: I, H_2O–MeOH; II, H_2O–EtOH.

simple. Plots of **Y** *vs.* weight % or volume % of water in aqueous ethanol and methanol have considerable curvature. The plot of **Y** *vs.* mole fraction of water, N_{H_2O}, is more nearly linear for these systems as illustrated in Fig. 2. The latter observation is useful for purposes of interpolation.

The parameters m and $\log k_0$ in equation 3 have been evaluated for a number of compounds by the method of least squares, using the values of k and **Y** in Tables I and II. The results are summarized in Table III together with the probable error of the fit,[15] r. The fit is satisfactory, particularly since the values of k often vary by 3 to 6 powers of ten, the mean value of r for the whole table being less than 0.05. The probable errors in m are of the order of 0.05 or less.

TABLE III

CORRELATION OF SOLVOLYSIS RATES IN VARIOUS SOLVENTS

No.	Compound	Temp., °C.	m	$\log k_0$	r
1	*t*-Butyl chloride	25.0	1.000	−5.034	...
2	*t*-Butyl bromide	25.0	0.917	−3.476	0.026
3	Neopentyl bromide	95.0	.712	−7.248	.059
4	α-Methylneopentyl *p*-bromobenzenesulfonate	70.0	.706	−2.837	.096
5	α-Methylallyl chloride	25.0	.894	−6.314	.052
6	Benzhydryl chloride	25.0	.757	−2.779	.004
7	α-Phenylethyl chloride[a]	50.0	1.195	−3.808	.072
8	*n*-Butyl bromide	59.4	0.392	−5.972	.026
		75.1	0.331	−5.419	.034

[a] The value of k for HOAc, 0.2 *M* KOAc (Table I), was not included since no value of **Y** is available at such high acetate concentration. From the above data $k = 1.74 \times 10^{-6}$ sec.$^{-1}$ at 0.025 *M* KOAc ($Y = -1.633$) in reasonable agreement with the value in Table I.

Equation 4 gives the variation of m with temperature T. This is slight since for most solvents the

$$2.303\ Y \frac{dm}{dT} = \frac{E^{\ddagger} - E_0^{\ddagger}}{RT^2} \qquad (4)$$

difference between the activation energy $E^{\ddagger}$ and the activation energy $E_0^{\ddagger}$ in "80%" ethanol is small for unimolecular-type solvolysis (Tables I, II).

Theoretical Interpretation. The Activity Postulate.—Application of the Brönsted theory to the variation of k_1 with solvent for unimolecular-type solvolysis leads to equation 5 where κ is the

$$k_1 = \kappa \frac{f_A}{f_A^{\ddagger}} \qquad (5)$$

specific rate in the standard state of unit activity and f_A and $f_A^{\ddagger}$ are the activity coefficients of reactant and transition-state. In the case of dilute solutions[16] of non-electrolytes it is useful to refer all activity coefficients to the gas phase so that equation 5 reduces to 6. In this equation H_A and $H_A^{\ddagger}$ are the Henry's law constants[16] of reactant

$$k_1 \kappa = (H_A/H_A^{\ddagger}) \qquad (6)$$

and transition-state.

Comparison of equations 6 and 3 leads to 7 which implies a linear relationship, 8, between

$$\log \frac{H_A}{H_A^{\ddagger}} = mY + \log \frac{k_0}{\kappa} \qquad (7)$$

$\log (H_A/H_A^{\ddagger})$ and $\log (H_B/H_B^{\ddagger})$ for any two com-

$$\log \frac{H_A}{H_A^{\ddagger}} = \frac{m_A}{m_B} \log \frac{H_B}{H^{\ddagger}} + \left(\frac{m_A}{m_B} \log \frac{\kappa_B}{k_{0B}} - \log \frac{\kappa_A}{k_{0A}}\right) \qquad (8)$$

pounds A and B solvolyzing by the unimolecular-type mechanism in a series of solvents. This deduction calls to mind the observation[17] that there exists an even simpler linear relationship, shown in equation 9, between $\log (f_B/f_{BH^+})$ for any two

$$\log \frac{f_B}{f_{BH^+}} = \log \frac{f_{B'}}{f_{B'H^+}} \qquad (9)$$

conjugate acid–base systems B and B′ in a series of solvents.

The success of equation 3 for correlating solvolysis rates of the unimolecular type may be due to the validity of a general relationship regarding ratios of activity coefficients. For systems undergoing similar changes of the type AZ → AZ′, BZ → BZ′, etc., the postulated general relationship may be expressed by equation 10, μ and β being parameters.

$$\log \frac{f_{AZ}}{f_{AZ'}} = \mu \log \frac{f_{BZ}}{f_{BZ'}} + \beta \qquad (10)$$

In the case of solvolysis by mechanism **A** the change AZ → AZ′ is from the dissolved halide or ester to the partly ionized and strongly solvated transition-state molecule. Equation 3 and thus 8 is successful for variations in the ionizing group to include chloride, bromide and bromobenzenesulfonate. Also, the change AZ → AZ′ is not restricted entirely to the A–Z bond. For example, resonance will diffuse any positive charge of the *alpha* carbon atom in the transition state to the *ortho* and *para* positions of an *alpha* phenyl group. Even in aliphatic cases the positive charge will be spread. Now evidently equations 3 and 8 hold for considerable variation in the R part of the solvolyzing molecule RX but further work is necessary to clearly outline the scope and limitations in this respect. The need for two sets of **Y** values for aqueous acetone mixtures is one of the limitations which has already appeared.

Solvolysis of *t*-Butyl Chloride.—The solvolysis rate of *t*-butyl chloride in a range of mixed aqueous solvents has previously been correlated by Olson and Halford[8] with the aid of the fugacity rate equation 11 where p_w and p_a are vapor

$$k = (k_w p_w + k_a p_a) H_{BuCl} \qquad (11)$$

pressures of water and alcohol, respectively. This equation, which empirically fits the rates but not

---

(15) Margenau and Murphy, "Mathematics of Physics and Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1943, p 502.

(16) Lewis and Randall, "Thermodynamics," McGraw–Hill Book Co., Inc., New York, N. Y., 1923, Chapter XX.

(17) Ref. 2, Chapter IX.

the products,[18] is based on assumed bimolecular reactions between halide and water or alcohol but it is set up according to an activity rate formulation, the respective terms not being divided by the activity coefficients of the corresponding transition states. Actually higher order[18] fugacity rate equations fit the rates at least as well as equation 11. Scrutinizing the data with our present approach, seeking generalizations regarding activity coefficients involved, we find that log k is a linear function of log H_{BuCl} for the range of solvents treated by Olson and Halford. Equation 12 fits

$$\log k^{\mathrm{BuCl}} = 1.232 \log H_{\mathrm{BuCl}} - 9.811 \qquad (12)$$

the data at 25.0° for all partly aqueous solvents (including also water and methanol) (Tables I, II, IV, ref. 8) with a probable error of 0.06. Thus, only two parameters are necessary.

The linear relation expressed in equation 12 indicates, according to equation 6, that a linear relation exists between log $H^{\pm}_{\mathrm{BuCl}}$ and log H_{BuCl} in the solvent range involved. This linear relation takes the form shown in equation 13.

$$\log H^{\pm}_{\mathrm{BuCl}} = -0.232 \log H_{\mathrm{BuCl}} + \text{Constant} \qquad (13)$$

TABLE IV

HENRY'S LAW CONSTANTS FOR *t*-BUTYL CHLORIDE AT 25.0°

Solvent	10^{-3} H_{BuCl}, mm.
HOH	5×10^3
EtOH	1.09 ± 0.09
HOAc, 0.025 *M* KOAc	1.23 ± 0.05
HOAc − Ac_2O, $N_{\mathrm{AcOH}} = 0.042$	0.786 ± 0.020

While there are indications that linear log–log relationships between the activity coefficients of non-electrolytes are fairly general,[19] the linear log–log relation expressed by equations 12 and 13 for *t*-butyl chloride and its solvolysis transition state breaks down when one proceeds to the more poorly ionizing solvents such as absolute alcohol or acetic acid–acetic anhydride combinations. The plot in Fig. 3 of log k^{BuCl} *vs.* log H_{BuCl} at 25.0° illustrates the linear relation for one range of solvents and the large departure for the slower solvents mentioned. Even with the departure from linearity the curve is smooth. However, a smooth curve is not necessarily to be expected and this feature may be fortuitous.

Further insight into the above-described situation is derived by reference again to equation 6. As shown in equation 14, (log H_{BuCl}–log k^{BuCl}) is a

$$\log H^{\pm}_{\mathrm{BuCl}} - \log \kappa = \log H_{\mathrm{BuCl}} - \log k^{\mathrm{BuCl}} \qquad (14)$$

measure of log $H^{\pm}_{\mathrm{BuCl}}$, and this quantity is plotted against log k^{BuCl} in Fig. 3. It can be seen that in the partly aqueous solvents where equation 12 holds the variation in k^{BuCl} is due largely to changes in H_{BuCl}. On the other hand, in the poorer ionizing media the variation in k^{BuCl} is due largely to changes in $H^{\pm}_{\mathrm{BuCl}}$.

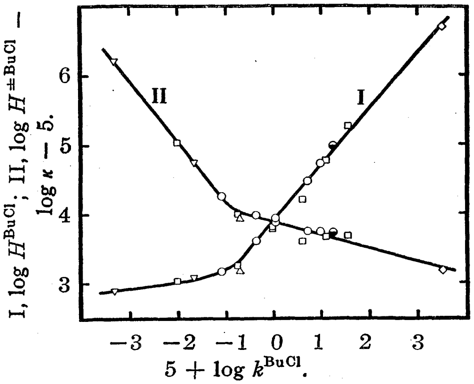


Fig. 3.—Plots of log H^{BuCl} and (log $H^{\pm\mathrm{BuCl}}$ − log κ) against log k^{BuCl}, 25.0°: □, H_2O–EtOH; ○, H_2O–MeOH; ◒, H_2O–dioxane; ▽, AcOH–Ac_2O; △, H_2O–acetone; ◇, H_2O.

Solvolysis of Isopropyl *p*-Bromobenzenesulfonate.—For the simple secondary alkyl compound, isopropyl *p*-bromobenzenesulfonate, without essentially prohibitive steric hindrance to nucleophilic attack on carbon such as evidently obtains in the case of pinacolyl *p*-bromobenzenesulfonate, the nucleophilic character of the solvent is very important. The first-order solvolysis rate constants k for isopropyl *p*-bromobenzenesulfonate are summarized in Table II and inspection reveals the contrast with the other compounds treated successfully by equation 3. For example, the rate constant in ethanol is much greater than in acetic acid although the **Y** value for acetic acid is the higher. This contrast is due to the fact that ionizing power and nucleophilic character of solvents do not go hand in hand. Instead of the rates in all solvents being manageable together it is now necessary to differentiate between basic solvents and others.

Quite a satisfactory understanding of the solvolysis rates of isopropyl *p*-bromobenzenesulfonate may be reached on the assumption that solvolysis proceeds by both mechanism types **A** and **B**, **B** being slight or negligible in the acidic type solvents such as acetic acid or its mixtures with acetic anhydride and serious in the more basic solvents.

In the acetic acid–acetic anhydride solvents the plot of log k for isopropyl *p*-bromobenzenesulfonate against log k' for pinacolyl *p*-bromobenzenesulfonate gives the least squares line shown in equation 15, the probable error[15] being 0.136. The

$$\log k = 1.204 \log k' + 0.031 \qquad (15)$$

straight line fit is not as satisfactory here as in the other cases, possibly because the acetolysis is not cleanly of the unimolecular type ($k = k_1$). It is not out of the question that acetic acid can func-

---

[18] (a) Bartlett, THIS JOURNAL, **61**, 1630 (1939); (b) Winstein, *ibid.*, **61**, 1635 (1939); (c) Bateman, Hughes, and Ingold, *ibid.*, **60**, 3080 (1938); (d) Bateman, Hughes and Ingold, *J. Chem. Soc.*, 881 (1938).

[19] Grunwald, Dissertation, University of California at Los Angeles, Calif., 1947, sections 6, 17.

tion in solvolysis by mechanism **B**. While the addition of $0.025M$ potassium acetate to glacial acetic acid gives no serious change in first-order rate constant the addition of $0.01M$ potassium acetate to the solvent rich in acetic anhydride produces a predominantly bimolecular reaction. However, the slope of the line represented by equation 15 is reasonable for solvolysis largely by mechanism **A**. The value of 1.204 combined with an m value of 0.706 for pinacolyl *p*-bromobenzenesulfonate (Table III) corresponds to 0.850 for m in the case of the isopropyl ester.

Assuming $k = k_1$ in the acidic solvents, equation 15 allows one to estimate k_1 in the nucleophilic alcoholic solvents. These estimates are listed in Table V along with k_x (*i. e.*, $k - k_1$) and the percentage of solvolysis by mechanism **A**, 100 k_1/k.

TABLE V

SOLVOLYSIS OF ISOPROPYL *p*-BROMOBENZENESULFONATE AT 70.0° IN NUCLEOPHILIC SOLVENTS

Solvent	10^4k sec.$^{-1}$	Calcd. 10^4k_1	Calcd. 10^4k_x	Calcd. $100k_1/k$
EtOH	2.64	0.108	2.53	4.1
MeOH	7.31	0.68	6.63	9.3
80% EtOH	17.0	3.86	13.1	22.7

It is interesting that k_x in the small range of comparably nucleophilic alcoholic solvents is fit by a linear equation of the same type as 3, equation 16 fitting the data in Table V with a probable

$$\log k_x = 0.360\,Y - 2.857 \qquad (16)$$

error of 0.046. In these solvents the rate of solvolysis by mechanism **B** seems to depend on the same properties of the solvent which control the rate of the **A** type, the slope m, however, being quite small.

It is an especially satisfactory feature of the assumed way of accounting for the solvolysis rates of isopropyl *p*-bromobenzenesulfonate that the slope in equation 16 is so small and so nearly equal to the one which is derivable for *n*-butyl bromide. There is reason to believe that the latter halide solvolyzes exclusively by mechanism **B** in alcoholic solvents, and Bird, Hughes and Ingold[20] have supplied rates of solvolysis in various aqueous ethanol and methanol solvents.[21] Using their data a plot of log k against log k^{BuCl} is linear as illustrated in Fig. 1 and equation 3 fits the data well as summarized in Table III. The values of m in aqueous methanol at 59.1° and aqueous ethanol at 75.1° are 0.392 and 0.331, respectively. In fact, values of m are also quite similar[22] for other primary halides apparently solvolyzing by mechanism **B**.

Experimental and Kinetic Part

Materials.—The *t*-butyl chloride was Eastman Kodak Co. "White Label" grade, b. p. 51.2° (752 mm.), n^{25}D 1.3820.

α-Methylneopentyl alcohol, b. p. 120.0–120.3° (754 mm.), was prepared by Miss Anita Suran from *t*-butyl magnesium chloride[23] and acetaldehyde.

α-Methylneopentyl *p*-bromobenzenesulfonate I and isopropyl *p*-bromobenzenesulfonate II were prepared in *ca.* 50% yield in 0.05 mole batches from the corresponding alcohols and *p*-bromobenzenesulfonyl chloride in pyridine by conventional methods.[24] I crystallized upon pouring the pyridine reaction mixture into ice-cold 6 *N* hydrochloric acid and was recrystallized several times from petroleum ether (b. p. 60–80°); m. p. 53.2–53.5; equivalent weight from quantitative solvolysis: calcd., 321.2; found, 323.2 (in acetic acid), 320.1 (in "80%" ethanol).

Anal. Calcd. for $C_{12}H_{17}O_3SBr$: C, 44.86; H, 5.34. Found: C, 44.99; H, 5.49.

II separated as an oil upon pouring the pyridine reaction mixture into 6 *N* hydrochloric acid. The oil was separated with the aid of *ca.* 40 ml. of carbon tetrachloride and the solution was dried over anhydrous potassium carbonate. After evaporation of the solvent at room temperature the viscous residue was induced to crystallize. The solid was purified by reprecipitation under petroleum ether (b. p. 60–80°); m. p. 32.3–34.1°. Equivalent weight from quantitative solvolysis: calcd. 279.2; found 282.1 (in acetic acid), 278.3 (in methanol). Analysis for carbon and hydrogen was unsuccessful because II decomposed rapidly on heating.

Solvents.—Synthetic methanol, containing less than 0.03% of water by the miscibility temperature with cyclohexane,[25] was used.

Ethanol was dried by the ethyl formate method[26] and contained less than 0.02% of water by Robertson's paraffin oil test.[26]

"80%" ethanol was prepared by adding 317.5 g. of conductivity water to 1000 g. of ethanol.

Acetic acid containing 0.0142 *M* (0.1%) acetic anhydride by Kilpi's anthranilic acid analysis[27] was prepared as described in a previous article.[3]

To 379.0 g. of Baker and Adamson "Reagent Grade" acetic anhydride, equivalent weight 51.20 ± 0.06 by hydrolysis and titration with standard aqueous base to the phenolphthalein endpoint (mole fraction of acetic acid 0.042), was added 80.6 g. of acetic acid containing 0.1 wt. % of acetic anhydride to give a solvent of equivalent weight 52.63 ± 0.06 (mole fraction of acetic acid 0.294).

In order to prepare solvents containing potassium acetate the Baker and Adamson "Reagent Grade" salt was dried to constant weight in a tared glass-stoppered flask at 110° *in vacuo* and dissolved in the desired weight of solvent.

Kinetic Measurements.—Rates were measured by the usual sealed ampoule technique. Titrations were made on 5-ml. aliquots from 5-ml. microburets. For the measurements in ethanol, methanol and "80%" ethanol, titration

---

[20] Bird, Hughes and Ingold, *J. Chem. Soc.*, 255 (1943).

[21] In the case of *n*-butyl bromide, the fugacity rate equation 11 has been found by Bird, Hughes and Ingold[20] to fit both rates and products. It must be noted that *H* may be expressed as the ratio of the vapor pressure of halide to either its mole fraction or its molarity. Olson and Halford[8] have used mole fraction as is also done in the present article, and Bird, Hughes and Ingold[20] have used molarity However, because of differences in molar volumes of various mixed solvents, if the use of molarity furnishes a fit for the product compositions, the use of mole fraction cannot furnish such a fit. A recalculation of the data of Bird, Hughes and Ingold, using mole fraction in evaluating *H*, shows that equation 11 will fit the rates but not the products.

[22] Winstein and Grunwald, unpublished work.

[23] Puntambeker and Zoellner, "Organic Syntheses," Vol. 23, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 510.

[24] Winstein, Grunwald and Ingraham, THIS JOURNAL, **70**, 821 (1948).

[25] Jones and Amstell, *J. Chem. Soc.*, 1321 (1930).

[26] Robertson, "Laboratory Practice of Organic Chemistry," Macmillan Co., New York, N. Y., 1943, pp. 178, 296.

[27] Kilpi, *Suomen Kemistilehti*, **13B**, 19 (1940); *C. A.*, **35**, 2445 (1941).

for acid was carried out with 0.05 *N* sodium hydroxide using brom thymol blue as indicator. Titrations in glacial acetic acid and mixtures of acetic acid and acetic anhydride were performed as described previously[3,24] except that 0.05 *N* *p*-toluenesulfonic acid was substituted for perchloric acid in the solvents containing large amounts of acetic anhydride. Reactions were usually followed to *ca.* 75% completion. Reaction mixtures were prepared gravimetrically except for the rate-runs involving *t*-butyl chloride where initial concentrations were obtained from the "infinite" titer of acid and/or from Volhard titration for chloride ion. In order to avoid errors due to the volatility of *t*-butyl chloride, the vapor space above the reaction solutions in the ampoules was kept quite small.

The observed kinetics were first-order within the experimental error of 1–2% in *k* over the range of concentrations investigated except for the solvolysis of isopropyl *p*-bromobenzenesulfonate (RX) in 4.2 mole % acetic acid in acetic anhydride in the presence of potassium acetate. A representative set of experimental data is shown in Table VI. These data were fitted satisfactorily by equation 17 which assumes a simultaneous first-order solvolysis and second-order reaction with potassium acetate.

$$-\mathrm{d}\ln(\mathrm{RX})/\mathrm{d}t = k_1 + k_2(\mathrm{KOAc}) \qquad (17)$$

Using the data obtained during the latter part of the run where the potassium acetate has been neutralized, k_1 was calculated from the slope (obtained by the method of least squares) of the linear plot of log (RX) *vs.* time, *t*. The derivative, $-\mathrm{d}\ln(\mathrm{RX})/\mathrm{d}t$, was then obtained at various concentrations of potassium acetate from a large-scale plot of ln (RX) *vs.* *t* with the aid of a tangent meter. Substitution in equation 17 gave satisfactorily constant values for k_2. The average value of k_2 for this and a duplicate run was $(3.61 \pm 0.07) \times 10^{-4}$ sec.$^{-1}$ *M*.$^{-1}$

TABLE VI

ACETOLYSIS OF ISOPROPYL *p*-BROMOBENZENESULFONATE (RX) IN 4.2 MOLE % ACETIC ACID IN ACETIC ANHYDRIDE AT 70.0°

Time, hr.	(RX) $10^3 M$	(KOAc) $10^3 M$	$-10^6 \frac{\mathrm{d}\ln(\mathrm{RX})}{\mathrm{d}t}$ (sec.$^{-1}$)
0.0	36.72	22.28	..
11.6	26.89	12.45	5.84
20.7	22.74	8.30	4.47
30.95	19.20	4.76	..
54.1	15.68	1.24	1.94
70.5	14.25	...	..
103.1	12.05	...	..
120.1	11.02	...	..
143.1	9.62	...	..

Equilibrium in the System *t*-Butyl Chloride, *t*-Butyl Acetate, Hydrogen Chloride.—In analogy with the report of Steigman and Hammett[14] for α-phenylethyl chloride, *t*-butyl chloride solvolyzes in initially neutral acetic acid to give an equilibrium mixture according to equation 18.

$$t\text{-BuCl} + \mathrm{HOAc} = t\text{-BuOAc} + \mathrm{HCl} \qquad (18)$$

The rate of establishment of equilibrium is considerably faster than the rate of solvolysis in the presence of potassium acetate. For example, at 40.0° *ca.* 97% of the equilibrium concentration of hydrogen chloride is produced from a solution of *t*-butyl chloride within 28 hours whereas the solvolysis in the presence of potassium acetate is only *ca.* 20% complete within the same period.

The pertinent equilibrium data are summarized in Table VII. The data were obtained by the sealed-ampoule technique described for the kinetic runs. The equilibrium titre of hydrogen chloride was constant within experimental error over a period of several days.

TABLE VII

EQUILIBRIUM IN THE SYSTEM *t*-BUTYL CHLORIDE, *t*-BUTYL ACETATE, HYDROGEN CHLORIDE

Initial *t*-BuCl $10^3 M$	*T*, °C.	(HCl) at equilibrium $10^3 M$	K^a
81.8	60.2	6.02 ± 0.2	2.1×10^3
158.3	60.2	$8.12 \pm .2$	2.3×10^3
81.8	40.0	$4.15 \pm .2$	4.5×10^3
158.3	40.0	$5.65 \pm .1$	4.8×10^3

[a] $K = (t\text{-BuCl})/(t\text{-BuOAc})(\mathrm{HCl})$.

Measurement of Henry's Law Constants.—Approximate Henry's law constants were determined as follows: A 500-ml. standard-taper round-bottom flask equipped with a graduated dropping funnel and an outlet tube leading by way of a T-joint to a manometer and an oil pump was placed in a thermostat and evacuated until the pressure was below 2 mm. A known volume of standard solution of *t*-butyl chloride in the appropriate solvent was introduced carefully from the dropping funnel and the increase in pressure read. Room temperature was maintained above that of the thermostat to avoid condensation of the vapors. A typical set of experimental data is given in Table VIII. In computing the mole fraction of *t*-butyl chloride, allowance was made for the materials in the known vapor space.

TABLE VIII

HENRY'S LAW CONSTANT OF *t*-BUTYL CHLORIDE IN ACETIC ACID CONTAINING 0.025 *M* POTASSIUM ACETATE, 25.0°

N_{BuCl}	*p*, mm.[a]	10^{-3} *H*, mm.
0.0000	16.0	..
.0338	53.6	1.13
.0359	59.1	1.22
.0293	52.3	1.26
.0137	33.5	1.29

[a] *p* = pressure increase due to the solution.

The Henry's law constant of *t*-butyl chloride in water was estimated from the vapor pressure and a rough determination of the solubility of the halide in water (*ca.* 3×10^{-3} *M*).

Summary

For compounds which appear to solvolyze by a rate determining ionization, plots of the logarithm of the first-order rate constant k in various solvents (either from the literature or here reported) against log k for t-butyl chloride are linear.

A set of values of the so-called ionizing power, **Y**, defined by the equation

$$\mathrm{Y} = \log k^{\mathrm{BuCl}} - \log k_0^{\mathrm{BuCl}}$$

(k^{BuCl} and $k_0{}^{\mathrm{BuCl}}$ being solvolysis rate-constants for t-butyl chloride at 25.0° in the given solvent and in 80% ethanol) has been set up for a number of solvents including water, methanol, ethanol, aqueous alcohols, formic acid and acetic acid. The solvolysis rate constants (varying sometimes by six orders of magnitude) are fitted by the equation

$$\log k = m\mathrm{Y} + \log k_0$$

with a mean probable error of less than 0.05 in the cases of t-butyl bromide, neopentyl bromide, α-methylneopentyl p-bromobenzenesulfonate, α-methylallyl chloride, α-phenylethyl chloride and benzhydryl chloride.

The observed linear relationships, interpreted on the basis of the Brönsted equation, lead to the equation

$$\log \frac{f_{\mathrm{A}}}{f^{\neq}_{\mathrm{A}}} = \frac{m_{\mathrm{A}}}{m_{\mathrm{B}}} \log \frac{f_{\mathrm{B}}}{f^{\neq}_{\mathrm{B}}} + \text{constant}$$

for the relationship among the pertinent activity coefficients (f_{A}, $f^{\neq}_{\mathrm{A}}$, *etc.*) for any two compounds A and B. It is postulated that linear logarithmic relationships among ratios of activity coefficients of this type may be quite general.

The solvolysis of t-butyl chloride is discussed in terms of the Brönsted equation. It is shown that, to a good approximation, log $f^{\neq}_{\mathrm{BuCl}}$ varies linearly with log f_{BuCl} in the partly aqueous solvents and that in these solvents the variation in k is due largely to changes in f_{BuCl}. On the other hand, in the more poorly ionizing solvents changes in k are attributable mainly to changes in $f^{\neq}_{\mathrm{BuCl}}$.

The reported method of correlating unimolecular type solvolysis rates is useful in elucidating the nature of the solvolysis of materials the rates of which depend markedly on the nucleophilic character of the solvent. For isopropyl p-bromobenzenesulfonate the rates of solvolysis in acetic acid and acetic acid–acetic anhydride mixtures furnish estimates of unimolecular solvolysis rates in ethanol, methanol and aqueous ethanol. The actual solvolysis rates are considerably larger in the latter solvents, the fractions of unimolecular solvolysis being low.

LOS ANGELES 24, CALIFORNIA RECEIVED AUGUST 15, 1947

[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

Hyperconjugation. II. The Competitive Bromination of Benzene and *t*-Butylbenzene

BY ERNST BERLINER AND FRANCES J. BONDHUS

When benzene and t-butylbenzene in an equimolecular mixture in 92% acetic acid are allowed to compete for an insufficient amount of bromine, the corresponding brominated hydrocarbons are formed in proportions which show that the ratio of the rates of bromination at 25° is about 115:1 in favor of t-butylbenzene. At 45° the ratio is about 72:1. Therefore the bromination of benzene requires a higher energy of activation than the bromination of t-butylbenzene.[1] Since under the same conditions toluene is brominated about four times faster than t-butylbenzene,[2,3] the rate of bromination of toluene appears to be about 465 times faster than that of benzene. Values for the individual rates of chlorination of toluene and benzene fix the ratio at about 345,[3,4] whereas in nitration with acetyl nitrate toluene reacts twenty-three times faster than benzene.[5]

The difference in the rates of bromination of toluene and t-butylbenzene was explained by no-bond resonance of the Baker–Nathan type,[2,3,6] which involves carbon–hydrogen bonds, but the much greater difference between t-butylbenzene and benzene clearly cannot be accounted for by such resonance, since no α-hydrogen atoms are available for conjugation.[7] On the other hand, it would be hard to see how the inductive effect, which, on the basis of the Baker–Nathan theory, should be operative in the absence of hydrogen atoms, could alone account for the great activation and strong *ortho–para* directive influence of the t-butyl group, particularly since inductive effects of alkyl groups are conceded to operate through a rather feeble relay mechanism. The definitions that make the Baker–Nathan type of resonance

---

[1] The bromination of different aromatic compounds is probably another case in which the differences in rate are primarily due to differences in the E term of the Arrhenius equation (Scheffer and Blanksma, *Rec. trav. chim.*, **45**, 522 (1928); Bradfield and Jones, *J. Chem. Soc.*, 1006 (1928)); *i. e.*, the relationship (log $k_1/k_2)_{T_1} = T_2/T_1$ (log $k_1/k_2)_{T_2}$ should hold. In the competitive bromination of toluene and t-butylbenzene the calculated ratio at 45° is 3.70 (found, 3.80); in the present bromination the agreement is less satisfactory (calculated ratio at 45°: 85.7, found: 71.5). This may be due to irregularities on account of the greater difference in rate.

[2] Berliner and Bondhus, THIS JOURNAL, **68**, 2355 (1946).

[3] De la Mare and Robertson, *J. Chem. Soc.*, 279 (1943).

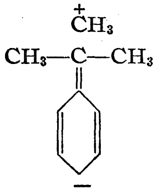
[4] This ratio is for 80% acetic acid; the ratio of the rate of chlorination of t-butylbenzene and benzene is 110.

[5] Ingold, Lapworth, Rothstein and Ward, *J. Chem. Soc.*, 1959 (1931).

[6] Baker and Nathan, *ibid.*, 1840 (1935).

[7] Baker, *ibid.*, 1150 (1939).

dependent upon the number of hydrogen atoms available for conjugation are, however, not inherent in the quantum mechanical treatment of the problem.[8] According to this approach any three single bonds can take part in hyperconjugation, if they are linked to a carbon atom which is conjugated with a multiple link. It has been more or less assumed that the carbon–hydrogen bond is capable of contributing more to hyperconjugation than an equally situated carbon–carbon bond, an idea that is supported by a fairly large number of reaction rates and equilibrium constants that have been studied by Baker and his school.[9] Although this concept seems thus fairly well established experimentally, it has also been stated that "...every carbon–carbon single bond can act as hyperconjugation donor wherever this is needed, without appreciable cost."[10] In view of the unexpectedly large contrast in the rates of bromination of benzene and *t*-butylbenzene, the *t*-butyl group must be considered to release electrons and partake in resonance through the contributions of structures of the type



The order of electron release of alkyl groups by this mechanism is identical with the order of the inductive effect, *i. e.*, *t*-butyl > *i*-propyl > ethyl > methyl,[11] and the reverse of the order of the hyperconjugation effect involving hydrogen atoms only (Baker–Nathan effect).

Reinterpretation of the inductive effect of alkyl groups as a resonance effect allows all observed electron release by these groups to be treated from a common basis. This might seem particularly advantageous in that the origin of the inductive effect has always been obscure.[12] It does not, *a priori*, answer the vexing question: why should there be two differing orders of electron release by alkyl groups, *i. e.*, why does carbon–hydrogen hyperconjugation contribute more in some cases, whereas in others resonance of carbon–carbon links takes precedence?[13] Thus, in the bromination of alkylbenzenes hyperconjugation appears to be predominant in toluene, but it must still be appreciable in *t*-butylbenzene, where only carbon–carbon hyperconjugation is possible.

Measurements of physical constants, on the whole, seem to reveal increasing contributions from resonance with increasing number of carbon–carbon links available for hyperconjugation, whereas rates and equilibrium constants indicate a greater tendency for carbon–hydrogen hyperconjugation. It is true that in many of the reactions that have been studied the differences in rate or equilibrium constants are very small, and in the majority of the cases the sequence of the alkyl groups is far from clean or regular, but enough well spaced series have been obtained to establish the Baker–Nathan order for reactions and equilibria with a good deal of certainty, even though only as a trend.[14,15]

Table I summarizes some of the pertinent data referring to both physical constants and chemical reactions. The new figures for the resonance energies of alkylbenzenes deserve some comment. It is generally agreed that small differences in experimental resonance energies must not be relied upon too strongly, since the values are obtained as small differences of two large figures, both subject to experimental errors.[16] The heats of combustion, on which the present data are based, have been determined on extremely pure samples by one reliable group at the National Bureau of Standards.[17] If one is justified in using thermochemical data for the calculation of resonance energies, the present set of data is surely reliable. The alkylbenzenes thus show resonance energies that increase with the amount of branching, *i. e.*, they follow the order produced by hyperconjugation of carbon–carbon bonds (line 1).[18,19,19a] In lines 2 and 3 of Table I are listed the dipole moments and molecular exaltations of the alkylben-

---

[8] Mulliken, *J. Chem. Phys.*, **7**, 339, 356 (1939).

[9] See Baker and Hemming, *J. Chem. Soc.*, 191 (1942), for the preceding references.

[10] Mulliken, Rieke and Brown, THIS JOURNAL, **63**, 41 (1941).

[11] Resonance structures of the type R^+ —Ar place the alkylbenzenes in the same order.

[12] Ingold, *Chem. Rev.*, **15**, 225 (1934).

[13] The problem of the order of the "inductive" effect *versus* the order of the resonance effect has been treated by Baker and his co-workers in terms of the relative energy levels (ref. 7 and 9, and *Trans. Faraday Soc.*, **37**, 632 (1941)) by which numerical values are assigned to the two effects. According to the present presentation it would not seem justified to assign a zero value to the resonance effect of the *t*-butyl group.

[14] For a general survey see: Deasy, *Chem. Rev.*, **36**, 145 (1945).

[15] The rates of chlorination of different alkyl phenyl ethers (Jones, *J. Chem. Soc.*, 1831 (1935)), the relative directive influence of alkoxyl groups (Robinson and Smith, *ibid.*, 392 (1926), 2647 (1927)), and of alkyl benzoates (Zaki, *ibid.*, 983 (1928)), that have often been cited in support of the pure order of the inductive effect, can actually be accounted for by a Baker–Nathan order. Since conjugation between the alkyl groups and the benzene ring is not possible through the intervening oxygen atom the increase in electron density on the ring will ultimately depend on the partial ionic bond character of the alkyl–oxygen bond, which in turn will depend on the stability of the alkyl carbonium ion (or something approaching it); see footnote 18.

[16] Wheland, "The Theory of Resonance," John Wiley & Sons, Inc., New York, N. Y., 1944, p. 63.

[17] Prosen, Johnson and Rossini, *J. Research Natl. Bur. Standards*, **36**, 455 (1946). The resonance energies are calculated from Pauling's bond energy values, ref. 16, p. 75.

[18] The figures, *inter alia*, also suggest that any effect based on the order *t-butyl* > methyl cannot be entirely due to induction, but must be, at least in part, a resonance effect, because no stabilization is assumed to accompany the inductive effect. However, the inductive effect of *all* groups is due to partial ionic bond character, and is thus a resonance effect.

[19] F. J. Bondhus, Ph.D. Dissertation, 1947, Bryn Mawr College, Bryn Mawr, Pa.

[19a] It might be argued that the bond energy values are not accurate enough to warrant an interpretation of the small differences; it is felt, however, that the observed *relative order* is significant. The calculations of Wheland and Pinkston (*J. Chem. Phys.*, **12**, 69 (1944)) refer only to second order hyperconjugation.

TABLE I

		Hydrogen	Methyl	Ethyl	*i*-Propyl	*t*-Butyl
1	Resonance energies of alkylbenzenes (kcal.)	39.5	42.4	42.3	43.5	44.9
2	Dipole moments of alkylbenzenes[a]	0	0.37	0.58	0.65	0.70
3	Molecular exaltations[b] EM_D at 20°	−0.124	0.169	0.221	0.262	0.207
	EM_D at 25°	−0.106	0.187	0.240	0.285	0.231
4	$k \times 10^4$ for R. of *p*-alkylbenzyl bromides with pyridine[6]	4.817[c]	7.983	6.733	6.500	6.467
5	First order solvolysis of *p*-alkylbenzhydryl chlorides[28] (a) alcoholysis	1	23.4	22.6	20	18.6
	(b) hydrolysis	1	21.4	17.3	13.8	10.9
6	10^3K for cyanohydrin reaction of *p*-alkylbenzaldehydes[9]	4.47	8.98	8.18	8.04	7.49
7	Chlorination of alkylbenzenes[3,4]	0.29	100	84	51	32
8	Bromination of alkylbenzenes[3]	...	100	76	44	23
9	Competitive bromination of alkylbenzenes	0.215	100	....	....	24.7
10	Per cent. dissociation of *p*-alkylhexaphenylethanes[f]	2.1[d]	16[e]	17[f]	26	33 (*s*-butyl)

[a] Baker and Groves, *J. Chem. Soc.*, 1144 (1939). [b] The molecular refractivities were taken from "Selected Values of Properties of Hydrocarbons," National Bureau of Standards, American Petroleum Institute, Research Project 44, Washington, D. C., Table 5b (June 30, 1945; May 31, 1947) and Table 14b (January 31, 1946; May 31, 1947). [c] Baker and Nathan, *J. Chem. Soc.*, 519 (1935). [d] Roy and Marvel, THIS JOURNAL, **59**, 2622 (1937). This degree of dissociation was determined in a 0.1 m. solution; in the other cases the molarity was 0.08. [e] Marvel, Rieger and Mueller, *ibid.*, **61**, 2769 (1939). [f] Marvel, Mueller, Himel and Kaplan, *ibid.*, **61**, 2771 (1939). (See footnote 36.)

zenes, which parallel the resonance energies, except for the exaltation of *t*-butylbenzene, which shows a reversal. Exaltation data have been used by Mulliken,[8] and by Hurdis and Smyth[20] to detect the presence of hyperconjugation. Data on the absorption spectra are only available for some alkylcyclohexenes,[21] and these do not demonstrate any differences.[22] No differences are shown in the heats of hydrogenations of alkylolefins,[23] but any differences would be expected to be smaller in the olefins than in the alkylbenzenes. Attention is also directed to the increasing stability of the free radicals formed from *p*-alkylhexaphenylethanes (line 10). The remainder of Table I records reaction rates and one equilibrium constant that show the opposite order (*i. e.*, the Baker–Nathan order) of the effect of alkyl groups.

Resonance involving the carbon–carbon bond was used at an early date by Wheland to account for the stability of free radicals formed from secondary or tertiary dialkyltetraarylethanes,[24] and later by Lewis and Kasha for the phosphorescence of di-isopropyl ketone.[25] It has recently been employed to explain the decreasing dipole moments of branched aliphatic amines.[26] The very small difference in dipole moments of *i*-propyl and *t*-butyl chloride as compared with the larger difference between methyl and ethyl chloride has been discussed by Smyth,[27] and can similarly be explained by the postulation of structures of the type $^-CH_3(CH_3)_2C{=}Cl^+$. The decreasing strengths of aliphatic branched acids can be accounted for in a like manner, as can other data, whenever alkyl groups are situated next to an atom having unshared electrons available for the formation of another bond.[19]

Why two opposing orders, based on the same effect, should be operative is at present not obvious. Since the data indicate that carbon–carbon hyperconjugation contributes more to the ground state of the resting molecule than carbon–hydrogen hyperconjugation, one might be justified in looking for deviations from the order required by carbon–carbon hyperconjugation in the energy and configurational requirements of the transition state.[28] Of the factors that might conceivably influence the stability of the transition state and be responsible for the inverted order of electron release by alkyl groups, the following might be of importance. Hydrogen is more electropositive than carbon on the electronegativity scale,[29] and a resonance structure that places a negative charge on the more electronegative atom (carbon) should, on this basis, be favored over other possible structures.[30a] Such an effect should be influenced by the solvent and the extent of solvation, and might be of considerable importance in reactions such as these, which have been carried out in strongly polar solvents or in the presence of acids and bases. It is perhaps significant in this connection that, whereas toluene does not exchange its hydrogens in neutral medium,[28] a slow deuterium exchange is reported to take place in alkaline solution.[31] This does not

---

(20) Hurdis and Smyth, THIS JOURNAL, **65**, 89 (1943).

(21) Bateman and Koch, *J. Chem. Soc.*, 600 (1944).

(22) In the case of the nitroalkylbenzenes there is a slight increase of the maximum at 2650 in the expected order, *p*-methyl < *p*-*i*-propyl < *p*-*t*-butylnitrobenzene, and also in the order *m*-methyl < *m*-*t*-butylnitrobenzene. Brown and Reagan, THIS JOURNAL, **69**, 1032 (1947).

(23) Conant and Kistiakowsky, *Chem. Rev.*, **20**, 181 (1937).

(24) Wheland, *J. Chem. Phys.*, **2**, 474 (1934).

(25) Lewis and Kasha, THIS JOURNAL, **66**, 2100 (1944).

(26) Rogers, *ibid.*, **69**, 457 (1947).

(27) Smyth, *ibid.*, **63**, 57 (1941).

(28) The problem of the transition states for these reactions has also been discussed by Hughes, Ingold and Taher, *J. Chem. Soc.*, 949 (1940).

(29) Pauling, "The Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, N. Y., 1940, pp. 60, 64.

(30) Remick, "Electronic Interpretations of Organic Reactions," John Wiley and Sons, New York, N. Y., 1943, p. (a) 463, (b) 462.

(31) Miklukhin and Brodskii, *Compt. Rend. Acad. Sci. U. R. S. S.*, **53**, 437 (1946). (*Chem. Abs.*, **41**, 2700 (1947.) The exchange probably takes place in the side chain rather than the nucleus, because *p*-nitrotoluene is reported to exchange much more readily than toluene.

mean that hyperconjugation implies an ionization, as has been suggested[32] and repudiated,[28] but resonance will be an important factor leading to dissociation.[33] Carbon–hydrogen hyperconjugation should also be favored by the greater polarizability of the carbon–hydrogen bond, than that of the carbon–carbon bond,[34] a factor that should be important for the transition state of reactions depending on accession of electrons to the seat of reaction (Ingold's time-variable electromeric polarizability).[30b] The above factors might contribute to the Baker–Nathan order, but unlike the bond polarizabilities and electronegativities, the bond energy is smaller for the carbon–carbon bond than for the carbon–hydrogen bond.[35] If bond energies influence the stability of structures contributing to a resonance hybrid, then carbon–carbon hyperconjugation should represent an energetically preferred state. Since bond energies, however, refer to symmetrical cleavage of the bonds, it might seem plausible that reactions involving free radicals should show an order depending on carbon–carbon hyperconjugation. Such resonance would then account for the observed degree of dissociation of *p*-alkylhexaphenylethanes into free radicals,[36] and the stability of alkyldiaryl free radicals, which according to Conant increases with increasing amount of branching of the alkyl group.[37] That this increase in stability is a result of hyperconjugation is indicated by some calculations of Wheland.[24]

Experimental

Preparation of Materials

Benzene.—Thiophene-free benzene was distilled once from sodium through a 20-inch, electrically heated column filled with glass helices. The fraction boiling at 79.8° (755.7 mm.), m. p. 5.3–5.4°, d^{25}_{25} 0.8754, $n^{25}\mathrm{D}$ 1.4972, was collected and stored over sodium in an amber bottle for use in the competitive brominations.

***t*-Butylbenzene.**—*t*-Butylbenzene was prepared as previously described.[2] Material boiling at 165–166° (755 mm.), d^{25}_{25} 0.8645, $n^{25}\mathrm{D}$ 1.4898, was used in the competition reactions.

Glacial Acetic Acid.—J. T. Baker C.P. analyzed glacial acetic acid was used without further purification.

Bromine and Iodine.—C.P. products were used without further purification.

Bromobenzene and Bromo-*t*-butylbenzene.—Individual brominations of benzene and *t*-butylbenzene were conducted under conditions duplicating those used in the competition reactions. In the bromination of benzene no evidence of the formation of dibromobenzene was obtained. The product boiled at 155° (755 mm.), $n^{25}\mathrm{D}$ 1.5557. The pure bromo-*t*-butylbenzene obtained upon bromination of *t*-butylbenzene had the following physical constants: b. p. 226° (752.5 mm.), d^{25}_{25} 1.2493, $n^{25}\mathrm{D}$ 1.5309. These materials were prepared for use in analyzing the mixtures obtained from the competitive brominations.

Competitive Brominations

The competitive brominations of benzene and *t*-butylbenzene were conducted as described in Part I. Bromination of a homogeneous mixture of 0.5 mole of each hydrocarbon dissolved in 500 cc. of 92% aqueous acetic acid with 0.5 mole of bromine dissolved in 50 cc. of 92% aqueous acetic acid was carried out for twenty-four hours at 25 ±0.5° and for eight hours at 45 ±0.5° using one-half mole per cent. of iodine as a catalyst. The results of the individual runs are recorded in Table II.

TABLE II

Run	Moles bromobenzene formed	Moles bromo-*t*-butylbenzene formed	k_1/k_2
1 at 25°	0.0021	0.1919	114.9
2 at 25°	.0020	.1886	118.1
3 at 25°	.0020	.1832	113.9
			Av. 115.6
4 at 45°	.0034	.1927	71.4
5 at 45°	.0035	.1977	71.6
			Av. 71.5

Analysis of the reaction mixtures by the procedure employed in Part I was supplemented by an analytical determination of bromine. This seemed particularly desirable because the amount of bromobenzene in the *t*-butylbenzene fraction was very small, and refractive indices could not be used for its detection. The products of the reaction were separated into a bromobenzene–*t*-butylbenzene mixture and a *t*-butylbenzene–bromo-*t*-butylbenzene mixture by fractional distillation. Determination of the density of each fraction supplied directly the weight per cent. of brominated hydrocarbon in each, by comparison with weight per cent.–density curves derived from artificial mixtures of the desired components. Data from which the weight per cent.–density curve of bromo-benzene-*t*-butylbenzene mixtures was plotted are recorded in Table III.

TABLE III

DENSITIES OF BROMOBENZENE–*t*-BUTYLBENZENE MIXTURES

Weight per cent. bromobenzene	d^{25}_{25}
0	0.8645
2.75	.8747
3.61	.8781
4.41	.8812
4.95	.8834

The density–weight per cent. relationship of *t*-butylbenzene–bromo-*t*-butylbenzene mixtures is linear (per cent. bromo-*t*-butylbenzene $= 180.2D - 125.12$) in the range 98–100% bromo-*t*-butylbenzene, the range required for analysis of the high boiling fraction obtained from the competition reactions.

The bromine content of each fraction was determined by subjecting weighed samples to Wurtz type reactions and titrating the bromide ion formed by the Volhard method.[38] The latter determinations checked the density determinations of brominated hydrocarbons within 0.2%.

In a control run containing 0.33 g. (0.0021 mole) of bromobenzene 0.32 g. (0.0020 mole, 97%) was recovered. The agreement was considered satisfactory, and no corrections were applied to the final figures.

In a representative run a mixture of 39.06 g. (0.5 mole) of benzene, 67.11 g. (0.5 mole) of *t*-butylbenzene, 500 cc. of 92% aqueous acetic acid and 0.625 g. of iodine was

---

[32] Robinson, *Chem. & Ind.*, **55**, 962 (1936).

[33] The solvent composition also has an appreciable effect on the spacing of the different rate constants in the first order solvolysis of the *p*-alkylbenzhydryl chlorides; see Table I, line 5.

[34] Smyth, "Dielectric Constant and Molecular Structure," The Chemical Catalog Company, Reinhold Publ. Corp., New York, N. Y., 1931, p. 152; see also Remick, ref. 30, p. 79.

[35] Pauling, ref. 29, p. 53.

[36] As long as the similar effect of groups in the *meta* position remains unexplained the data on the degree of dissociation have to be treated with reserve. See also Wheland, ref. 16, p. 194.

[37] Conant, *J. Chem. Phys.*, **1**, 427 (1933).

[38] For similar determinations see Rauscher, *Ind. Eng. Chem., Anal. Ed.*, **9**, 296 (1937), and the references given there.

placed in a 1-liter, 3-necked, round-bottomed flask equipped with a reflux condenser, dropping funnel, and electrically driven glass stirrer and brought to constant temperature in a thermostat maintained at 25 ± 0.5°. One-half mole of bromine dissolved in 50 cc. of aqueous acetic acid was added to the solution through the dropping funnel, with constant stirring, over a period of one hour. Stirring at constant temperature was continued for twenty-three hours after completion of the addition of bromine. The reaction mixture was then poured into cold water and stirred with bisulfite to remove the unreacted bromine. The diluted mixture was divided into two portions. Each portion was extracted with two 200-cc. portions of ether. The ethereal extract was washed with aqueous sodium carbonate until all evolution of carbon dioxide had ceased. The alkaline washings were combined and extracted with 100 cc. of ether. The combined ethereal extracts were dried over anhydrous sodium carbonate for distillation. The ether and unreacted benzene were removed and discarded. Separation of the residue was effected by means of a twenty-inch electrically heated column filled with glass helices. The first fraction, containing bromobenzene and *t*-butylbenzene, distilled at 150–170°, d^{25}_{25} 0.8678, amount 37.4 g. The column was allowed to drain and was replaced by a small distillation outfit through which the entire residue, consisting of *t*-butylbenzene and bromo-*t*-butylbenzene, was distilled. This second fraction contained 41.2 g. of material, d^{25}_{25} 1.2453.

The density of the first fraction corresponds to 0.88% bromobenzene (0.0021 mole). The density of the second fraction corresponds to 99.28% bromo-*t*-butylbenzene (0.1919 mole).

A 4.3390 g. (5 cc.) sample of fraction I was dissolved in 40 cc. of ether and allowed to stand in contact with 1 g. of sodium wire overnight at room temperature. The sodium which had not reacted in twelve hours was destroyed with ethanol. The sodium bromide formed was extracted with water. The aqueous solution was diluted to 50 cc., of which 10-cc. portions were treated with 5 cc. of 0.1 *N* silver nitrate solution. The excess silver nitrate was titrated with 8.65 cc. of 0.0522 *N* potassium thiocyanate. This value corresponds to 0.0021 mole of bromobenzene in fraction I.

A 1.2453 g. (1-cc.) sample of fraction II was dissolved in 40 cc. of benzene and refluxed with 2 g. of sodium, cut into small pieces, for five hours. The aqueous extract of the sodium bromide formed was diluted to 100 cc.; 10-cc. portions were treated with 10 cc. of 0.1 *N* silver nitrate. The excess silver nitrate was titrated with 8.05 cc. of 0.0522 *N* potassium thiocyanate. The titration value corresponds to 0.1918 mole of bromo-*t*-butylbenzene in fraction II.

Applying the equation of Ingold, *et al.*,[5,39] $k_x/k_y = (\log x/x_0)/(\log y/y_0)$, where x and y represent the final concentrations of *t*-butylbenzene and benzene and x_0 and y_0 the initial concentrations, the ratio of velocities is 114.9/1.

Acknowledgment.—We gratefully acknowledge the assistance afforded by a grant from the Penrose Fund of the American Philosophical Society.

Summary

1. *t*-Butylbenzene is brominated about 115 times faster than benzene at 25°. This is explained by hyperconjugation involving carbon–carbon bonds.

2. It is pointed out that the so-called inductive effect of alkyl groups may be explained by hyperconjugation, and it is suggested that this may explain the entire effect. The factors that influence the operation of the effect are discussed.

---

[39] Ingold and Smith, *J. Chem. Soc.*, 905 (1938).

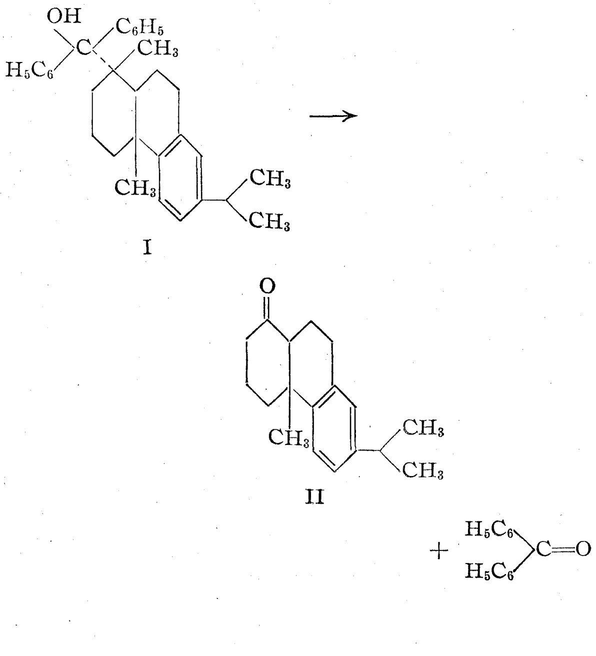
BRYN MAWR, PA. RECEIVED AUGUST 8, 1947

[CONTRIBUTION FROM RIDBO LABORATORIES, INC.]

Studies on Resin Acids.[1] II. The Oxidation of Diphenyl-*t*-dehydroabietinol. A Postulated Mechanism

BY HAROLD H. ZEISS

The oxidation of tertiary alcohols is not a reaction generally employed in the laboratory principally because of product complexity and low yields. In the course of our study of the resin acids the previously reported tertiary resin alcohol, diphenyl-*t*-dehydroabietinol (I),[1] has been subjected to chromic acid oxidation in glacial acetic acid from which the cyclic ketone, 1-keto-12-methyl-7-isopropyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (II), is obtained in yields as high as 67%, together with benzophenone. It is to be noted that this oxidation differs from the Barbier–Wieland type of oxidative degradation in that there cannot be a preceding dehydration of the carbinol to an olefin, since no hydrogen atoms are attached to the carbon atoms at which oxidation occurs.



Fifteen years ago Vocke[2] submitted the diphenyl carbinol of tetrahydroabietic acid to the

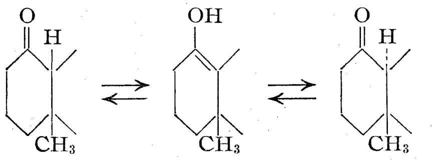
---

[1] Paper I, THIS JOURNAL, **69**, 302 (1947).

[2] Vocke, *Ann.*, **497**, 247 (1932).

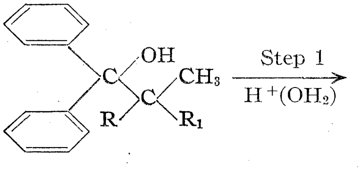
action of chromic acid at room temperature and with warming from which only benzophenone and benzoic acid were reported in the reaction mixture in addition to a considerable amount of unoxidized carbinol. At 50° diphenyl-*t*-dehydroabietinol is also largely unchanged by chromic acid and at 90° is oxidized to acidic material at the expense of the ketone (II). The optimum temperature for this oxidation has been found to be 80°, at which temperature the maximum yield of (II) is obtained with no unreacted carbinol (I) present and a minimum amount of acidic products, probably arising from ring cleavage.

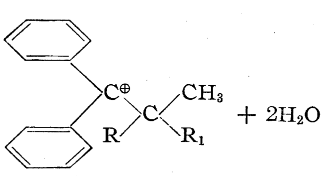
The cyclic ketone (II) is isolated, presumably, as a stereoisomeric mixture resulting from keto–enol tautomeric equilibrium. The ease of this tautomerism is adequately supported by Hückel,[3] who reported the facile conversion of *cis*-α-decalone to *trans*-α-decalone by simple distillation at atmospheric pressure. After purification through the sodium bisulfite addition product and through the use of Girard reagent T, the ketone (II) was obtained analytically pure as a pale yellow, viscous liquid from which the crystalline 2,4-dinitrophenylhydrazone derivative has been prepared. The sodium bisulfite addition product, combustion analyses and molecular refraction data leave little doubt that the structure of the cyclic ketone is as represented by (II). The identity of the benzophenone was established by mixed melting point determination and the 2,4-dinitrophenylhydrazone derivative.



As a gross approximation this reaction may be described as a dealcoholation (loss of methyl alcohol) followed by cleavage of the resulting double bond to form (II) and benzophenone. This of course is a highly oversimplified explanation but one which stipulates that any reasonable mechanism must account for the loss of the elements of methyl alcohol. One such mechanism is postulated solely as the basis of a working hypothesis.

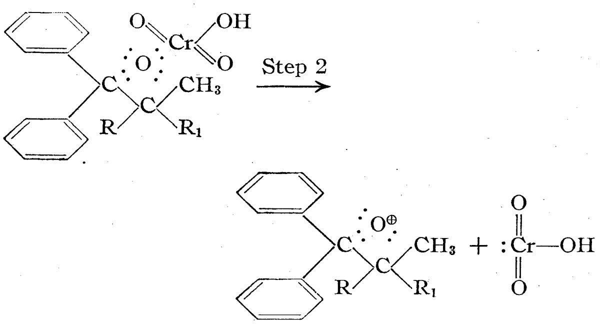
The first step is a proton transfer reaction to form a tertiary carbonium ion stabilized by resonance contributions from two phenyl groups (Step 1).



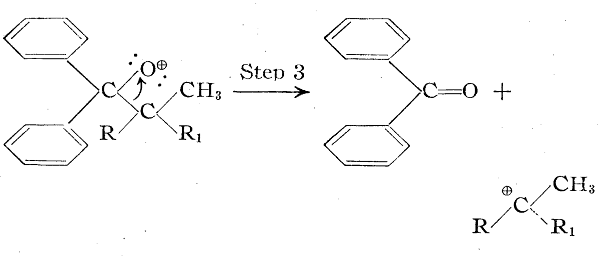


R = —CH$_2$
R$_1$ = —CH

The resultant center of low electron density is susceptible to nucleophilic attack by chromate ion to form a chromium complex which may then dissociate into two fragments (Step 2), the chromium atom now having a full share in the electron pair and the tertiary carbon fragment possessing a positively charged oxygen atom. The other alternative is a Wagner–Meerwein rearrangement leaving the electron deficient center on the carbon atom bearing the R and R$_1$ substituents. This latter possibility is unlikely to predominate because of the higher energy of the resulting carbonium ion.



In order to relieve the situation in which the oxygen atom is bearing a positive charge, the electron pair of the carbon–carbon bond must migrate (Step 3) since the phenyl-carbon bonds are unavailable.

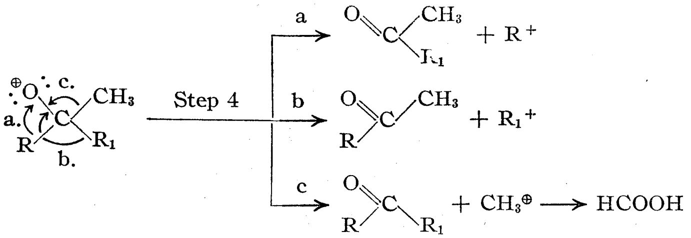


This shift releases the diphenylmethyl structure as benzophenone and leaves the positive charge on the carbon atom carrying the methyl group.

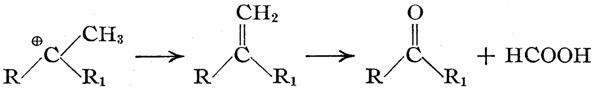
Repetition of chromate ion attack on the new carbonium ion and subsequent formation of positive oxygen leaves three possibilities open for electron shift. By Steps 4a or 4b the acidic byproducts are explained. Step 4c accounts for the formation of (II) but invites high speculation as to the formation of the very high energy methyl carbonium ion. Another explanation is one in which the carbonium ion rearranges to form the exocyclic double bond which immediately is

---

(3) Hückel, *Ann.*, **441**, 1 (1925).



cleaved by chromate ion to (II) and formaldehyde or formic acid. In this connection it is



interesting to note that Phillipov,[4] on oxidation of 1-methylcyclohexanol-1 with permanganate in aqueous solution, obtained cyclohexanone and formic acid on the one hand and acetic acid and glutaric acid on the other. The latter reaction was preponderant, however, under these conditions.

This oxidation is being further investigated as to the mechanism involved and its general application to tertiary alcohols as a class.

Experimental

1-Keto-12-methyl-7-isopropyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (II): (a) **Oxidation at 90°.**—A solution of 42 g. of chromic trioxide in 30 ml. of water and 280 ml. of glacial acetic acid was added dropwise to a stirred solution of 33 g. of diphenyl-*t*-dehydroabietinol[5] in 300 ml. of glacial acetic acid at 90°. The addition extended over a period of one and one-half hours after which time heating and stirring were continued for three hours. The acetic acid was removed by distillation at the water pump and the remaining residue treated with sulfurous acid and dilute sulfuric acid on the steam-bath. The oily layer appearing on the surface of the cooled green solution was then extracted with ether. After washing the ethereal layer with water, the acidic material[6] was extracted with 1% sodium hydroxide. The ether layer was then washed free of alkali, dried over magnesium sulfate and the ether evaporated. The orange-red oil thus obtained gave two main fractions on fractional distillation: fraction 1, distilling at 140–150° (3 mm.) as a yellow fluid, and fraction 2, distilling at 220–230° (7 mm.) as an orange-red, viscous oil. Crystallization from methanol of fraction 1 gave large, transparent rods of benzophenone melting at 46.5–47.5°. Its 2,4-dinitrophenylhydrazone was prepared which gave a m. p. at 238–239°. A mixed m. p. of the crystals from fraction 1 with authentic benzophenone showed no depression. The yield of fraction 2, compound (II), was 9 g. (46%) and was identified as described under (b).

(b) **Oxidation at 80°.**—85 g. of diphenyl-*t*-dehydroabietinol was oxidized in exactly the same manner as in (a) with 103 g. of chromic trioxide with the one exception that the solution was maintained at 80 ± 0.5° during the oxidation. Fractional distillation of the neutral portion of the oxidation mixture gave 31.5 g. (63.5%) of crude ketone (II), boiling at 165–215° (1 mm.), and 16.2 g. (46%) of benzophenone.

The ketone was purified for analysis by the following methods: redistillation of the crude ketone, precipitation of the sodium bisulfite addition product in the cold (too unstable for characterization), regeneration and redistillation of (II), treatment with Girard reagent T, regeneration and final distillation of (II) as a pale yellow, viscous liquid at 208–212° (3 mm.[7]); $[\alpha]^{23}\text{D}$ 46° (4% in abs. alcohol); $[\eta]^{22}\text{D}$ 1.5572; d^{22} 1.0582.

Anal.[8] Calcd. for $C_{18}H_{24}O$: C, 84.38; H, 9.36. Found: C, 84.42, 84.54; H, 9.60, 9.41; M_R calcd., 77.65; found, 78.01.

The 2,4-dinitrophenylhydrazone of (II) was prepared in the usual manner which, after three recrystallizations from ethyl acetate, gave a sharp m. p. of 176.5–177°. A mixed m.p. with 2,4-dinitrophenylhydrazine showed a 12° depression.

Anal.[8] Calcd. for $C_{24}H_{28}N_4O_4$: N, 12.84. Found: N, 12.43, 12.32.

Acknowledgment.—The author is grateful to Dr. M. Frisch for experimental assistance in this work.

Summary

The oxidation of the tertiary alcohol, diphenyl-*t*-dehydroabietinol, to the cyclic ketone, 1-keto-12-methyl-7-isopropyl-1,2,3,4,9,10,11,12-octahydrophenanthrene, is described in which dehydration preliminary to oxidation cannot occur. A mechanism for the oxidation of this diphenyl carbinol has been postulated.

PATERSON, NEW JERSEY RECEIVED SEPTEMBER 3, 1947

---

[4] Phillipov, *J. prakt. Chem.*, [2] **93**, 162 (1916).

[5] $[\alpha]^{23}\text{D}$ 91° (4% in absolute alcohol).

[6] These by-products were not investigated.

[7] All distillations for the purification of (II) were carried out in a short path still with a central take-off; see footnote (51), Woodward and Doering, THIS JOURNAL, **67**, 860 (1945).

[8] Combustion analysis by Dr. Carl Tiedcke Microlaboratories, New York.

NOTES

Condensation Products from Acetaldehyde

By A. H. Andersen, R. M. Kitchen and C. H. Neufeld

Nord, *et al.*,[1] condensed acetaldehyde with magnesium aluminum alkoxide catalysts and isolated from the reaction product the monoacetate of 1,3-butanediol. No mention is made in their papers of the ethyl ester of β-hydroxybutyric acid which we have found to be present in the reaction mixture in approximately equimolecular proportion to the monoacetate of 1,3-butanediol. Similar proportions of the diol and the hydroxy acid have also been found in an oily by-product obtained in the commercial preparation of ethyl acetate from acetaldehyde.[2]

Experimental.—The procedure adopted for separating the constituents of the high-boiling oils was as follows:

(1) Acid hydrolysis with excess water and butanol: the mixture was heated in a flask provided with a packed distillation column. The overhead temperature was kept at the boiling point of the butyl acetate–butanol–water ternary azeotrope by adjusting the reflux ratio. The ester-containing top layer of the distillate was drawn off while the water layer was decanted back to the flask. This was continued until the temperature could no longer be kept below 90° by refluxing. The excess butanol was then removed in the same manner at a temperature of 92°.

(2) Neutralization and saponification: the saponification equivalent of the aqueous residue was determined, and just sufficient sodium hydroxide was added in 10% solution to neutralize the free acid and saponify the remaining esters. The mixture was boiled for an hour and cooled.

(3) Filtration to remove any resinous by-products.

(4) Vacuum distillation of filtrate: the excess water and the butanediol are removed leaving a fused residue of crude sodium β-hydroxybutyrate.

The glycol was purified by fractionation, b. p. 207°, $n^{20}\text{D}$ 1.441.

The sodium β-hydroxybutyrate was purified by recrystallization from butanol, m. p. 157–158°. It was identified by comparison with an authentic sample prepared through crotonic acid,[3] m. p. 157–158°; mixed m. p. 157–158°.

The butyl ester of β-hydroxybutyric acid was prepared from the sodium salt, hydrochloric acid and butanol, b. p. 103–104° (14 mm.).

The separation has also been carried out using potassium hydroxide. The potassium β-hydroxybutyrate melts at 148–149°. Care must be exercised since all the derivatives of β-hydroxybutyric acid so far examined by us are heat labile, dehydrating rather readily to the crotonates.

From our observations we conclude that termolecular condensation of acetaldehyde occurs under the influence of the coördination catalyst of Nord[1] and also to a much smaller extent under the influence of aluminum alkoxides. We believe that this reaction results from an initial aldolization followed by a condensation between the aldol and aldehyde molecules. This condensation can occur in either of two ways

$$CH_3CHO + CH_3CHOHCH_2CHO \longrightarrow CH_3CHOHCH_2CH_2OCOCH_3$$

Monoacetate of 1,3-butanediol (1)

$$CH_3CHO + CH_3CHOHCH_2CHO \longrightarrow CH_3CH_2OCOCH_2CHOHCH_3$$

Ethyl ester of β-hydroxybutyric acid (2)

Tischtschenko[4] mentions the formation of the ethyl ester of β-hydroxybutyric acid from acetaldehyde, and our observations confirm this and indicate that the ethyl ester is formed in similar quantities to the glycol ester.

---

[1] (a) Kulpinski and Nord, *J. Org. Chem.*, **8**, 256–270 (1943); (b) Villani and Nord, This Journal, **68**, 1674 (1946); (c) F. F. Nord, U. S. Patent 2,403,876.

[2] Benson and Cadenhead, *J. Soc. Chem. Ind.*, **53**, 40–3T (1934).

[3] Biilman, *Ber.*, **43**, 579 (1910).

[4] Tischtschenko, *Chem. Centr.*, **77**, II, 1309 (1906).

Shawinigan Chemicals Limited
Shawinigan Falls
Quebec, Canada

Received September 15, 1947

The Addition of Dimethylamine to Benzoquinone

By Richard Baltzly and Emil Lorz

In the usual procedure for the preparation of *bis*-(dialkylamino)-quinones from benzoquinone two-thirds of the quinone is employed as an oxidizing agent so that, at best, only around 30% of the starting quinone can be isolated as the product.[1]

It has been found that re-oxidation of the intermediates can be accomplished by a stoichiometric amount of cupric salt or by a smaller quantity when the reaction mixture is stirred with oxygen. The latter procedure is preferable since the product crystallizes in virtually pure form from solution, uncontaminated by cuprous salts. The method was unsuccessful with methylamine, aniline and ammonia.

Procedure

A one-liter three-necked flask equipped with mercury-seal and stirrer was connected to a two-liter graduated cylinder having a levelling bulb and a stopcock for admission of oxygen. The system was flushed out with oxygen and a solution containing 20 g. (0.1 mole) of cupric acetate monohydrate and 27 g. (0.6 mole) of dimethylamine in 300 cc. of methanol was introduced. One-tenth mole (10.8 g.) of benzoquinone in 200 cc. of methanol was then added and the system was closed. The stirrer was started and the reaction was followed by the oxygen absorption which was initially about 120 cc. per minute. Considerable heat was evolved at the start of the reaction and the temperature was held near 25° by ice-water cooling. About five minutes after the beginning of the reaction, crimson platelets of *bis*-(dimethylamino)-benzoquinone became visible on the sides of the flask. After oxygen-absorption had ceased the flask was refrigerated overnight and the product was collected. This material melted at 171° (lit., 173°). A further crop of 2.5 g. was obtained by concentration of the filtrate (total yield, 93%).

bis-(Dimethylaminobenzoquinone is not itself oxidized

---

[1] (a) Mylius, *Ber.*, **18**, 463 (1885); (b) Kehrmann, *Ber.*, **23**, 897 (1890); (c) Anslow and Raistrick, *J. Chem. Soc.*, 1449 (1939).

under the above conditions but benzoquinone (and perhaps the intermediate quinones) can be. If the concentration of cupric ion is significantly diminished such oxidations take place and the yield is less. In the presence of 0.01 mole of cupric acetate the oxygen-absorption was about the same but the bisaminoquinone was then obtained in 72–76% yield.

THE WELLCOME RESEARCH LABORATORIES
TUCKAHOE 7, NEW YORK RECEIVED OCTOBER 14, 1947

Isolation of a Saponin from the Leaves of *Solidago canadensis* L.

BY R. C. BURRELL AND FORREST G. HOUSTON

In the course of the investigation of the chemical composition of several common weeds, leaves of *Solidago canadensis* L. were examined for the possible presence of a saponin. There are several reports of the recognition of both acid and neutral saponins in various other species of goldenrod,[1,2,3] but none of actual isolation.

Experimental

Method of Isolation.—Leaves of *Solidago canadensis* L. were gathered in late July, 1946, dried at room temperature, and ground to a fine powder. A 230-g. sample of this powder in a small cloth bag was exhaustively extracted, first with acetone, then with ether and finally twice with 95% ethyl alcohol. The combined alcoholic extracts were concentrated to a small volume (about 100 cc.) and 5 volumes of ether added with shaking. This produced a gummy, white precipitate. After decanting the ether, this precipitate was dissolved in the least possible amount of hot methanol. This solution, which had a light yellow color, was treated with acetone added from a large pipet while shaking the mixture vigorously. A flocculent white precipitate formed from which the liquid was decanted. The precipitate was once more dissolved in hot methanol and the acetone precipitation repeated. The final white flocculent precipitate was amorphous and very hygroscopic. It produced a stable creamy foam with water and stabilized an emulsion of kerosene in water. Fehling solution showed no reduction.

Preparation of the Sapogenin.—The moist saponin preparation was brought into solution in 50 cc. of 10% hydrochloric acid, 25 cc. of 95% ethyl alcohol added to reduce foaming and this solution refluxed for three hours. A grainy precipitate formed which consisted of microscopic, colorless needles. The supernatant liquid gave a positive Fehling reaction. The crystals were filtered off and brought into solution by refluxing with methanol. This solution was concentrated to about 50 cc. and on cooling some 500 mg. of colorless needles were isolated, representing a yield of 0.22% of the dried leaves.

Properties of the Sapogenin.—The crystals, which melted at 310–315° with decomposition, were slightly soluble in ethanol methanol, acetone, ether and ethyl acetate, insoluble in water, but dissolved easily in cold concentrated sulfuric acid, giving a faintly yellow colored solution which became deep red on warming or on the addition of a few drops of acetic anhydride, suggesting the behavior of a triterpene. The Rast method indicated a molecular weight of approximately 500.

Anal. Calcd. for $C_{30}H_{50}O_5$ (490.4): C, 73.41; H, 10.28. Found: C, 72.97; H, 10.02.

Insolubility in hot alkali and a neutral reaction in alcoholic solution indicates the absence of a carboxyl group. The acetate was prepared as flat rectangular crystals which melt at 182–183°. A search of the literature failed to reveal a compound approximating $C_{30}H_{50}O_5$ which possesses the above properties.

CONTRIBUTION FROM THE
DEPARTMENT OF AGRICULTURAL CHEMISTRY
THE OHIO STATE UNIVERSITY
COLUMBUS, OHIO RECEIVED SEPTEMBER 27, 1947

---

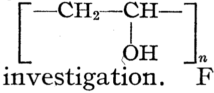
[1] L. Krober, *Heil-gewurz Pflanzen*, **12**, 131 (1930).

[2] F. P. Rey, *Rev. farm.* (*Buenos Aires*), **74**, 93 and 131 (1932).

[3] E. Wagner, *Seifensieder-Ztg.*, **68**, 35 (1941).

The Infrared Spectrum of Polyvinyl Alcohol

BY ELKAN R. BLOUT AND ROBERT KARPLUS

Despite two previously reported measurements on the infrared spectrum of polyvinyl alcohol[1,2] we should like to record some of our data, using carefully purified samples, because of their possible bearing on the details of the molecular structure of this material. The presence of chemical groups and arrangements other than those of the poly-1,3-glycol  $\left[\begin{array}{c}\text{—CH}_2\text{—CH—} \\ \quad\;\;| \\ \quad\;\;\text{OH}\end{array}\right]_n$ has been shown by chemical investigation. For example, terminal acetal,[3] keto or ketal[4] and 1,2-glycol groups[5] have been shown to be present in low percentage in the material known as polyvinyl alcohol.

The infrared spectra for the region 700–4000 cm.$^{-1}$ of carefully purified and dried films of polyvinyl alcohols of various degrees of polymerization are shown in Fig. 1. These spectra correspond in most salient features to those reported by Thompson and Torkington[2] except that there is no evidence of a band at 1650 cm.$^{-1}$. Other samples prepared so that water was not rigidly excluded at the time of measurement show a characteristic absorption band in this region. Another band typical of incompletely hydrolyzed polyvinyl alcohol is seen at 1710 cm.$^{-1}$ in Fig. 2, curve A. This figure also shows the effect of careful acid hydrolysis (removal of residual acetate groups) and drying on the spectrum in the region 1400–1800 cm.$^{-1}$.

It is difficult to correlate absorption bands definitely with molecular structure except through mathematical analysis. In the spectra shown in Fig. 1 the assignments of the bands above 1400 cm.$^{-1}$, *viz.*, 3350 cm.$^{-1}$ (O—H stretching), 2940 cm.$^{-1}$ (C—H stretching) and 1435 cm.$^{-1}$ (C—H bending) seem reasonable, based on analogy with the spectra of simple molecules and on the calculated characteristic frequency of various molecular groups.[6] In the region 1000 cm.$^{-1}$ to 1400 cm.$^{-1}$ five bands are observed at 1380, 1330, 1240 1135 and 1085 cm.$^{-1}$ which are probably associ-

---

[1] Barnes, Liddel and Williams, *Ind. Eng. Chem., Anal. Ed.*, **15**, 659 (1943).

[2] Thompson and Torkington, *Trans. Far. Soc.*, **41**, 246 (1945).

[3] Marvel and Inskeep, THIS JOURNAL, **65**, 1710 (1943).

[4] Clarke and Blout, *J. Pol. Sci.*, **1**, 419 (1946).

[5] Flory and Leutner, "The Occurrence of Head-to-Head Arrangements of the Structural Units in Polyvinyl Alcohol and Acetate," paper presented at the New York meeting of the American Chemical Society, September 15, 1947.

[6] Herzberg, "Infrared and Raman Spectra," D. Van Nostrand Co., New York, N. Y., 1945.

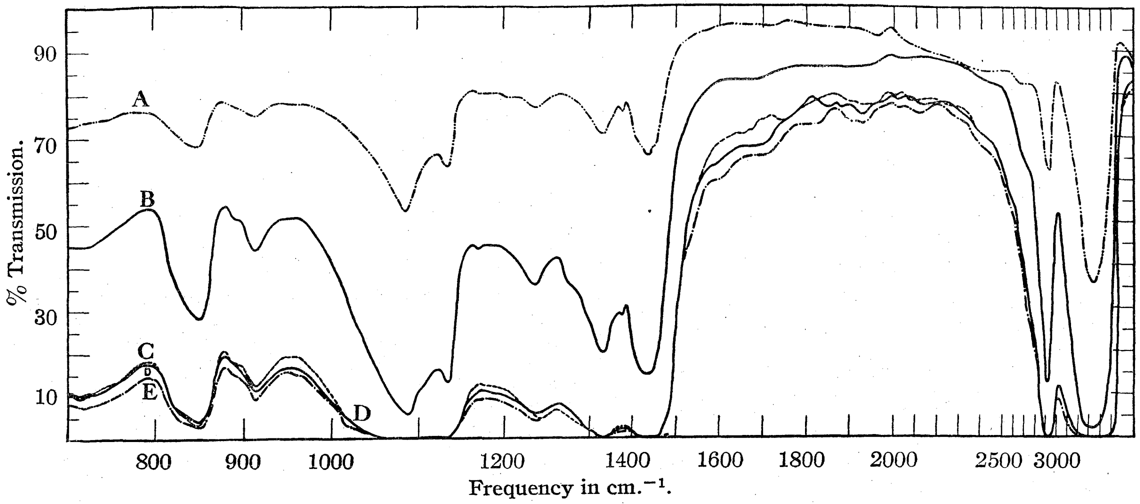


Fig. 1.—Polyvinyl alcohols after acid hydrolysis and drying: curve A, ··—··—··—, JRG-8200 (0.0002″ film); curve B, ————————, RH-391 (0.0003″ film); curve C, — — — — — — —, RH-393 (0.001″ film); curve D, ————————, RH-391 (0.001″ film); curve E, ·—·—·—·, RH-349 (0.001″ film).

ated with the motions of the substituent groups in the material, the last band arising from stretching of the C—O bond.[7] The absorption bands below 1000 cm.$^{-1}$ cannot be identified except as due to motions of the carbon skeleton. We find that the band at 1240 cm.$^{-1}$ is not removed by acid hydrolysis although a band at 1265 cm.$^{-1}$ in unpurified samples is removed simultaneously with the 1710 cm.$^{-1}$ band. This fact suggests that the 1240 cm.$^{-1}$ band is not associated with the acetate groups of polyvinyl alcohol, as has been previously pointed out.[2]

It is interesting to note that the band at 1380 cm.$^{-1}$, which is present even after repeated acid hydrolysis, is located in the region characteristic of the symmetrical deformation frequency of the C—CH_3 group.[6,8,9] This suggests the possibility that either the polymer contains methyl groups branching off the chain, or the chain ends are methyl groups or perhaps both.

Experimental

Materials.—The various polyvinyl alcohols were obtained as white powders.[7,10] Since they are prepared by the hydrolysis of polyvinyl acetate, further purification was undertaken to assure complete absence of residual acetate groups. This was accomplished by hydrolyzing 5% aqueous solutions with 0.02 *N* hydrochloric acid for twenty-four hours at 90° followed by precipitation and thorough washing with ethanol. The material so obtained was air-dried, then dissolved in water (approximately 15% solution) and cast into thin films (0.0002″–0.001″ thick) on glass plates at room temperature. To remove the

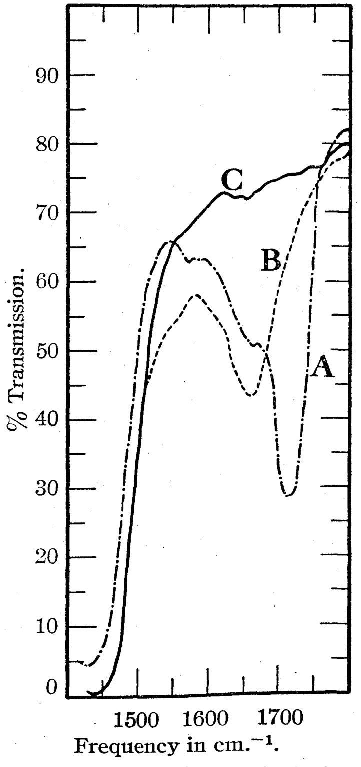


Fig. 2.—Polyvinyl alcohol (JRG-8200): curve A, ·—·—·—·, cast as received (0.0006″ film); curve B, — — — — — —, cast after acid hydrolysis (0.001″ film); curve C, ————————, dried film cast after acid hydrolysis (0.001″ film).

---

(7) *Cf.* analogous compounds in refs. 1 and 6.

(8) Thompson and Torkington, *Proc. Roy. Soc.* (*London*), **184,** 3 (1945).

(9) Fox and Martin, *ibid.*, **175,** 208 (1940).

(10) All polyvinyl alcohols referred to in this paper were obtained from E. I. du Pont de Nemours and Co. The designations used are those of the du Pont Co.

Grade	Viscosity	Approximate viscosity centipoises of 4% in aqueous solutions at 20°C.	%Residual[a] acetate
RH-393	Low	5	1
RH-349	Medium	24	1
RH-391	High	55	1
JRG-8200[b]	High	115	4

[a] After acid hydrolysis as described below there were no acetate groups detectable by saponification. [b] Experimental sample obtained through the courtesy of Dr. R. E. Burk, E. I. du Pont de Nemours & Co., Wilmington, Delaware.

5–10% of retained water the films were heated at 160° for one hour immediately before spectral analysis. Determinations showed that during the time it took to measure the spectra no appreciable absorption of moisture occurred.

Instrument.—The spectral measurements[11] were made on a Perkin–Elmer infrared spectrometer Model 12-A using a 40-cycle chopper, a Strong nickel-strip bolometer, an a. c. amplifier and a Brown Instrument Company potentiometer. The data were obtained on a point-to-point basis, the points being taken from 5 to 10 cm.$^{-1}$ apart at frequencies up to 1900 cm.$^{-1}$ and at larger intervals at higher frequencies.

---

[11] We are indebted to Mr. Dwight Merrill for some of the spectral measurements.

CHEMICAL RESEARCH LABORATORY
POLAROID CORPORATION
CAMBRIDGE 39, MASSACHUSETTS
RECEIVED JULY 18, 1947

A Convenient Synthesis of Octahydropyrrocoline and 2-(γ-Hydroxypropyl)-piperidine

BY V. BOEKELHEIDE AND S. ROTHCHILD[1]

It has been found that octahydropyrrocoline, which has previously been prepared in poor yield by procedures involving three or more steps,[2] can be obtained readily in excellent yield by the direct hydrogenation of 2-(γ-hydroxypropyl)-pyridine[3] at 200° and 2500 lb. pressure with Raney nickel catalyst.

When the reduction was carried out at 125° instead of 200°, the product was not octahydropyrrocoline but rather 2-(γ-hydroxypropyl)-piperidine. The yield of 2-(γ-hydroxypropyl)-piperidine is practically quantitative and this is undoubtedly the best method for its preparation.[4] At temperatures intermediate between 125 and 200° the reduction gave mixtures of octahydropyrrocoline and 2-(γ-hydroxypropyl)-piperidine. Although it is probable that 2-(γ-hydroxypropyl)-piperidine is an intermediate in the formation of octahydropyrrocoline, 2-(γ-hydroxypropyl)-piperidine is not readily affected by heat and can be distilled repeatedly without change.

Experimental[5]

Octahydropyrrocoline.—A mixture of freshly distilled 2-(γ-hydroxypropyl)-pyridine (9.0 g., 0.066 mole), Raney nickel (2 g.), and absolute alcohol (10 cc.) was heated at 200° with shaking under an initial pressure of 2540 p. s. i. of hydrogen. At the end of one hour the drop in hydrogen pressure corresponded to that calculated. After removal of the catalyst by filtration, the oily product was distilled yielding 6.4 g. (78%) of a colorless oil; b. p. 71–72° at 32 mm.; $n^{21.2}$D 1.4702.

For purposes of identification, there were prepared the following derivatives: picrate, m. p. 228–9° (lit.,[2] m. p. 226°, 231–232°); gold chloride double salt, m. p. 188–192° (lit.,[2] m. p. 191–193°).

The methiodide of octahydropyrrocoline was formed in benzene and proved to be unstable in the presence of air. The amorphous solid, obtained from benzene, decomposed at 280–283° and was analyzed directly without further purification.

Anal. Calcd. for $C_9H_{18}NI$: C, 40.46; H, 6.79. Found: C, 40.00; H, 7.10.

2-(γ-Hydroxypropyl)-piperidine.—A mixture of freshly distilled 2-(γ-hydroxypropyl)-pyridine (14.0 g., 0.102 mole), Raney nickel (2 g.), and absolute alcohol (4 cc.) was heated at 125° with shaking under an initial pressure of 2500 p. s. i. of hydrogen. At the end of four hours the pressure drop corresponded to that calculated. After removal of the catalyst and solvent, the product was distilled yielding 12.5 g. (85%) of a colorless oil; b. p. 101–102° at 3 mm.; $n^{21.5}$D 1.4882.

For identification there was prepared the hydrochloride, m.p. 128–129° (lit.,[2b] m. p. 127–128°), and the mercuric chloride complex, m. p. 180–182° (lit.,[2a] m. p. 182–183°).

---

[1] Aided by a Grant from the National Foundation for Infantile Paralysis.

[2] (a) Loeffler and Kaim, *Ber.*, **42**, 94 (1909); Loeffler and Flugel *ibid.*, **42**, 3423 (1909), and Tullock and McElvain, THIS JOURNAL, **61**, 961 (1939); (b) Clemo and Ramage, *J. Chem. Soc.*, 2969 (1932); (c) Wibaut and Beets, *Rec. trav. chim.*, **60**, 905 (1940); (d) Diels and Alder, *Ann.*, **498**, 16 (1932).

[3] 2-(γ-Hydroxypropyl)-pyridine is available from Reilly Tar and Chemical Co., Indianapolis, Indiana.

[4] Previous methods for preparing 2-(γ-hydroxypropyl)-piperidine are given in ref. (2a).

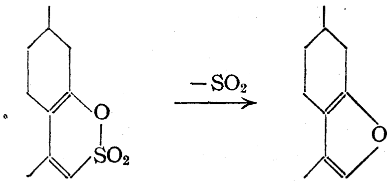
[5] Analysis by Mrs. G. L. Sauvage. All melting points are corrected.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, NEW YORK
RECEIVED NOVEMBER 14, 1947

The Sulfonation of Mesityl Oxide

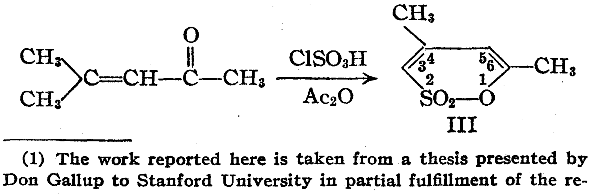
BY RICHARD H. EASTMAN AND DON GALLUP[1]

In seeking a convenient method for the synthesis of alkylated furans we have sought to extend to simple α,β-unsaturated ketones and aldehydes the observation of Treibs[2] that pulegone on treatment in acetic anhydride at ice temperature with concentrated sulfuric acid yields cyclopulegenol-sulfonic ester (I) from which menthofuran (II) is obtained in excellent yield on pyrolysis with zinc oxide at atmospheric pressure.



I II

We have attempted the sulfonation under varied conditions of concentration and temperature, using both sulfuric acid and chlorosulfonic acid, of crotonaldehyde, cyclohexylidenecyclohexanone, 3,4-dimethylhexene-3-on-2 and mesityl oxide. A clean-cut reaction was obtained only in the case of the sulfonation of mesityl oxide which on sulfonation with chlorosulfonic acid in acetic anhydride gave the cyclic sulfonic ester III in good yield. Pyrolysis of the cyclic sulfonic ester of mesityl oxide (III) at atmospheric pressure,



III

---

[1] The work reported here is taken from a thesis presented by Don Gallup to Stanford University in partial fulfillment of the requirements for the degree of Master of Science.

[2] W. Treibs, *Ber.*, **70B**, 85 (1937).

under reduced pressure and in an atmosphere of nitrogen did not effect the transformation analogous to I→II, but led rather to intractable tars.

Bromination of III with one mole of bromine resulted in a substitution product, formulated tentatively as the 5-bromo derivative of III. Treatment of III with an excess of bromine led to an unstable compound $C_6H_7O_3SBr_3$, formulated tentatively as the 5-bromo-3,4-dibromide of III.

Experimental

Mesityl Oxide Cyclic Sulfonic Ester (III).—Mesityl oxide (19.6 g.) was added to 41 g. acetic anhydride and the mixture was cooled to 0°. Chlorosulfonic acid (22.3 g.) was added dropwise while the temperature was kept at 0° with an ice–salt-bath. The mixture was stirred for one-half hour after the addition of the acid was complete, and then placed in the cold-room overnight. The reaction mixture was decomposed by pouring it into an equal volume of ice–water with vigorous stirring. The light-yellow precipitate which formed was separated and purified by crystallization from methanol to yield 13 g. (41%) of stout, colorless prisms of m. p.[3] 65–67°.

Anal. Calcd. for $C_6H_8O_3S$: C, 45.0; H, 5.03. Found: C, 45.1; H, 5.19.

After several weeks a sample of the compound suddenly decomposed with violence, the production of sulfur dioxide and a black tar.

Bromination of the Cyclic Sulfonic Ester of Mesityl Oxide.—A 5.0-g. sample of the ester (III) was dissolved in carbon tetrachloride (25 ml.) and bromine was added dropwise during ten minutes until the decolorization of it became slow. A precipitate formed rapidly and hydrogen bromide was evolved. A slight excess of bromine was removed with sodium thiosulfate solution and the solvent was removed by distillation. The crude product was crystallized from alcohol to give 3.0 g. of white, crystalline material of m. p. 75–76° (mixed with III, m. p. 46–47°).

Anal. Calcd. for $C_6H_7O_3SBr$: C, 30.1; H, 2.95. Found: C, 30.4; H, 3.36.

The substance is a powerful skin irritant and is formulated as the **5-bromo derivative** of the cyclic sulfonic ester of mesityl oxide (III).

A 5.0-g. sample of the cyclic sulfonic ester (III) was dissolved in 25 ml. of carbon tetrachloride and 10 g. of bromine was added rapidly. The mixture was allowed to stand for a day and the precipitate that formed was separated and washed thoroughly with methanol–water (1:1). The white crystalline product turned dark near its melting point and then melted with decomposition at 156–60°.

Anal. Calcd. for $C_6H_7O_3SBr_3$: C, 18.2; H, 1.88. Found: C, 18.3; H, 1.77.

This substance is formulated as the **5-bromo-3,4-dibromide** of the cyclic sulfonic ester (III).

---

(3) Melting points are not corrected.

Department of Chemistry
Stanford University
Stanford University, California

Received August 28, 1947

The Reaction of *t*-Butylmagnesium Chloride with Ethyl Oxalate

By G. F. Hennion and Charles F. Raley

In connection with another problem we have recently had occasion to re-examine the reaction of *t*-butylmagnesium chloride with ethyl oxalate.[1] Our observations are not entirely in accord with the previous report which states that the reaction gives a mixture of products containing *t*-butylglycolic acid, ethyl *t*-butylglycolate, α-ethoxy-β,β-dimethylbutyric acid and smaller amounts of substances thought to be *t*-butyl neopentyl ketone and *sym*-di-*t*-butylglycol. *t*-Butylglycolic acid and its ethyl ester were obtained in the present study but the other products could not be found; instead, several other compounds were isolated.

We have carried out the reaction in three ways: addition of ethyl oxalate to the Grignard reagent (1:4); addition of the Grignard reagent to the ester (2:1); and simultaneous reaction of magnesium (2.5), *t*-butyl chloride (2.0), and ethyl oxalate (1.0). In each case there was considerable evolution of gas, evidently isobutylene, and after working up the products in the usual way complex mixtures were encountered. In view of the latter fact the reaction seems to have little preparative value.

Experimental

A. **Direct Addition.**—When 0.385 mole of ethyl oxalate was added dropwise to 1.54 moles of *t*-butylmagnesium chloride in anhydrous ether (previously filtered through glass wool), 0.7 mole of isobutylene was recovered by absorption in sulfuric acid. After hydrolysis of the reaction mixture with ice and hydrochloric acid in the usual way, extraction of the ether layer with sodium bicarbonate solution removed 18 g. of impure *t*-butylglycolic acid. The neutral components, after removal of the ether, were saponified and thus yielded an additional 10 g. of the acid. It was best purified by vacuum distillation (b. p. 110–117° at 4 mm.), followed by crystallization from water; m. p. 85–86°. Smaller amounts of other products were formed also; of these only hexamethylethane and diisobutylene were recognized.

B. **Reverse Addition.**—In this experiment, when 1.35 moles of filtered Grignard reagent was added to 0.676 mole of ester, the only acidic substance recovered was 2.5 g. of impure oxalic acid. There was obtained by distillation of the ether layer after hydrolysis, etc., 27 g. of ethyl *t*-butylglycolate and 30 g. of a substance whose analysis corresponds to $C_{12}H_{24}O_3$. There was good evidence that the latter compound is the previously unknown ethyl di-*t*-butylglycolate, $(t\text{-}C_4H_9)_2C(OH)COOC_2H_5$. In addition to these two compounds there was 26 g. of higher boiling material.

C. **Barbier Reaction.**—When this method was employed with 2.5 gram atoms of magnesium, 2.0 moles of *t*-butyl chloride and 1.0 mole of ethyl oxalate (the latter mixed and added slowly to the magnesium under ether), hydrolysis and removal of the ether left 137 g. of pale yellow oil. Distillation *in vacuo* through a helix-packed column yielded 38 g. of impure ethyl *t*-butylglycolate and 40 g. of ethyl di-*t*-butylglycolate. The remainder of the product was distilled at 2.5–3.0 mm. without the column and appeared to decompose somewhat in the process. The distillate (39 g.) deposited a crystalline solid; after removal and crystallization from aqueous alcohol it melted at 113–113.5°. The analytical data corresponded with the formula $C_{14}H_{28}O_2$. Despite the oxygen content this substance gave none of the tests specific for alcohols, carbonyl compounds, etc. It was tentatively decided that the compound is di-*t*-butylpivaloycarbinol, $(t\text{-}C_4H_9)_2C(OH)COC(CH_3)_3$. Decomposition by strong heating and the failure to respond to functional group reactions are consistent with this structure.

The physical properties and the analytical data for purified samples of the various products are summarized below.

***t*-Butylglycolic acid**: b. p. 118° at 9 mm.; m. p. 85–86°. Calcd. for $C_6H_{12}O_3$: C, 54.52; H, 9.15; neutral equiv.,

---

(1) Egorova, *J. Russ. Phys.-Chem. Soc.*, **41**, 1454 (1909); *Chem. Zentr.*, **81**, 1003 (1910).

132.2. Found: C, 54.50; H, 9.06; neutral equiv., 133.6.

Ethyl *t*-butylglycolate: b. p. 53° at 5 mm.; n^{25}_{D} 1.4210; d^{25} 0.9661. Calcd. for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.26; H, 10.03.

Ethyl di-*t*-butylglycolate: b. p. 70° at 3.5 mm.; n^{25}_{D} 1.4431; d^{25} 0.9525. Calcd. for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18; $-OC_2H_5$, 20.84. Found: C, 66.51; H, 11.05; $-OC_2H_5$, 18.73.

Di-*t*-butylpivaloylcarbinol (?): m. p. 113–113.5°. Calcd. for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.48; H, 12.56.

Ethyl *t*-butylglycolate failed to react with semicarbazide, as expected, but did yield a derivative, m. p. 166°, with 2,4-dinitrophenylhydrazine, probably due to oxidation at the *alpha* carbon atom.

The analyses for carbon and hydrogen were carried out by Mr. Charles W. Beazley, Micro-Tech Laboratories, Skokie, Ill.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NOTRE DAME
NOTRE DAME, INDIANA
RECEIVED AUGUST 20, 1947

Some New 1,1,1-Trichloro-2,2-bis-(*p*-alkylphenyl)-ethanes

BY G. F. HENNION AND JOSEPH G. WALSH

The condensations of chloral hydrate with toluene,[1] two of the xylenes,[2] *t*-butylbenzene[3] and benzene itself[4] are known to yield crystalline derivatives structurally analogous to DDT. We have recently extended the reaction to several other alkylbenzenes to determine whether it may be used to prepare solid derivatives useful for identification purposes. Furthermore, an assortment of 1,1,1-trichloro-2,2-bis-(*p*-alkylphenyl)-ethanes (I) was desired to explore the possibility of preparing 4,4′-dialkyldiphenylacetylenes (III) from them by elimination of hydrogen chloride and chlorine.

$$\underset{\mathrm{I}}{(R-C_6H_4)_2CH-CCl_3} \xrightarrow{\mathrm{KOH}} \underset{\mathrm{II}}{(R-C_6H_4)_2C=CCl_2} \xrightarrow{2\mathrm{Na}}$$

$$\underset{\mathrm{III}}{R-C_6H_4-C\equiv C-C_6H_4-R}$$

The reactions of the alkylbenzenes with chloral hydrate were carried out in concentrated sulfuric acid (96.9%) in the ordinary manner. Toluene and *t*-butylbenzene gave solid products identical with those previously described.[1,3] Ethylbenzene, isopropylbenzene, *n*-butylbenzene, *s*-butylbenzene and 2-*s*-amylbenzene, however, yielded viscous oils which could not be induced to crystallize. The isolation and purification of these products proved somewhat troublesome because dilution of the crude reaction products with water gave emulsions, probably due to appreciable sulfonation as a side reaction. The emulsions were broken with ether and salt and the ethereal extracts finally distilled three times *in vacuo*. The physical constants, yields after the first distillation, and analyses for these compounds are given in Table I.

TABLE I

1,1,1-TRICHLORO-2,2-*bis*-(*p*-ALKYLPHENYL)-ETHANES

Alkyl group	B. p., °C.	Press., mm.	Yield, %	n^{25}_{D}	Chlorine, % Calcd.	Chlorine, % Found
Ethyl[a]	183	0.8	51	1.5780	31.2	31.1
Isopropyl	199	1.4	40	1.5672	28.8	28.5
n-Butyl	203	0.4	42	1.5611	26.8	25.6
s-Butyl	204	0.4	36	1.5597	26.8	25.7
2-*s*-Amyl	210	0.4	27	1.5515	25.0	24.2

[a] Wild, *Helv. Chim. Acta*, **29**, 497 (1946), reported the boiling point to be 180° at 0.2 mm. The refractive index was not given.

Each of the seven products (I) was treated with alcoholic potassium hydroxide to prepare the corresponding dichloroethylenes (II). Again the toluene and *t*-butylbenzene derivatives gave solids, as previously reported, while all the other yielded oils. In all cases the dichloroethylenes were insoluble in liquid ammonia and failed to react well with sodium in this medium. An ethereal solution of the di-*p*-tolyl compound, for example, decolorized only a fraction of the theoretical amount of sodium in liquid ammonia and yielded an insoluble, infusible, polymeric substance containing chlorine. All attempts to prepare acetylenes (III) in this manner failed.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NOTRE DAME
NOTRE DAME, INDIANA
RECEIVED AUGUST 20, 1947

---

[1] Fischer, *Ber.*, **7**, 1190 (1874).

[2] Elbs, *J. prakt. Chem.*, [2] **39**, 300 (1889).

[3] Cristol, Hayes and Haller, THIS JOURNAL, **68**, 913 (1946).

[4] Baeyer, *Ber.*, **5**, 25 (1872).

Nitration of (*p*-Bromophenyl)-cyclopentane

BY RICHARD D. KLEENE

It was desired to prepare an acetamino derivative of (*p*-bromophenyl)-cyclopentane by the method of Ipatieff and Schmerling[1] for alkyl benzenes. The product obtained was free of halogen as described below.

(3,5-Diacetaminophenyl) - cyclopentane.—One gram of the bromo compound[2] was nitrated with 5 ml. of a mixture of one part of 70% nitric acid and one part of 98% sulfuric acid by volume. The red oil so obtained was dissolved in alcohol and reduced with tin and 36% hydrochloric acid. The amine was then acetylated with acetic anhydride and the resulting solid was recrystallized three times from dilute alcohol. Very fine hair-like needles were formed which melted at 233–234° (uncor.); yield 50%. Analysis showed the complete absence of bromine.

Anal. Calcd. for $C_{15}H_{20}O_2N_2$: C, 69.2; H, 7.70; N, 10.8. Found: C, 68.4; H, 7.57; N, 10.4.

A mixture of this new compound with (2,4-diacetaminophenyl)-cyclopentane[1] (m. p. 228°) melted at 220–225°. The two compounds also appeared dissimilar under the microscope. The removal of the bromine atom indicates that it is probably activated by both nitro groups. This reduces the possibility that the new compound is the 2,5- or the 2,6-diacetamino isomer.

---

[1] V. N. Ipatieff and L. Schmerling, THIS JOURNAL, **59**, 1056 (1937); **60**, 1476 (1938).

[2] R. D. Kleene, *ibid.*, **62**, 2883 (1940).

The removal of halogens from aromatic compounds during the reduction of two activating nitro groups is a well-known phenomenon. Thus the reduction of 2,4-dibromo-3,5-dinitrotoluene with tin and hydrochloric acid gives 3,5-diaminotoluene.[3]

In contrast to the nitration with mixed acid as described above, nitration with 70% nitric acid alone according to the method of Mayes and Turner[4] led to a mixture of products from which a considerable amount of 1-nitro-4-bromobenzene was isolated. The other products were not identified.

---

(3) W. A. Davis, *J. Chem. Soc.*, **81**, 873 (1902).

(4) H. A. Mayes and E. E. Turner, *ibid.*, 500 (1929).

CHICAGO, ILLINOIS RECEIVED MAY 29, 1947

The Acylation of Thiophene and Furan by Means of Boron Trifluoride[1]

BY HOWARD D. HARTOUGH AND ALVIN I. KOSAK[2]

The acetylation of thiophene and furan to form the respective 2-acyl derivatives has been effected previously by means of several catalysts.[3] This reaction has now been effected by means of catalytic amounts of boron trifluoride complexes in ether, methanol, and acetic acid. The yields were satisfactory (70%) with 0.03–0.075 mole of the catalyst per mole of acetic anhydride. When acetyl chloride was used instead of acetic anhydride the yield was poor. The analogous reaction with benzoyl chloride was effected in 22% yield.

Although the nucleus of 2-acetylthiophene is acetylated in the presence of zinc chloride, orthophosphoric acid and phosphorus pentoxide,[3] acetylation at the side chain of this ketone occurred in the presence of a molecular equivalent of boron trifluoride to form a triacetylthiophene in 17% yield; however, the product has not been identified. Acetylation at the side chain might have been anticipated from the work of Meerwein, Pannwitz and Vossen[4] and Hauser and Adams.[5]

With furan, acetic anhydride and a catalytic amount of boron trifluoride in methanol, 2-acetylfuran was obtained in 46% yield.

Boron Trifluoride Complexes.—The boron trifluoride etherate was used as received from the Eastman Kodak Co. The boron trifluoride methanol complex and the boron trifluoride acetic acid complex were prepared by saturating methanol and acetic acid with boron trifluoride gas at 100 p. s. i. pressure in a stirring autoclave.

2-Acetylthiophene.—To a mixture of 252 g. (3 moles) of thiophene and 107 g. (1 mole) of 95% acetic anhydride cooled to 10° by means of an ice-bath was added 4 g. of boron trifluoride–methanol complex (60% boron trifluoride). The temperature rose to 13° and when it finally subsided after five minutes to 5° the ice-bath was removed and the flask warmed to 50° for two hours. Two hundred milliliters of water was added, the mixture agitated for fifteen minutes, the lower organic layer drawn off, washed with 10% sodium carbonate solution until neutral, and distilled. Thiophene, 180 g., was recovered and 84 g. (70%) of 2-acetylthiophene, b. p. 87–88° (8 mm.),[6] $n^{20}_{\rm D}$ 1.5666, was obtained.

2-Benzoylthiophene.—To 126 g. (1.5 moles) of thiophene and 141 g. (1 mole) of benzoyl chloride was added 4 g. of boron trifluoride–acetic acid complex. No heat of reaction was noted and the mixture was heated at 90–95° for six hours. After cooling, the reaction mixture was washed with 10% sodium hydroxide solution until neutral. Distillation yielded thiophene, 42 g. (22%) of 2-benzoylthiophene, b. p. 146–147° (5 mm.), m. p. 56.5–57°,[7] after recrystallization from ASTM naphtha, and 21 g. of tarry residue.

"2-Triacetylthiophene."—To 42 g. (0.33 mole) of 2-acetylthiophene was added 107 g. (1 mole) of 95% acetic anhydride and 110 g. (0.84 mole) of boron trifluoride etherate. The temperature rose to 38° and after fifteen minutes the mixture was warmed on a steam-bath at 55° for thirty minutes. The hot mixture was poured slowly into one liter of water containing 120 g. of sodium acetate and shaken until the oily liquid crystallized. The crystals were filtered, washed with cold benzene, and purified by vacuum sublimation, yielding 12 g. (17%) of bright yellow crystals, m. p. 176–177°.[8]

Anal. Calcd. for $C_{10}H_{10}O_3S$: S, 15.31, Found: S, 14.92.

Oxidation with alkaline permanganate gave 2-thiophenecarboxylic acid, m. p. and mixed m. p. 127–128.5°.

2-Acetylfuran.—A procedure, analogous to that employed for to 2-acetylthiophene, was used but the temperature of the reaction mixture was maintained at 25° instead of 50° for two hours. Distillation yielded 53 g. (48%) of 2-acetylfuran, b. p. 89–90° (43 mm.),[9] m. p. 30–32°,[9] $n^{30}_{\rm D}$ 1.5015.

Acknowledgments.—The authors wish to thank Dr. D. E. Baderscher for advice and interest in this problem and Miss Loretta G. Conley who helped with a number of the laboratory experiments.

---

(1) Paper VII of this series.

(2) Present address: Ohio State University, Columbus, Ohio.

(3) (a) Hartough and Kosak, THIS JOURNAL, **68**, 2639 (1946); (b) **69**, 1012 (1947); (c) **69**, 3093 (1947); (d) **69**, 3098 (1947); (e) Hartough, Kosak and Sardella, *ibid.*, **69**, 1014 (1947); (f) Hartough and Conley, *ibid.*, **69**, 3096 (1947).

(4) Meerwein, *Ber.*, **66B**, 411 (1933); Meerwein and Pannwitz, *J. prakt. Chem.*, **141**, 123 (1934); Meerwein and Vossen, *ibid.*, **141**, 149 (1934).

(5) Hauser and Adams, THIS JOURNAL, **66**, 345 (1944).

(6) Reported data (ref. 3a): b. p. 77–78° (4 mm.) and $n^{20}_{\rm D}$ 1.5666.

(7) Reported data (ref. 3b); b. p. 143–144 (4 mm.) and m. p. 56.5–57°.

(8) Alternate purification procedures involved numerous recrystallizations from benzene or precipitation of the material from ethyl acetate by addition of petroleum ether yielding brown crystals, m. p. 173–175°.

(9) Reported data (ref. 3c): m. p. 30–32° and b. p. 45–50° (5 mm.).

SOCONY-VACUUM LABORATORIES
RESEARCH AND DEVELOPMENT DEPARTMENT
PAULSBORO, N. J.

RECEIVED SEPTEMBER 23, 1947

Derivatives of Diethylamino Compounds

BY NELSON J. LEONARD, FELICE MARY KRAFT AND VIVIAN WOLFMAN

In connection with studies in progress on reactions of aminoalcohols and aminoketones involving possible rearrangement, it was desirable to obtain readily identifiable derivatives of certain diethylamino compounds. The compounds of interest included amines, aminoethers, aminoalcohols and aminoketones, in all of which the amine function was tertiary. Derivatives have been formed with picric acid, picrolonic acid and ethyl iodide. Diethyl-*n*-propylamine has been obtained pure, as have β-ethoxyethyldiethylamine and γ-ethoxypropyldiethylamine. 2-Diethylamino-2-methyl-1-propanol has been prepared by a method similar to the previously unsuccessful diethylation of 2-amino-2-methyl-1-propanol[1] and the successful ethylation of 2-ethylamino-2-methyl-1-propanol.[2]

Experimental[3]

Diethyl-*n*-propylamine.—A mixture of 70 g. of *n*-propyl bromide, 32 g. of ethylene glycol and 61 g. of diethylamine was refluxed for forty hours. The amine was liberated with alkali and extracted with ether. After the ether solution was dried over potassium hydroxide the ether was removed, and 19 g. (27%) of diethyl-*n*-propylamine was distilled at 111.5–112.5° (750 mm.); n^{20}_{D} 1.4064; d^{20}_{4} 0.742.

Anal. Calcd. for $C_7H_{17}N$: C, 72.97; H, 14.88; N, 12.16; MR_D, 38.35. Found: C, 73.10; H, 15.01; N, 12.14; MR_D, 38.18.

The **ethiodide** melted at 262–263° (cor.) with decomposition (von Auwers and Mauss reported 255–256°[4]).

The **picrate** was prepared in and recrystallized from ether as long yellow needles, m. p. 82–84° (cor.).

Anal. Calcd. for $C_{13}H_{20}N_4O_7$: C, 45.34; H, 5.86; N, 16.27. Found: C, 45.41; H, 5.91; N, 16.14.

The **picrolonate** was prepared in ether and recrystallized from ethanol–ether as orange-yellow elongated prisms, m. p. 140–141° (cor.).

Anal. Calcd. for $C_{17}H_{25}N_5O_5$: C, 53.81; H, 6.64; N, 18.46. Found: C, 53.92; H, 6.69; N, 18.41.

Diethylisopropylamine Picrolonate.—Prepared from diethylisopropylamine[5] in ether, the picrolonate was recrystallized from absolute ethanol in leafy clusters of yellow prisms, m. p. 164–165.5° (cor.).

Diethylisopropylamine Ethiodide.—Formed by refluxing diethylisopropylamine in benzene with excess ethyl iodide, the microcrystalline ethiodide melted at 264–266° (cor.) with decomposition.

β-Ethoxyethyldiethylamine.—A mixture of a six to one molar proportion of diethylamine (50 g.) and β-ethoxyethyl bromide (16.7 g.) was heated under reflux for twenty-four hours. The product was isolated as in the method for diethyl-*n*-propylamine; b. p. 63–64° (25 mm.); n^{20}_{D} 1.4179.

Anal. Calcd. for $C_8H_{19}NO$: C, 66.15; H, 13.18; N, 9.64. Found: C, 65.81; H, 12.96; N, 9.64.

No picrate, picrylsulfonate, picrolonate, methiodide or mineral acid salt could be formed.

γ-Ethoxypropyldiethylamine.—Fifty grams of diethylamine and 19 g. of γ-ethoxypropyl bromide were heated under reflux and the product was isolated in the usual manner; b. p. 78–81° (25 mm.); n^{20}_{D} 1.4223.

Anal. Calcd. for $C_9H_{21}NO$: C, 67.87; H, 13.29; N, 8.80. Found: C, 68.01; H, 13.01; N, 8.84.

Prepared in and recrystallized from ethanol, the **picrolonate** melted with decomposition at 213–215° (uncor.).

Anal. Calcd. for $C_{19}H_{29}N_5O_6$: C, 53.89; H, 6.93. Found: C, 53.75; H, 6.92.

2-Diethylamino-2-methyl-1-propanol.—2-Diethylamino-2-methyl-1-propanol was prepared by a method similar to that of Olson and Whitacre and Bachman and Mayhew[2]; b. p. 82–83° (22 mm.); n^{20}_{D} 1.4421.

Anal. Calcd. for $C_8H_{19}NO$: N, 9.64. Found: N, 9.61.

The **picrolonate** was recrystallized from benzene containing a small amount of ethanol as elongated yellow prisms; m. p. 185.5–187° (uncor.) with decomposition.

Anal. Calcd. for $C_{18}H_{27}N_5O_6$: C, 52.80; H, 6.65. Found: C, 52.73; H, 6.67.

The **picrate** was recrystallized from ethanol–petroleum ether solution as yellow prisms; m. p. 156° (uncor.).

Anal. Calcd. for $C_{14}H_{22}N_4O_8$: C, 44.92; H, 5.92. Found: C, 45.00; H, 5.89.

Diethylaminoacetone Picrolonate.—Formed from diethylaminoacetone[6] in ether and recrystallized from ethanol, the picrolonate formed clusters of yellow prisms, m. p. 143–144° (cor.).

Anal. Calcd. for $C_{17}H_{23}N_5O_6$: C, 51.90; H, 5.89; N, 17.80. Found: C, 51.74; H, 6.11; N, 17.81.

5-Diethylamino-2-pentanone Picrolonate.—Prepared from Noval ketone in ether and recrystallized from ethanol–ether, the picrolonate formed stout yellow prisms, m. p. 105–107° (cor.).

Anal. Calcd. for $C_{19}H_{27}N_5O_6$: C, 54.14; H, 6.46; N, 16.62. Found: C, 54.32; H, 6.67; N, 16.67.

---

[1] Olson and Whitacre, This Journal, **65**, 1019 (1943).

[2] Bachman and Mayhew, *J. Org. Chem.*, **10**, 243 (1945).

[3] The microanalyses were performed by Miss Theta Spoor. Boiling points are uncorrected for emergent stem error.

[4] von Auwers and Mauss, *Ber.*, **61**, 2411 (1928).

[5] Caspe, This Journal, **54**, 4457 (1933).

[6] Stoermer and Dzimiski, *Ber.*, **28B**, 2220 (1895).

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

RECEIVED MAY 7, 1947

Conversion of Benzylamine to N-Substituted Thiobenzamides

BY FREEMAN H. MCMILLAN[1]

In a previous publication[2] the modified Willgerodt reaction[3] was applied to styrene in the presence of a series of amines and the yield of phenylacetic acid obtained by hydrolyzing the crude reaction mixture was measured. In some instances there was isolated from the crude reaction mixture a little of the pure thioamide for characterization and analysis. It has been found that the compound isolated and called N-benzylphenylthioacetamide was in reality N-benzylthiobenzamide. Since there was no doubt that it was phenylacetic acid which was obtained from the hydrolysis of the crude reaction mixture, the hydrolysis of pure N-benzylthiobenzamide was investigated. It was found that this thioamide was very slowly attacked by refluxing 50% (by weight) sulfuric acid (the conditions used for hydrolyzing the crude thioamides), thus explaining the absence of benzoic acid in the hydrolysate from the crude reaction mixture of styrene, sulfur and benzylamine. The identity of N-benzylthiobenzamide was established by hydrolysis with refluxing 65% (by weight) sulfuric acid followed by isolation of benzoic acid and benzylamine in the form of its picrate.

Since none of the other amines used to prepare thioamides reported in ref. 2 had the possibility of undergoing a reaction analogous to that which benzylamine underwent, there is no reasonable doubt as to their identity.

Although it is possible that the N-benzylthiobenzamide could have arisen through cleavage[4]

---

[1] Present address: Warner Institute for Therapeutic Research, 113 West 18th St., New York, N. Y.

[2] King and McMillan, This Journal, **68**, 2335 (1946).

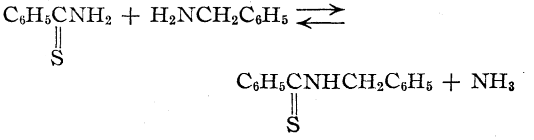
[3] Schwenk and Bloch, *ibid.*, **64**, 3051 (1942).

[4] For discussion of cleavage in Willgerodt reaction *cf.* McMillan and King, *ibid.*, **69**, 1207 (1947).

of styrene, such cleavage has not been observed with other amines, *e. g.*, morpholine, where the yield of phenylthioacetmorpholide is very good, and consequently this mode of formation is not considered probable. An alternative mode of formation is by oxidation (replacement of two hydrogens by sulfur) of part of the benzylamine used.[5]

It was found that by heating equimolecular portions of benzylamine and sulfur a 91% yield of N-benzylthiobenzamide was obtained. Wallach[6] reported that the reaction of benzylamine with sulfur in a sealed tube at 180° gave thiobenzamide. The discrepancy between our results and those of Wallach may be explained by the fact that ammonia was given off copiously from our reaction. Any reaction in which ammonia is one of the products would be favored in an open reaction vessel where the ammonia could escape and would be suppressed in a sealed tube where it would remain at the site of the reaction. Two such possible reactions which would lead to our product would be

$$C_6H_5CH_2NH_2 + H_2NCH_2C_6H_5 \rightleftarrows C_6H_5CH_2NHCH_2C_6H_5 + NH_3 \quad (1)$$



$$C_6H_5\underset{\underset{S}{\|}}{C}NH_2 + H_2NCH_2C_6H_5 \rightleftarrows C_6H_5\underset{\underset{S}{\|}}{C}NHCH_2C_6H_5 + NH_3$$

(2)

It was also found that heating an equimolecular mixture of benzylamine and morpholine with sulfur gives thiobenzmorpholide, presumably by the same route as the benzylamine–sulfur reaction.

Acknowledgment.—The author wishes to acknowledge the helpful criticisms of Dr. John A. King in the preparation of this manuscript.

Experimental[7,8]

Reaction of Benzylamine with Sulfur.—A mixture of benzylamine (21.4 g., 0.20 mole) and sulfur (8.0 g., 0.25 mole) was heated at reflux for forty-five minutes. Evolution of ammonia was noticed almost immediately after heating was begun. The cooled reaction mixture was treated with Skellysolve "C" (100 ml.) and then filtered. The solid material weighed 19.5 g. (91%) and melted at 81–83°. After crystallization from Skellysolve "C" (250 ml.) it melted at 84–85°.

Anal. Calcd. for $C_{14}H_{13}NS$: N, 6.16; S, 14.10. Found: N, 5.85; S, 14.10.

There was no depression in melting point when this compound was mixed with the material reported to be N-benzylphenylthioacetamide[2] but now known to be N-benzylthiobenzamide.

Hydrolysis of above Reaction Product.—The compound melting at 84–85° (2.0 g.) was refluxed for one hour with 65% (by weight) sulfuric acid (30 ml.). The hydrolysis mixture was cooled and extracted with two 30-ml. portions of ether. The combined ether extracts were extracted with 25 ml. of 10% sodium hydroxide solution and the caustic extract was acidified with dilute hydrochloric acid. The acidified solution was extracted with two 30-ml. portions of ether; the ether solution was dried over anhydrous sodium sulfate and the ether was removed under vacuum. The residue was crystallized from water giving white crystals (0.4 g.) melting at 120–121°, undepressed when mixed with an authentic sample of benzoic acid.

The hydrolysis mixture was made alkaline with 10% sodium hydroxide solution and then extracted with three 100-ml. portions of ether. The ether was dried over anhydrous potassium carbonate and the ether was removed under vacuum. The residue was treated with saturated alcoholic picric acid solution and gave a picrate which after crystallization from alcohol melted at 193–195°, undepressed when mixed with an authentic sample of benzylamine picrate.[9]

Reaction of Benzylamine, Morpholine and Sulfur.—A mixture of benzylamine (10.7 g., 0.10 mole), morpholine (8.7 g., 0.10 mole) and sulfur (6.4 g., 0.20 mole) was heated at 160° for one hour. The cooled reaction mixture was taken up in 150 ml. of boiling alcohol and then chilled. The solid that formed weighed 8.4 g. (40.6%) and melted at 137–138°, undepressed when mixed with an authentic sample of thiobenzmorpholide.[5]

---

[5] For discussion of this type of oxidation see McMillan and King, submitted for publication in THIS JOURNAL.

[6] Wallach, *Ann.*, **259**, 300 (1890).

[7] Melting points uncorrected.

[8] Analyses performed under the direction of Mr. M. E. Auerbach.

[9] Moureu and Lazennec, *Bull. soc. chim.*, [3] **35**, 1183 (1906).

STERLING–WINTHROP RESEARCH INSTITUTE
RENSSELAER, NEW YORK
RECEIVED APRIL 16, 1947

Diffusion Coefficient of Nitroglycerin in Rocket Powder and in Cellulose Acetate[1]

BY S. S. PENNER[2] AND S. SHERMAN[3]

Double base rocket powders, consisting of approximately 60% nitrocellulose, 40% nitroglycerin and some minor components, constitute one type of widely used rocket propellant. These powders burn easily over their entire exposed surface. In order to restrict burning to a preferred direction and thereby lengthen the total burning time it is necessary to cover a portion of the powder surface with a strongly bonded inert material such as cellulose acetate. These wrappings of cellulose acetate, though initially almost noncombustible, lose their protective action in the course of time because of the diffusion of nitroglycerin into the cellulose acetate. By determining the nitroglycerin concentration as a function of the distance from the cellulose acetate–powder interface at a given time, it is possible to ascertain the average diffusion coefficient of nitroglycerin in cellulose acetate and in powder. Knowledge of the maximum allowable nitroglycerin concentration in the cellulose acetate permits calculation of maximum safe storage times at all temperatures for which diffusion coefficients are available.

A complete experimental study was not carried through. In view of the limited experimental

---

[1] This paper is based on OSRD report No. 4963 (PB report No. 50864) on the "Diffusion of Nitroglycerin in Wrapped Powder Grains." The diffusion study was carried out at the Allegany Ballistics Laboratory, Cumberland, Maryland, operated by the George Washington University under OSRD contract OEMsr-273. Analytical work was performed by J. J. Donovan and N. Marans.

[2] Present address: Jet Propulsion Laboratory, California Institute of Technology, Pasadena, California.

[3] Present address: 413 Eckart Hall, University of Chicago, Chicago, Ill.

data available for calculation of the diffusion coefficient, an approximate treatment was employed which is strictly applicable only if the cellulose acetate and the powder have identical physical properties as regards the diffusion of nitroglycerin. The theoretical treatment of diffusion through a composite cylinder for the boundary values of interest in connection with the present study has been reported elsewhere.[4]

More extensive experimental investigations along the lines discussed in this report were carried out independently by B. H. Sage[5] and, at a later date, by J. J. Donovan.[5]

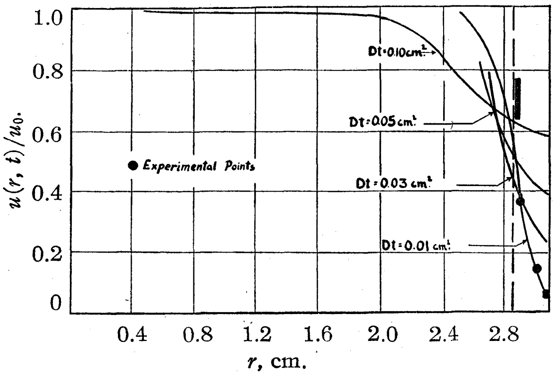


Fig. 1.—Comparison between experimental and calculated data.

Theoretical Treatment.—Consider an infinite cylinder of radius b surrounded by a cylindrical shell of thickness $c - b$. The initial concentration of diffusing material is U_0 in the cylinder and zero in the shell. From these data the boundary value problem may be formulated as follows[6]

$$\partial u/\partial t = \mathrm{D}[\partial^2 u/\partial r^2 + (1/r)(\partial u/\partial r)],\ 0 \leqslant r < c,\ t > 0 \quad (1)$$

$$u(r,0) = U_0,\ 0 \leqslant r < b \quad (2)$$

$$u(r,0) = 0,\ b < r < c \quad (3)$$

$$\partial u(c - 0,t)/\partial r = 0 \quad (4)$$

Here $u(r,t)$ represents the concentration of diffusing material at any point at any time, D is the coefficient of diffusion, r is the radial distance from the axis of the cylinder, and t represents the time. Condition (4) arises from the assumption that no nitroglycerin is lost through the outer boundary of the cellulose acetate wrapping. The general solution of the problem specified by equations (1) to (4) may be written as[7]

$$u(r,t)/U_0 = b^2/c^2 + (2b/c^2) \sum_{j=1}^{\infty} J_1(\lambda_j b) J_0(\lambda_j r) e^{-D\lambda_j^2 t}/\lambda_j [J_0(\lambda_j c)]^2 \quad (5)$$

where the positive eigen values λ_j satisfy the condition

$$J_1(\lambda_j c) = 0$$

and J_0 and J_1 represent, respectively, Bessel functions of order zero and order one of the first kind.

Calculation of Diffusion Coefficient.—The particular grain of wrapped powder for which analyses for nitroglycerin were available consisted of a long cylindrical powder stick 2.858 cm. in radius, wrapped with cellulose acetate 0.228 cm. thick. The powder grain was stored for a period of two months at an average temperature close to room temperature. At the end of this time it was sectioned and nitroglycerin analyses were carried out according to U. S. Army Specification R11B. The material to be analyzed is extracted with ether. The ether in the extract is then replaced by glacial acetic acid. Finally, the nitroglycerin is reduced with ferrous chloride and the concentration of ferric ion determined with titanous chloride.

By use of equation (5) it is possible to calculate the ratio $u(r,t)/U_0$ as a function of r for various values of the parameter Dt. The results of this calculation are represented in Fig. 1. Since the storage time was two months or 1440 hours, D in sq. cm. per hour is 1/1440 of the value of Dt for which theoretical and experimental results agree. Reference to Fig. 1 indicates that a satisfactory value for Dt is 0.01 sq. cm. so that D is 7×10^{-6} sq. cm. per hour.

The theoretical curve for $Dt = 0.01$ sq. cm. lies considerably below the experimental points closest to the cellulose acetate–powder interface. This discrepancy may probably be ascribed to contamination during sectioning of the sample closest to the interface with some powder, thereby causing abnormally large values of the nitroglycerin concentration and also impairing the reproducibility of the results.

The curves for different values of Dt show that the theoretical curve is quite sensitive to the value chosen for Dt. In view of the close agreement between experimental and calculated curves for $Dt = 0.01$ sq. cm., it follows that the calculated value for the average diffusion coefficient in powder and cellulose acetate is of the correct order of magnitude.

The boundary value problem specified by equations (1) to (4) may be simplified for the particular powder grain used for the present study. Thus, the composite cylinder may be approximated by a powder slab of thickness b in contact with a slab of cellulose acetate of thickness $c - b$. The composite slab treatment leads to the same value for Dt as the cylindrical treatment given here. Equally good results are obtained if the powder is considered to be a semi-infinite solid. However, it is not permissible to represent the relatively thin cellulose acetate coating by a semi-infinite solid.

ALLEGANY BALLISTICS LABORATORY
CUMBERLAND, MARYLAND
RECEIVED JUNE 21, 1947

---

(4) Penner and Sherman, *J. Chem. Phys.*, **15**, 569 (1947).

(5) Unpublished data in classified OSRD reports.

(6) For application of the Laplacian in cylindrical coördinates see Churchill, "Fourier Series and Boundary Value Problems," McGraw-Hill Book Co., New York, N. Y., 1941.

(7) For methods of solution of boundary value problems see ref. 1; also Byerly, "Fourier Series and Spherical Harmonics," Ginn and Co., London, 1893.

N-β-Bromoethylaniline Hydrobromide

BY WILLIAM M. PEARLMAN

Although a product designated[1,2] as N-β-bromoethylaniline hydrobromide has been reported to be formed by converting N-phenylethanolamine into its hydrobromide at 100° with gaseous hydrobromic acid and then heating to 150–160°, no identification was made and no yields were given. In addition, the indicated procedures are cumbersome. It was found that the desired product could be obtained in 85% yield from β-hydroxyethylaniline and hydrobromic acid by a slight modification of the procedure of Cortese.[3]

Experimental

β-Hydroxyethylaniline (100 g.) was precooled to 0° and 310 ml. of precooled (0°) 48% hydrobromic acid was added dropwise with stirring and cooling. When all of the hydrobromic acid had been added the mixture was distilled with an efficient fractionating column until a constant boiling distillate was reached. The residue was cooled slightly, placed in a large, open dish in a vacuum desiccator and evacuated with a water jet overnight. The resulting slurry was filtered and the solid recrystallized from absolute ethanol. The yield of nearly colorless needles was 180 g. (85.5%), m. p. 136–139°. A sample recrystallized from benzene was colorless, m. p. 137–138°.

Anal. Calcd. for $C_8H_{11}Br_2N$: C, 34.19; H, 3.95; N, 4.99. Found: C, 33.87; H, 4.16; N, 4.97.

---

(1) French Patent 800,369; abstracted in *C. A.*, **30**, 8241^5 (1936).

(2) Julius v. Braun, *Ber.*, **70**, 979 (1937).

(3) "Organic Syntheses," Coll. Vol. II, 91, ed. by Blatt, John Wiley and Sons, Inc., New York, N. Y., 1943.

RESEARCH LABORATORIES
PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN
RECEIVED SEPTEMBER 11, 1947

Oxidation–Reduction Potentials and Ionization Constants of the Reversible Series: Hexahydroxybenzene – Tetrahydroxyquinone – Rhodizonic Acid

BY PAUL W. PREISLER, LOUIS BERGER AND EDGAR S. HILL

Professor G. Schwarzenbach of the Universität at Zürich has recently called our attention to omission of reference in our publication[7] to the prior work and publication by Schwarzenbach and Suter[6] with the same substances. The oxidation–reduction potentials and ionization constants of this series of related compounds has been reported on several occasions.[1–7] It is regretted that there was no discussion of the work of Schwarzenbach and Suter[4,6] in our publications,[5,7] which oversight resulted from their being no abstract of the thesis of Suter[4] in *Chemical Abstracts* and no indication in the abstract[6a] of their joint publication[6] that they had worked with any compound of the rhodizonic acid series oxidation–reduction systems.

The two reports[6,7] differ mainly in the estimation of the ionization constants of rhodizonic acid. Our constants of $pK_1 = 4.1$ and $pK_2 = 4.5$ should be rejected in favor of those of Schwarzenbach and Suter, who found $pK_1 = 3.15$ and $pK_2 = 4.9$, since our values were estimated from the E_0'–pH curve of the rhodizonic acid–tetrahydroxyquinone system in a range where the curve is quite flat, while their values were determined by colorimetric and photometric methods.

Accepting their constants, 3.15 and 4.9, curves of $E_0' - p$H may be drawn which fit our experimentally determined points reasonably well. These changes do not affect the tetrahydroxyquinone–hexahydroxybenzene curve; the estimated ionization constant of tetrahydroxyquinone being unchanged at $pK_1 = 4.8$. Our E_0' values at $p\text{H} = 0$ become altered: for rhodizonic acid–tetrahydroxyquinone to $E_0' = +0.426$ volt (increase of +0.016) and for tetrahydroxyquinone–hexahydroxybenzene to $E_0' = +0.388$ volt (increase of +0.008).

These extrapolated values for $p\text{H} = 0$ and our measured potentials agree as well as may be expected for systems of this type with the potentials of Schwarzenbach and Suter. However, we experienced no difficulties in obtaining rapidly adjusting stable potentials in the entire pH range studied from 3.5 to 9.9. Therefore, where the slopes of our E_0'–pH curves are sufficiently well established, as for the tetrahydroxyquinone–hexahydroxybenzene system, we consider the ionization constants reported,[7] for tetrahydroxyquinone $pK_2 = 6.8$ and for hexahydroxybenzene $pK_1 = 9.0$, to be reliably estimated.

---

(1) P. W. Preisler, E. S. Hill, E. Ronzoni and L. Young, *J. Biol. Chem.*, **123**, XCV (1938).

(2) G. E. Carpeni, Thesis, Paris, 1938.

(3) P. W. Preisler, *Cold Spring Harbor Symposia on Quantitative Biology*, **7**, 94 (1939).

(4) H. Suter, Thesis, Zürich, 1940.

(5) P. W. Preisler and L. Berger, paper presented at the meeting of the American Chemical Society, April, 1941; THIS JOURNAL, **64**, 67 (1942).

(6) G. Schwarzenbach and H. Suter, *Helv. Chim. Acta*, **24**, 617 (1941).

(6a) *Chemical Abstracts*, **35**, 7806 (1941).

(7) P. W. Preisler, L. Berger and E. S. Hill, THIS JOURNAL, **69**, 326 (1947).

DEPARTMENT OF BIOLOGICAL CHEMISTRY
WASHINGTON UNIVERSITY MEDICAL SCHOOL
ST. LOUIS 10, MO.
RECEIVED SEPTEMBER 15, 1947

Freezing Point Depression of Sulfuric Acid by Siloxanes

BY FRASER P. PRICE

Since sulfuric acid is used as an equilibrating agent in the preparation of silicones,[1] it is of interest to investigate the kinds of particles produced when siloxanes are dissolved in this acid. It was hoped that such an investigation would shed some light on the mechanism of siloxane rearrangement.

The molal freezing point depressions and the van't Hoff "*i*" factors in approximately 100% sulfuric acid were determined by the method of Hammett and Deyrup.[2] The only departure from their method was that the weight of solvent

---

(1) Patnode and Wilcock, *ibid.*, **68**, 358 (1946).

(2) Hammett and Deyrup, *ibid.*, **55**, 1900 (1933).

was determined by weighing the freezing point tube containing the solute and acid at the end of the run and subtracting the weight of solute and tube.

The nomenclature used in this paper is a modification of that developed in this Laboratory for the simplified representation of polymethylpolysiloxane structures[3]: M = $(CH_3)_3Si$, D = $(CH_3)_2Si$, T = CH_3Si, Q = Si. The results of the study are given in Table I.

TABLE I

VAN'T HOFF "*i*" FACTORS FOR SEVERAL SILOXANES IN 100% SULFURIC ACID

Solute	[Solute]	$[H_2O]$	ϑ(°C.)	*i*	*i* (av.)
MOM	0.0368	0.066	0.947	4.29	
	.0802	.066	2.053	4.27	4.28
$(DO)_4$	$.148 \times 10^{-3}$	.134	0.277	11.88[a]	
	$.487 \times 10^{-3}$	.134	0.965	12.60	
	1.01×10^{-3}	.134	1.951	12.58	12.59
$(MO)_3T$	8.59×10^{-3}	.092	0.425	8.20	
	21.0×10^{-3}	.092	1.035	8.25	
	39.0×10^{-3}	.092	1.874	8.23	8.23
$(MO)_4Q$	7.84×10^{-3}	.092	0.449	9.48	
	15.66×10^{-3}	.092	0.889	9.46	
	$26.6 \quad 10^{-3}$	.092	1.507	9.57	9.50

[a] This figure rejected as it is too far out of line.

Previous work with silyl sulfates[4] shows that only the normal sulfate is isolated when hexamethyldisiloxane is treated with sulfuric acid. However, the freezing point data for this siloxane indicate that the major reaction is

$$\text{MOM} + 3H_2SO_4 \longrightarrow 2MHSO_4 + H_3O^+ + HSO_4^- \quad (1)$$

which gives an "*i*" of 4. The slightly higher value observed is presumably due to the partial ionization of the $MHSO_4$. If the formation of the normal sulfate were the major reaction, then an "*i*" of only 3 would be observed or it would be necessary to assume that the reaction

$$M_2SO_4 \longrightarrow M^+ + MSO_4^-$$

went to completion in order to explain the observed value. Furthermore, it seems highly improbable that in this acid medium anything other than the acid sulfate could exist in appreciable quantity. It is more likely that the previous workers' results are due to the normal sulfate having a much higher solubility than the bisulfate in the extracting solvents. Hence, any small amount of sulfate that was formed would be removed and the equilibrium would shift to make up the deficiency.

The result obtained with the cyclic tetramer $(DO)_4$ is explained by the reaction

$$(DO)_4 + 12H_2SO_4 \longrightarrow 4D(HSO_4)_2 + 4H_3O^+ + 4HSO_4^- \quad (2)$$

The deviation from the integral value of 12 is probably due to ionization of the $D(HSO_4)_2$.

The deviations of the "*i*" factors from integers for both MOM and $(DO)_4$ are 0.28 and 0.59, respectively. However, when these deviations are made comparable by dividing by the number of silicon atoms, practically identical values are obtained. It then appears that the ionizations of $MHSO_4$ and $D(HSO_4)_2$ both proceed to about the same extent and that the replacement of methyl by bisulfate has little effect.

The two remaining siloxanes contain units capable of producing a three dimensional network Furthermore, these networks, if they form, will be quite insoluble in the acid. If these siloxanes reacted in a manner analogous to the two discussed above, the "*i*" factors should be 10 and 13 for $(MO)_3T$ and $(MO)_4Q$, respectively. Since the observed values are much lower, it is obvious that some type of polymerization must have occurred to remove T or Q units.

For the $(MO)_3T$ case the equations which most closely approximate the observed "*i*" value are

$$(MO)_3T + 6H_2SO_4 \longrightarrow 3MHSO_4 + \frac{1}{x}[T(HSO_4)O]_x + 2H_3O^+ + 2HSO_4^- \quad (3)$$

$$(MO)_3T + 7.5H_2SO_4 \longrightarrow 3MHSO_4 + 0.5[T(HSO_4)_2]_2O + 2.5H_3O^+ + 2.5HSO_4^- \quad (4)$$

Assuming that *x* in Equation 3 is large, these equations give values of "*i*" of 7 and 8.5 for Equations 3 and 4, respectively. It is, therefore, probable that both these reactions take place.

Consideration of the possible reactions for the $(MO)_4Q$ system leads to

$$(MO)_4Q + 7.5H_2SO_4 \longrightarrow 4MHSO_4 + \frac{.5}{x}[Q_2(HSO_4)_2O_3]x + \frac{5}{2}H_3O^+ + \frac{5}{2}HSO_4^- \quad (5)$$

$$(MO_4)Q + 9H_2SO_4 \longrightarrow 4MHSO_4 + \frac{1}{x}[Q(HSO_4)_2O]_x + 3H_3O^+ + 3HSO_4^- \quad (6)$$

with "*i*" factors of 9 and 10 for Equations 5 and 6, respectively. Whereas in the case of the $(MO)_3T$ the reaction lay between the cyclic polymer, $[T(HSO_4)O]_x$ and the dimer, $[T(HSO_4)_2]_2O$, here it lies between the three-dimensional gel and the cyclic polymer. In no case, however, does the number of HSO_4 radicals attached to silicon exceed two.

When freshly prepared polysiloxane hydrolysates are equilibrated with sulfuric acid, catalytic amounts, *ca.* 5%, of 95% acid are used. Hence, the conditions observed in the freezing point experiments are not exactly those prevailing during equilibration. In spite of these differences, in view of the non-integral values of "*i*" for MOM and $(DO)_4$ a probable active intermediate in the rearrangement is a positive siliconium ion which attacks the oxygen of the unreacted siloxane, forming a new Si–O bond and ejecting a new siliconium ion which repeats the process.

RESEARCH LABORATORY
GENERAL ELECTRIC CO.
SCHENECTADY, N. Y.

RECEIVED JULY 21, 1947

---

(3) Sauer, THIS JOURNAL, **68**, 954 (1946).

(4) Sommer, Pietrusza, Kerr and Whitmore, *ibid.*, **68**, 156 (1946).

A Side Reaction of Acid Hydrazides in Qualitative Organic Analysis

By Louis Sattler and F. W. Zerban

In the course of the identification of small amounts of carbonyl derivatives obtained from heated fructose solutions which had been subsequently fermented with baker's yeast, *p*-nitrobenzhydrazide[1] and diphenylacethydrazide[2] were used.

With the *p*-nitrobenzhydrazide in 50% acetic acid, we obtained a small amount of a by-product of *s*-bis-(*p*-nitrobenzoyl)-hydrazine which crystallized in the form of yellow needles, and which on recrystallization from nitrobenzene melted at 288°.[3a] Previously reported melting points are 291°[3b] and 283°[3c].

Anal. Calcd. for $C_{14}H_{10}O_6N_4$: C, 50.91; H, 3.05. Found: C, 50.52; H, 3.21.

Similarly, diphenylacethydrazide in 60% ethanol plus 2 drops of glacial acetic acid[2b] yielded a white crystalline by-product of *s*-bis-(diphenylacetyl)-hydrazine. It was purified by recrystallization from a mixture of equal volumes of dioxane and 99% isopropyl alcohol. The pure crystals melted at 307°.

Anal. Calcd. for $C_{28}H_{24}O_2N_2$: C, 79.97; H, 5.75; N, 6.67. Found: C, 79.65; H, 5.60; N, 6.70.

Strain[4] has pointed out that while aqueous solutions of *m*-nitrobenzhydrazide are stable over long periods of time, strong acid solutions and elevated temperatures cause the formation of the symmetrical *bis*-hydrazine. It is evident that in addition to the normal reaction of acid hydrazides, a side reaction can also take place even in the absence of prolonged heating or strong acids. The ease with which these by-products are formed and isolated complicates the identification of expected derivatives. Consequently, due caution should be exercised in using hydrazides as derivatives of carbonyl compounds.

The authors express their thanks to Dr. Francine Schwartzkopf for the micro analyses.

---

[1] Eastman Kodak Co., #3341.

[2a] Aspelund, *Ber.*, **63B**, 1197 (1930), has described this compound but we found it more convenient to prepare it from ethyl diphenylacetate according to the general procedure (b) Sah and Ma, *J. Chinese Chem. Soc.*, **2**, 40 (1934).

[3a] The melting points are uncorrected.

[3b] Dann and Davies, *J. Chem. Soc.*, 1050 (1929).

[3c] Heller and Ebeling, *J. prakt. Chem.*, **142**, 274 (1935).

[4] Strain, This Journal, **57**, 758 (1935).

BROOKLYN COLLEGE, BROOKLYN, N. Y.
NEW YORK SUGAR TRADE LABORATORY
113 PEARL STREET
NEW YORK, N. Y.

RECEIVED NOVEMBER 6, 1947

4-Phenyl-*m*-dioxane

By Robert W. Shortridge

4-Phenyl-*m*-dioxane is produced in small amounts when styrene and formaldehyde react in acetic acid solution in the presence of a mineral acid catalyst such as sulfuric acid. The major product is 1-phenyl-1,3-diacetoxypropane, formed by the participation of the acetic acid in the reaction.

Prins,[1] in his original study of this reaction, erroneously formulated the products as derivatives of 2-phenyl-1,3-propanediol. Later, Fourneau, Benoit and Firmenich[2] proved their correct structure as derivatives of 1-phenyl-1,3-propanediol. Recently the structure of these compounds has been discussed by Emerson[3] on the basis of the results of the earlier workers.

It became necessary in the course of some research in this Laboratory to prepare moderate amounts of 4-phenyl-*m*-dioxane. To this end it was decided to study the reaction of Prins with a view to increasing the yield of the desired compound and the convenience of obtaining it.

An obvious change in the Prins procedure was to employ an inert mutual solvent in place of the acetic acid; such a change, of course, would eliminate entirely the formation of the undesired 1-phenyl-1,3-diacetoxypropane. It might be expected that the corresponding glycol would be formed under these changed conditions; this, however, proved not to be the case. When styrene and formaldehyde (in the form of trioxane) in a molar ratio of 1:2 were allowed to stand at room temperature in dioxane solution in the presence of sulfuric acid, a 78% yield of 4-phenyl-*m*-dioxane was obtained. There was no evidence of glycol formation and the remainder of the yield was accounted for by the production of polymers of styrene and of formaldehyde.

In a further step toward simplification the mutual solvent was eliminated completely and the reaction was run as a heterogeneous system, containing styrene, 37% aqueous formaldehyde and sulfuric acid. It was found necessary in this instance to work at reflux temperature. Carried out under these conditions the reaction yielded a maximum of 88% of 4-phenyl-*m*-dioxane. The sole identifiable by-products were polymers of styrene and of formaldehyde.

Since the completion of these studies, a patent[4] has issued claiming the preparation of a phenyl-*m*-dioxane in undisclosed yield by the reaction of styrene and 37% aqueous formaldehyde in the presence of hydrochloric acid and an inert hydrocarbon diluent. It is stated that only resinous products are obtained in the absence of the diluent. It appears, however, that under the conditions specified in the present paper the use of such a diluent is unnecessary.

Experimental

Reaction in Dioxane Solution.—A mixture of 220 g. of dioxane, 32 g. of 96% sulfuric acid, 30 g. of trioxane (du Pont) and 52 g. of styrene (Dow N-99) was allowed to stand at room temperature over a week-end. At the end of this time the reaction mixture was poured into 600 ml. of water and the organic layer was separated. The aqueous layer was extracted with three 50-ml. portions of benzene and the combined organic layer and extracts were washed with three portions of water and distilled. After removal of the benzene 64 g. (78%) of 4-phenyl-*m*-dioxane was obtained, b. p. 94–104° at 3 mm.

Reaction as a Heterogeneous System.—A mixture of 104 g. of styrene, 300 ml. of 37% aqueous formaldehyde and 16 g. of 96% sulfuric acid was refluxed and stirred overnight. The organic layer was washed successively

---

[1] Prins, *Proc. Acad. Sci. Amsterdam*, **22**, 51 (1919).

[2] Fourneau, Benoit and Firmenich, *Bull. soc. chim.*, **47**, 894 (1930).

[3] Emerson, *J. Org. Chem.*, **10**, 464 (1945).

[4] Engel, U. S. Patent 2,417,548 (March 18, 1947).

with dilute sodium carbonate solution, dilute sodium bisulfite solution and water. It was then dried by azeotropic distillation with 100 ml. of benzene. Further distillation yielded 144 g. (88%) of 4-phenyl-*m*-dioxane, b. p. 121–123° at 11 mm.

In several repetitions of the preceding preparation, the yields varied from 84 to 88%. The combined products were fractionated through a Vigreux column. A center cut from this distillation had these physical properties: b. p. 95° at 2 mm., $n^{25}{}_D$ 1.5288, d^{25} 1.101. Prins[1] reported b. p. 128–30° at 13 mm., $n^{18}{}_D$ 1.53063, $d^{18}{}_4$ 1.1111.

ORGANIC CHEMISTRY DEPARTMENT
MIDWEST RESEARCH INSTITUTE
KANSAS CITY, MISSOURI
RECEIVED AUGUST 21, 1947

The Vapor Pressures of Solutions of Sodium and Potassium Bisulfates at 25°

BY R. H. STOKES

As part of a general study of the vapor pressure–concentration curves of a number of mono-sodium and mono-potassium salts of dibasic acids which is in progress in this Laboratory, isopiestic vapor pressure measurements have been made on sodium and potassium bisulfates. Owing to the relatively large second dissociation constant[1] of sulfuric acid (K_2 = 0.012 at 25°) these two salts have little in common with the others being investigated and are therefore reported separately.

Stock solutions of the two bisulfates were prepared by dissolving the calculated amount of the anhydrous normal sulfate in sulfuric acid which was previously analyzed by weight-titration against sodium carbonate. The resulting solutions were equilibrated (in platinum dishes) against sodium chloride as reference substance by the usual technique,[2] the molalities of pairs of solutions of equal vapor pressure being given in Table I. From these results and the standard values[3] for sodium chloride the vapor pressures at round concentrations were computed and are given in Table II in the form of $(p_0 - p)/mp_0$. A graph of this relative molal vapor pressure lowering against m shows a rapid rise below 1*M* as is to be expected in consequence of the increasing dissociation of the bisulfate ion with dilution. There seems, however, to be little justification for attempting a quantitative estimate of the amounts of the various ionic species present. The calculation of activity coefficients is also complicated by this dissociation which makes extrapolation to infinite dilution difficult. Consequently, though the data are of good accuracy (0.1–0.2%) no solute activity data derived from them are included in Table II.

TABLE I

(a) Isopiestic solutions of sodium bisulfate and sodium chloride at 25°

m_{NaHSO_4}	0.1041	0.1237	0.1482	0.1529	0.2039	
m_{NaCl}	0.1190	0.1400	0.1664	0.1713	0.2255	
m_{NaHSO_4}	0.2823	0.4272	0.6425	0.7774	1.084	1.174
m_{NaCl}	0.3078	0.4573	0.6763	0.8119	1.119	1.210
m_{NaHSO_4}	1.340	1.382	1.632	2.398	3.065	4.067
m_{NaCl}	1.376	1.420	1.671	2.456	3.138	4.140
m_{NaHSO_4}	4.191	5.112	5.240	5.610	6.320	
m_{NaCl}	4.265	5.122	5.228	5.555	6.147	

(b) Isopiestic solutions of potassium bisulfate and sodium chloride at 25°

m_{KHSO_4}	0.1068	0.1277	0.1361	0.1445	0.2423	0.4216
m_{NaCl}	0.1199	0.1425	0.1505	0.1595	0.2584	0.4311
m_{KHSO_4}	0.5287	0.7233	0.7538	1.002	1.156	1.502
m_{NaCl}	0.5300	0.7038	0.7307	0.9471	1.074	1.359
m_{KHSO_4}	1.664	1.827	2.259	2.653		
m_{NaCl}	1.485	1.614	1.943	2.235		

TABLE II

RELATIVE MOLAL VAPOR PRESSURE LOWERINGS $(p_0 - p)/mp_0$ OF SODIUM AND POTASSIUM BISULFATES AT 25° (CALCULATED RELATIVE TO p_1 = 23.756 MM.)

m	$NaHSO_4$	$KHSO_4$	*m*	$NaHSO_4$	$KHSO_4$
0.1	0.03838	0.03775	1.2	0.03425	0.03074
.125	.03778	.03722	1.4	.03435	.03035
.15	.03737	.03669	1.6	.03456	.03000
.2	.03671	.03589	1.8	.03482	.02977
.3	.03590	.03469	2.0	.03508	.02957
.4	.03537	.03384	2.5	.03582	.02916
.5	.03502	.03316	3.0	.03658	
.6	.03477	.03266	3.5	.03731	
.7	.03460	.03223	4.0	.03795	
.8	.03445	.03188	4.5	.03847	
.9	.03436	.03156	5.0	.03882	
1.0	.03432	.03129	6.0	.03912	

I am indebted to the Commonwealth Research Grant to Australian Universities for funds which made possible the purchase of equipment used in this work.

CHEMISTRY DEPARTMENT
UNIVERSITY OF WESTERN AUSTRALIA
NEDLANDS, W. A.
RECEIVED SEPTEMBER 5, 1947

---

[1] W. J. Hamer, THIS JOURNAL, **56**, 860 (1934).

[2] R. A. Robinson and D. A. Sinclair, *ibid.*, **56**, 1830 (1934).

[3] R. A. Robinson, *Trans. Roy. Soc. New Zealand*, **75** (II), 203 (1946); see also appendix to R. H. Stokes and B. J. Levien, THIS JOURNAL, **68**, 333 (1946).

Quinazolines. IV. Synthesis and Hydrolysis of 3-(4′-Quinazoyl)-4-quinazolone[1]

BY ARTHUR J. TOMISEK AND BERT E. CHRISTENSEN

In the attempts to prepare 4-cyanoquinazoline by fusion of 4-chloroquinazoline with either silver or cuprous cyanide[2] only small amounts of a fibrous material were isolated. This product appeared to be pure, and analysis suggested that it might be a diquinazolyl ether. Since 4-chloroquinazoline is easily hydrolyzed by traces of water, it is possible to account for diquinazolyl ether as resulting from the condensation of the 4-chloroquinazoline with small amounts of hydroxyquinazoline impurity.

There is no record in the literature of a diquinazolyl ether. Bogert and May attempted the syn-

---

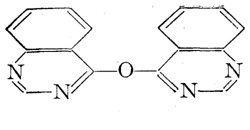
[1] Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 115, School of Science.

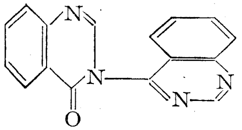
[2] Tomisek and Christensen, THIS JOURNAL, **67**, 2114 (1945).

thesis by refluxing sodium 4-quinazolonate with 4-chloroquinazoline in a benzene medium.[3] Attributing their failure to the insolubility of sodium 4-quinazolonate in benzene, the work was repeated in this laboratory using a dry dioxane solvent. This modified procedure gave a product which was found to be identical with that resulting from the cyanide fusions.

A diquinazolyl ether synthesized as above could have either of two possible structures: di-4-quinazolyl ether (I) or 3-(4′-quinazolyl)-4-quinazolone (II). Among the alkylquinazolyl ethers, O-ethers (I) or N-ethers[4] (II) are synthesized depending on which radical contains the halide and which the —ONa group (Fig. 1). When both radicals are quinazolyl, analogy to the alkylquinazolyl ethers fails to distinguish between the two possible isomers.

O-Ethers are very easily cleaved by acid in contrast to N-ethers which are stable.[3] The diquinazolyl ether prepared above reacted very readily with dilute hydrochloric acid to yield almost quantitatively a product ($C_{15}H_{13}N_3O$) which contained a quinazoline unit bound apparently to a degraded quinazoline nucleus. The failure to obtain 4-hydroxyquinazoline as the hydrolysis product, together with the fact that the two nuclei remain attached after hydrolysis, suggests an N-ether type of linkage. The stability of the ether toward boiling alcohol or water and to dry heat (m. p. 232° without decomposition or rearrangement) lends additional support to this point of view. The O-ethers are generally unstable under these conditions.[5]


I


II

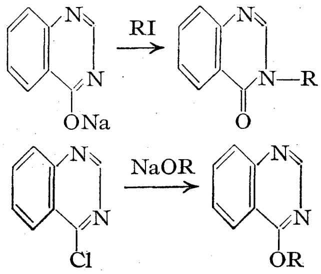


Fig. 1.

Experimental[6]

3-(4′-Quinazolyl)-4-quinazolone.—Twelve and seventenths grams of 4-hydroxyquinazoline was added to a solution containing 4.5 g. of potassium hydroxide (0.08 mole) in 75 ml. of absolute alcohol. The solvent was then removed on a steam-bath and the quinazolinate throughly dried under high vacuum. One hundred milliliters of dry dioxane and 14.6 g. of 4-chloroquinazoline (0.088 mole) were added to the pulverized residue and the mixture was refluxed for three days. Potassium chloride was removed by filtration while the reaction mixture was still hot. 3-(4′-Quinazolyl)-4-quinazolone separated from the liquors on cooling. Additional product was obtained by evaporating the mother liquors to dryness. The combined fractions were then triturated with dilute sodium hydroxide solution. The crude product (16.1 g., 74%), purified by charcoal treatment of a hot alcohol solution, yielded 14.1 g. (64%) of pure 3-(4′-quinazolyl)-4-quinazolone. The product recrystallized from alcohol as thin, wool-like fibers, m. p. 232.5°, was insoluble in water, soluble in both dioxane and hot benzene. It was stable to long boiling in water.

Anal. Calcd. for $C_{16}H_{10}N_4O$: C, 70.06; H, 3.68; N, 20.43: Found, C, 70.02; H, 3.85; N, 20.43.

Acid Hydrolysis Product of 3-(4′-Quinazolyl)-4-quinazolone.—The 3-(4′-quinazolone)-4-quinazolone (10.6 g.) was dissolved in hot dilute hydrochloric acid. In a few seconds the hydrochloride of the cleavage product precipitated. The mixture was cooled and filtered. The solid material and liquors were separately treated with excess sodium bicarbonate. The free base was then filtered, washed with water and dried. Combined fractions amounted to 9.3 g. (96%) of the crude product. After recrystallization from pyridine–water, fine, white, needle-like crystals melting at 244–225° were obtained.

Anal. Calcd. for $C_{15}H_{13}N_3O$; C, 71.69; H, 5.21; N, 16.72; mol. wt., 251. Found: C, 71.69; H, 5.23; N, 16.87; mol. wt.,[7] 255, 232, 257.

---

[3] Bogert and May, THIS JOURNAL, **31**, 507 (1909).

[4] For other examples of this terminology, see ref. 3, p. 508.

[5] Bogert and Seil, THIS JOURNAL, **29**, 526 (1907).

[6] All melting points are corrected. All N-analyses are by the Dumas method.

[7] Niederl and Niederl, "Micromethods of Quantitative Organic Analysis," 2d ed., John Wiley & Sons, New York, N. Y., 1942, p. 217.

DEPARTMENT OF CHEMISTRY
OREGON STATE COLLEGE
CORVALLIS, OREGON

RECEIVED JULY 14, 1947

Investigation of the Oxidative Condensation of 2-Methoxy-4-nitrotoluene. The Use of Oxidative Catalysts

BY GINO R. TREVES

The oxidation of various substituted 4-nitrotoluenes to stilbenes was described by Green and Baddiley.[1] They also prepared 2,2′-dimethoxy-4,4′-dinitrostilbene by a two stage air oxidation of 2-methoxy-4-nitrotoluene. Recently Ashley and Harris[2] repeated the work of Green and Baddiley but were unable to obtain the stilbene. They report that the reaction ceased at the bibenzyl stage. When we carried out the reaction only minute quantities of condensation products were obtained. It was then decided to run the reaction with oxygen instead of air under more carefully controlled conditions.

The reaction mixture was shaken in the Adams shaker and the rate of oxygen consumption observed. The contact was continued for twenty-two hours and the product consisted of a mixture of the bibenzyl and the stilbene in 30% yield.

Compounds of high oxidation potential were tried in the hope that they would catalyze the reaction by functioning as hydrogen carriers. Results are shown in Fig. 1. Of special interest was the fact that cyclohexanol was almost as effective as cyclohexanone. This indicates that cyclo-

---

[1] Green and Baddiley, *J. Chem. Soc.*, **93**, 1721 (1908).

[2] Ashley and Harris, *ibid.*, 567 (1946).

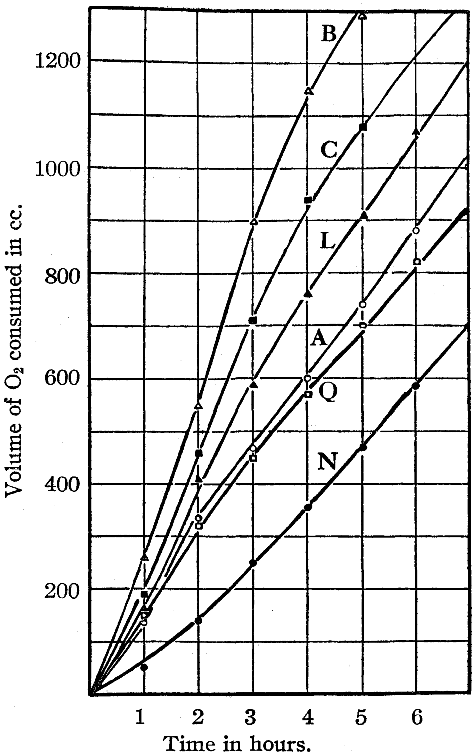


Fig. 1.—Effect of the addition of 0.001 M quantities of oxidation catalysts on the oxygen uptake in the oxidative condensation of 2-methoxy-4-nitrotoluene: ●, no catalyst, N; □, anthraquinone, Q; ○, acetone, A; ▲, cyclohexanol, L; ■, cyclohexanone, C; △, benzoquinone, B.

hexanol may be oxidized first to cyclohexanone which then acts as a catalyst. The total oxygen consumption was well above the expected theoretical amount. Therefore, oxygen was also used up in some side reaction.

Atmospheric oxygen as in the original method[1] was then tried in the presence of a catalyst and it proved to be effective. When benzoquinone was used and air bubbled through the reaction mixture for seven hours a 55% yield of the bibenzyl was obtained. When acetone was used and air bubbled through for twenty-two hours, 60% yield of a mixture of two parts of the bibenzyl and one part of the stilbene was obtained.

Experimental

Preparation of 2,2′-Dimethoxy-4,4′-dinitrobibenzyl.—Air is bubbled through a suspension of 10 g. of pure 2-methoxy-4-nitrotoluene in 200 ml. of 33% solution of methanolic potassium hydroxide containing one gram of benzoquinone for seven hours. The product is filtered, washed with dilute hydrochloric acid then with hot methanol and recrystallized from ethyl acetate, m. p. 179°; yield 5.5 g. On bromination it gives α,α'-dibromo-2,2′-dimethoxy-4,4′-dinitrobibenzyl, m. p. 247–249°.

Preparation of 2,2′-Dimethoxy-4,4′-dinitrobibenzyl and 2,2′-Dimethoxy-4,4′-dinitrostilbene.—Forty grams of 2-methoxy-4-nitrotoluene is placed in 800 ml. of 33% methanolic potassium hydroxide and 20 ml. of acetone. The mixture is well stirred and air is bubbled through at room temperature. After twenty-two hours the precipitate is filtered off. The mixture is then taken up in boiling ethyl acetate which dissolves the bibenzyl. The stilbene is filtered off and weighs 7.5 g. On cooling 16 g. of bibenzyl is collected from the ethyl acetate. The stilbene on bromination gives the same α,α'-dibromo-2,2′-dimethoxy-4,4′-dinitrobibenzyl as was obtained by brominating the bibenzyl.

Procedure Followed to Determine the Rate of Oxygen Consumption (see Fig. 1).—Ten grams of 2-methoxy-4-nitrotoluene and 0.001 M quantities of the different oxidation catalysts were placed in 200 ml. of 33% methanolic potassium hydroxide and shaken for twenty-two hours in the Adams shaker in the presence of oxygen at atmospheric pressure. The yield of mixture of the bibenzyl and the stilbene for all the catalysts tried varied between 30% and 38%. The mixture contained about equal quantities of the two substances.

RESEARCH LABORATORIES
SCHIEFFELIN & CO.
NEW YORK 3, N. Y.
RECEIVED SEPTEMBER 5, 1947

COMMUNICATIONS TO THE EDITOR

STUDIES ON THE MECHANISM OF THE DEAMINATION OF DIAZONIUM SALTS WITH HYPOPHOSPHOROUS ACID

Sir:

In an attempt to introduce a deuterium atom into the *meta* position of nitrobenzene, a deamination reaction with hypophosphorous acid[1] was carried out. Thus, to a solution of diazotized *m*-nitroaniline containing 30% deuterium oxide was added a solution of hypophosphorous acid in water which contained 50% of deuterium oxide. Before use the hypophosphorous acid solution was allowed to stand at room temperature for twenty-four hours. Much to our surprise *the nitrobenzene which was obtained was found to contain no deuterium.* This was determined for us by Mrs. James L. Johnson and Dr. Foil A. Miller with an infrared spectrometer.[2] Similarly, aniline hydrochloride prepared from this sample of nitrobenzene was found to show no absorption in the region of the C–D stretching frequencies (2270 cm.$^{-1}$).

We are not yet in a position to comment on the mechanism of the reaction, but this result is par-

---

(1) See Kornblum, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 277.

(2) The lower limit of the sensitivity of this method for the detection of deuterium in an aromatic ring has not yet been completely determined. From dilution experiments conducted with deuterobenzene in benzene, however, it appears that if 1–2% of the nitrobenzene molecules contained deuterium, it could be detected.

ticularly interesting in view of the fact that the work of Erlenmeyer, Schoenauer and Schwarzenbach[3] indicates that all three hydrogen atoms of hypophosphorus acid exchange rapidly with deuterium oxide. Apparently in the deamination reaction a hydrogen atom was extracted from another aromatic nucleus, since that is the only source of hydrogen which is not equilibrated with deuterium.

[3] Erlenmeyer, Schoenauer and Schwarzenbach, *Helv. Chim. Acta*, **20**, 732 (1937); see also Franke and Mönch, *Ann.*, **550**, 1 (1941).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS
ELLIOT R. ALEXANDER
ROBERT E. BURGE

RECEIVED DECEMBER 22, 1947

CAUSE OF EXPLOSIONS OCCASIONALLY OBSERVED DURING EVAPORATION OF SOLUTIONS OF ALUMINUM HYDRIDE AND RELATED COMPOUNDS

Sir:

In experiments involving dimethyl ether solutions of aluminum hydride, as well as of lithium and sodium aluminum hydrides, explosions have occasionally occurred. The details to be described have demonstrated that the explosions were caused by carbon dioxide present as an impurity in some samples of the ether.

Explosions have occurred toward the end of distillations undertaken to remove the solvent from dimethyl ether solutions of lithium aluminum hydride. That the explosions were due to an impurity more volatile than dimethyl ether was indicated by the facts (1) that later samples of the ether taken from a cylinder caused less violent explosions than the first few samples, and (2) ether taken from another cylinder at no time caused these explosions. These facts, as well as chemical tests to prove their absence, excluded aldehydes, alcohols or peroxide as the offending impurity. Considerable carbon dioxide was present in the cylinders whose contents led to explosions; its removal by fractionation *in vacuo* rendered the contents harmless. After carbon dioxide was reintroduced into the purified sample, the explosions recurred. It was then found that diethyl ether solutions of lithium aluminum hydride, which can ordinarily be safely evaporated, may also cause explosions if first treated with carbon dioxide in considerable amount.

Evaporation of dimethyl ether solutions of aluminum hydride and subsequent slow heating of the residue may result in a very rapid reaction in which, at slightly above 40°, relatively large quantities of gaseous material are suddenly released, but which is not accompanied by detonation, unless a large excess of aluminum chloride is present. But carbon dioxide-free ether leads to a residue which begins to decompose *slowly* above 70°, if aluminum chloride is not present in large amount; even in the presence of a large excess of the latter (2.5 moles/l.), the decomposition above 40° is sudden but without detonation. Other experiments have shown that aluminum chloride accelerates the decomposition of aluminum hydride.

On one occasion a violent explosion occurred when the residue resulting from evaporation of a dimethylcellosolve solution of aluminum hydride was warmed. The aluminum hydride was contaminated with aluminum chloride, which is known to decrease the stability of the former, and the dimethylcellosolve was impure. No explosion resulted when the experiment was repeated with purified materials.

Lithium aluminum hydride is considerably more stable than aluminum hydride. Approximately two hundred different reactions using the former reagent have been carried out in this Laboratory without untoward results although no precautions were taken to exclude carbon dioxide. We are, therefore, convinced that it may be used with perfect safety if the precautions suggested by the facts herein reported are followed. In other words, we recommend that in the reduction of organic compounds the normal procedure of hydrolyzing the initial reaction product before evaporation of the solvent be employed. If, as would rarely be the case, it is desired to evaporate the solvent before hydrolysis of the initially produced organic salts, the safety of the procedure should first be tested by use of a small sample.

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF CHICAGO
CHICAGO 37, ILL.
GERALDINE BARBARAS
GLEN D. BARBARAS
A. E. FINHOLT
H. I. SCHLESINGER

RECEIVED DECEMBER 15, 1947

CRYSTALLINITY OF HYDRO-CELLULOSES

Sir:

Hydrolytic methods are being used at present for evaluating the intramolecular structure of cellulose. It has been suggested in a paper to be published in THIS JOURNAL that such methods might possibly cause additional crystallization in the initial stages of hydrolysis. We have succeeded in obtaining data which indicate that such changes do occur. Consequently, it would seem necessary to reinterpret accessibility measurements based on hydrolysis rates in terms of two competing processes: hydrolysis and further crystallization.

The data in Table I were obtained on a beechwood pulp that had been digested in boiling 2.5 N hydrochloric acid–0.6 M ferric chloride solution constantly saturated with air.

TABLE I

Time treated, minutes	Percentage of samples destroyed	Specific vol. of bone-dry hydrocellulose, ml./g.	Percentage increase in crystallinity from Sp V. change, %
0	0	0.652	
10	4.8	.647	15
19	6.0	.646	18
28	39.0	.645	19

The specific volume was obtained from density, which was measured by flotation in carbon tetrachloride. The percentage increase in crystallinity was calculated using the values given by H. Mark[1] for the density of crystalline cellulose, 1.59 g./ml. (Sp V = 0.629). The density of amorphous cellulose was taken to be 1.50 g./ml. (Sp. V = 0.667) as estimated by P. H. Hermans.[2] The following relation was used to calculate the increase in crystallinity

$$\frac{\text{Sp. } V \text{ of untreated sample} - \text{Sp. } V \text{ of treated sample}}{\text{Difference in Sp. } V \text{ of amorphous and crystalline cellulose}}$$

A rayon of specific volume 0.653 showed a weight loss of 10% when treated with the reagent for five minutes. The specific volume of the treated sample was 0.647, indicating an increase of 16% in the crystallinity.

If the only process involved in the initial stages of this treatment is the attack and removal of the amorphous portion of the fiber, the density increase should predict a change of crystallinity of the same order of magnitude as the weight of material lost. However, the actual increase in density is much larger. This may indicate that with the rupture of a cellulose chain in an amorphous portion of the fiber a process of crystallization is initiated.

---

(1) H. Mark, "Physik und Chemie der Cellulose," Berlin, 1932.

(2) P. H. Hermans, "Contribution to the Physics of Cellulose Fibres," Elsevier Publishing Co., Inc., 1946.

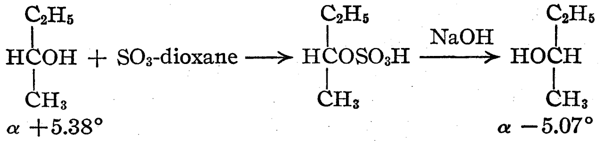
INST. OF POLYMER RESEARCH F. C. BRENNER
POLYTECHNIC INST. OF BROOKLYN V. FRILETTE
BROOKLYN, N. Y. H. MARK

RECEIVED DECEMBER 9, 1947

A NEW WALDEN INVERSION

Sir:

The following reaction sequence constitutes a new Walden inversion



$$\begin{array}{c}C_2H_5\\|\\HCOH\\|\\CH_3\end{array} + SO_3\text{-dioxane} \longrightarrow \begin{array}{c}C_2H_5\\|\\HCOSO_3H\\|\\CH_3\end{array} \xrightarrow{NaOH} \begin{array}{c}C_2H_5\\|\\HOCH\\|\\CH_3\end{array}$$

α +5.38° α −5.07°

The second step resembles the displacement of *p*-toluenesulfonate ion from secondary alkyl esters of the sulfonic acid by ethoxide or acetate ions, a reaction which has been shown to invert the configuration of the carbinol carbon.[1]

We previously[2] prepared (+)*s*-butylsulfuric acid by action of Suter's sulfur trioxide–dioxane reagent on (+)*s*-butyl alcohol and found that upon its acid hydrolysis a (+)alcohol was recovered whose rotation was 30% of that of the starting material. We had assumed that the racemization was confined to the hydrolytic step and that the formation of the alkylsulfuric acid proceeded with little if any racemization. This is now confirmed.

Since the action of chlorosulfonic acid and of sulfuric acid upon (+)alcohol gave (+)*s*-butylsulfuric acid, and since it was difficult to see how all these methods could involve breaking the carbon–oxygen bond of the alcohol, it was considered that the alkylsulfuric acid had the same configuration as the alcohol. If this is true, and its plausibility is increased by our finding that the sulfur trioxide–pyridine complex[3] also gives a (+)alkylsulfuric acid, then the saponification involves the displacement of a sulfate ion by a hydroxide ion with inversion of configuration. Since this reaction is one between two ions of like charge it is comparatively slow.

The alkylsulfuric acid was prepared by action of the sulfur trioxide–dioxane complex upon an alcohol of α +5.38. In one saponification, 8 g. of (+)sodium *s*-butylsulfate (from neutralizing the alkylsulfuric acid reaction mixture with sodium hydroxide, evaporating and extracting the sodium alkylsulfate with methanol) and 10 g. of sodium hydroxide were dissolved in 50 cc. of water. At 100° the reaction required two days for substantial completion. Alcohol was recovered in 54% yield with a rotation 6% below that of the starting alcohol and of opposite sign. About 8% of gas, apparently butylene, was evolved. A similar alcohol was obtained from the barium salt in a more concentrated potassium hydroxide solution, but several times as much butylene resulted.

Further investigation now under way at this laboratory should reveal the degree to which this reaction is common to secondary alcohols.

---

(1) This work of Kenyon, Phillips and co-workers is reviewed by Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 160–163.

(2) Burwell, THIS JOURNAL, **67**, 220 (1945).

(3) Sobel, Drekter and Natelson, *J. Biol. Chem.*, **115**, 381 (1936).

DEPARTMENT OF CHEMISTRY ROBERT L. BURWELL, JR.
NORTHWESTERN UNIVERSITY HOWARD E. HOLMQUIST
EVANSTON, ILL.

RECEIVED DECEMBER 18, 1947

FORMYLFOLIC ACID, A FUNCTIONAL DERIVATIVE OF FOLIC ACID

Sir:

Previous studies from this Laboratory have indicated that a coenzyme containing *p*-aminobenzoic acid is involved in combining a single carbon unit into the pyrimidine ring of purines[1] and that folic acid functions in the biosynthesis of purines.[2] Seeking functional derivatives which could act as "carriers" of formate, we prepared *p*-aminobenzoylhistidine and condensed it with α,β-dibromopropionaldehyde and 2,4,5-triamino-6-hydroxypyrimidine to obtain pteroylhistidine. No pronounced activity was obtained with either of these histidine derivatives. The announcement of the structure of rhizopterin[3] which is *p*-[N-(2-amino-4-hydroxypyramido-[4,5-b]pyrazin-6-ylmethyl)-formamido]-benzoic acid gave a clue as

---

(1) Shive, *et al.*, THIS JOURNAL, **69**, 725 (1947).

(2) Rogers and Shive, *J. Biol. Chem.*, in press.

(3) Wolf, *et al.*, THIS JOURNAL, **69**, 2753 (1947).

to how formate may be carried by a functional derivative of folic acid. Accordingly, formylfolic acid was prepared by heating 2 cc. of 98% formic acid and 0.5 cc. of acetic anhydride with 26 mg. of folic acid (pteroylglutamic acid) for one hour at 100°. The volatile reactants were removed *in vacuo*, and the light yellow product was precipitated from an alkaline solution by acetic acid. For analysis, a sample was hydrolyzed, and formic acid determined (Calcd.: 9.8%. Found.: 9.5%). The formylfolic acid was as effective as folic acid in stimulating the growth of *Streptococcus faecalis R* and *Lactobacillus casei*.

However, in an inhibition analysis with 7-methylfolic acid,[4] formylfolic acid was approximately thirty times as active as folic acid in preventing the toxicity of the inhibitor for *S. faecalis R;* the antibacterial index was 3,000 for formylfolic acid as compared with 100 for folic acid over a range of inhibitor concentrations from 10 to 100γ per 10 cc. In 10 cc. of medium,[2] a mixture of 0.3 γ of folic acid with 0.03 γ of formylfolic acid was no more effective than 0.03 γ of formylfolic acid alone in preventing the toxicity of the inhibitor. Synthetic rhizopterin[3] was two to three times as effective as folic acid in preventing the toxicity of the inhibitor. The toxicity of methylfolic acid was increased several fold by treating with 98% formic acid at 100° for two hours. For *L. casei* formylfolic acid was only slightly more effective than folic acid in preventing the toxicity of the inhibitor.

These results indicate that formylfolic acid is a functional derivative of folic acid and is competitively inhibited by methylfolic acid. The activity of rhizopterin indicates that it probably is converted directly to formylfolic acid.

These and other unpublished experiments offer additional evidence that the biochemical functions of *p*-aminobenzoic and folic acid derivatives involve the introduction of the single carbon unit into purines, pyrimidines and probably histidine.

The possibility of enhanced activity and decreased toxicity for formylfolic acid as compared with folic acid in treatment of pernicious anemia indicates the desirability for clinical testing.

---

[4] Crude product from the condensation of α,β-dibromobutyraldehyde, 2,4,5-triamino-6-hydroxypyrimidine and *p*-aminobenzoylglutamic acid obtained from Dr. E. L. R. Stokstad (Franklin, *et al.*, *J. Biol. Chem.*, **169**, 427 (1947)).

THE BIOCHEMICAL INSTITUTE AND
THE DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF TEXAS, AND
THE CLAYTON FOUNDATION FOR
RESEARCH, AUSTIN, TEXAS

MALCOLM GORDON
JOANNE MACOW RAVEL
ROBERT E. EAKIN
WILLIAM SHIVE

RECEIVED DECEMBER 29, 1947

CONCERNING THE STRUCTURE OF PHTHIOIC ACID

Sir:

Polgar and Robinson[1] have recently proposed, partly on the basis of the highly questionable degradative evidence of Wagner-Jauregg,[2] that phthioic acid,[3] isolated from tubercle bacillus, may be 3,13,19-trimethyltricosanoic acid. This acid was synthesized, but since it contains three asymmetric carbons the *dl*-mixture was of no value for comparison with the natural product. By use of the data which have now been collected concerning the optical rotation of fatty acids containing branching methyl groups, it is possible to estimate with some accuracy the maximum rotation to be expected of an acid such as 3,13,19-trimethyltricosanoic acid. Data of interest to this discussion appear in Table I.

TABLE I

Acid	$[\alpha]_D$	$[M]_D$
(+)-2-Methylhexacosanoic[4]	6.8°[a]	28°
(+)-2-Methyldodecanoic[4]	13.2°	28.3°
(+)-4-Methylhexanoic[5]	8.4°	11.0°
(+)-12-Methyltetradecanoic[6]	4.7°	11.4°
(+)-10-Methyloctadecanoic[7]	0.06°	0.2°
(+)-3-Methylhendecanoic[7]	5.0°	10.1°

[a] Taken in chloroform solution, remaining values obtained homogeneous.

As shown by the above data and elsewhere,[6] the molecular rotation remains reasonably constant for a given relationship of methyl group to the ends of the chain. Variables such as solvent and temperature have appreciable but not large effects in these compounds. For the case of 3,13,19-trimethyltricosanoic acid, it seems safe to assume that (a) the contribution of each asymmetric carbon to the rotation is unaffected by the presence of the other branching groups, (b) the contribution of carbon-19 is less than the rotation of the third or fourth acids listed in Table I, (c) the contribution of carbon-13 is similar to that of the fifth acid in Table I, (d) the contribution of carbon-3 is the same as the rotation of the sixth acid in Table I. It follows that the maximum molecular rotation for 3,13,19-trimethyltricosanoic acid should be approximately 22°, less than half the value of 49.7° observed for phthioic acid. Thus, it seems impossible that phthioic acid could have the structure suggested by Polgar and Robinson.

It is of interest that 2,3,21-trimethyltricosanoic acid has a calculated maximum molecular rotation of approximately 49.5° (ignoring any effect caused by the proximity of the 2- and 3-methyl groups), and all other trimethyltricosanoic acids would have a lower rotation. Thus, if phthioic acid is a long-chain acid with several branching methyl groups (evidence supporting this proposition seems doubtful), three of these groups are probably in the 2-, 3- and anteiso positions. Additional methyl groups between the 3- and anteiso positions should contribute little to the rotation.

---

[1] Polgar and Robinson, *J. Chem. Soc.*, 389 (1945).

[2] Wagner-Jauregg, *Z. Physiol. Chem.*, **247**, 135 (1937).

[3] Spielman and Anderson, *J. Biol. Chem.*, **112**, 759 (1936).

[4] Ställberg-Stenhagen, *Arkiv Kemi, Mineral. Geol.*, **23**, No. 15 (1946).

[5] Welt, *Compt. rend.*, **119**, 855 (1894).

[6] Weitkamp, THIS JOURNAL, **67**, 447 (1945).

[7] Prout, Cason and Ingersoll, *ibid.*, **69**, 1233 (1947).

It would appear, however, that the absence of rings and quaternary carbons in phthioic acid has hardly been demonstrated.

CHEMICAL LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA JAMES CASON
FURMAN CHEMICAL LABORATORY
VANDERBILT UNIVERSITY
NASHVILLE, TENN. FRANKLIN S. PROUT

RECEIVED OCTOBER 14, 1947

THE EXCHANGE REACTION BETWEEN THE TWO OXIDATION STATES OF THALLIUM IN PERCHLORIC ACID SOLUTIONS

Sir:

We have studied the exchange reaction between thallous and thallic ions in aqueous perchloric acid and wish to make a preliminary report of the results. This reaction is of interest in that it involves transfer of two electrons between the reacting species and in that it is found to proceed at a slow and measurable rate, in contrast to the several other electron-transfer exchange reactions which have been reported to be fast.[1] Earlier studies of this reaction[2,3] were handicapped by the short half-life of the radioactive tracer used (ThC″, half-life 3.1 min.) and gave results which are difficult to interpret.

Using $Tl^{204,206}$ (half-life *ca.* 3 years), we have observed the exchange reaction and have investigated the dependence of the rate of exchange on the concentrations of thallous and thallic perchlorates, on the acid concentration, and on the temperature. The thallous perchlorate concentration was varied from 0.003 f. to 0.015 f., that of thallic perchlorate from 0.0006 f. to 0.003 f.

The method employed was to mix stock solutions of active thallic perchlorate and inactive thallous perchlorate in a stoppered flask immersed in a constant temperature bath, to withdraw samples at intervals, and to determine the distribution of activity between the two oxidation states of thallium. Thallous chromate was precipitated from the sample by the addition of a mixture containing chromate, cyanide, ethanol and excess ammonia. This method was found to give a reasonably clean separation, and not to induce a significant amount of exchange during precipitation.

The activity in the thallous fraction was found to vary with time in the simple exponential manner expected for an exchange reaction occurring at chemical equilibrium.[4,5] The rate of exchange was found to be proportional to the first power of the concentration of each reactant. The specific rate constant is 2.0 moles^{-1} liter hours^{-1} at 49.5° (perchloric acid 0.4 f.). The experimental activation energy is 12 kcal./mole. The addition of a neutral salt ($LiClO_4$ 0.6 f.) increased the rate, suggesting that ions of like sign participate in the exchange.

When the acid concentration was varied, the rate constant showed a maximum at about 1 f. ($k = 2.5$) and decreased to 0.9 at 3.9 f. This behavior doubtless results from the combined effects of ionic strength and hydrolysis of thallic ion.

We have also observed the exchange in 0.2 f. hydrochloric acid and find that the rate is markedly greater than in perchloric acid.

We are continuing these studies.

We are grateful to the Los Alamos Laboratory, in particular to Mr. J. W. Starner and Mr. E. L. Bentzen, for neutron irradiation of the thallium. We also are indebted to Dr. Norman Davidson for his interest and helpful advice.

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA GARMAN HARBOTTLE[6]
R. W. DODSON[6]

RECEIVED DECEMBER 8, 1947

---

(1) See for example G. T. Seaborg, *Chem. Rev.*, **27**, 199 (1940).

(2) J. Zirkler, *Z. Physik*, **99**, 669 (1936), *et al.*

(3) V. Majer, *Z. physik Chem.*, **A179**, 51 (1937).

(4) H. A. C. McKay, *Nature*, **142**, 997 (1938).

(5) R. B. Duffield and M. Calvin, THIS JOURNAL, **68**, 557 (1946).

(6) Now at Chemistry Department, Columbia University, New York, N. Y.

EXCHANGE REACTION BETWEEN THALLIUM (I) AND THALLIUM (III) IONS IN PERCHLORIC AND NITRIC ACID SOLUTIONS

Sir:

We have measured the rate of the exchange reaction between thallium(I) and thallium(III) ions in aqueous solutions of perchloric and nitric acid and have found it to be slow and measurable. The data from earlier work[1,2] on this reaction are difficult to interpret because the short lived tracer, ThC″ (3.1 m.), limited the duration of the experiments.

Part of the $Tl^{204,206}$ (*ca.* 3.5 y) used as tracer in our experiments was prepared by the Tl(d, p) reaction in the Washington University cyclotron, the rest by the Tl(n,γ) reaction in the Oak Ridge pile. Our procedure was to mix acid solutions of thallium (I) perchlorate (nitrate) and active thallium (III) perchlorate (nitrate), remove aliquots at definite intervals of time, separate the two oxidation states, and assay and count the two fractions. Two methods of separation were used. (1) Thallium (III) hydroxide was precipitated with ammonium hydroxide; both fractions being subsequently weighed and counted as thallium (I) chromate. (2) Thallium (I) bromide was precipitated with sodium bromide solution, both fractions being weighed and counted as thallium (I) bromide.

A fast, incomplete, but reproducible exchange was induced at the time of separation. The induced exchange (exchange measured at zero time) could be varied from 45 to 70% for the hydroxide separation and from 8 to 13% for the bromide separation by adding the reagents in a different

---

(1) J. Zirkler, *Z. Physik*, **87**, 410 (1934); **98**, 75 (1935); **99**, 669 (1936); *Z. physik Chem.*, **A187**, 103 (1940).

(2) V. Majer, *ibid.*, **A179**, 51 (1937).

order or at different rates. However, the induced exchange was reproducible when conditions were held constant so we were able to correct for it using the equation

$$\% \text{ exchange} = \frac{\% \text{ exchange (measured)} - \% \text{ exchange (induced)}}{100 - \% \text{ exchange (induced)}} (100)$$

The corrected values (always three or more excluding the value at zero time) obeyed the exponential exchange law.[3,4] The half-times for the exchange rates are summarized in Table I. As expected the exchange rate is not dependent on the method of separation when proper account is taken of the induced exchange.

TABLE I

Tl(I)-Tl(III) EXCHANGE RATES

0.0244 f. Tl(I), 0.0244 f. Tl(III)

Acid	Temperature	Method of separation	Exchange, half-time hr.
1.0 f. HNO_3	*ca.* 25°C.	Bromide	2.5 ± 0.2
1.5 f. HNO_3	24.8 ± 0.2°	Bromide	1.8 ± 0.
1.5 f. HNO_3	24.8 ± 0.2°	Hydroxide	1.6 ± 0.2
1.5 f. $HClO_4$	24.8 ± 0.2°	Hydroxide	36 ± 4
1.5 f. $HClO_4$	24.8 ± 0.2°	Bromide	35 ± 4
1.5 f. $HClO_4$	24.8 ± 0.2°	Bromide	33 ± 4
2.5 f. $HClO_4$	24.8 ± 0.2°	Bromide	45 ± 4
3.5 f. $HClO_4$	24.8 ± 0.2°	Bromide	67 ± 5

We are extending this work to determine the effect of temperature, ionic strength, and concentrations of the reactants on the exchange rate.

(3) H. A. C. McKay, *Nature*, **142**, 997 (1938).

(4) R. B. Duffield and M. Calvin, THIS JOURNAL, **68**, 557 (1946).

DEPARTMENT OF CHEMISTRY
WASHINGTON UNIVERSITY
ST. LOUIS, MISSOURI
RENÉ J. PRESTWOOD
ARTHUR C. WAHL

RECEIVED DECEMBER 10, 1947

THE STRUCTURE OF THE DECABORANE MOLECULE

Sir:

We are studying the structure of crystalline decaborane, $B_{10}H_{14}$, by single crystal X-ray diffraction methods. We have established the approximate positions of the ten boron atoms and four of the hydrogen atoms, and have assigned probable positions to the remaining ten hydrogen atoms. (Hydrogen atoms are well resolved in fourier sections.)

The $B_{10}H_{14}$ molecule has the symmetry C_{2v}–mm2. The bond distances are as follows (see figure): B_1–B_1', B_1–B_4, B_2–B_3, B_2–B_4, B_3–B_4, are all 1.74 ±0.04 kX; B_1–B_2 and B_4–B_4' are 1.96 ± 0.04 kX; B_4–H_4 is 1.34 ± 0.04 kX,[1] and all other B–H distances are assumed the same, except B_4–H_6 which is assumed to be 1.54 ± 0.04 kX. (B_4–B_4''' and B_4'–B_4'' are 2.76 ± 0.04 kX and are not bond distances.) Each hydrogen atom, except H_6 and H_6' is bound to a single boron atom; H_6 and H_6' are each bound to two boron atoms. Each boron atom has three boron neighbors at 1.74 ± 0.04 kX and one hydrogen neighbor at 1.34 ± 0.04 kX. In addition, B_4, B_4', B_4'' and B_4''' each has a boron neighbor at 1.96 ± 0.04 kX and another hydrogen neighbor at 1.54 ± 0.04 kX; B_1, B_1', B_2, B_2', each has two boron neighbors at 1.96 ± 0.04 kX; B_3 and B_3', each has another hydrogen neighbor at 1.34 ± 0.04 kX.

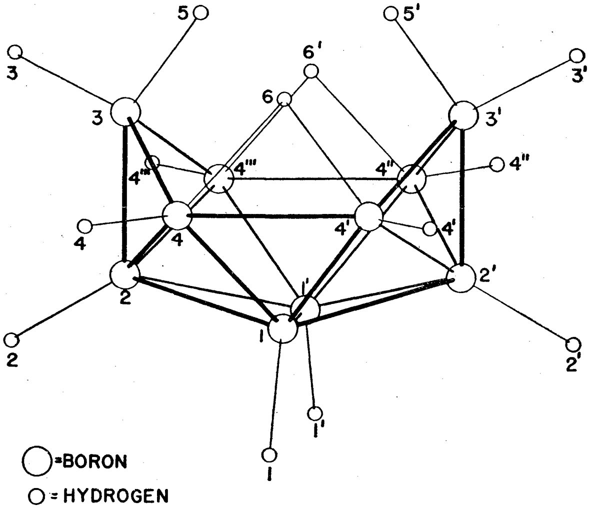


Fig. 1.

Each boron atom is bound to five or six other atoms, but the bonds are not all equivalent. Inasmuch as a bond distance of 1.96 kX has about half the "bond number"[2] of a bond distance of 1.74 kX, one can say that each boron forms five bonds of bond number 0.60. The corresponding radius, R(0.60) = 0.87 kX. Consequently, R(1) = 0.80 kX in agreement with Pauling.[2]

This structure for $B_{10}H_{14}$ gives excellent agreement with the observed X-ray diffraction intensities and also with the electron diffraction observations of S. Bauer.[3]

A detailed discussion of the determination of the structure of crystalline decaborane will be published soon.

(1) H_4, H_4', H_4'' and H_4''' were located on an electron density map; the positions of the other hydrogen atoms are assumed.

(2) L. Pauling, THIS JOURNAL, **69**, 542 (1947).

(3) S. Bauer, *ibid.*, **70**, 115 (1948).

RESEARCH LABORATORY
GENERAL ELECTRIC COMPANY
SCHENECTADY, NEW YORK.
JOHN S. KASPER
C. M. LUCHT
DAVID HARKER

RECEIVED JANUARY 21, 1948

HETEROGENEITY OF CRYSTALLINE BETA-LACTOGLOBULIN

Sir:

That crystalline β-lactoglobulin is not a homogeneous protein was indicated by the solubility measurements of Grönwall[1] and by the electrophoretic results of Li.[2] Our experiments with

(1) Grönwall, *Compt. rend. trav. lab. Carlsberg*, **24**, no. 8–11, 185 (1942).

(2) Li, THIS JOURNAL, **68**, 2746 (1946).

this protein confirm these reports and indicate a relationship between the solubility of the protein and its composition as defined by the electrophoretic patterns obtained at *p*H 4.7.

β-Lactoglobulin was prepared by the method of Palmer[3] which involves the fractionation of milk whey with ammonium sulfate after the removal of casein with acid. The isolated β-lactoglobulin was recrystallized four times by dialyzing away the salt from sodium chloride solutions at the isoelectric point. Electrophoretic studies on a 1% solution of this material in acetate buffer of ionic strength 0.1, *p*H 4.8, showed the presence of a two component system. The same preparation was electrophoretically homogeneous on the alkaline side of the isoelectric point.

Fractionation experiments on the whey proteins from the filtrate after the partial removal of crystalline β-lactoglobulin gave crystalline fractions with a mobility comparable to that of the usual β-lactoglobulin at *p*H 8.3. Electrophoresis *p*H 4.8, however, indicated a variation in the concentration of the components in each of the fractions. These new crystalline fractions also varied from the standard preparation in that they showed a greater solubility in water and in dilute salt solutions.

Crystallization of the standard preparation by dialysis from an acetate buffer solution, varied with respect to *p*H, gave fractions with a partial separation of the components as indicated electrophoretically. Partial separation of β-lactoglobulin has also been obtained by fractionation with alcohol at low temperatures. The fractions obtained by alcohol have properties in agreement with the data reported in the table below for preparations obtained by the other methods. These results will be reported subsequently.

The solubility experiments were made as described by Grönwall.[1] In every case a suspension of the crystalline material containing 7.6 ± 0.1 mg. protein nitrogen per ml. was equilibrated for a twenty-four hour period. The protein nitrogen was then determined on the supernatant liquid after centrifugation. The table illustrates the variations in the electrophoretic components of a number of preparations at *p*H 4.8 and the solubility of these crystalline fractions at *p*H 5.2 ± 0.1.

Preparation	% Composition, $\mu \times 10^5$ 1.4–1.5	% Composition, $\mu \times 10^5$ 2.2–3.2	Solubility (mg. N/cc.) at 25° in H_2O	Solubility (mg. N/cc.) at 25° in 0.02 *M* NaCl
B[a]	28	72	0.08	1.1
A[a]	38	62	.10	1.3
Standard	40	60	.12	1.5
K[b]	46	54	.18	1.7
L[b]	54	46	.13	1.6
M[b]	59	41	.19	1.9

[a] Preparations made from the standard preparation by means of acetate buffer of varying *p*H. [b] From filtrate of standard β-lactoglobulin preparation.

The variation in solubility in salt solutions of preparations with different electrophoretic compositions is an adequate explanation for the divergent solubility data reported by Palmer[3] and Grönwall.[1]

EASTERN REGIONAL RESEARCH LAB. T. L. MCMEEKIN
U. S. DEPARTMENT OF AGRICULTURE B. D. POLIS
AGRICULTURAL RESEARCH ADMINIS. E. S. DELLAMONICA
PHILADELPHIA 18, PA. J. H. CUSTER

RECEIVED DECEMBER 15, 1947

---

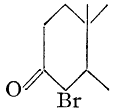
[3] Palmer, *J. Biol. Chem.*, **104**, 359 (1934).

THE PREPARATION OF 3-KETO-Δ^4-STEROIDS

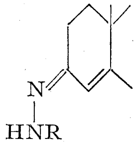
Sir:

For the introduction of a double bond at $C_4 : C_5$ in 3-ketosteroids hydrogen bromide has been eliminated from the 4-bromo derivative by treatment in boiling pyridine.[1] However, the yields have not been good. A new method for dehydrobromination has been found in which the reactivity of the bromine at C_4 is greatly increased through formation of a hydrazone at C_3. For a model compound, methyl 3,11-diketo-12-bromocholanate[2] was brominated to give methyl 3,11-diketo-4,12-dibromocholanate (I), m. p. 157.5–158.5°, $[\alpha]_D +13 \pm 2°$ (*c* 0.96 in chloroform). Calcd. for $C_{25}H_{36}O_4Br_2$: C, 53.58; H, 6.48; Br, 28.52. Found: C, 53.56; H, 6.69; Br, 28.5.

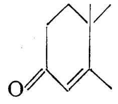
When 2,4-dinitrophenylhydrazine (1.2 equivalents) in the absence of molecular oxygen was added to an acetic acid solution of I which contained 5 equivalents of sodium acetate, a hydrazone was formed and hydrogen bromide was eliminated to give methyl 3,11-diketo-12-bromo-Δ^4-cholenate-3-(2,4-dinitrophenylhydrazone) (II). Hydrogen bromide also was eliminated quantitatively without the use of sodium acetate. Red needles, m. p. 238–239°; $\lambda_{max.}$ 387 mμ, log ε 4.48 (chloroform); yield, 82%. Calcd. for $C_{31}H_{39}O_7BrN_4$: C, 56.45; H, 5.96; Br, 12.12. Found: C, 56.21; H, 5.89; Br, 11.93.



I



II



III

The hydrazone (II) was converted into III by treatment in 20 cc. of chloroform, 30 cc. of pyruvic acid and 2.2 cc. of 2.3 *N* hydrogen bromide in acetic acid at 45°. After two and one-half hours the pyruvic acid 2,4-dinitrophenylhydrazone was removed with aqueous sodium bicarbonate, any C_{24}-carboxyl was esterified and III was separated in about 90% yield. The product was identical with a sample of III prepared by dehydrobromination of I in pyridine, m. p. 190–191°, $[\alpha]_D +29 \pm 2°$ (*c* 1.00 in chloroform); $\lambda_{max.}$ 238 mμ, log ε 4.22 (methanol). Calcd. for $C_{25}H_{35}O_4Br$: C,

---

(1) Adolf Butenandt and Josef Schmidt, *Ber.*, **67**, 1901 (1934).

(2) R. B. Turner, V. R. Mattox, L. L. Engel, B. F. McKenzie and E. C. Kendall, *J. Biol. Chem.*, **166**, 345 (1946).

62.62; H, 7.36; Br, 16.67. Found: C, 62.44; H, 7.57; Br, 16.77.

A solution of hydrazone II is autoxidizable and should be protected from molecular oxygen with an inert gas. Before autoxidation of the unsaturated hydrazone was recognized dehydrobromination of the 4-bromo intermediates to give the adrenal hormones dehydrocorticosterone acetate (IV) and 17-hydroxydehydrocorticosterone acetate (V) was carried out. The yields of bromide ion, unsaturated hydrazone and IV were 96, 59 and 80% respectively. Slightly lower yields of V were obtained. The preparation of IV and V under more favorable conditions is planned as soon as the essential intermediate compounds again become available.

For the precursors of the adrenal hormones we are indebted to Merck and Co., Inc., Rahway, New Jersey.

DEPARTMENT OF BIOCHEMISTRY
MAYO FOUNDATION
ROCHESTER, MINNESOTA
VERNON R. MATTOX
EDWARD C. KENDALL

RECEIVED JANUARY 19, 1948

VALENCE INDUCTIVITY

Sir:

Experiments conducted in this Laboratory on supported transition group oxides have led to what appears to be a new general principle in inorganic chemistry.

The effect was first observed in supported oxides of manganese. Thermal decomposition of manganous nitrate is well known to yield manganese dioxide. But if the manganous nitrate is first impregnated on high-area *gamma*-alumina, the oxidation state of the manganese becomes dependent on the concentration of the manganese. On an alumina with area of about 200 sq. m. per g., and with a manganese concentration less than 5%, all the manganese is in the +3 oxidation state. At higher concentrations the manganese reverts increasingly to the +4 state. The oxidation state is established both by direct titration, and by measurement of the magnetic moment.

This observation suggests that the manganese oxide tends to assume the crystal structure of the alumina, even to the extent of changing oxidation state in order to do so. It is well known that the *gamma* form of manganese(III) oxide is isomorphous with *gamma*-alumina.

Confirmation of this view is obtained by supporting the manganese on a high area (94 sq. m. per g.) rutile, which is isomorphous with pyrolusite. In this case the oxidation state of the manganese remains at +4, even at very low concentrations.

The experiments leading to the above results were performed by Marylinn Ellis and Kathryn Wethington. The effect described is strikingly shown by supported nickel in experiments performed by Fred N. Hill.

Magnesia is isomorphous with nickel(II) oxide. Supported nickel prepared by impregnation and ignition of high area magnesia is all in the +2 oxidation state. But dilute nickel oxide supported on high area alumina has the nickel in the +3 oxidation state. This state is established by direct quantitative uptake of hydrogen during reduction, and by magnetic measurements. It has proved possible to obtain up to 10% of nickel, all in the +3 state, by using multiple impregnation. This supported oxide is pale blue in color.

On the other hand, copper supported on alumina shows no tendency to assume the +3 state, nor does supported silver. It appears, therefore, that the effect is shown only when the supported positive ion may fairly readily assume a charge and radius similar to that of the positive ion in the support.

The effect illustrated for manganese and nickel may be described as a leading of the supported ion to take a different oxidation state than it would normally assume. Following a suggestion by Prof. Robert L. Burwell, Jr., we offer "valence inductivity" as a name for this effect. The general principle illustrated may be described as an induced change of valence brought about when a transition group ion is supported on a high area surface with which it may become isomorphous, and in which the ions may become isometric. The effect is somewhat related to the phenomenon of oriented overgrowth. It may be expected to aid in the understanding of several problems in catalysis and promoter action, and to be useful in the fields of mineralogy, crystallography, and coprecipitation.

DEPARTMENT OF CHEMISTRY
NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS
P. W. SELWOOD

RECEIVED JANUARY 29, 1948

EXCHANGE REACTION BETWEEN FERRIC AND FERROUS IONS IN PERCHLORIC ACID USING A DIFFUSION SEPARATION METHOD

Sir:

Equilibrium exchange was found to occur by Nahinsky in Professor Ruben's laboratory[1] when ferrous and tagged ferric ions mixed in perchloric acid solution were immediately separated by a chemical method. In a chemical separation of the ions, other ionic or molecular species formed through chemical change during the separation may exchange. For the perchlorate system, for example, ether–hydrochloric acid extraction of iron (III) leads to erroneous conclusions, because in 6 *M* hydrochloric acid ferrous and ferric iron exchange rapidly.[2] If separation is achieved by a physical method, without changing the environment of the ions, exchange incidental to chemical changes during separation may be avoided. Since catalytic effects of trace impurities and surfaces cannot be excluded, the results must still be interpreted cautiously.

---

(1) Nahinsky, Ph.D. Thesis, University of California, 1942.

(2) Seaborg, *Chem. Rev.*, **27**, 256 (1940).

We have investigated electronic exchange between ferric and ferrous ions in 3 M perchloric acid using radioferric ion[3] as indicator. The concentration ratio of ferric to ferrous ions (R_0) was consistently close to 0.25 and the total iron concentration was 0.023 M. Exchange was allowed to proceed for periods up to nine days. No measurable oxidation of ferrous to ferric ion by air occurred in this time. Hydrolysis of ferric ion was slight.[4]

Measurement of exchange was dependent on partially separating ferric and ferrous ions by their diffusion from the exchange mixture across a sintered glass membrane[5] into 3 M perchloric acid.

Ferric and ferrous ion concentrations were determined colorimetrically at 480 mμ employing the thiocyanate method.

In thirty-minute diffusion periods at 25° ratios (R) of around 0.54 were obtained for ferric to ferrous ion concentrations in the diffusate. The average separation factor ($S = R_0/R$) of about 0.47 indicates ferric ion diffuses relatively more rapidly than ferrous ion.

If the half time for exchange is much greater than the time required for diffusion separation, it is possible to derive the relation

$$F = \left(\frac{A}{a_0 W} - 1\right)\frac{R_0 + 1}{S - 1}$$

where the fraction of equilibrium exchange (F) is related to the radioactivity of the diffusate (A, in counts min.$^{-1}$), the specific activity of ferric ion (a_0, in counts min.$^{-1}$ mmol.$^{-1}$), and the millimoles of ferric ion in the diffusate (W) through the separation terms previously defined.

Initial results, subject to deviations of $\pm 5\%$ by virtue of the separation technique used, are: for thirty minutes, 2.2 and 3.8% of equilibrium exchange and for one case of poor separation, 9.6%; for two days, 8.7%; for five days, 13.9%; for seven days, 26.2%; and for nine days, 30.7%. These figures give a half time for exchange[6] of 18.5 ± 2.5 days.

We gratefully acknowledge the interest shown by Professor T. de Vries. Experimental results for ferric–ferrous ion exchange under other conditions will be the subject of a later communication.

CHEMISTRY DEPARTMENT
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

L. VAN ALTEN
C. N. RICE[7]

RECEIVED DECEMBER 13, 1947

---

(3) Supplied by U. S. Atomic Energy Commission.

(4) Rabinowitch and Stockmayer, THIS JOURNAL, **64**, 338 (1942).

(5) Northrop and Anson, *J. Gen. Physiol.*, **12**, 543 (1929).

(6) Mackay, *Nature*, **144**, 997 (1938).

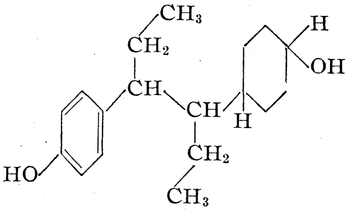
(7) Present address: The Lilly Research Laboratories, Indianapolis 6, Indiana.,

---

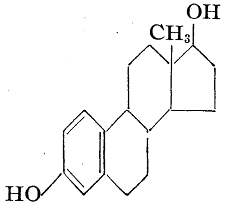
THE HEXAHYDRO DERIVATIVES OF *meso*-HEXESTROL

Sir:

After it was discovered that hexestrol is a highly potent estrogen, it became of considerable interest to prepare the hexahydro derivatives I since these bear a closer resemblance to the phenolic alcohol estradiol (II) than does the diphenol hexestrol itself. The activity of I would be of considerable significance in deciding whether the high physiological activities of hexestrol and diethylstilbestrol result from their superficial resemblance to the natural hormone II.



I



II

Our efforts to synthesize I (begun in 1940) have now proved successful, leading to the two stereoisomers corresponding in configuration at the bridge carbon atoms to *meso*-hexestrol. Recently Ungnade and Ludutsky [THIS JOURNAL, **69**, 2629 (1947)] reported the synthesis of the isomers of I related in configuration to the much less potent racemic hexestrol. In our synthesis hexestrol monomethyl ether was hydrogenated in the presence of copper chromium oxide catalyst at 240° and 425 atmospheres pressure, to obtain selective reduction of the phenolic ring. Demethylation of the mixture of methyl ethers by heating with methylmagnesium iodide at 170–190° gave a mixture of the phenolic alcohols I (soluble in Claisen alkali) in 40–50% yield. By recrystallization from dilute alcohol and benzene isomer A, m. p. 183–184° (cor.), was obtained. *Anal.* Calcd. for $C_{18}H_{28}O_2$: C, 78.2; H, 10.2. Found: C, 78.2; H, 9.9. The monobenzoate of A (Schotten–Baumann) melted at 68–69°. *Anal.* Calcd. for $C_{25}H_{32}O_3$: C, 78.9; H, 8.5. Found: C, 79.0; H, 8.6. Isomer B was obtained from the original filtrate and purified through the monobenzoate, m. p. 129.5–130° (cor.). *Anal.* Found: C, 79.0; H, 8.3. Saponification of the pure monobenzoate gave isomer B, which showed a variable melting point behavior. Recrystallization from benzene and from dilute methanol gave samples with the m. p. 133–134°; sublimation at 120° (0.01 mm.) resulted in material of m. p. 128–129.5°. When the 134° material was dried at 60° (0.1 mm.) the m. p. broadened to 134–141.5° (*Anal.* Found: C, 78.2; H, 10.0). Other samples melting as high as 143–145° were obtained. This behavior is indicative of polymorphism. Isomer B may be the same as the compound, m. p. 144–145°, obtained by Hoehn and Ungnade [THIS JOURNAL, **67**, 1617 (1945)] in low yield by hydrogenation of diethylstilbestrol.

Preliminary physiological assays carried out under the direction of Drs. R. K. Meyer and Elva Shipley Meyer of the Department of Zoology, indicate that both isomers are definitely weaker in estrogenic activity in rats than diethylstilbestrol. Further tests are in progress.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON 6, WISCONSIN
A. L. WILDS
WILLIAM B. MCCORMACK

RECEIVED JANUARY 19, 1948

STREPTOMYCIN, VII. DEGRADATION OF O-TETRAMETHYLSTREPTAMINE TO D,L-DIMETHOXYSUCCINIC ACID

Sir:

N,N′-Diacetylstreptamine (1,3-diacetamido-2,4,5,6-tetrahydroxycyclohexane)[1] was converted with dimethyl sulfate and sodium hydroxide to O-tetramethyl-N,N′-diacetylstreptamine (m. p. > 300°; *Anal.* Calcd. for $C_{14}H_{26}O_6N_2$: C, 52.81; H, 8.23; N, 8.81; CH_3O, 39.07. Found: C, 52.99; H, 8.28; N, 8.67; CH_3O, 40.1), which on hydrolysis with hydrochloric acid afforded O-tetramethylstreptamine dihydrochloride (m. p. > 300°; *Anal.* Calcd. for $C_{10}H_{22}O_4N_2 \cdot 2HCl$: C, 39.09; H, 7.87; N, 9.12; Cl, 23.08. Found: C, 38.76; H, 7.71; N, 8.98; Cl, 23.4). The free base (m. p. 83–84°; *Anal.* Calcd. for $C_{10}H_{22}O_4N_2$: C, 51.26; H, 9.46; N, 11.96. Found: C, 51.18; H, 9.38; N, 11.71) was oxidized with neutral potassium permanganate at room temperature. The methyl ester mixture formed from the oxidation products with methanolic hydrogen chloride yielded on distillation several fractions which were treated separately with methanolic ammonia or methylamine. From the lower-boiling fractions there were obtained D,L-dimethoxysuccinic acid diamide (m. p. 266–268° (dec.)[2]; *Anal.* Calcd. for $C_6H_{12}O_4N_2$: C, 40.90; H, 6.87; N, 15.90; CH_3O, 35.2. Found: C, 41.14; H, 6.76; N, 16.19; CH_3O, 35.0) and D,L-dimethoxysuccinic acid di-N-methylamide (m. p. 188–189°; *Anal.* Calcd. for $C_8H_{16}O_4N_2$: C, 47.04; H, 7.90; N, 13.72; CH_3O, 30.4. Found: C, 47.46; H, 8.05; N, 13.96; CH_3O, 30.5). Synthetic specimens of these hitherto undescribed amides, prepared from D,L-tartaric acid, showed the same melting points, undepressed by admixture of the degradation products. The diamide[3] and di-N-methylamide[4] of *meso*-dimethoxysuccinic acid melted at 255–257° (dec.) and 210–210.5°, respectively. The *meso*-diamide strongly depressed the melting point of the diamides derived from streptamine and from D,L-tartaric acid.

If, as appears highly probable, streptamine and streptidine are *meso* compounds, it follows from the above results that the 5-hydroxyl group is oriented *trans* with respect to the 4- and 6-hydroxyl groups (*xylo*-configuration), a spatial arrangement also encountered at the corresponding positions in *meso*inositol. This would limit the number of possible *meso* forms for streptamine to four.

Furthermore, there was isolated from high-boiling ester fractions prior to amidation a compound $C_{10}H_{17}O_6N$ (m. p. 109–110°; *Anal.* Calcd C, 48.57; H, 6.93; N, 5.67; $4CH_3O$, 50.1. Found: C, 48.74; H, 6.87; N, 5.65; CH_3O, 49.2) which should be either the 2,6-lactam of a 2-amino-3,4,5-trimethoxyadipic acid-1-methyl ester, or the 3,6-lactam of a 3-amino-2,4,5-trimethoxyadipic-1-methyl ester.

DIVISION OF ORGANIC CHEMISTRY
SQUIBB INSTITUTE FOR MEDICAL RESEARCH
NEW BRUNSWICK, NEW JERSEY
O. WINTERSTEINER
ANNA KLINGSBERG

RECEIVED JANUARY 19, 1948

---

[1] R. L. Peck, C. E. Hoffhine, E. W. Peel, R. P. Graber, F. W. Holly, R. Mozingo and K. Folkers, THIS JOURNAL, **68**, 776 (1946).

[2] All melting points reported are corrected.

[3] W. N. Haworth and E. L. Hirst, *J. Chem. Soc.*, 1858 (1926).

[4] W. N. Haworth and D. I. Jones, *ibid.*, 2349 (1927).

NEW BOOKS

SMALL WONDER—The Story of Colloids. By GESSNER G. HAWLEY. Alfred A. Knopf, New York, N. Y., 1947. 220 pp. Price $3.50.

The author certainly deserves full credit for his courage and, as many parts prove, skill in attempting to explain "to those who have the curiosity but lack the time to study more erudite treatises" what the term "colloid" implies. In his preface he also states, however, that "there is such a thing as having an embarrassment of subject matter" and "it is easy to become bewildered and get lost in it all." That has happened, and it is unfortunate because the reader who takes many of the written words at their face value will not get a more general, but often a wrong, understanding of colloids. This refers specifically to the author's definition of colloids, the history of this branch of science, to the explanation of their electrical properties, to the discussion of how natural rubber is obtained, or synthetic rubber produced.

The discussion of the electron microscope is by far too extensive for a book of this type, so much the more since its use in attempting to pry deeper into the structure of lyophilic colloids is becoming more and more questionable. It would have been far more appropriate to explain to the reader the tremendous developments of ultramicroscopic techniques and what has been achieved by their use.

The author has made a few serious mistakes which must be corrected. Plate XV is a cut-away view of a Sharples *super*- and not ultracentrifuge. The statement that the first periodical given over exclusively to colloid chemistry is the "Journal of Colloid Science," which appeared for the first time in January, 1946, is incorrect; the Germans have had the periodicals "Kolloid Zeitschrift" and "Kolloidchemische Beihefte" since 1906, the French have had the "Revue Generale du Colloides" since 1923, and we in the United States have had the "Colloid Symposium Monographs," also since 1923. The fact that no credit was given to many of the most outstanding colloid chemists, like Freundlich, Weiser, Holmes, v. Weimarn, Duclaux and Houwink, only to mention a few, is unfortunate.

Despite these criticisms, the reviewer hopes that this book will accomplish its purpose: namely, to arouse more general interest in this world of dimensions which has been overlooked for too long. Then it will be up to us colloid chemists to keep the ball rolling.

ERNST A. HAUSER

Thermodynamics for Chemists. By SAMUEL GLASSTONE, formerly Research Associate of Princeton University, and Professor of Chemistry in the University of Oklahoma. D. Van Nostrand and Co., Inc., 250 Fourth Ave., New York, N. Y., 1947. viii + 522 pp. Illustrated. 15.5 × 23.5 cm. Price, $5.00.

This is a typical Glasstone book, a mosaic of pieces shaped and fitted together with skill. When the individual pieces can be made from adequate reviews the result is excellent, but when the best literature is out of date or highly specialized, it may not be so good.

The proof reading seems to have been very carefully done. The only typographical errors I found were omissions of the bar denoting a partial molal quantity in a few cases where the omissions are relatively harmless. There are more important errors which the instructor will need to correct if the students are to grasp the subject. Some of the more striking are:

"Energy is defined as *any property which can be produced from or converted into work*, including, of course, work itself" (p. 6).

The partial molal volume of a component of an ideal gas mixture is defined as RT divided by the partial pressure of that component, instead of by the total pressure (pp. 219, 261).

"The general conclusion to be drawn, therefore, is that *upon mixing two liquids which yield a system exhibiting positive deviations from Raoult's law there is an absorption of heat*" (p. 331).

The author has even succeeded in copying two errors from Lewis and Randall; there are not many more.

The limit at zero pressure of $d\alpha/dP$ [$\alpha = (RT/P) - V$ for a gas] is taken as zero. Figure 17 of Glasstone is not so unreal as the figure on page 195 of Lewis and Randall, but it is still misleading, as is the discussion on pages 253 and 255.

"TABLE XXXII. ACTIVITY COEFFICIENTS OF THALLOUS CHLORIDE IN PRESENCE OF VARIOUS ELECTROLYTES AT 25° C." is given as experimental evidence for the "ionic strength principle." The first three of the seven rows, which are the ones which show agreement, are in the range where there is neither added salt nor measurements. The fourth is only 25% above the solubility of pure thallous chloride.

There is more from Lewis and Randall which was good in 1923 but is not so good in 1947. For example, the chapters on electrolytes would be greatly improved if the author had made up his mind how much of the Debye theory he trusted, and had started with that. This would permit presentation of the limitations of the ionic strength principle, Brønsted's specific ion attraction theory and at least a qualitative discussion of the treatment of the higher terms in the expansion of the Boltzmann exponential.

The following topics might well have been included: pH and single ion activities with appropriate reservations; the Donnan equilibrium; the vapor pressure of a liquid in a capillary; and particularly, the effect of gravitational, centrifugal and electrical fields on thermodynamic properties and on concentrations.

In the preface the author claims three points of distinction which give a good indication of the character of the book.

(1) There are more than a hundred illustrative numerical problems solved in the text, and about three hundred and sixty exercises to be solved by the reader. These vary from drill in the relative magnitudes of various units to derivation of some of the general equations. They seem to be very well chosen, and should serve the author's purpose of making thermodynamics a live subject to the chemist.

(2) The theory of corresponding states as developed by American chemical engineers has been used "whenever feasible" under the name "generalized procedures." It is an excellent idea to present the method as an approximation which is valuable when specific data are lacking, but the emphasis here is much greater than the accuracy of the approximation warrants.

(3) The use of statistical methods is emphasized. The partition function is introduced early and often and its relation to the classical thermodynamic functions is clearly shown. This is one of the best features of the book.

The author does not tell the maturity of the reader for whom he wrote, but there are few chemists who cannot profit by this book.

GEORGE SCATCHARD

BOOKS RECEIVED

December 10, 1947–January 10, 1948

D. E. H. FREAR. "Catalogue of Insecticides and Fungicides." Vol. I, "Chemical Insecticides." The Chronica Botanica Company, Waltham, Mass. (Stechert-Hafner, Inc., 31 East 10th Street, New York, N. Y.). 203 pp. $6.50.

PAUL KARRER, translated by A. J. Mee. "Organic Chemistry." Third English Edition. 957 pp. $8.50.

OTTO L. KOWALKE. "Fundamentals in Chemical Process Calculations." The Macmillan Company, 60 Fifth Avenue, New York 11, N. Y. 158 pp. $2.50.

JOSEPH MICHELMAN. "Violin Varnish." Published by Joseph Michelman, 5050 Oberlin Blvd., Cincinnati, Ohio. 185 pp. $3.75.

R. V. V. NICHOLLS. "An Introduction to Practical Organic Chemistry." Sir Isaac Pitman and Sons (Canada) Ltd., Publishers, 381–383 Church Street, Toronto, Ontario, Canada. 187 pp. $2.25.

R. L. SHRINER, EDITOR-IN-CHIEF. "Organic Syntheses." Vol. 27. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 121 pp. $2.25.

ROLAND M. WHITTAKER. "Rudiments of Chemistry. The Chemist's View of the Nature of Matter." The Roland Press Company, Publishers, 15 East 26th Street, New York 10, N. Y. 310 pp. $3.00.

"Nordisk Cerealkemist-Forenings. Kongress I Stockholm." Uppsala, 1947. Appelbergs Boktryckeriaktiebolag, Publishers. 258 pp.

"Research. A Journal of Science and Its Applications." Published by Butterworths Scientific Publications Ltd., 4, 5, 6 Bell Yard, Temple Bar, London, W. C. 2. 96 pp. $10.00.

JOURNAL OF THE
AMERICAN CHEMICAL SOCIETY

VOLUME 70 APRIL 3, 1948 NUMBER 3

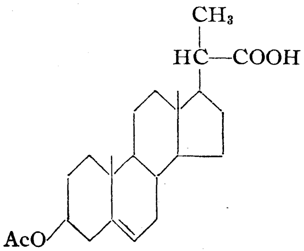
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Sterols. IV. Δ^{20}-Pregnenes from *bisnor*-Steroid Acids

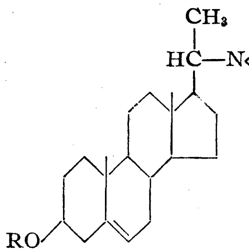
BY PERCY L. JULIAN, EDWIN W. MEYER AND HELEN C. PRINTY

Intensive studies in these Laboratories over the past few years have resulted in making 3-acetoxy-5-*bisnor*-cholenic acid a relatively cheap and useful raw material for the synthesis of most of the major steroid hormones. This communication presents one of the promising and convenient methods for degrading this acid to key intermediates in such a synthetic approach. The emphasis in this particular investigation centers upon the Δ^{20}-pregnenes prepared from 3-acetoxy-5-*bisnor*-cholenic acid and analogous steroid acids. The ease of preparation and the excellent yields encountered make the Δ^{20}-pregnenes focal points of interest in the general picture involving degradation and synthesis of physiologically active steroids.

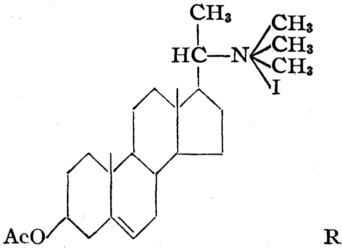
3-Acetoxy-5-*bisnor*-cholenic acid (I) was converted to 3-acetoxy-20-amino-5-pregnene (II) in practically quantitative yield *via* the acid chloride by the Curtius method.[1] Methylation of the 20-amine (II) with formic acid and formaldehyde[2] gave 3-acetoxy-20-dimethylamino-5-pregnene (III) and this compound reacted smoothly with methyl iodide to yield the desired quaternary halide (V). All steps to this point gave yields which were excellent. Decomposition of the ammonium iodide (V) by treatment with potassium hydroxide in ethylene glycol solution afforded 3-hydroxy-5,20-pregnadiene (VI) in only 65% yield, but the major portion of the remaining 35% was recovered as the 3-hydroxy-20-dimethylamine (IV). Thus this reaction, too, in the end, becomes nearly quantitative. Of the two competing reactions involved in the degradation of the quaternary base, namely, the loss of trimethylamine and the loss of methyl alcohol, the former predominates in this case sufficiently to make this procedure one of the cleanest of side-chain degradations. The decomposition of the halide (V) by silver oxide-pyrolysis gave a poorer yield of the pregnadiene (VI).



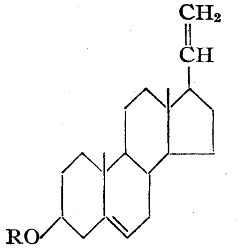
(I)



(II), R = Ac, R' = H
(III), R = Ac, R' = CH_3
(IV), R = H, R' = CH_3



(V)



(VI), R = H
(VII), R = Ac
(VIII), R = $C_7H_7SO_2$

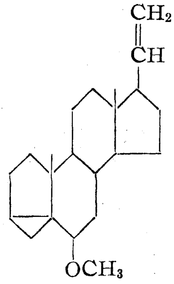
The structure of the pregnadiene (VI) was demonstrated by conversion into the *i*-ether (IX) followed by oxidation with potassium permanganate in pyridine and subsequent "rearrangement" and esterification with acidulated methanol to yield methyl 3-methoxy-5-*etio*-cholenate (X) identical with the compound prepared from 3-hydroxy-5-*etio*-cholenic acid. Oxidation of 3-hydroxy-5,20-pregnadiene (VI) offers the first authentic and clean-cut preparation of 3-keto-4,20-pregnadiene

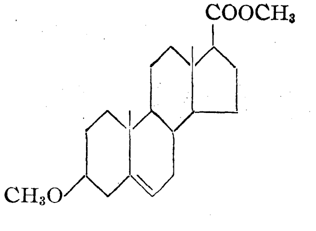
---

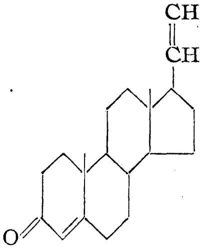
[1] Bochmühl, Ehrhart and Ruschig, U. S. Patent 2,108,646; Ruschig, *Med. u. Chem.*, **4**, 327 (1942) (*C. A.*, **38**, 4954 (1944)).

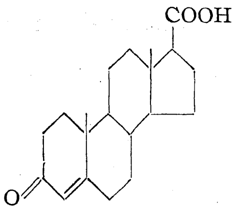
[2] Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(XI). This material melted at 126.5° and gave a good yield of 3-keto-4-*etio*-cholenic acid (XII) upon mild treatment with ozone. The structure of the pregnadiene is, therefore, indisputably established.


(IX)

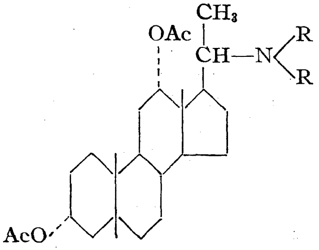

(X)

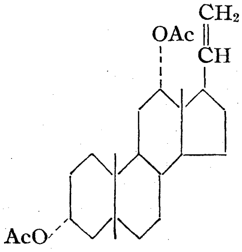

(XI)


(XII)

Ruzicka and co-workers[3a] posed the possibility that their substance of melting point 132–133°, prepared by the reduction of 3,17-dihydroxy-17-ethynyl-5-androstene with sodium in ethanol–xylene, might have the structure of our pregnadiene (VI). These authors, however, in a later communication,[3b] presented satisfactory proof that their compound did not possess the first proposed structure but was instead the 3-hydroxy-5,17-pregnadiene.

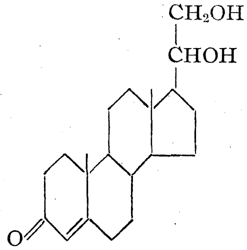
The application of the above-described degradative scheme to 3(α),12(α)-diacetoxy-*bisnor*-cholanic acid afforded equally as facile a route to 3(α),12(α)-diacetoxy-20-pregnene (XV) *via* the aminopregnane derivatives (XIII) and (XIV). Oxidation of this pregnene gave a good yield of 3(α),12(α)-diacetoxy-*etio*-cholanic acid.


(XIII), R = H
(XIV), R = CH_3


(XV)

This preparation of *etio*-acids from *bisnor*-acids *via* the Δ^{20}-pregnenes constitutes, in our opinion, the most satisfactory route to *etio*-acids yet proposed. The preparation of 3-acetoxy-5-*etio*-cholenic acid by Steiger and Reichstein[4] gave, according to these investigators, only a 9.0% yield based upon 3-hydroxy-5-*bisnor*-cholenic acid. Hoehn and Mason[5] prepared 3(α),12(α)-dihydroxy-*etio*-cholanic acid in 14.5–17% yield by an improved procedure from 3(α),12(α)-dihydroxy-*bisnor*-cholanic acid. Our preparation gives a minimum yield of 33% of 3-keto-4-*etio*-cholenic acid based on the 3-acetoxy-5-*bisnor*-cholenic acid. Thus the Δ^{20}-pregnenes occupy a significant role in the classical route to the cortical hormones.

The Δ^{20}-pregnenes offer other interesting approaches to the typical ketol structure of the cortical hormones. The pregnadiene (XI) underwent hydroxylation with osmium tetroxide giving both of the expected diastereoisomeric 20,21-diols (XVI) which have been separated and characterized. One diol melted at 168°, $[\alpha]^{27}_D$ + 98°, and the other melted at 194°, $[\alpha]^{35}_D$ + 97°. The first of these agrees in its properties with the so-called "α-form" of the diol which Steiger and Reichstein[6] prepared from desoxycorticosterone. These workers, however, apparently did not have the β-modification in pure form as they give a melting point of 185° and indicate that they had too little material for analysis and complete characterization. These diols and their derivatives offer attractive routes to the cortical hormones[7] and we shall report more in detail later upon this phase of the investigation.


(XVI)

Experimental[8,9]

3-Acetoxy-20-amino-5-pregnene (II).—In a flask protected with a calcium chloride tube, a suspension of 50.0 g. of 3-acetoxy-5-*bisnor*-cholenic acid in 1000 ml. of anhydrous ether was treated with 29 ml. of freshly distilled thionyl chloride. After the addition of a few drops of 10% pyridine in benzene, the mixture was swirled occasionally. The acid dissolved within one-half hour. After two hours, the solvent was removed *in vacuo* with gentle warming. To remove the last traces of thionyl chloride, the residue was dissolved successively in several small portions of dry benzene and this solvent was removed *in vacuo*. The acid chloride remained as a white, crystalline cake.

---

(3) (a) Ruzicka, Goldberg and Hardegger, *Helv. Chim. Acta*, **22**, 1294 (1939); (b) Ruzicka, Goldberg and Hardegger, *ibid.*, **25**, 1297 (1942).

(4) Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 1040 (1937).

(5) Hoehn and Mason, THIS JOURNAL, **60**, 1493 (1938).

(6) Steiger and Reichstein, *Helv. Chim. Acta*, **21**, 171 (1938).

(7) *Cf.* Sarett, *J. Biol. Chem.*, **162**, 601 (1946); THIS JOURNAL, **68**, 2478 (1946).

(8) The carbon-hydrogen analyses were performed by Mr. C. W. Beazley of the Micro-Tech Laboratories, Skokie, Illinois.

(9) We are indebted to Miss Isabelle Ryden of this Laboratory for certain technical assistance.

The acid chloride was dissolved in 900 ml. of acetone and chilled in an ice-bath to 10°. A solution of 16.0 g. of sodium azide in 75 ml. of water was then added dropwise, with mechanical stirring, at such a rate that the temperature of the solution was maintained at 10–13°. After fifteen minutes of stirring, 1000 ml. of ice-cold water was added and the white crystalline azide was filtered. The moist cake which weighed 160 g. was added to a mixture of 1000 ml. of glacial acetic acid and 142 ml. of water. The mixture was warmed on a steam-bath with swirling. At about 38° nitrogen was evolved and the azide went into solution. After heating for one hour at 60–65°, the solution was steam distilled (about 2–3 l. of distillate). To the residual mixture, while still hot, a solution of 80 g. of sodium hydroxide in 300 ml. of water was added portionwise with good agitation. Upon cooling, the 3-acetoxy-20-amino-5-pregnene acetate formed needle-like crystals. The mass was filtered, washed with a small quantity of cold water and dried. The acetate weighed 51.7 g. (96%) and melted at 200–205° after softening slightly at about 185°. This material which contains a small quantity of sodium acetate is of sufficient purity for further experimentation.

A 5.0-g. sample of the acetate was dissolved in a small amount of methanol and treated with dilute sodium carbonate solution. After addition of ether, the ethereal solution was washed with water (it was necessary to add a small amount of methanol from time to time to solubilize the amine which is only moderately soluble in ether) and dried. The solid remaining after removal of ether was dissolved in hot methanol, filtered, and precipitated by the cautious addition of water. It was recrystallized several times from a concentrated methanol solution—white silky needles resulted, m. p. 116–120° (loss of solvent).

A convenient derivative for this amine was the benzal derivative, 3-hydroxy-20-benzaldimino-5-pregnene. For preparation, the 20-amine described above was hydrolyzed with 2% methanolic potassium hydroxide and this solution was treated with benzaldehyde. The benzal compound crystallized readily in the form of glistening plates. For analysis it was recrystallized from benzene–methanol, m. p. 191°.

Anal. Calcd. for $C_{28}H_{39}ON$: C, 82.90; H, 9.69. Found: C, 82.57; H, 9.31.

3-Acetoxy-20-dimethylamino-5-pregnene (III).—A solution of 20.5 g. of 3-acetoxy-20-amino-5-pregnene acetate in 17.8 g. of 90% formic acid and 13.2 g. of 35% aqueous formaldehyde was heated on a steam-bath under reflux for five hours. At the outset the evolution of carbon dioxide was vigorous but this subsided to a slow steady rate. The mixture was diluted with water and extracted with ether after the addition of dilute hydrochloric acid. The aqueous layer containing suspended insoluble hydrochloride was separated and combined with the water washings of the ethereal layer. The aqueous mixture was made alkaline with dilute sodium hydroxide and extracted well with ether. The ether solution was washed with water and dried. Upon removal of solvent, there remained 17.8 g. (92%) of a white, crystalline residue melting at 155–175°, which was sufficiently pure for the preparation of (V). For analysis, however, several recrystallizations from a small volume of ether gave glistening plates which melted at 184.5–187.5°; $[\alpha]^{34}D$ $-50 \pm 1°$ (77.2 mg. made up to 5 ml. with chloroform, α $-0.77°$, l, 1 dm.).

Anal. Calcd. for $C_{25}H_{41}NO_2$: C, 77.47; H, 10.66. Found: C, 77.65; H, 10.76.

3-Hydroxy-20-dimethylamino-5-pregnene (IV).—A 1.94-g. sample of the 3-acetoxy-amine was dissolved in a solution of 0.5 g. of potassium hydroxide in 50 ml. of methanol and 10 ml. of benzene. This solution was refluxed for three hours. It was then diluted with water and extracted with ether. The water-washed ether solution was concentrated to a crystalline mass which was recrystallized from ether–petroleum ether (b. p. 35–60°). The product, 1.7 g. of white prisms, melted at 162–171°. Recrystallization from ether gave material melting at 169–170°; $[\alpha]^{33}D$ $-54 \pm 2°$ (23.3 mg. made up to 5 ml. with chloroform, α $-0.25°$, l, 1 dm.).

Anal. Calcd. for $C_{23}H_{39}ON$: C, 79.94; H, 11.37. Found: C, 80.17; H, 11.08.

3-Acetoxy-5-*ternor*-cholenyltrimethylammonium Iodide (V).—Ten and four-tenths grams of the crude 3-acetoxy-dimethylamine was dissolved in 40 ml. of warm benzene, chilled and treated with 6 ml. of methyl iodide. The solution was refluxed for two hours. During this period a heavy crop of crystalline material separated. The mixture was slurried with ether, filtered, and the solid washed with ether. The mother liquor was concentrated to remove ether and was retreated with methyl iodide in the same fashion to obtain a second crop of material. The total yield of white, crystalline quaternary iodide amounted to 12.7 g. (89.2%), m. p. 255–265°, dec. Recrystallization from methanol gave plates which decomposed at 270°.

Anal. Calcd. for $C_{26}H_{44}O_2NI$: C, 58.97; H, 8.38. Found: C, 58.75; H, 8.23.

The ammonium iodide can be converted to the quaternary base, **3-hydroxy-5-*ternor*-cholenyltrimethylammonium hydroxide** by treatment with moist silver oxide. In one experiment, a solution of 1.0 g. of the iodide in 10 ml. of methanol was shaken with the moist silver oxide prepared from 1.0 g. of silver nitrate. After three hours the solution was filtered and the oxide washed with methanol. No attempt was made to isolate the base; however, it was converted directly to the picrate by the addition of 1.0 g. of picric acid in methanol to the methanolic solution of the base. After concentration the picrate was crystallized from methanol–ether; 0.8 g. of orange prisms melting at 188–194°. Recrystallization from methanol raised the melting point to 192–194.5°.

Anal. Calcd. for $C_{30}H_{44}O_8N_4$: C, 61.20; H, 7.54. Found: C, 60.92; H, 7.35.

3-Hydroxy-5,20-pregnadiene (VI).—A solution of 7.2 g. of 3-acetoxy-5-*ternor*-cholenyltrimethylammonium iodide in a mixture of 14.0 g. of potassium hydroxide, 15 ml. of water and 55 ml. of ethylene glycol was boiled, allowing the water vapor to escape until the solution reached a temperature of about 135°. Then heating was continued under reflux. Slowly oil globules separated and trimethylamine was liberated. After six hours the mixture was chilled, diluted with water and extracted with ether. The ether solution was washed with water, dried and treated with glacial acetic acid until a slight excess was present. The mixture was chilled and the white solid was separated by filtration and washed with ether (saved for amine recovery). The ether filtrate was then washed with dilute alkali, water and dried. Upon concentration there remained 2.8 g. (approximately 65% discounting water of crystallization) of a crystalline, white solid which lost water at 110–120° and melted 130–133°. Several recrystallizations from methanol gave colorless plates which frothed at 125–127° and melted 138–139.5°. Upon standing exposed to the atmosphere these crystals became opaque and slowly disintegrated; $[\alpha]^{27}D$ $-85 \pm 1°$ (46.0 mg. made up to 5 ml. with chloroform, α $-0.78°$, l, 1 dm.). For analysis the product was dried for five hours at 1 mm. over boiling chloroform.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.95; H, 10.72. Found: C, 83.64; H, 11.00.

The solid acetate, 3-hydroxy-5-*ternor*-cholenyldimethylammonium acetate, which was recovered from the reaction mixture weighed 1.4 g. Accounting for this material which may be re-used, the yield of the pregnadiene is 90%.

Upon titration of the pregnadiene in chloroform solution with a solution of bromine in chloroform, this substance absorbed the equivalent of two moles of bromine per mole of compound without liberation of hydrogen bromide. The first mole was absorbed more rapidly than the second but no sharp end-point existed between the two.

Treatment of the 3-hydroxy-pregnadiene with acetic acid–acetic anhydride at steam-bath temperature for one hour afforded **3-acetoxy-5,20-pregnadiene (VII)**. This material after two recrystallizations from methanol existed as white prisms which melted at 132.5–135°. $[\alpha]^{37}\text{D}$ $-76.8 \pm 1°$ (62.5 mg. made up to 5 ml. with chloroform, α $-0.96°$, l, 1 dm.).

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.64; H, 10.01. Found: C, 80.53; H, 9.94.

3-Hydroxy-5,20-pregnadiene has also been prepared by conversion of the quaternary iodide to the ammonium hydroxide with moist silver oxide and subsequent pyrolysis of the quaternary base. In one experiment, 1.5 g. of the iodide was treated in 50 ml. of methanol with moist silver oxide prepared from 7.5 g. of silver nitrate. After twelve hours the oxide was separated and the pale yellow filtrate was concentrated *in vacuo*. The residue was pyrolyzed at 210° for fifteen minutes at 1 mm. It was then dissolved in ether, washed with dilute hydrochloric acid and water and dried. The gum which remained after removal of ether was crystallized from petroleum ether (b. p. 35–60°); 0.2 g. of white solid melting at 134° after losing solvent at 113–116°. Decomposition of the quaternary base was also effected by refluxing it in methanolic potassium hydroxide solution. This procedure was also effective in converting the quaternary iodide directly into the diene without employing moist silver oxide for the preparation of the intermediate base. However, the last two methods gave erratic results especially when applied to larger batches. Substitution of ethanol for methanol did not alter the situation.

3-*p*-Toluenesulfonoxy-5,20-pregnadiene (VIII).—A 5.8-g. sample of the 3-hydroxy-diene was dissolved in 13 ml. of pyridine. By warming on the steam-bath, 5.8 g. of *p*-toluenesulfonyl chloride was dissolved in this solution. The mixture was allowed to stand overnight, then diluted with water and extracted with ether. The ether solution was washed successively with dilute hydrochloric acid, water, dilute sodium carbonate solution. The residue remaining after removal of ether from the dried solution was crystallized from ether–petroleum ether (b. p. 35–60°). There resulted 7.4 g. (84%) of white solid which melted at 94–97°. After one crystallization from benzene–petroleum ether and another from petroleum ether, the colorless needles melted at 93.5–96°: $[\alpha]^{26}\text{D}$ $-65 \pm 1°$ (65.0 mg. made up to 5 ml. with chloroform, α $-0.84°$, l, 1 dm.).

Anal. Calcd. for $C_{28}H_{38}O_3S$: C, 73.96; H, 8.42. Found: C, 74.14; H, 8.39.

6-Methoxy-Δ^{20}-*i*-pregnadiene (IX).—A mixture of 5.2 g. of the *p*-toluenesulfonoxy derivative and 150 ml. of methanol containing 10 g. of freshly-fused potassium acetate was refluxed for two hours and allowed to stand overnight. It was then diluted to about 1.5 liters with water and extracted with ether. The extract was washed with water, dilute sodium carbonate solution, water and dried. Upon concentration (finally *in vacuo*) there remained 3.8 g. of a pale yellow sirup. This was dissolved in 50 ml. of petroleum ether (b. p. 35–60°) and treated with 10 g. of activated alumina (Aluminum Ore Company; grade F, −80 mesh). After shaking intermittently for fifteen minutes, the alumina was separated by filtration and washed with 150 ml. of petroleum ether. The filtrate was concentrated *in vacuo* to 3.2 g. (88.5%) of a colorless sirup: $[\alpha]^{27}\text{D}$ $+28.6 \pm 2°$ (43.7 mg. made up to 5 ml. with chloroform, α $+0.25$, l 1 dm.).

Anal. Calcd. for $C_{22}H_{34}O$: C, 84.01; H, 10.91. Found: C, 83.65; H, 10.72.

Methyl 3-Methoxy-5-*etio*-cholenate (X).—To a stirred solution of 2.5 g. of 6-methoxy-Δ^{20}-*i*-pregnadiene in 50 ml. of pyridine and 5 ml. of water, 5.0 g. of powdered potassium permanganate was added portionwise over a period of three hours. The manganese dioxide was filtered and washed with pyridine and water. The filtrate which remained clear upon dilution with water was acidified with dilute acetic acid and extracted with ether. The ether solution was washed with cold dilute sulfuric acid, with water and dried. The sirup which remained upon removal of ether was dissolved in 50 ml. of methanol. Fifteen drops of concd. sulfuric acid was added and the solution was refluxed for three and one-half hours. Water was added cautiously to the chilled solution until crystallization began. After completion of crystallization, the white solid was filtered, washed with aqueous methanol and dried. The solid, 1.5 g., melted at 115–128°. Several recrystallizations from a concentrated methanol solution gave 1.0 g. of white needles melting at 133–134°, $[\alpha]^{38}\text{D}$ $-23 \pm 2°$ (44.3 mg. made up to 5 ml. with chloroform, α, $-0.20°$, l, 1 dm.).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.90. Found: C, 76.10; H, 9.71.

The constitution of this *etio*-ester was proven by an independent synthesis. 3-Acetoxy-5-*etio*-cholenic acid was converted to the acid chloride with thionyl chloride in dry ether. The acid chloride when refluxed in methanol for a short period gave methyl 3-hydroxy-5-*etio*-cholenate (m. p. 175–178°). The 3-*p*-toluenesulfonoxy derivative (m. p. 155–157.5°) was prepared from this ester. The former upon refluxing in methanol yielded, as indicated by mixed m. p., the same compound as described above, namely, methyl 3-methoxy-5-*etio*-cholenate.

3-Keto-4,20-pregnadiene (XI).—Nine grams of 3-hydroxy-5,20-pregnadiene was dissolved in a mixture of 100 ml. of toluene and 54 ml. of cyclohexanone and then a few ml. of toluene was distilled in order to remove traces of moisture. After the addition of 9.2 g. of aluminum isopropoxide in 60 ml. of hot toluene, the solution was refluxed for one hour. The solution was then chilled, diluted with dilute hydrochloric acid and extracted with ether. The extract was washed with water, concentrated and then steam distilled. The residue was taken up in ether, washed with water, dilute sodium hydroxide solution and water. The pale yellow, crystalline residue remaining after the removal of ether from the dried solution was recrystallized from a concentrated methanol solution. The product, 7.3 g. (81.6%) of pale yellow prisms, melted at 120–125°. This material is soluble in ether, acetone, methanol, hexane and petroleum ether (b. p. 35–60°). After it was recrystallized several times from a concentrated methanol solution, the diene, practically colorless prisms, melted at 123.5–126.5°: $[\alpha]^{39}\text{D}$ $+106 \pm 1°$ (82.5 mg. made up to 5 ml. with chloroform, α $+1.75°$, l, 1 dm.).

Anal. Calcd. for $C_{21}H_{30}O$: C, 84.52; H, 10.12. Found: C, 84.56; H, 10.13.

3-Keto-4,20-pregnadiene formed a white, crystalline semicarbazone which melted at 243–244°, dec., after recrystallization from chloroform–methanol.

Anal. Calcd. for $C_{22}H_{33}ON_3$: C, 74.32; H, 9.37. Found: C, 74.13; H, 9.20.

3-Keto-4-*etio*-cholenic Acid (XII).—A solution of 2.0 g. of 3-keto-4,20-pregnadiene in 60 ml. of chloroform was ozonized (4.5% O_3 by volume at 0.5 l./min.) for ten minutes at ice-bath temperature. The solution was then steam distilled and the residual waxy solid dissolved in ether. The ether solution was washed with water and then extracted with cold dilute sodium hydroxide solution. Upon acidification of the alkaline solution with dilute hydrochloric acid, a white, crystalline solid separated. The solid was filtered, washed with water and dried; 1.2 g. (56.6%), m. p. 235–250°. After recrystallization from acetone–hexane and from acetone, the acid melted at 250–255°. This material showed no depression in melting point when mixed with an authentic sample of 3-keto-4-*etio*-cholenic acid prepared by the oxidation of 3-hydroxy-5-*etio*-cholenic acid. Reozonization of the neutral fraction yielded an additional quantity of *etio*-acid.

3(α),12(α)-Diacetoxy-20-aminopregnane (XIII).—A solution of 7.2 g. of 3(α),12(α)-diacetoxy-*bisnor*-cholanic acid in 20 ml. of dry benzene and 40 ml. of dry ether was treated with 4.2 ml. of freshly-distilled thionyl chloride. After standing at room temperature for one hour and forty minutes, the solvent was removed *in vacuo* with gentle warming. The last traces of thionyl chloride were removed by sweeping out, *in vacuo*, with several small portions of benzene. At this stage the acid chloride, which had begun to crystallize, was dissolved in 130 ml. of acetone. The solution was chilled in an ice–salt-bath to 0–5° and treated dropwise, with mechanical agitation, over a period of ten minutes with a solution of 2.3 g. of sodium azide in 10 ml. of water. Sodium chloride separated. After an additional twenty minutes of stirring, 200 ml. of cold water was dribbled in with continued stirring. The crystalline azide (a sample of this material melted at 86–90°, dec.) was then filtered, washed with cold water and suspended in 130 ml. of 80% acetic acid. This mixture was heated to 50–60° and held there for one hour. The azide dissolved rapidly and then decomposed with evolution of nitrogen. The solution was filtered, steam distilled for thirty minutes, filtered again and made alkaline with cold dilute sodium carbonate solution. The amine was extracted with ether and washed with water. Upon removal of solvent *in vacuo* from the dried solution there remained 6.2 g. (96.7%) of yellow amorphous material. Attempts to crystallize this material have not been overly successful. A small sample when crystallized from ether and ether–petroleum ether (b. p. 35–60°) melted at 207–209° but was not analytically pure.

The crude amine readily gave an acetamide upon treatment with acetic anhydride in acetic acid; 800 mg. with 4 ml. of acetic acid and 2 ml. of acetic anhydride gave 910 mg. of amide melting at 210–220°. After several recrystallizations from aqueous methanol, it melted at 220–221°.

Anal. Calcd. for $C_{27}H_{43}O_5N$: C, 70.24; H, 9.60. Found: C, 70.14; H, 9.44.

A sample of the crude azide upon warming with ethanol formed the urethan. After several recrystallizations from aqueous ethanol, it melted at 172–173°.

Anal. Calcd. for $C_{28}H_{45}O_6N$: C, 68.39; H, 922. Found: C, 68.23; H, 9.23.

3(α),12(α)-Diacetoxy-20-dimethylaminopregnane (XIV).—A mixture of 5.2 g. of the crude 20-aminopregnane, 6 ml. of 90% formic acid and 4 ml. of 35% aqueous formaldehyde was heated on the steam-bath under reflux for four hours. The orange liquid was poured into cold dilute sodium hydroxide solution and extracted with ether. The ether solution was washed with water, dried and concentrated *in vacuo*. There remained 5.5 g. (99%) of an orange glass. This material when crystallized from petroleum ether (b. p. 35–60°) gave 3.0 g. of white solid, m. p. 115–125° (cloudy). The residue (2.5 g.) in the mother liquor was also reserved for further processing. Several recrystallizations of the solid material from petroleum ether gave small, white needles melting at 134–137°.

Anal. Calcd. for $C_{27}H_{45}O_4N$: C, 72.45; H, 10.14. Found: C, 72.71; H, 10.52.

From one run there was isolated a small portion of material melting at 167–174°. Several recrystallizations from acetone gave fine, white needles melting at 184–187.5°. This material analyzed for an acetoxy-hydroxy-20-dimethylaminopregnane.

Anal. Calcd. for $C_{25}H_{43}O_3N$: C, 74.03; H, 10.68. Found: C, 73.90; H, 10.57.

3(α),12(α)-Diacetoxy-20-pregnene (XV).—A 2.2-g. sample of the crystalline 20-dimethylaminopregnane was dissolved in 20 ml. of benzene, treated with 5 ml. of methyl iodide and refluxed for two hours. The solution was diluted with ether, chilled, and the solid material separated. After washing with petroleum ether (b. p. 35–60°), the dry, pale yellow crystalline quaternary iodide was dissolved in a mixture of 6 ml. of water and 30 ml. of ethylene glycol containing 6 g. of potassium hydroxide. The mixture was refluxed (temperature of boiling solution about 135°) for seven and one-half hours, diluted with water and extracted with ether. The ether solution was then washed with water, dilute hydrochloric acid, water and dried. Concentration of the solution gave a pale yellow glass. This was dissolved in 10 ml. of acetic acid–3 ml. of acetic anhydride and treated with 1 ml. of 5 *N* perchloric acid[10] in acetic acid at ice-bath temperature and then allowed to stand for thirty minutes. Upon dilution with water, a white crystalline solid separated. This was filtered, washed with water and dried; 1.5 g. (75.7%), m. p. 162–175°. Several recrystallizations from methanol gave large needle-like prisms which melted at 184–185°.[11] $[\alpha]^{37}\text{D} + 102 \pm 2°$ (60.9 mg. made up to 5 ml. with chloroform, α 1.24°, *l*, 1 dm.).

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.58; H, 9.52. Found: C, 74.63; H, 9.73.

The non-crystalline fraction (2.5 g.) of the diacetoxy-20-dimethylaminopregnane, when treated as described above gave 1.4 g. (62.2%) of crystalline material melting at 162–175°. Recrystallization from methanol raised the melting point to 184–185°.

3-Keto-20,21-dihydroxy-4-pregnene (XVI).—A solution of 1.1 g. of 3-keto-4,20-pregnadiene in 20 ml. of anhydrous ether was added to a solution of 1.0 g. of osmium tetroxide in a like amount of ether. After twenty-two hours at room temperature, the brown solid was separated and washed with ether–petroleum ether (b. p. 35–60°). It was then suspended in 75 ml. of 95% ethanol to which 8 g. of sodium sulfite in 40 ml. of water was added. The mixture was refluxed for four hours and, while hot, filtered to remove the black solid. After washing the solid with hot ethanol, the filtrate was concentrated *in vacuo* to about 20 ml. Upon addition of water, a white solid separated. This was chilled, filtered, washed with water and dried; 0.9 g., m. p. 170–175° after shrinking at 150°. Recrystallization from anhydrous ether gave 0.6 g. of white solid which melted at 176–183°. Four recrystallizations from acetone gave fine, colorless prisms melting at 192.5–194.5°; $[\alpha]^{35}\text{D} + 97 \pm 1°$ (47.3 mg. made up to 5 ml. with chloroform, $\alpha + 0.92°$, *l*, 1 dm.).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.87; H, 9.69. Found: C, 75.75; H, 9.85.

The residual material from the crystallization was chromatographed over 30 g. of activated alumina (Aluminum Ore Co. grade F, −80 mesh) in ether–methanol (9–1). The separation was not sharp, but an intermediate fraction eluted with ether–methanol (9–1) gave a small amount of white solid melting at 164–170° but softening at 140°. Several recrystallizations from acetone gave fine needles melting at 166–168°; $[\alpha]^{27}\text{D} + 98 \pm 1°$ (83.8 mg. made up to 5 ml. with chloroform, α, + 1.65°, *l*, 1 dm.). This material when mixed with a portion of the 192.5–194.5° material melted at 115°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.87; H, 9.69. Found: C, 75.83; H, 9.87.

3(α),12(α)-Diacetoxy-*etio*-cholanic Acid.—A solution of 1.0 g. of 3(α),12(α)-diacetoxy-20-pregnene in 30 ml. of acetic acid was ozonized for thirty minutes (4.5–5% O_3 at 0.5 l./min.). The solution was then treated with zinc dust, warmed, filtered and steam distilled after the addition of a few ml. of 30% hydrogen peroxide. The residue was dissolved in ether and washed with water. The ether solution was then extracted with cold dilute sodium hydroxide solution. The neutral material remaining in the ether was retreated with ozone and worked for acidic material. Upon addition of dilute hydrochloric acid to the alkaline solution a solid separated. This was filtered, washed with water and dried. It was then acetylated in 8 ml. of acetic acid with 3 ml. of acetic anhydride employing 1 ml. of 5 *N* $HClO_4$ in acetic acid for catalyst.[10] The product was precipitated by addition of water and dried—0.7 g. (67%), m. p. 190–199°. After one recrystallization from ether–pentane the *etio*-acid melted at 195–199° (reported 196–198°[12]).

Summary

1. *bisnor*-Steroid acids have been degraded to Δ^{20}-pregnenes *via* the Curtius procedure to 20-

---

(10) Whitman and Schwenk, THIS JOURNAL, **68**, 1865 (1946).

(11) This pregnene may be identical with the compound of m. p. 176–178.5° described by Brink, Clark and Wallis, *J. Biol. Chem.*, **162**, 695 (1946).

(12) Reichstein and von Arx, *Helv. Chim. Acta*, **23**, 747 (1940).

amino-derivatives, followed by Hofmann degradation.

2. Ozonization of 3-keto-4,20-pregnadiene constitutes a better route than any hitherto suggested to 3-keto-4-*etio*-cholenic acid. Likewise ozonization of 3(α),12(α)-diacetoxy-20-pregnene gave 3(α),12(α)-diacetoxy-*etio*-cholanic acid in good yield.

3. Hydroxylation of 3-keto-4,20-pregnadiene gave the isomeric 20,21-diols which have been separated and characterized.

4. This degradation of *bisnor*-acids facilitates the preparation of compounds containing the ketol structure of the cortical hormones.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 15, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE]

Studies in the Quinoline Series. IX. The Mononitrophenyllepidylcarbinols and Related Compounds

BY R. STUART TIPSON AND ANNE FARLEY WALTON

In a recent communication,[1] methods were described for the preparation of the three mononitrophenylquinaldylcarbinols and certain of their derivatives. We now describe related work on the lepidyl isomers.

In an attempt to prepare *p*-nitrophenyllepidylcarbinol by Bulach's[2] method (used for the preparation, in good yield, of the corresponding quinaldyl compounds[1]) the yield was only 7% of the theoretical; this is in agreement with Eibner's work[3] showing that a methyl group at position 4 reacts less readily with aldehydes than one at position 2. However, on lengthening the reaction time to eight hours, and changing the method of isolating the product, the yields of the lepidylcarbinols were: *o*- and *p*-, 24%; *m*-, 19%. A lower yield of *m*-derivative had also been noted[1] in the quinaldyl series. The *o*- and *p*-derivatives were isolated directly; because of the greater solubility of the *m*-derivative, it was found more convenient to extract it as the hydrochloride and to reconvert the latter to the base.

When *two* moles of lepidine were used to one of aldehyde, the yield of *m*-carbinol (after eight hours at 120°) was increased to 24%, but for the *o*- and *p*- isomers there was no great improvement in yield of isolable product (presumably because these compounds were, to a somewhat greater extent, retained in solution in the excess lepidine, and the dissolved part could not be readily separated from it). Various attempts were made to increase the yield of *m*-derivative still further. It was found that heating the reaction mixture at 120° for twenty-four hours, or at 145° for eight hours, always gave a mixture of the carbinol and the corresponding *styryl* compound. Moreover, after cooling to room temperature, the reaction mixture was invariably found to be acid to litmus and it was concluded that this acid, presumably formed from the aldehyde during the reaction, had facilitated conversion of some of the carbinol to the styryl derivative. (The ability of acid to catalyze this dehydration has already been proved[1] for the corresponding quinaldyl carbinols.) It was therefore decided to add to the reaction mixture some substance which would neutralize acid as fast as it was formed. After examining the effect of a number of materials, anhydrous sodium carbonate was finally selected, and the reaction mixture was heated at 145° for twenty-four hours. At the end of this time, the reaction mixture was still alkaline to litmus, and *no* styryl derivative had formed, but the yield obtained (33%), though higher, was scarcely increased enough to warrant using this method.

Just as for the three quinaldyl isomers, we find the three nitrophenyllepidylcarbinols exhibit two melting points, depending on whether heated rapidly or slowly. On cooling until crystallized and remelting, the melting point is found to be lower in each case, presumably owing to partial conversion to the corresponding styryl derivative on heating. The carbinols were transformed to their monohydrochlorides which were isolated as colorless, crystalline substances showing no tendency to become dehydrated to the styryl derivatives during five months at room temperature, as evidenced by the recovery of pure carbinol on reconversion to the base. The acetyl derivatives of the three carbinol compounds were also prepared. Attempts to reduce each nitro carbinol to the corresponding amino derivative gave inconclusive results suggestive of formation of some β-hydroxylamino derivative[4]; we were unable to purify the products satisfactorily by fractional recrystallization.

It has been shown previously[5] that the reaction of *p*-dimethylaminobenzaldehyde with quinaldine gives rise to the corresponding styryl derivative *plus* *p*-dimethylaminobenzylidene diquinaldine (β-*p*-dimethylaminophenyl-α,γ-di-2-quinolylpropane) and that a preponderance of either product is obtainable by appropriate choice of the conditions. Similarly, on attempting to prepare the pure *styryl* derivatives by condensation of the appropriate nitrobenzaldehyde with lepidine in

---

[1] Walton, Tipson and Cretcher, THIS JOURNAL, **67**, 1501 (1945).

[2] Bulach, *Ber.*, **20**, 2046 (1887).

[3] Eibner, *Ber.*, **37**, 3605 (1904); Fischer, *et al.*, *J. prakt. Chem.*, **100**, 91 (1920).

[4] Fieser and Hershberg, THIS JOURNAL, **62**, 1640 (1940).

[5] Tipson, *ibid.*, **67**, 507 (1945).

TABLE I

MELTING POINTS AND ANALYSES OF THE MONONITROPHENYLLEPIDYLCARBINOLS AND THE 4-(NITROSTYRYL)-QUINOLINES

Vol. (cc.) of absolute ethanol (E) plus chloroform (C) for recryst. of 10 g. -phenyllepidylcarbinol	M. p., °C.			Formula	Analyses, %					
	Initial		Second Cooled and reheated		Calculated			Found		
	Fast	Slow			C	H	N	C	H	N
o-Nitro 150 (E) + 120 (C)	191–192	182–184	180	$C_{17}H_{14}N_2O_3$	69.36	4.8	9.53	69.66	5.2	9.46
m-Nitro 160 (E)	166–167	162–163	157	$C_{17}H_{14}N_2O_3$	69.36	4.8	9.53	69.45	5.1	9.34
p-Nitro 150 (E) + 120 (C)	187–188	182–184	180	$C_{17}H_{14}N_2O_3$	69.36	4.8	9.53	69.18	5.0	9.79
-styryl)-quinoline										
4-*o*-Nitro 150 (E) + 50 (C)			172–173[a]	$C_{17}H_{12}N_2O_2$	73.88	4.4	10.15	73.77	4.5	10.43
4-*m*-Nitro			133–134[b]	$C_{17}H_{12}N_2O_2$	73.88	4.4	10.15	73.83	4.3	10.14
4-*p*-Nitro			227–229[c]	$C_{17}H_{12}N_2O_2$	73.88	4.4	10.15	73.70	4.5	9.95

[a] Loew (*Ber.*, **36**, 1666 (1903)) gave m. p. 162°. [b] Heymann and Koenigs (*Ber.*, **21**, 2167, 1424 (1888)) gave m. p. 131–132° and 135–136°; Kaslow and Stayner (THIS JOURNAL, **67**, 1716 (1945)) gave 130.5–131.5°. [c] Loew, ref. *a*, gave 221°.

the presence of an inorganic acid, it was found that the *dilepidine* derivatives are formed together with the nitrostyryl compounds. Indeed, the *m*- and *p*-nitrobenzylidene dilepidines could be isolated in good yield (77% and 63%, respectively, of the theoretical amount) by heating one mole of the appropriate aldehyde with two moles of lepidine in the presence of concentrated sulfuric acid for three hours at 165° (bath temperature). On the other hand, on treating lepidine with the *o*-aldehyde under the same conditions, a violent reaction ensued, resulting in extensive decomposition. At a reaction temperature of 100°, a mixture of the *o*-nitrostyryl-quinoline and its corresponding *carbinol* derivative was formed.

The three 4-(nitrostyryl) derivatives have now been isolated in pure form and are found to have melting points higher than those previously recorded in the literature. The *o*-nitrostyryl derivative was readily prepared pure since it was the *sole* product resulting either on boiling a solution of the pure carbinol compound in acetic anhydride,[2,6] or on boiling a solution of the *o*-aldehyde and lepidine in acetic anhydride.

The 4-(*m*-nitrostyryl)-quinoline could not be obtained as the *sole* product in any of the reactions attempted. On performing the reactions involving acetic anhydride (successfully used to prepare the pure *o*-styryl compound), the *m*-nitrostyryl derivative formed was contaminated with a higher melting, more insoluble compound (either the carbinol or dilepidine derivative, depending on the conditions). When propionic anhydride (b. p. 165–168°) was used instead of acetic anhydride, a mixture of the styryl and carbinol derivatives resulted. Again, on heating equimolecular proportions of aldehyde and lepidine in the presence of hydrochloric or sulfuric acids, a mixture of the styryl and dilepidine compounds was obtained. It was difficult to separate pure *m*-nitrostyryl compound from these more insoluble derivatives, but we succeeded in isolating it by fractional recrystallization of its mixture with the dilepidine compound.

On boiling pure *p*-nitrophenyllepidylcarbinol with acetic anhydride, the product consisted essentially of the styryl derivative plus a trace of *p*-nitrobenzaldehyde, which was detected by sublimation. This scission of *p*-nitrobenzaldehyde from the nitrophenyllepidylcarbinol molecule was presumably accompanied by formation of the corresponding amount of the dilepidine derivative. When lepidine was heated with *p*-nitrobenzaldehyde in the presence of hydrochloric acid, the styryl derivative was formed together with the dilepidine compound (which could not be removed by repeated crystallization), but the pure *p*-styryl compound was separable therefrom by conversion to the hydrochloride; the hydrochloride of the dilepidine derivative is fairly soluble in boiling water, whereas that of the *p*-nitrostyryl derivative is difficultly soluble.

Experimental

o- and p-Nitrophenyllepidylcarbinols.—The nitrobenzaldehyde (10.6 g., completely free from acid[1]) was treated with distilled lepidine (10 g.) at 120° (temperature of reaction mixture) during eight hours, and then allowed to stand overnight at room temperature. Chloroform (50 cc.) was now added to the partly crystalline mixture, the suspension cooled in ice during several hours, and filtered. The crystals were washed with two 10-cc. portions of chloroform and dried in the vacuum desiccator over phosphorus pentoxide.

A small second crop was obtained by extracting the chloroform filtrate with three 50-cc. portions of 5 *N* hydrochloric acid. The *aqueous* layer was separated from the chloroform layer (A), made alkaline to litmus with 8 *N* sodium hydroxide solution, and the lepidine plus product extracted with chloroform. The chloroform extract was washed, dried over anhydrous sodium sulfate, and evaporated to dryness. Heptane (50 cc.) was added to the resulting dark oil, and, on scratching and chilling, a second crop of crystals appeared. (The *chloroform* layer (A) was freed from acid by shaking with dilute sodium hydroxide solution, washed, dried, filtered and evaporated to dryness, giving unchanged aldehyde which could be used directly for another preparation.)

The crude product was recrystallized from a boiling mixture of ethanol and chloroform (see Table I); the hot solution was filtered and the filtrate cooled and kept overnight in the refrigerator. The *o*- and *p*-nitrophenyllepidylcarbinols were obtained as pale yellow crystals, fairly soluble in hot methanol, ethanol, chloroform, and acetone, and sparingly soluble in ether, benzene, and heptane. They were more soluble in methanol than in any of the other solvents mentioned. The *o*-compound was slightly more soluble than the *p*- in all these solvents.

---

(6) Wartanian, *Ber.*, **23**, 3644 (1890).

m-Nitrophenyllepidylcarbinol.—*m*-Nitrobenzaldehyde (10.6 g., free from acid) was heated, as in the previous section, but with *two* molar proportions of distilled lepidine (20 g.), and then kept overnight at room temperature. The resulting oil was washed into a flask with 50 cc. of chloroform and 5 *N* hydrochloric acid (50 cc.) was added, whereupon the fairly insoluble, colorless carbinol hydrochloride slowly separated out in the aqueous layer. The mixture was kept in an ice-bath for two hours, and the solid was then filtered off and washed successively with 5 *N* hydrochloric acid (25 cc.) and chloroform. The hydrochloride was now suspended in about 50 cc. of water, and 8 *N* sodium hydroxide solution was added until, after vigorous shaking, the suspension remained alkaline to litmus. The precipitated base was dissolved by extracting with chloroform, and the chloroform solution washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The yield of crude product was 24% of the theoretical. It was recrystallized from boiling ethanol (see Table I) and was obtained as colorless crystals. It was more soluble than the corresponding *o*- or *p*-compounds in all the solvents tested.

The yield was increased to 33% of the theoretical amount by heating 2 moles of lepidine plus 1 mole of the aldehyde and 0.5 mole of anhydrous sodium carbonate, with continuous stirring, during twenty-four hours at 145°.

Nitrophenyllepidylcarbinol Monohydrochlorides.—The base (2 g.) was dissolved in the minimum volume of cold chloroform and the calculated amount of concentrated hydrochloric acid (0.25 g.), dissolved in 10 cc. of absolute ethanol, was added rapidly to the solution, with stirring. A colorless precipitate of hydrochloride appeared slowly; after keeping the mixture overnight at room temperature, this was filtered off, washed successively with 10 cc. of ethanol and 10 cc. of chloroform, and dried.

All three hydrochlorides were obtained as colorless crystals which were stable at room temperature but started to decompose at about 200°. They were slightly soluble in water and sparingly soluble in absolute ethanol, the salt of the *m*-compound being more soluble than the hydrochlorides of either the *o*- or *p*-derivatives.

Anal. Calcd. for $C_{17}H_{14}N_2O_3 \cdot HCl$: N, 8.48. Found: (*o*-), N, 8.53; (*m*), N, 8.63; (*p*-), N, 8.51.

Samples of each were stored at room temperature for five months and then reconverted to the free base; there was no change in m. p. or analysis.

Acetylation of the Nitrophenyllepidylcarbinols.—The carbinols were acetylated as previously described[1] for the acetylation of *m*-nitrophenylquinaldylcarbinol; yield, quantitative.

o-Nitrophenyllepidylcarbinyl Acetate.—The crude compound was recrystallized from 10 volumes of hot absolute ethanol, the resulting crystals were dissolved in 3 volumes of chloroform, hexane (10 volumes) was added to faint opalescence, and the solution kept overnight in the refrigerator; colorless crystals; m. p. 103–105°.

Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.83; H, 4.8; N, 8.34. Found: C, 68.19; H, 5.0; N, 8.16.

m-Nitrophenyllepidylcarbinyl Acetate.—The crude compound was first recrystallized from 9 volumes of methanol by adding 6.5 volumes of water. The resulting crystals were dried, extracted with 20 volumes of cold, dry ether, and the pure, colorless, acetyl derivative filtered off and dried; m. p. 95–97°.

Anal. Calcd. for $C_{19}H_{1}\ {}_{2}O_4$: C, 67.83; H, 4.8; N, 8.34. Found: C, 67.81, H, 4.8; N, 8.40.

p-Nitrophenyllepidylcarbinyl Acetate.—The crude compound was recrystallized from 7 volumes of boiling absolute ethanol; pale yellow crystals, m. p. 120–121.5°.

Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.83; H, 4.8; N, 8.34. Found: C, 67.87; H, 5.0; N, 8.22.

m-Nitrobenzylidene Dilepidine.—A mixture of lepidine (10 g.), *m*-nitrobenzaldehyde (5.3 g.) and concentrated sulfuric acid (1.4 g.) was heated for three hours at 165° (glycerol bath) in a two-necked flask (thermometer). It was then cooled to room temperature and dilute sodium hydroxide solution added to the reaction mixture. After standing overnight at room temperature, the lumps of solid were readily broken up, the solid was transferred to a large beaker with water, 8 *N* sodium hydroxide was added until the solution was alkaline to litmus, and the mixture allowed to stand for about seven hours. The solid was then filtered off, washed with water until the washings were free from sulfate (barium hydroxide test), and dried; weight (cocoa-colored solid), 14.2 g.

The crude product was treated with 10 volumes of boiling absolute ethanol during one hour, the suspension cooled in ice, and the light-brown solid filtered off and dried. The weight of crude dilepidine compound was 11.2 g. (77%); m. p., 226–232° (shrinks at 220°).

The alcoholic mother liquor was evaporated to dryness (2.9 g.) and found to consist essentially of the styryl derivative.

Recrystallization of the crude dilepidine compound from boiling chloroform and absolute ethanol was unsatisfactory. One gram of material (partially purified thus) was treated with 75 cc. of water plus 2 cc. of concentrated hydrochloric acid. A trace of undissolved solid was filtered off and 8 *N* sodium hydroxide (about 3 cc.) was added to the filtrate until the solution was alkaline to litmus. The pure, colorless dilepidine compound which separated was filtered off and dried (0.8 g.); shrinks at 220°, followed by partial melting, and melts to brown liquid at 227–232°. This melt would not resolidify on cooling to room temperature.

Anal. Calcd. for $C_{27}H_{21}N_3O_2$: C, 77.29; H, 5.1; N, 10.03. Found: C, 77.24; H, 4.7; N, 9.89.

p-Nitrobenzylidene Dilepidine.—The procedure for preparing the *p*-dilepidine compound was initially similar to the one used for the corresponding *m*-compound but, after filtering it from the first alkaline solution, the cocoa-colored solid was suspended in water and enough 5 *N* hydrochloric acid was added to bring the solution to *p*H 1–3. The undissolved material was filtered off, suspended in dilute sodium hydroxide solution, the orange-colored product filtered off, washed with water and dried (13.3 g.).

The crude product was treated with a boiling mixture of absolute ethanol (10 volumes) and chloroform (15 volumes) during one hour, cooled to room temperature, and the undissolved solid was filtered off and dried; 6.1 g. of pink crystals. A second crop (3.2 g.) was obtained by allowing the mother liquor of this first crop to stand in the refrigerator for several days; total yield of crude product, 63%.

The mother liquor of the second crop was evaporated to dryness (4.1 g.) and found to be mainly composed of the styryl derivative.

The crude dilepidine compound (2 g.) was treated with 150 cc. of boiling 1% hydrochloric acid, the hot suspension filtered, and dilute sodium hydroxide added to the filtrate, giving colorless, free base; shrinks at 220°, followed by partial melting, and melts to a dark brown liquid at 237–240°.

Anal. Calcd. for $C_{27}H_{21}N_3O_2$: C, 77.29; H, 5.1; N, 10.03. Found: C, 77.25; H, 5.4; N, 10.15.

4-(o-Nitrostyryl)-quinoline.—A solution of pure *o*-nitrophenyllepidylcarbinol (2 g.) in 8 cc. of acetic anhydride was boiled under reflux for two hours, and the solution cooled and poured into 250 cc. of ice plus water, with stirring. The product was filtered off, washed with water until the washings were neutral to litmus, and dried; yield of crude product, 80% of the theoretical (increased to quantitative yield by working up the aqueous mother liquor). It was recrystallized from 15 volumes of boiling absolute ethanol plus 5 volumes of chloroform, giving bright yellow crystals having a silvery sheen.

4-(*o*-Nitrostyryl)-6-methoxyquinoline was prepared as for the 4-styryl derivative[7]; unchanged starting materials were removed by distillation[7] at 0.05 mm. The still residue was crystallized from absolute ethanol (m. p., 122–124°) and recrystallized from pyridine (10 volumes) plus water (10 volumes), giving bright yellow crystals, m. p., 128–129°.

---

[7] Campbell, Tipson, *et al.*, *J. Org. Chem.*, **11**, 803 (1946).

Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.56; H, 4.6; N, 9.15. Found: C, 70.48; H, 4.5; N, 9.44.

4-(*m*-Nitrostyryl)-quinoline.—After repeated recrystallization, the styryl compound was finally obtained in pure form from a mixture with the corresponding dilepidine derivative.

Lepidine (5 g.), *m*-nitrobenzaldehyde (5.3 g.), and 3 cc. of concentrated hydrochloric acid were heated in a two-necked flask at 120° (inside temperature) during three hours. After cooling to room temperature, chloroform (50 cc.) was added and the mixture kept in an ice-bath for two hours. The solid was then filtered off, washed with 50 cc. of chloroform, the yellow-brown crystals suspended in water, and made alkaline to litmus with 8 *N* sodium hydroxide solution. The yellow solid was dissolved in chloroform, the solution washed with water, dried over anhydrous sodium sulfate, filtered, and the filtrate evaporated to dryness, giving 6.2 g. of yellow solid.

The crude product was dissolved in 15 volumes of boiling absolute ethanol plus 8 volumes of chloroform, filtered, and the filtrate kept in the refrigerator overnight. A small crop of cream-colored crystals which separated was filtered off and dried (0.7 g.); m. p. 220–230°. Microchemical analysis indicated that it was slightly impure dilepidine derivative. The mother liquor was kept in the refrigerator for a week, giving a second crop of cream-colored solid (0.5 g.); m. p. 217–231°.

The mother liquor of the second crop was evaporated to dryness (4.9 g.); m. p. 130–134°. It was recrystallized from 8 volumes of boiling absolute ethanol. The pure *m*-styryl compound separated on cooling, and was filtered off and dried (3.7 g.).

4-(*p*-Nitrostyryl)-quinoline.—When prepared as described for the *m*-styryl compound, in the presence of hydrochloric acid, the *p*-styryl derivative could not be separated from its impurity (probably the dilepidine compound) by repeated recrystallization. The most satisfactory method for obtaining the pure *p*-styryl compound when the impurity was the dilepidine derivative (*not* the carbinol compound) was by treatment with hydrochloric acid, as follows:

Impure *p*-styryl derivative (4 g.) was treated with 240 cc. of chloroform and a trace (0.1 g.) of insoluble material (which seemed to consist mainly of the more insoluble dilepidine derivative) filtered off. To the filtrate was added 100 cc. of 5% hydrochloric acid and the mixture swirled. The hydrochlorides which separated were filtered off, suspended in 150 cc. of 1% hydrochloric acid, the suspension boiled for a few minutes, filtered while hot, and the yellow solid washed with about 50 cc. of hot 1% hydrochloric acid. The solid hydrochloride was then suspended in dilute sodium hydroxide solution, the base extracted with chloroform, the chloroform solution washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness (2.5 g.). This material was now recrystallized by dissolving in 15 volumes of boiling absolute ethanol plus 25 volumes of chloroform. The solution was kept in the refrigerator overnight, and the crystals filtered off and dried (2.2 g.).

Summary

The three mononitrophenyllepidylcarbinols and their acetates and monohydrochlorides have been prepared and some of their properties are described. The corresponding styryl derivatives were isolated in pure form.

A method has been developed for the preparation of the *m*- and *p*-nitrobenzylidene dilepidines in good yield, and some of their properties are recorded.

PITTSBURGH 13, PA. RECEIVED OCTOBER 3, 1947

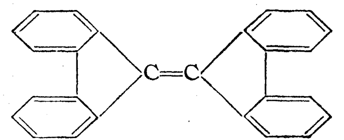
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Addition of Grignard Reagents to the Olefin, Bidiphenyleneethylene

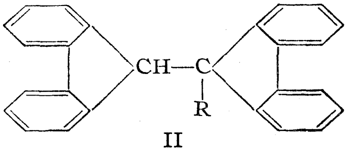
BY REYNOLD C. FUSON AND HERSCHEL D. PORTER[1]

Attempts to add Grignard reagents to olefins, involving a large number of hydrocarbons and a wide range of experimental conditions, have yielded only negative results.[2,3,4] Apparently successful attempts reported in some instances,[5,6] were subsequently found to have been misleading.[7]

The demonstration by Pinck and Hilbert[8] that bidiphenylethylene (I) as well as its tetrabromo derivative was capable of reacting additively with various carbonyl reagents suggested that this highly conjugated olefin might also combine with Grignard reagents. This idea was favored by the discovery of Ziegler and Schäfer[9] that phenyllithium condensed with bidiphenyleneethylene to give 1-phenyl-1,2-bidiphenyleneethane (II, R = C_6H_5).



I



II

In the present work it has been found that certain Grignard reagents will react with bidiphenyleneethylene to produce the corresponding substituted ethanes (II). It appeared that the best chance of success was to employ *t*-butyl or benzyl Grignard reagents, shown by Kharasch and Weinhouse[10] to be the most reactive.

When *t*-butylmagnesium chloride was allowed to react with bidiphenyleneethylene, 1-*t*-butylbidiphenyleneethane (II, R = C_4H_9) was produced in good yield. Similarly, benzylmagnesium chlo-

---

[1] Rohm and Hass Research Assistant, 1946–1947.

[2] Gilman and Crawford, THIS JOURNAL, **45**, 554 (1923).

[3] Kinney and Larsen, *ibid.*, **57**, 1054 (1935).

[4] Gilman and Peterson, *ibid.*, **48**, 423 (1926).

[5] Rupe and Bürgin, *Ber.*, **43**, 172 (1910).

[6] Rupe, *Ann.*, **402**, 149 (1913).

[7] Gilman and McGlumphy, *Rec. trav. chim.*, **47**, 418 (1928).

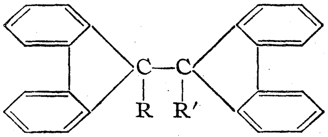
[8] Pinck and Hilbert, THIS JOURNAL, **57**, 2398 (1935); **68**, 2014 (1946).

511, 101 (1934).

[10] Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

ride gave 1-benzylbidiphenyleneethane (II, R = $C_6H_5CH_2$). In one experiment with the benzyl reagent the chief product was 1,2-dibenzylbidiphenyleneethane (III, R = R′ = $C_6H_5CH_2$). It seemed likely that this product formed through benzylation of the primary adduct by excess benzyl chloride present in the solution of the Grignard reagent. In confirmation of this surmise, it was found that the dibenzyl derivative could be made in good yield by treating the olefin with benzylmagnesium chloride and then adding benzyl chloride to the resulting reaction mixture.

p-Chlorobenzylmagnesium chloride reacted in much the same way as the benzyl Grignard reagent. The structures assigned to the alkylated ethanes are indicated by analogy with the products obtained in other addition reactions of the olefin. They are given additional support by the following observations.



III

Treatment of the addition product from the olefin and benzylmagnesium chloride with *p*-chlorobenzyl chloride yielded 1-benzyl-2-*p*-chlorobenzylbidiphenyleneethane (III, R = $C_6H_5CH_2$, R′ = $ClC_6H_4CH_2$). The same derivative was formed by benzylation of the adduct from *p*-chlorobenzylmagnesium chloride and the olefin.

The bidiphenyleneethylene was prepared by the action of methanolic potassium hydroxide on 9-bromofluorene according to the directions of Thiele and Wanscheidt.[11] The bromofluorene was synthesized by a new method—treatment of fluorene with N-bromosuccinimide by the procedure of Ziegler, Späth, Schaaf, Schumann and Winkelmann.[12] The bromofluorene was made also by photochemical bromination of fluorene by the procedure of Sampey and Reid.[13] This method has the advantage of extreme simplicity and affords higher yields.

Attempts to condense less reactive Grignard reagents with bidiphenyleneethylene failed. Neither phenylmagnesium bromide nor methylmagnesium iodide proved to be capable of undergoing addition.

Inasmuch as Ziegler, Späth, Schaaf, Schumann and Winkelmann[12] have been able to add phenyllithium to benzalfluorene, it seemed possible that the Grignard reagent might react in a similar manner. Efforts to bring about condensation of this olefin with *t*-butylmagnesium chloride were, however, unsuccessful.

Experimental

9-Bromofluorene.—A solution of 99.6 g. of commercial fluorene (m. p. 108–111°) in 500 ml. of dry thiophene-free benzene was heated for four hours under reflux with an equimolar amount (106.8 g.) of N-bromosuccinimide, prepared (in 71% yield) by the directions of Ziegler, Späth, Schaaf, Schumann and Winkelmann.[12] The precipitate of succinimide which formed during this process was removed by filtration, the solvent distilled from the filtrate, and the residue taken up in 500 ml. of hot, high-boiling petroleum ether. Cooling caused long needle-like crystals of 9-bromofluorene to precipitate; yield 69 g., 47%; m. p. 103–104°.

The bromofluorene was also prepared, in approximately the yields reported, by the photochemical bromination of fluorene according to the directions of Sampey and Reid.[13]

Bidiphenyleneethylene.—The general directions of Thiele and Wanscheidt[11] were followed. A solution of 20 g. of 9-bromofluorene in 150 ml. of acetone was caused to react at room temperature with a solution of 10 g. of potassium hydroxide in 30 ml. of methanol. After one hour, 100 ml. of water was added, with vigorous stirring. The precipitate of bidiphenyleneethylene was collected by filtration and allowed to dry in the air overnight. The products of two such preparations were taken up in 50 ml. of boiling benzene, and precipitation was induced by the addition of 50 ml. of boiling alcohol; yield 64%; m. p. 188–190° (uncor.).

1-*t*-Butyl-1,2-bidiphenyleneethane.—A solution of *t*-butylmagnesium chloride, prepared from 9.25 g. of *t*-butyl chloride, 2.43 g. of magnesium and 130 ml. of absolute ether, was freed of magnesium by forcing it through a glass wool plug by means of nitrogen pressure. The *t*-butylmagnesium chloride was added to a solution of 3.28 g. of bidiphenyleneethylene in 100 ml. of a mixture of equal parts of dry benzene and absolute ether. After the material had been heated for eighteen hours under reflux in an atmosphere of nitrogen, with constant stirring, it was poured on an ice–hydrochloric acid mixture. The organic layer was separated and washed with very dilute hydrochloric acid. After the solvent had been removed by distillation, the residue was taken up in 15 ml. of boiling chloroform; precipitation was induced by the addition of 30 ml. of 95% ethanol; yield 2.63 g., or 68%. After the above purification procedure had been repeated ten times, the material was found to be analytically pure; m. p. 221–223° (cor.).

Anal. Calcd. for $C_{30}H_{26}$: C, 93.22; H, 6.78. Found: C, 93.24; H, 6.90.

1-Benzyl-1,2-bidiphenyleneethane.—A solution of benzylmagnesium chloride, prepared from 5.06 g. of benzyl chloride, 0.97 g. of magnesium and 100 ml. of absolute ether, was heated under reflux for one hour. Bidiphenyleneethylene (3.28 g.) was added in the form of small crystals. The solution was stirred overnight under gentle reflux, poured on an ice–hydrochloric acid mixture and processed as in the preceding experiment. A precipitate of 2.42 g. of light yellow needles melting at 223–231° (uncor.) was obtained; yield 57.6%. The sample for analysis did not reach a constant melting point until it had been subjected to twelve purifications in the manner described for the purification of 1-*t*-butyl-1,2-bidiphenyleneethane; m. p. 240–241° (cor.).

Anal. Calcd. for $C_{33}H_{24}$: C, 94.24; H, 5.75. Found: C, 94.25; H, 5.92.

1-*p*-Chlorobenzyl-1,2-bidiphenyleneethane.—A solution of *p*-chlorobenzylmagnesium chloride was prepared by the dropwise addition of 3.22 g. of *p*-chlorobenzyl chloride to 0.49 g. of magnesium in 50 ml. of absolute ether. After the solution was stirred under reflux for one hour, 3.28 g. of bidiphenyleneethylene was added in the form of small crystals. The solution was heated under reflux in an atmosphere of dry nitrogen for sixteen hours and worked up in the usual manner. Removal of the solvent produced a red oil which deposited yellow crystals when triturated with 100 ml. of low-boiling petroleum

---

[11] Thiele and Wanscheidt, *Ann.*, **376**, 269 (1910); Wittig and Lange, *ibid.*, **536**, 266 (1938).

[12] Ziegler, Späth, Schaaf, Schumann and Winkelmann, *ibid.*, **551**, 80 (1942).

[13] Sampey and Reid, THIS JOURNAL, **69**, 235 (1947).

ether. The compound was purified in the manner described for 1-*t*-butyl-1,2-bidiphenyleneethane; m. p. 234–235° (cor.); yield 12.5%.

Anal. Calcd. for $C_{33}H_{23}Cl$: C, 87.11; H, 5.10. Found: C, 86.97; H, 5.38.

1,2-Dibenzyl-1,2-bidiphenyleneethane.—A solution of benzylmagnesium chloride was formed by the addition of 0.67 g. of benzyl chloride to 0.14 g. of magnesium in 16 ml. of absolute ether. One gram of bidiphenyleneethylene was added immediately after the addition of the benzyl chloride was complete. The reaction mixture was diluted with 50 ml. of absolute ether, heated under reflux overnight and processed in the usual manner. The analytical sample was prepared by repeated recrystallization from a solvent composed of six parts of benzene and one part of toluene; m. p. 204–205° (cor.); yield 36%.

Anal. Calcd. for $C_{40}H_{30}$: C, 94.07; H, 5.93. Found: C, 93.80; H, 6.27.

A solution of benzylmagnesium chloride, prepared from 2.53 g. (0.02 mole) of benzyl chloride, 0.48 g. of magnesium and 50 ml. of absolute ether, was protected from the air by a stream of dry nitrogen and stirred for one hour to ensure completion of the reaction. A solution of 3.28 g. (0.01 mole) of bidiphenyleneethylene in 50 ml. of dry benzene and 30 ml. of absolute ether was then added. After the solution had been heated under reflux for four hours, 3 g. of benzyl chloride was added. The mixture was heated under reflux for fifteen hours and processed in the usual manner. The product was purified by dissolving in hot chloroform and reprecipitating by the addition of boiling alcohol. After two such operations the melting point was 196–198° (uncor.); a mixed melting point with the 1,2-dibenzyl-1,2-bidiphenyleneethane obtained previously was not depressed (196–198°).

1-Benzyl-2-*p*-chlorobenzyl-1,2-bidiphenyleneethane.—The benzylmagnesium chloride was prepared as in the preceding experiment and allowed to react with 3.28 g. of bidiphenyleneethylene dissolved in 100 ml. of a solvent composed of equal parts of dry benzene and absolute ether. After the solution had been heated under reflux for eighteen hours, 3.50 g. of *p*-chlorobenzyl chloride was added, and the reaction mixture was heated overnight under reflux, with mechanical stirring. The reaction mixture was poured on an ice–hydrochloric acid mixture, and the organic layer was washed with water. The reddish oil that remained, after removal of the solvent and trituration with low-boiling petroleum ether, deposited 1.69 g. of yellow, sandy crystals. Purification was accomplished by dissolving the compound in hot chloroform, and reprecipitating it by the addition of boiling alcohol. The analytical sample consisted of white needles and possessed a melting point of 203–205° (uncor.).

Anal. Calcd. for $C_{40}H_{29}Cl$: C, 88.13; H, 5.36. Found: C, 87.87; H, 5.66.

The addition product of *p*-chlorobenzylmagnesium chloride and bidiphenyleneethylene was prepared as in the preparation of 1-*p*-chlorobenzyl-1,2-bidiphenyleneethane. After the reaction mixture had been heated under reflux for eight hours, 2.78 g. of benzyl chloride was added, and the solution was heated under reflux overnight. The reaction mixture was poured on an ice–hydrochloric acid mixture; the organic layer was separated, washed with water and evaporated to dryness. The residual, red oil was triturated with a mixture of 8 ml. of benzene and 4 ml. of carbon tetrachloride in a bath of solid carbon dioxide; a precipitate of 0.37 g. (7%) was deposited. The material was purified as in the above experiment. Softening occurred at 195–199° and melting took place at 199–202°. A mixture with the product obtained in the preceding experiment softened at 196–199° and melted at 199–203°.

Attempted Reaction with Phenylmagnesium Bromide.—A solution of phenylmagnesium bromide, prepared from 3.14 g. of bromobenzene, was protected at all times from the air by an atmosphere of nitrogen. Bidiphenyleneethylene (3.2 g.) was added, and the solution was heated under reflux for twenty-five hours. It was then poured on an ice–hydrochloric acid mixture and worked up in the usual manner. A total of 2.84 g. (89%) of the original hydrocarbon was recovered.

Attempted Reaction with Methylmagnesium Iodide.—An ether solution, containing 0.02 mole of methylmagnesium iodide, was heated overnight under reflux with 3.28 g. (0.01 mole) of bidiphenyleneethylene. In addition to 2.53 g. (77%) of bidiphenyleneethylene recovered, a small amount of bidiphenyleneethane was obtained; m. p. 247–248° (cor.).

Anal. Calcd. for $C_{26}H_{18}$: C, 94.50; H, 5.49. Found: C, 94.45; H, 5.75.

Attempted Reaction of Grignard Reagents with Benzalfluorene.—The Grignard solution was prepared as described in the preparation of 1-*t*-butyl-1,2-bidiphenyleneethane. A solution of 2.55 g. of benzalfluorene, prepared in 70% yield according to the directions of Henle,[14] in 50 ml. of absolute ether was added, and the solution heated overnight under reflux in an atmosphere of nitrogen. A total of 2.11 g. (83%) of unchanged benzalfluorene was obtained.

In a similar experiment 5.10 g. (0.02 mole) of benzalfluorene was added to a solution of 0.04 mole of benzylmagnesium chloride, and the solution was heated under reflux for twenty-four hours. A total of 4.33 g. (84%) of unchanged benzalfluorene was recovered.

Summary

Grignard reagents have been found to react additively with the olefin, bidiphenyleneethylene. Reaction with *t*-butyl-, benzyl- or *p*-chlorobenzylmagnesium chlorides converts the olefin to the corresponding 1-alkylbidiphenyleneethane.

When the adduct obtained with benzylmagnesium chloride was treated with *p*-chlorobenzyl chloride, the product was 1-benzyl-2-chlorobenzylbidiphenyleneethane. The same compound was produced by the action of benzyl chloride on the adduct formed by *p*-chlorobenzylmagnesium chloride and the olefin. These facts show that the two points of attachment of the Grignard reagent are symmetrically situated.

URBANA, ILLINOIS RECEIVED SEPTEMBER 15, 1947

---

[14] Henle, *Ann.*, **347**, 290 (1906).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF OREGON, AND THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF OREGON MEDICAL SCHOOL]

Studies on the Reactions between Formaldehyde and Enediols.[1a] I

BY F. J. REITHEL AND E. S. WEST

Krishnamurthy[1b] showed that ascorbic acid reacted with formaldehyde as evidenced by a marked decrease in reducing power when titrated with 2,6-dichlorophenol-indophenol or iodine. Lugg[2] found that ascorbic acid reacted readily with formaldehyde at *p*H 3.5 but slowly at *p*H 1.5, that some reducing substances reacted readily at both *p*H values, and still others, among them a crude preparation of reductone, reacted with formaldehyde at neither *p*H value. A critical study of Lugg's work was made by Snow and Zilva,[3] who found that reductone did react with formaldehyde but more slowly. Mapson[4] has also published some observations.

The prime purpose of these investigators was to develop a method for determining ascorbic acid in foods and biological products which would be more accurate than the simple method of dye titration. In addition, both Lugg[2] and Snow and Zilva[3] attempted to discover the nature of the reaction between enediols and formaldehyde. Extensive data were obtained on reaction velocities and equilibrium constants were determined but the reaction products could not be isolated.

In 1937, one of the present authors[5] noted the fact that formaldehyde abolished the reducing power of ascorbic acid. A study of this phenomenon produced evidence that *l*-ascorbic acid, *d*-isoascorbic acid, *d*-gluco-ascorbic acid, α-hydroxytetronic acid, reductone, and dihydroxymaleic acid lost the ability to reduce 2,6-dichlorophenol-indophenol when they were treated with formaldehyde. Furthermore, it was found that under the proper conditions mixtures of ascorbic acids and formaldehyde and similar mixtures of α-hydroxytetronic acid and formaldehyde slowly evolved carbon dioxide.

Like Snow and Zilva[3] we attempted to isolate a reaction product from mixtures of *l*-ascorbic acid and formaldehyde but no crystalline product was ever obtained. The sirupy material formed on removal of excess formaldehyde and evaporation of such reaction mixtures was investigated by many of the standard methods of carbohydrate chemistry such as methylation, acetylation, tritylation, periodic acid oxidation and permanganate oxidation. An acetone derivative and a semicarbazide were obtained in crystalline form but in very small yield. We concluded that a complex mixture of compounds was formed.

The following is a study of the reactions between enediols and formaldehyde at *p*H 3.5–6.0, utilizing carbon dioxide production as a criterion of reaction.

Experimental

1. **Carbon Dioxide Formation by Ascorbic Acid–Formaldehyde Mixtures.**—Two-hundred fifty milligrams of ascorbic acid was dissolved in 25 ml. of carbon dioxide- and oxygen- free water and neutralized to *p*H 7.2 with sodium hydroxide. Two and five-tenths milliliters of 37% formaldehyde was added and the mixture introduced into a small flask with a side arm arranged so that any carbon dioxide produced could be swept into an absorbing spiral immersed in barium hydroxide by a stream of nitrogen (purified over hot copper). The mixture was allowed to react at 60° for four hours, then acidified: carbon dioxide found, 52.8 mg.; theoretical (assuming one mole of carbon dioxide per mole of ascorbic acid), 62.5 mg.

In an exactly similar experiment calcium hydroxide was used to bring the *p*H to 7.65. Reaction was allowed to proceed for four hours at 60°, then acidified to liberate carbon dioxide from the calcium carbonate precipitate; carbon dioxide found, 57.7 mg.

A third experiment was done using the same quantities and conditions except that no alkali was added. After five hours at 60°, 62.2 mg. of carbon dioxide was produced.

Other variables were checked and the following observations made. Never was there obtained more than one mole of carbon dioxide per mole of ascorbic acid. The reaction proceeded somewhat more rapidly in alkaline than in acid solution. The reaction was slower at 30° than at 60° but the rate was appreciable. In blank experiments where no formaldehyde was added no carbon dioxide was obtained from ascorbic acid.

Several experiments were conducted to determine the effect of formaldehyde on the optical rotation of ascorbic acid. We found, as did Snow and Zilva, that the phenomenon was not simple. If the reaction mixture was allowed to remain in polariscope tubes for several days it was observed, upon opening them, that a considerable pressure of carbon dioxide had developed.

Following are the data from a typical experiment. One gram of ascorbic acid was dissolved in 19% formaldehyde and made up exactly to 50 ml.

TABLE I

Time	$[\alpha]^{25}_D$
0 hr.	+33.4
4	+51.5
24	+50.7
2 days	+45.0
5	+25.0
10	0.0
13	−11.2
17	−25.0
19	−22.5[a]

[a] Reading was made after releasing gas pressure in tube.

2. **Rates of Carbon Dioxide Production under Varying Conditions of *p*H, Temperature and Concentration.**—In

---

[1a] A portion of this work was taken from a thesis by F. J. Reithel presented to the Faculty of the University of Oregon Medical School in partial fulfillment of the requirements for the Ph.D. degree in June, 1942. This work was presented at the Northwest Regional Meeting of the A.C.S. at Pullman, Wash., May 2, 1947.

[1b] Krishnamurthy, *J. Indian Chem. Soc.*, **18**, 383 (1941).

[2] Lugg, *Nature*, **150**, 577 (1942); *Australian J. Exp. Biol. and Med. Sci.*, **20**, 273 (1942).

[3] Snow and Zilva, *Biochem. J.*, **37**, 630 (1943); **38**, 458 (1944).

[4] Mapson, *J. Soc. Chem. Ind.*, **62**, 223 (1943).

[5] West and Ney, *Proc. Am. Soc. Biol. Chem.*, **cii**, 31st Annual Meeting (1937).

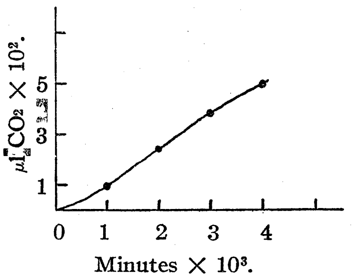


Fig. 1.—85 mg. of ascorbic acid in 10 ml. of 5.54% formaldehyde (0.0483 *M* ascorbic and 1.85 *M* formaldehyde), 40°, *p*H 3.5.

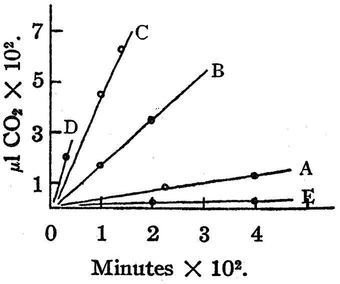


Fig. 2.—(A) 87.1 mg. of ascorbic acid in 10 ml. of formaldehyde (5% in 0.1 *M* phthalate buffer), *p*H 4.0; (B) 85.4 mg. of ascorbic acid in 10 ml. of formaldehyde (5% in 0.1 *M* phthalate buffer), *p*H 5.0; (C) 17 mg. of ascorbic acid in 2 ml. of formaldehyde (5.3% in *M* acetate buffer), *p*H 5.4; (D) 17 mg. of ascorbic acid in 2 ml. of formaldehyde (5% in 0.2 *M* phosphate buffer), *p*H 6.0; (E) portion of curve in Fig. 1 for comparison. All experiments carried out at 40°.

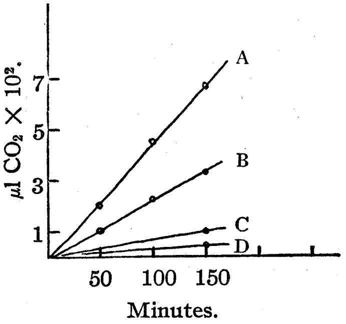
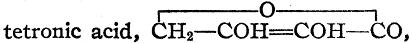


Fig. 3.—(A) 17 mg. of ascorbic acid in 2 ml. of formaldehyde (5.3% in *M* acetate buffer, *p*H 5.4), 0.0484 *M* ascorbic; (B) same except 0.0242 *M* ascorbic; (C) same except 0.0086 *M* ascorbic; (D) same except 0.0048 *M* ascorbic; all experiments carried out at 40°.

the following experiments the liberation of carbon dioxide from ascorbic acid–formaldehyde mixtures was followed in the Warburg manometric apparatus. All solutions were saturated with carbon dioxide before use and equilibrated with carbon dioxide while in the manometer flasks. The total volume of the reaction mixture was 2.0 ml. In most of the experiments the ascorbic acid was made up in buffer and tipped into the formaldehyde in the body of the Warburg flask after equilibration. (Figs. 1–5.)

3. Liberation of Carbon Dioxide from Mixtures of α-Hydroxytetronic Acid and Formaldehyde.—α-Hydroxy tetronic acid,  $\overbrace{CH_2—COH{=}COH—CO}^{O}$, was prepared by the method of Micheel and Jung.[6] (Fig. 6.)

4. The Effect of Formaldehyde on the Acidity of Solutions of Enediols.—A solution of 0.1000 *M* ascorbic acid in 37% formaldehyde was allowed to stand at 23° until it no longer reduced 2,6-dichlorophenolindophenol. As measured with a Beckmann *p*H meter this solution had a *p*H of 5.11. Five milliliters of this solution plus 2.50 ml. of 0.1000 *N* sodium hydroxide had a *p*H of 7.23. This corresponds to the *pK*. Our ascorbic acid (0.1000 *M* in water) had a *pK* of 4.08.

A similar experiment with reductone indicated a *pK* of 7.7 in 37% formaldehyde and 5.03 in water.

Two hundred and fifty milligrams of ascorbic acid was dissolved in 25 ml. of distilled water and 25 ml. of 37% formaldehyde added. The mixture was allowed to react in an atmosphere of nitrogen at 50°. At the beginning the *p*H was 4.4, at the end of eighteen hours the *p*H was 4.63.

Discussion

The foregoing data indicate that more than one reaction can occur in mixtures of formaldehyde and enediols. It is likely that Snow and Zilva were able to obtain reaction rates and equilibrium constants for an apparent single "condensation" reaction between enediols and formaldehyde because they worked with enediol concentrations of about 0.5 *M* and near room temperature. Under such conditions the liberation of carbon dioxide is very slow.

The hypothesis of Snow and Zilva that formaldehyde adds to carbons three and six of the ascorbic acid molecule is based on two lines of evidence. First, carbon number three was assumed to be involved because the *p*H of ascorbic acid solutions rose as reaction with formaldehyde progressed. This is confirmed by our data. Second, they found that six-substituted derivatives of ascorbic acid reacted at a different rate than ascorbic acid.

It would appear likely that such a reaction would lead to a product which is essentially neutral. Thus as reaction proceeds the *p*H should rise and sodium hydroxide titration values should decrease. However, Snow and Zilva found sodium hydroxide titration values to remain essentially the same throughout the course of reaction. They claim that this is due to reversal of the reaction by alkali. Krishnamurthy's data show that more ascorbic acid reacts at *p*H 6.0 than at 3.5 and our data show a marked acceleration of carbon dioxide liberation as the *p*H approaches 6.

Further we found that under our conditions little change in *p*H occurred during the course of carbon dioxide liberation. We interpret these findings as indicating that reaction with formaldehyde involves carbon number three and that the lactone ring breaks to free the potential carboxyl group. The carbon dioxide liberated probably arises from such a reaction product. That the lactone ring is involved is suggested by the fact that only those enediols possessing such a structure yield carbon dioxide when treated with formaldehyde.

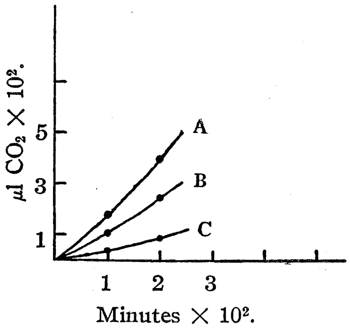


Fig. 4.—(A) 8.5 mg. of ascorbic acid in 2 ml. of formaldehyde (1.41 *M* in *M* acetate buffer, *p*H 5.4), 40° (B) same except 0.71 *M* formaldehyde; (C) same except 0.18 *M* formaldehyde.

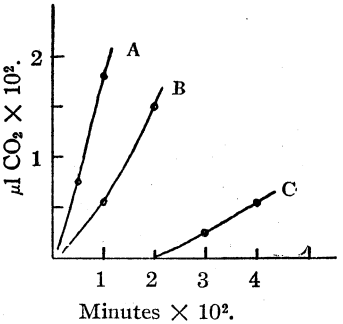


Fig. 5.—(A) 8.5 mg. of ascorbic acid in 2 ml. of formaldehyde (5.85% in *M* acetate buffer, *p*H 5.4), 40°; (B) same except 32°; (C) same except 25°.

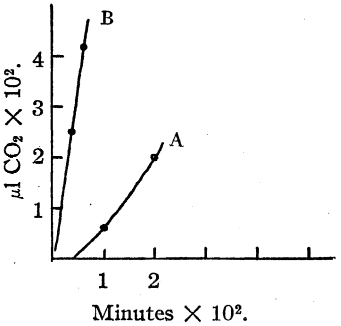


Fig. 6.—(A) 8.5 mg. of α-hydroxytetronic acid in 2 ml. of formaldehyde (5.85% in *M* acetate buffer, *p*H 5.4): 25.8° (B) same except 40°.

the phenomena described in this paper may lead to a quantitative method for determining ascorbic acid which is more specific than any yet devised.

Summary

1. It has been shown that ascorbic acid and α-hydroxytetronic acid react with formaldehyde and that under certain conditions one of the products of the reaction is carbon dioxide.

2. The rate of carbon dioxide formation in reaction mixtures of ascorbic acid and formaldehyde has been studied in relation to *p*H, temperature and concentration of reactants.

3. A similar study has been made on an α-hydroxytetronic acid–formaldehyde system.

4. The present work has been discussed in relation to previous studies which employed diminution of the reducing action of enediols as a criterion of reaction.

EUGENE, OREGON RECEIVED MAY 31, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

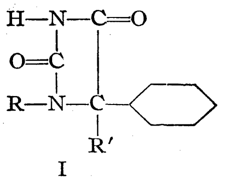
The Synthesis of 1-R-5-R'-5-Phenylhydantoins

BY LOREN M. LONG, C. A. MILLER AND H. D. TROUTMAN

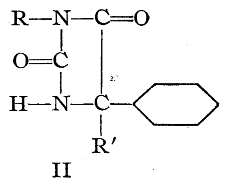
The discovery by Putnam and Merritt[1] of the efficacy of Dilantin[2] in the treatment of epilepsy has resulted in the synthesis and subsequent testing of a large number of related compounds. The activity of many of these against electrically induced convulsions has been reported by Merritt and Putnam.[3] On examining this report one notes that the majority of the hydantoins which have been studied are those substituted in the 5-position only. It was logical, then, to extend the types of hydantoins studied to include those containing an N-substituent.

Since a search of the literature revealed that an appreciable number of 3,5-substituted hydantoins have been prepared,[4] it seemed that the synthesis of hydantoins substituted in the 1- and 5-positions offered a better opportunity of finding new and useful anticonvulsants. Indeed, in reference to 3-substituted hydantoins, a derivative of 5-ethyl-5-phenylhydantoin (nirvanol) has been introduced recently[5] as being effective in reducing the number of convulsions exhibited by epileptic patients. However, the use of this drug, 3-methyl-5-ethyl-5-phenylhydantoin, may result in rash formation similar to that caused by nirvanol.

Another possible advantage of compounds unsubstituted in the 3-position, as in structure (I), was thought to be the retention of dilute alkali solubility in contrast to the dilute alkali insolubility of compounds of structure (II). Thus, in many cases the sodium salts of cyclic ureides are preferred over the free compounds, *i. e.*, Dilantin[2] and phenobarbital.



I



II

A few derivatives of type (I) have been prepared

---

(1) Putnam and Merritt, *Science*, **85**, 525 (1937).

(2) Dilantin—registered trade-mark of Parke, Davis & Co. for 5,5-diphenylhydantoin.

(3) Merritt and Putnam, *Epilepsia*, **3**, 51 (1945).

(4) British Patents 430,255, 430,282, 430,283, 430,473; French Patent 769,667; German Patent 611,057; Swiss Patents 166,004, 168,947, 168,948, 169,509, 171,982, 176,827, 177,411, 179,255, 179,690, 179,692.

(5) Lascalzo, *J. Nerv. Ment. Dis.*, **101**, 537 (1945).

TABLE I

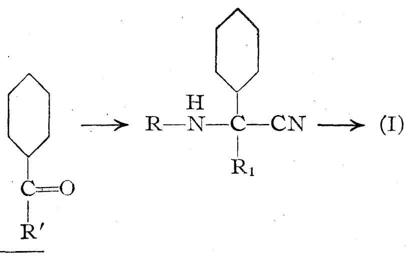
1-R-5-R′-5-PHENYLHYDANTOINS

					Analyses, %[b]			
					Carbon		Hydrogen	
R	R′	M. p., °C.	Yield, %[a]	Formula	Calcd.	Found	Calcd.	Found
Methyl[c]	H	177–179	59	$C_{10}H_{10}N_2O_2$	63.14	63.23	5.30	5.36
Methyl[d]	Methyl	186–188	53	$C_{11}H_{12}N_2O_2$	64.69	64.78	5.93	6.00
Methyl[e]	Ethyl	210	47	$C_{12}H_{14}N_2O_2$	66.03	66.13	6.47	6.14
Methyl	*n*-Propyl	235	49	$C_{13}H_{16}N_2O_2$	67.21	67.15	6.94	6.74
Methyl	Phenyl	224–226	14	$C_{16}H_{14}N_2O_2$	72.16	72.27	5.30	5.29
Ethyl	H	109–111	61	$C_{11}H_{12}N_2O_2$	64.69	64.78	5.93	5.81
Ethyl	Methyl	176–177	43	$C_{12}H_{14}N_2O_2$	66.03	66.08	6.47	6.40
Ethyl	Ethyl	164–166	45	$C_{13}H_{16}N_2O_2$	67.21	67.44	6.94	6.83
Ethyl	*n*-Propyl	210	37	$C_{14}H_{18}N_2O_2$	68.27	68.85	7.37	7.10
Ethyl	Phenyl	185–187	20	$C_{17}H_{16}N_2O_2$	72.84	72.60	5.75	5.70
n-Propyl	H	108–110	62	$C_{12}H_{14}N_2O_2$	66.03	66.19	6.47	6.44
n-Propyl	Methyl	133–135	57	$C_{13}H_{16}N_2O_2$	67.21	67.27	6.94	6.93
n-Propyl	Ethyl	127	52	$C_{14}N_{18}N_2O_2$	68.27	68.49	7.37	7.05
n-Propyl	*n*-Propyl	135	45	$C_{15}H_{20}N_2O_2$	69.20	69.23	7.74	7.77
i-Propyl	H	173–174	35	$C_{12}H_{14}N_2O_2$	66.03	66.33	6.47	6.55
Allyl	H	94–96	65	$C_{12}H_{12}N_2O_2$	66.65	66.95	5.60	5.35
Allyl	Methyl	98–99	40	$C_{13}H_{14}N_2O_2$	67.80	67.56	6.13	6.16
Allyl	Ethyl	117–119	48	$C_{14}H_{16}N_2O_2$	68.83	68.94	6.60	6.66
Allyl	*n*-Propyl	137	42	$C_{15}H_{18}N_2O_2$	69.74	69.91	7.02	6.80
n-Butyl	H	141–142	67	$C_{13}H_{16}N_2O_2$	67.21	67.63	6.94	6.96
n-Butyl	Methyl	100–101	50	$C_{14}H_{18}N_2O_2$	68.27	68.39	7.37	7.32
n-Butyl	Ethyl	149–152	45	$C_{15}H_{20}N_2O_2$	69.20	69.02	7.74	7.70
n-Butyl	*n*-Propyl	98–100	51	$C_{16}H_{22}N_2O_2$	70.04	70.37	8.08	8.06
Cyclohexyl	H	190–193	32	$C_{15}H_{18}N_2O_2$	69.74	69.85	7.02	6.95
n-Heptyl	H	103–105	51	$C_{16}H_{22}N_2O_2$	70.04	70.35	8.08	8.01
n-Heptyl	Methyl	94–95	43	$C_{17}H_{24}N_2O_2$	70.80	70.57	8.39	8.42
n-Heptyl	Ethyl	118–119	45	$C_{18}H_{26}N_2O_2$	71.46	71.53	8.70	8.78
β-Phenethyl	H	173–175	65	$C_{17}H_{16}N_2O_2$	72.84	72.84	5.75	5.89
α-Methyl-β-phenethyl	H	149–152	64	$C_{18}H_{18}N_2O_2$	73.45	73.34	6.16	5.86
β-Hydroxyethyl	H	155–157	52	$C_{11}H_{12}N_2O_3$	59.99	60.00	5.49	5.40
β-Hydroxyethyl	Methyl	115	43	$C_{12}H_{14}N_2O_3$	61.52	61.43	6.02	6.07
β-Hydroxyethyl	Ethyl	102	44	$C_{13}H_{16}N_2O_3$	62.88	62.61	6.50	6.57
α-Dimethyl-β-hydroxyethyl	H	229	33	$C_{13}H_{16}N_2O_3$	62.88	62.51	6.50	6.43
β-Bromoethyl	H	131–133	70	$C_{11}H_{11}BrN_2O_2$	46.66	46.81	3.92	3.78

[a] Based on the amount of aldehyde or ketone employed. [b] The analytical data reported in this paper were determined by Arthur W. Spang. [c] Gabriel, *Ann.*, **350**, 124 (1906). [d] Swiss Patent 179,692. [e] German Patent 611,057; French Patent 769,667; Swiss Patent 169,509.

previously. The emphasis, however, has been on those representing 1-substituted nirvanol,[4] although an attempt was made to produce effective germicides by synthesizing 1,5-dihydroxyphenylhydantoins.[6]

Although the details of the procedure employed in the synthesis of the compounds listed in Table I were varied to improve yields, the general method was essentially the same throughout and may be represented by the following scheme.



This procedure is similar to that employed by other investigators[4,6] and is necessary since on alkylating 5,5-substituted hydantoins the first group entering the ring does so at the 3-position as in (II).

Since with primary amines benzaldehyde readily forms benzylidenimines which in turn react with hydrogen cyanide to form aminonitriles, such a procedure was utilized in preparing the 1-substituted-5-phenylhydantoins. It was found unnecessary to isolate any of the compounds intermediate between the imine and the hydantoin. In general the best method of synthesis consisted of mixing benzaldehyde with the appropriate amine. The resulting mixture was then added to cold 70–80% acetic acid containing about one-half of the required sodium or potassium cyanide. The remainder of the cyanide was then added and was followed shortly by the portion-wise addition of a slight excess of potassium cyanate. The resulting mixture, when treated with concentrated hydrochloric acid, gave yields of 35–70% of the expected hydantoin.

The procedure with ketones such as acetophenone and propiophenone was changed in that the ketone was first treated with liquid hydrogen cyanide. When the cyanohydrin thus formed reacted with an amine, water split out and the resulting aminonitrile was treated with potassium cyanate. In several reactions of this type results indicated that the presence of a strong mineral acid, either with or without acetic acid, offers some advantage over acetic acid alone.

The problem of preparing 1-alkyl derivatives of 5,5-diphenylhydantoin differs somewhat from that involved in either of the above types. Although it has been shown that diaryl ketones such as benzophenone, contrary to the findings of Bucherer and Lieb,[7] do in fact form hydantoins,[8] it is true that benzophenone exhibits very little tendency toward cyanohydrin formation with hydrogen cyanide.[9] In confirmation of this fact, all attempts to prepare aminonitriles from benzophenone itself ended in failure. However, this difficulty was overcome by treating dichlorodiphenylmethane with an amine as in the method used by Moore[10] in preparing benzophenone imine from dibromodiphenylmethane and ammonia. The substituted benzophenone imine thus produced reacted readily with hydrogen cyanide and the resulting amino-nitrile was converted to 1-alkyl-5,5-diphenylhydantoin by the use of cyanic acid.

Pharmacology.—The results of preliminary studies by Merritt and Putnam, part of which have been published,[3] and especially by Chen[11] of this Laboratory indicate that although many of the compounds in Table I exhibit anticonvulsant activity, the maximum inhibition of variously induced convulsions is attained with the 1-R-5-phenylhydantoins, where R represents a hydrocarbon radical of from two to four carbon atoms inclusive. Like other types of derivatives of 5,5-diphenylhydantoin,[3] the 1-alkyl-5,5-diphenylhydantoins have no inhibitory effect on electrically induced convulsions.

Experimental

1-Propyl-5-phenylhydantoin.—Two hundred and sixty-five grams (2.5 moles) of benzaldehyde was placed in a 1-liter flask fitted with a stirrer, a reflux condenser and a dropping funnel. The flask was cooled in a cold water-bath and 154 g. (2.6 moles) of *n*-propylamine (Sharples) was added with stirring. The addition, which was completed in twenty minutes, was made at such a rate as to cause the mixture to reach a temperature of 60°. Stirring was continued for one-half hour after the last of the amine had been added. The mixture was then cooled in an ice-bath.

One liter of 75% aqueous acetic acid was placed in an open 3-liter flask fitted with a stirrer and a thermometer and cooled to 0° in an ice-salt-bath. The acid was stirred slowly while 71 g. of sodium cyanide was added so that the temperature remained below 5°. The benzylidene–propylamine–water mixture was then added dropwise, keeping the temperature below 10°. The remainder of the sodium cyanide (70 g.) was added in 10-g. portions.

Stirring was continued, and when the aminonitrile solution had again cooled to 0°, a total of 212 g. of potassium cyanate was added over a period of one-half hour. The temperature increased to 5°. After one hour the slowly stirred mixture was heated to 70° for fifteen minutes on a steam-bath.

Concentrated hydrochloric acid (750 ml.) was added cautiously to the warm solution. After the acidified mixture had been heated on the steam-bath for an hour, it was diluted to 3 liters with cold water and thoroughly cooled in an ice-bath. The oily layer on top solidified slowly. The resulting mixture was filtered and the solid product washed with cold water and dried. Purification was accomplished by solution in 5% aqueous alkali, charcoaling and reprecipitation with Dry Ice. The final product was a white, crystalline solid weighing 337 g.

1-Allyl-5-phenylhydantoin.—Four hundred and twenty-four grams (4.0 moles) of benzaldehyde was mixed with 500 ml. of water in a 2-liter flask fitted with a stirrer, reflux condenser and a dropping funnel. The mixture was stirred and 234 g. (4.1 moles) of allylamine was added at a moderate rate. The temperature increased to about 65°. After refluxing for one-half hour, the mixture was cooled and extracted twice with 300-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate, concentrated on a steam bath and the residue distilled at reduced pressure. The product, 517 g. or 89%, distilled at 96–99° (20 mm.).[12]

One hundred and forty-five grams (1.0 mole) of benzylidene allylamine was placed in a 500-ml. flask fitted with a stirrer, reflux condenser and a dropping funnel and cooled in an ice–salt mixture. While the imine was stirred slowly, 27 g. (1.0 mole) of liquid hydrogen cyanide was added dropwise. The resulting aminonitrile was allowed to warm up to room temperature.

The aminonitrile was dissolved in 350 ml. of 80% aqueous acetic acid cooled to 0°. To the cold solution was added in small portions with slow stirring 89 g. (1.1 mole) of potassium cyanate. The remainder of the process was carried out as in the preparation of 1-propyl-5-phenylhydantoin. The yield of white, crystalline product based on the benzylidene allylamine was 73%.

1-Methyl-5-methyl-5-phenylhydantoin.—One hundred and twenty grams (1.0 mole) of acetophenone was mixed with 29.7 g. (1.1 mole) of liquid hydrogen cyanide in a pressure bottle. A few drops of saturated sodium carbonate solution were added, and the bottle closed and allowed to stand at room temperature for twenty-four hours. The solution was then cooled and methylamine was passed in until one mole had been absorbed. On standing at 25° for twenty hours, an appreciable quantity of water separated.

The crude aminonitrile was added slowly to 1 liter of dilute hydrochloric acid cooled to 0°. A large part of the nitrile dissolved. The mixture was stirred slowly while 89 g. (1.1 mole) of potassium cyanate was added in small portions. After twenty minutes a white solid precipitated. The mixture was kept in the ice-bath for an additional hour. It was then heated on a steam-bath and 100 ml. of concentrated hydrochloric acid was added. After an hour the mixture was thoroughly cooled and filtered. The product was dissolved in an excess of 5% aqueous sodium hydroxide and the resulting mixture extracted twice with small portions of ether to remove unreacted ketone. The solution was then charcoaled, filtered and the product reprecipitated with Dry Ice. The purified product was a white crystalline solid.

1-Ethyl-5-diphenylhydantoin.—To a solution of 23.6 g. (0.1 mole) of benzophenone chloride[13] in 50 ml. of toluene

---

[7] Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

[8] Henze and Long, This Journal, **63**, 1941 (1941); Henze, U. S. Patents 2,409,754, 2,409,755, 2,409,756.

[9] Lapworth and Manske, *J. Chem. Soc.*, 2533 (1928).

[10] Moore, *Ber.*, **43**, 563 (1910).

[11] Private communication.

[12] Borsche and John, *Ber.*, **57**, 664 (1924).

[13] Norris, Thomas and Brown, *ibid.*, **43**, 2958 (1910).

in a small metal bomb was added 22.5 g. (0.5 mole) of anhydrous ethylamine. The bomb was closed and heated to 100–105° for twenty hours. It was then cooled, opened and the contents filtered. The solid consisted of ethylamine hydrochloride (16.1 g.). The yellow filtrate was concentrated *in vacuo*. The cooled residue was mixed with 2.7 g. (0.1 mole) of liquid hydrogen cyanide. The solution became warm. It was cooled and mixed with 500 ml. of cold, dilute hydrochloric acid. Treatment with 8.9 g. (0.11 mole) of potassium cyanate and purification of the product as previously described in the preparation of 1-methyl-5-methyl-5-phenylhydantoin yielded a crystalline product.

1-β-Hydroxyethyl-5-phenylhydantoin.—Fifty-three grams (0.5 mole) of benzaldehyde and 14.9 g. (0.55 mole) of liquid hydrogen cyanide were mixed together in a small pressure bottle (ice-bath) and allowed to stand at 25° for two hours. The product was cooled and 30.5 g. (0.5 mole) of ethanolamine was added. Heat was evolved. The resulting mixture was cooled and added to a cold solution of 50 ml. of concentrated hydrochloric acid and 200 ml. of water. After the solution had cooled to 0°, 44.6 g. (0.55 mole) of potassium cyanate was added. Within a few minutes a yellow, semi-solid material precipitated. The mixture was left in the ice-bath for an hour before being heated on the steam-bath with an additional 100 ml. of concentrated hydrochloric acid. After the mixture was thoroughly chilled, it was filtered. The yellow solid was purified by dissolving in 800 ml. of boiling water, charcoaling and cooling to reprecipitate the product.

1-β-Bromoethyl-5-phenylhydantoin.—Twenty-two grams (0.1 mole) of 1-β-hydroxyethyl-5-phenylhydantoin was mixed with 50 ml. of dry chloroform and cooled in an ice-bath. Ten grams of phosphorus tribromide in 50 ml. of chloroform was added with stirring. After one-half hour the mixture was placed on a steam-bath and warmed for an hour. The resulting solution was poured with stirring into an excess of chipped ice. The solid product was filtered off and recrystallized from ethanol and water.

Summary

A series of 1-R-5-R′-5-phenylhydantoins, most of which are new compounds, has been prepared and tested for anticonvulsant activity.

Maximum activity is exhibited by those derivatives having a lower hydrocarbon group in the 1-position and only a phenyl group in the 5-position.

DETROIT, MICHIGAN RECEIVED OCTOBER 4, 1947

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

The Preparation of Some Substituted Quinoxalines

BY R. W. BOST AND E. E. TOWELL[1,2]

The reaction between aromatic ortho-diamines and alpha-diketones to form quinoxalines has been utilized to prepare a series of 2,3-disubstituted quinoxalines and 2,3-disubstituted-6-methoxyquinoxalines, with the purpose of studying their pharmacological properties.

The two diamines used were *o*-phenylenediamine and 3,4-diaminoanisole in the form of its hydrochloride, which was prepared in the laboratory from 4-amino-3-nitroanisole. The 4-amino-3-nitroanisole was prepared from commercial *p*-anisidine by the method of Reverdin,[3] with minor modifications. The diacetyl was obtained from the Forest Products Company. 3,5-Dicarboethoxycyclopentanedione-1,2 was prepared by the condensation of ethyl oxalate and ethyl glutarate in the presence of sodium ethoxide.[4] The following benzoins were prepared from the corresponding aldehydes by the "benzoin" condensation in the presence of alcoholic potassium cyanide: 4,4′-dimethoxybenzoin, *p*-dimethylaminobenzoin, 3,3′,4,4′-bis-(methylenedioxy)-benzoin, 2,2′,3,3′-tetramethoxybenzoin, 4-methoxy-3′,4′-methylenedioxybenzoin, and *p*-diethylaminobenzoin. *alpha*-Furoin and benzil were available in the laboratory. The following diketones were prepared by oxidation of the corresponding hydroxyketone with copper sulfate in pyridine[5]: 4,4′-dimethoxybenzil, *p*-dimethylaminobenzil, 3,3′,4,4′-bis-(methylenedioxy)-benzil, 2,2′,3,3′-tetramethoxybenzil[6]; 4-methoxy-3′,4′-methylenedioxybenzil, alpha-furil, and *p*-diethylaminobenzil (not obtained in crystalline form; alcoholic solution used to prepare the quinoxaline).

Attempts to prepare the quinoxaline from 2,3,2′-3′-tetramethoxybenzil and *o*-phenylenediamine were unsuccessful. An explanation of this anomalous behavior of an alpha-diketone toward an aromatic ortho-diamine has been offered by Schönberg and co-workers.[7]

Bennett and Willis[8] have shown that the methyl groups in 2,3-dimethylquinoxaline react with certain aromatic aldehydes in an excess of boiling acetic anhydride to form mono- and di-styrylquinoxalines. Attempts were made by us to bring about a similar reaction between 2,3-dimethylquinoxaline and formaldehyde, acetaldehyde and *n*-butyraldehyde, respectively, using the method of Bennett and Willis. Since no identifiable products could be isolated from the reaction mixtures, the experimental details are not given in this paper. An unsuccessful attempt was made to carry out a

---

[1] This paper is a portion of a dissertation presented by E. E. Towell in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the University of North Carolina, June, 1944.

[2] New York Community Trust Fund Fellow, 1942–1943; Wm. S. Merrell Co. Fellow, 1943–1944. Present address: Department of Chemistry, College of Charleston, Charleston, S. C.

[3] Reverdin, *Ber.*, **29**, 2595 ff. (1896).

[4] Adams, *et al.*, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 284.

[5] "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 87; Kinney, THIS JOURNAL, **51**, 1595 (1929); Hartmann and Dickey, *ibid.*, **55**, 1228 (1933).

[6] Hartwell and Kornberg, *ibid.*, **67**, 1607 (1945).

[7] Schönberg and co-workers, *Ber.*, **55B**, 1174 ff., 3746 ff., 3755 (1922).

[8] Bennett and Willis, *J. Chem. Soc.*, 1960 (1928); 256 (1929).

Mannich[9] type reaction using 2,3-dimethylquinoxaline, methylamine hydrochloride and formaldehyde.

Experimental

3,4-Diaminoanisole.—This compound has been reported by Meldola and Eyre,[10] and has been prepared in the pure state by Bergeim,[11] *et al.*, by the reduction of 4-amino-3-nitroanisole with stannous chloride and hydrochloric acid. The free base has also been prepared by the reduction of 4-amino-3-nitroanisole with hydrogen and Raney nickel catalyst.[12] The authors prepared and used the compound in the form of its crude hydrochloride, since in this form it was less susceptible to oxidation by the air. In a typical run, 4-amino-3-nitroanisole (50.4 g., 0.30 mole) and fluid Raney nickel catalyst (8–9 cc.) were added to anhydrous ether (150 cc.) and reduced catalytically under pressure in the presence of hydrogen in the usual manner at an initial pressure of 1500 p. s. i. and an initial temperature of 30°. The reduction was complete within thirty to forty minutes. As soon as possible after opening the bomb, the straw-colored ether solution was poured rapidly through a glass-wool filter into chilled, anhydrous ether (1000 cc.), previously saturated with dry hydrogen chloride gas, and contained in a three-liter, three-necked, round-bottomed flask fitted with stirrer and gas trap. The diamine hydrochloride, pale purple in color, formed immediately, and the product from each run was allowed to remain in the flask until several runs had been made. The product was then filtered, washed with anhydrous ether, dried in air for two hours, and stored in the dark. One series of five runs gave 276 g. of the crude hydrochloride (87%). The product was used to prepare quinoxaline without further purification. A small sample reacted with benzoyl chloride in 20% sodium hydroxide solution to form the dibenzoyl derivative which, after recrystallization from glacial acetic acid, melted at 248–249°. Reported m. p. 251–252°.[10]

Benzoins.—The usual methods[13] of preparing benzoins, both simple and mixed, were employed, with certain modifications as to proportions of reagents used, time of reflux and standing, and method of isolating and purifying the product. In general, it was found that yields were improved by filtering off the first batch of product, returning the filtrate to the reaction vessel, adding a fresh portion of potassium cyanide solution and refluxing again. In some instances, this process was repeated more than once. The yields ranged from 25% for 4-methoxy-3′,4′-methylenedioxybenzoin to 74% for 3,3′,4,4′-bis-(methylenedioxy)-benzoin.

***p*-Diethylaminobenzoin.**—*p*-Diethylaminobenzaldehyde (53.1 g., 0.30 mole), freshly distilled benzaldehyde (41.8 g., 0.30 mole) and 150 cc. of 95% ethanol were warmed on the steam-bath until solution was complete. Potassium cyanide solution (5 g. in 100 cc. of water) was added, the whole refluxed for two hours, then allowed to stand overnight. A second portion of potassium cyanide solution (8 g. in 50 cc. of water) was added, the whole refluxed for three hours, and allowed to stand overnight. Chilling failed to produce crystallization, the reaction mixture persisting as two layers, the lower being dark orange-red in color. The mixture was steam-distilled until about five liters of distillate had come over. The residue was allowed to stand overnight, after which the aqueous layer was decanted, and the viscous orange-red lower layer taken up in 50 cc. of 95% ethanol. The solution was diluted with water (150 cc.), the resulting suspension warmed on the steam-bath, and 95% ethanol added gradually until the solution just became clear. The solution was boiled with Norite, filtered, and allowed to stand at room temperature for six hours whereupon 30.8 g. of lustrous golden-yellow flakes were obtained. After recrystallization twice from 95% ethanol, lustrous white flakes, m. p. 105–106°, were obtained.

Anal. Calcd. for $C_{18}H_{21}O_2N$: N, 4.94. Found: N, 4.97.

Benzils.—The oxidation of the benzoins to the corresponding benzils by copper sulfate in pyridine was found to give good yields (better than 60%) in nearly every case. The products were easily isolated and purified. An exception was the product from the oxidation of *p*-diethylaminobenzoin, which could be obtained only as a sticky yellow gum adhering to the walls of the vessel. This material was taken up in 95% ethanol, in which it was readily soluble, and the solution used to prepare the corresponding quinoxaline by reaction with *o*-phenylenediamine.

2,3,2′,3′-Tetramethoxybenzil.—This compound was obtained in an 84% yield when 2,3,2′,3′-tetramethoxybenzoin was oxidized by the above procedure. It consists of white needles, m. p. 140–142°. *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.05: H, 5.29.

The 2,4-dinitrophenylhydrazone of this compound was prepared according to the method of Allen,[14] being obtained as brilliant orange crystals, m. p. 169–171° (uncor.), after three recrystallizations from a chloroform–methanol mixture.

Anal. Calcd. for $C_{24}H_{22}O_9N_4$: N, 10.99. Found: N, 11.11.

Quinoxalines.—The general procedure for preparing the 2,3-disubstituted quinoxalines was as follows[15]; equimolar portions (approx. 0.10 mole) of *o*-phenylenediamine and the benzil were refluxed for two to three hours in boiling glacial acetic acid (200–400 cc.), the reaction mixture allowed to cool, then poured, with vigorous stirring, into cold water (1000–2000 cc.). The resulting suspensions in most cases yielded precipitates on standing, or were broken with 20% sodium hydroxide solution. The products were recrystallized from ethanol, after treatment with Norite. The yields ranged from 85 to 99%. The 2,3-disubstituted-6-methoxyquinoxalines were prepared generally by the same procedure, except that the crude diamine hydrochloride was used instead of the free base. The yields ranged from 41 to 81%, it being found that the sooner the diamine hydrochloride was used after its preparation, the higher was the yield. The 2,3-dimethylquinoxalines were prepared in 10% acetic acid medium as given below.

2,3-Dimethyl-6-methoxyquinoxaline.—Crude 3,4-diaminoanisole hydrochloride (42.2 g., approx. 0.20 mole) was taken up in 10% acetic acid (300 cc.). Diacetyl (20 g., 0.23 mole) in 50 cc. of 10% acetic acid was added dropwise, with stirring, the mixture being heated on the steam-bath throughout the addition and for thirty minutes afterward. The dark-green mixture was allowed to cool to room temperature, diluted with water (750 cc.) and made alkaline to litmus with 20% sodium hydroxide solution. The brownish-black precipitate which formed was filtered, washed with water, taken up in dilute ethanol (1:1, 1000 cc.), boiled with Norite, then filtered. This operation was repeated four times, until the filtrate became pale straw-colored. Upon chilling, cream-colored crystals formed. Repeated recrystallization from dilute ethanol gave cream-colored crystals of constant m. p. 99–100° (uncor.).

Anal. Calcd. for $C_{11}H_{12}ON_2$: N, 14.89. Found: N, 14.81.

2,3-Dimethylquinoxaline Sulfate.—2,3-Dimethylquinoxaline (15.8 g., 0.10 mole), prepared according to the procedure given above, was taken up in anhydrous ether

---

[9] Adams, *et al.*, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 303 ff.

[10] Meldola and Eyre, *J. Chem. Soc.*, **81** [2], 990 (1902).

[11] Bergeim, Losee and Lott, This Journal, **69**, 586 (1947).

[12] Cavagnol and Wiselogle, *ibid.*, **69**, 796 (1947).

[13] Buck and Ide, *ibid.*, **52**, 223 (1930); **52**, 4107 (1930); **53**, 2352 (1931); **54**, 3305 (1932); Jenkins and co-workers, *ibid.*, **52**, 4496 (1930); **52**, 5201 (1930); **54**, 1159 (1932); Wöhler and Liebig, *Ann.*, **3**, 276 (1832); Perkin, *J. Chem. Soc.*, **59**, 164 (1891); Staudinger, *Ber.*, **46**, 3537 (1913); Tiffeneau and Levy, *Bull. soc. chim.*, [4] **49**, 725 (1931).

[14] Allen, This Journal, **52**, 2957 (1930).

[15] Fuson, Emerson and Gray, *ibid.*, **61**, 482 (1939), prepared quinoxalines by the reaction of arylglyoxals and *o*-phenylenediamine in boiling glacial acetic acid.

TABLE I

2,3-DISUBSTITUTED QUINOXALINES

Substituents	Yield, %	M. p., °C. (uncor.)	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
2,3-Dimethyl	90	104–106	$C_{10}H_{10}N_2$	17.72	17.66
2,3-Diphenyl	87	124	....	...	...
2,3-Di-*p*-anisyl	85	145.5–146	$C_{22}H_{18}O_2N_2$	8.18	8.06
2,3-Di-α-furyl	92	131–132	$C_{16}H_{10}O_2N_2$	10.68	10.58
2,3-Piperonyl	99	199–200	....	...	...
2,3-Di-(3′,5′-dicarboethoxy)-cyclopentane	94	202–203	$C_{17}H_{18}O_4N_2$	8.91	8.92
[a]2-Phenyl-3-(*p*-dimethylamino)-phenyl	88	120–121	$C_{22}H_{19}N_3$	12.91	12.70
[a]2-Phenyl-3-(*p*-diethylamino)-phenyl	..	126- 127	$C_{24}H_{23}N_3$	11.89	10.22
2,3-DISUBSTITUTED-6-METHOXYQUINOXALINES					
[a]2,3-Dimethyl[b]	49	99–100	$C_{11}H_{12}ON_2$	14.89	14.81
2,3-Diphenyl	77	154.5–155	....	...	...
[a]2,3-Di-*p*-anisyl[b]	81	131–132	$C_{23}H_{20}O_3N_2$	7.52	7.43
[a]2,3-Di-α-furyl	42	109–110	$C_{17}H_{12}O\ N_2$	9.58	9.35
[a]2,3-Dipiperonyl[c]	55	171–172	$C_{23}H_{16}O_5N_2$	6.99	7.29

[a] These compounds have not hitherto been reported. [b] Specific preparation given. [c] A sample of this quinoxaline with an authentic sample of piperil, m. p. 171.5°, gave a mixed m. p. 145–155°.

(400 cc.). Ten cubic centimeters of concentrated sulfuric acid (sp. gr. 1.84, 96–98% H_2SO_4) was added dropwise, with vigorous stirring. A voluminous pale yellow solid formed, and as the mass became too thick for efficient stirring, 100-cc. portions of dry ether were added at three successive intervals. The yellow solid was filtered and washed with dry ether. Two recrystallizations from absolute ethanol (300 cc.) gave 20 g. (78%) of pale green flakes, m. p. 151–152° (d.). The salt is readily soluble in water.

Anal. Calcd. for $C_{10}H_{10}N_2{\cdot}H_2SO_4$: neutral equivalent, 256.27. Found: neutral equivalent, 256.01.

2,3-bis-(*p*-Methoxyphenyl)-6-methoxyquinoxaline.—4,4′-Dimethoxybenzil (10 g., 0.04 mole) and crude 3,4-diaminosanisole hydrochloride (20 g., approx. 0.10 mole) were taken up in glacial acetic acid (300 cc.). The mixture was refluxed for two hours, allowed to stand overnight at room temperature, then refluxed again for two hours. After cooling, the mixture was poured, with vigorous stirring, into cold water (2500 cc.). The resulting light tan suspension was diluted with water (2500 cc.) and broken by the addition of 20% sodium hydroxide solution. The flocculent solid was filtered, washed with water, and recrystallized from 95% ethanol (300 cc.), after treatment with Norite. The cream-colored crystals weighed 7.6 g. after drying in air. A second crop (3.5 g.) was obtained by diluting the mother liquor to a volume of one liter with water and allowing to stand several hours. The combined yield of 11.1 g. was 81% of the theoretical, based on the 4,4′-dimethoxybenzil. Repeated recrystallization from 95% ethanol gave a product of constant m. p. 131–132° (uncor.).

Anal. Calcd. for $C_{23}H_{20}O_3N_2$: N, 7.52. Found: N, 7.43.

The 2,4-dinitrophenylhydrazone of 2,3-dimethoxybenzaldehyde was prepared, being obtained as brilliant red crystals, m. p. 218–219° (uncor.), after two recrystallizations from chloroform.

Anal. Calcd. for $C_{15}H_{14}O_6N_4$: N, 16.22. Found: N, 16.07.

Pharmacological Properties.—The pharmacological studies on these quinoxalines were carried out by the Wm. S. Merrell Co. of Cincinnati, Ohio, through the courtesy of Dr. Robert S. Shelton, to whom the authors are deeply grateful. The results will be reported elsewhere.

Acknowledgment.—The authors wish to express their appreciation to the Wm. S. Merrell Company through whose generous support this work was carried out.

Summary

1. A series of 2,3-disubstituted quinoxalines and 2,3-disubstituted-6-methoxyquinoxalines have been prepared.

2. A method for the preparation of 3,4-diaminoanisole hydrochloride in sizeable quantities has been developed.

3. The 2,4-dinitrophenylhydrazones of 2,3-dimethoxybenzaldehyde and 2,3,2′,3′-tetramethoxybenzil have been prepared.

CHAPEL HILL, N. C. RECEIVED SEPTEMBER 11, 1947

[Contribution from Western Regional Research Laboratory[1]]

The Molecular Weight of Lysozyme Determined by the X-Ray Diffraction Method

By K. J. Palmer, M. Ballantyne and J. A. Galvin

A method for growing single crystals of the several salts of lysozyme, including the chloride, bromide and iodide, has been described recently.[2,3] Since lysozyme has a comparatively small molecular weight (13,900) and forms chloride, bromide and iodide salts which can be crystallized, it appears probable that a comprehensive X-ray diffraction investigation of these salts may reveal some interesting information about the structure of a native protein molecule. With this end in view a coöperative investigation of the structure of the salts of lysozyme has been started by this Laboratory and the California Institute of Technology. The results of this joint endeavor will be published when available. The present paper is concerned with a preliminary account of the X-ray diffraction results obtained from air-dried lysozyme chloride crystals and the determination of the molecular weight of lysozyme.

Results and Discussion.—Two crystalline modifications of lysozyme chloride have been reported.[2] When the mother liquor has a *p*H between about 3.5 and 6, tetragonal, bipyramidal crystals appear,[2] whereas at a *p*H between about 7 and 11, needle-shaped orthorhombic crystals appear.[3] Both the tetragonal and orthorhombic crystals give rise to a large number of X-ray reflections when in the presence of their mother liquors. When air-dried, however, it has been possible to obtain a diffraction pattern from the tetragonal crystals only. Diffraction spots have been observed for *d* values down to about 5.7 kX from the air-dried tetragonal crystal as compared to 2.0 kX or less from the wet crystals. The fact that the air-dried tetragonal crystals give a diffraction pattern makes the X-ray method ideally suited for a determination of its molecular weight.

The tetragonal lysozyme chloride crystals used in this investigation were grown by the method of Alderton, Ward, and Fevold[2] at a *p*H of 4.5. Crystals suitable for X-ray diffraction analysis were obtained by allowing the crystals to grow on the side of an Erlenmeyer flask until they had attained a size of from 0.5 to 1.0 mm. on a side. The mother liquor was then decanted and the crystals allowed to dry. Many of the resulting crystals were transparent and had sharp edges and no apparent flaws. The crystals when air-dried are relatively hard and can be scraped from the wall of the flask without difficulty. Suitable crystals were mounted on the ends of thin glass fibers by means of clear shellac.

The optical and crystallographic properties of lysozyme chloride crystals grown at a *p*H of 4.5 have been determined.[4] This microscopic investigation showed that the crystals have positive uniaxial birefringence and appear to be tetragonal, tabular bipyramids of the first order. The tetragonal symmetry has been confirmed by taking several sets of 5° oscillation photographs 90° apart around the *c* axis. In all cases, these pairs of photographs appear to be identical.

Complete rotation and 5° oscillation photographs through a range of 90° have been taken around the [101], [110] and [001] axes. The unit cell size of the air-dried crystals has been determined from layer line measurements to be a = 71.1 kX and c = 31.3 kX. The volume of the unit cell is, therefore, $V = a^2c = 15.82 \times 10^4$ $(\text{kX})^3$. The approximately 1200 reflections have been indexed by using reciprocal lattice plots. The only systematic absences appear to be (h00) when $h \neq 2n$ and (0k0) when $k \neq 2n$. These latter restrictions are based on the appearance of only even orders through (14,0,0). No (00l) reflections have been observed from the air-dried crystals in spite of the fact that special care has been taken to observe them. When a tetragonal lysozyme chloride crystal is in the presence of its mother liquor, (00l) reflections are observed only when $l = 4n$. Since reflections are observed from the air-dried crystal only down to *d* values of about 5.7 kX, it is apparent that if the air-dried crystals, like the wet crystals, have a 4_1 or 4_3 screw axis, the first (00l) reflection that could appear (7.8 kX) would be expected to be weak because of the rapid falling off of intensity with angle. Since no conclusion can be drawn with regard to the *c* axis in the air-dried tetragonal crystal, the space groups compatible with the X-ray data are D_4^2—$P42_1$; D_4^4—$P4_12_1$; D_4^6—$P4_22_1$; D_4^8—$P4_32_1$; and D_{2d}^3—$P\bar{4}2_1m$. The space group D_{2d}^3—$P\bar{4}2_1m$ can be eliminated because lysozyme is optically active. None of these enantiomorphic space groups is in accord with the external holohedral appearance of the crystals.[4] This discrepancy is probably due to the fact that only the simple prism faces {101} appear. More complicated faces probably would reflect the non-holohedral symmetry.

Following the suggestion of McMeekin and Warner[5] the density of the lysozyme chloride crystals was determined with organic liquids by the suspension method. Since the relative humidity at the time the X-ray photographs were taken was approximately 40%, the crystals to be used for the density determination were first equilibrated in an atmosphere having this relative humidity.

---

[1] Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

[2] Gordon Alderton, W. H. Ward and H. L. Fevold, *J. Biol. Chem.*, **157**, 43 (1945).

[3] Gordon Alderton and H. L. Fevold, *ibid.*, **164**, 1 (1946).

[4] F. T. Jones, This Journal, **68**, 854 (1946).

[5] T. L. McMeekin and R. C. Warner, *ibid.*, **64**, 2393 (1942).

A crystal was placed in a mixture of toluene and ethylene bromide and the composition of the liquid was quickly adjusted until the crystal remained suspended. A fresh crystal was then added to be sure that excessive dehydration of the original crystal had not occurred. In all cases where the time for adjusting the composition did not exceed a few minutes the second crystal appeared to have the same density as the original. A series of determinations of the density on several different air-dried crystals from two different preparations (both at *p*H 4.5) of tetragonal lysozyme chloride gave an average value of 1.312 ± 0.003 g./cc. at 27°. This value of the density must be corrected because all of the lysozyme chloride crystals have a small amount of sodium chloride associated with them. The sodium chloride results from the evaporation of the mother liquor adhering to the lysozyme chloride crystals after decanting. The major portion of the sodium chloride is probably encrusted on the external faces of the crystals as it can often be seen under the microscope.[4] That the sodium chloride is present as a separate phase is also shown by the fact that lysozyme chloride crystals give, on long exposure, a sodium chloride X-ray pattern.

To determine the correction to be applied to the observed densities, microchemical analyses for sodium and chloride were made[6] on the preparations from which the crystals were obtained for both the X-ray and density measurements. The averaged results, expressed as per cent. of air-dried weight, are shown in columns 1 and 2 of Table I.

TABLE I

ANALYTICAL DATA ON AIR-DRIED TETRAGONAL LYSOZYME CHLORIDE

Na, %	Cl, %	NaCl, %	Cl bound to lysozyme, %	Corrected density (27°C.)
0.50	3.15	1.27	2.38	1.305 g./cc.

The amount of sodium chloride was calculated by assuming that all of the sodium is present as sodium chloride. The result is given in Column 3 of Table I. Column 4 gives the amount of the remaining chloride which is presumably attached to the amino groups of lysozyme as the hydrochloride. On the assumption that the volumes of sodium chloride and lysozyme chloride are additive the observed density was corrected by the formula

$$\rho \text{ corr.} = \frac{m_0}{\dfrac{100}{\rho_2} - \dfrac{m_1}{\rho_1}}$$

where m and ρ are the per cent. by weight and density, respectively, and the subscripts 0, 1 and 2 refer to lysozyme chloride, sodium chloride, and the mixture, respectively. The corrected density is given in Column 5 of Table I.

Oncley[7] has determined approximate values for the molecular weight of lysozyme by osmotic pressure (17,500) and sedimentation–diffusion (14,000–17,000). Assuming a value of 16,000 for the molecular weight of lysozyme, the number of molecules in the unit cell can be calculated to be

$$N = \frac{(1.305)(15.82 \times 10^4)}{(1.65)\ (16{,}000)} = 7.8$$

It is evident, therefore, that there must be eight molecules in the unit cell.

The weight of a lysozyme chloride molecule in the air-dried crystal is then

$$M = \frac{(1.305)(15.82 \times 10^4)}{(1.65)(8)} = 15{,}680$$

This value is an upper limit for the molecular weight and must be corrected for both water of hydration and attached hydrochloric acid.

The weight of a lysozyme molecule, free of hydrochloric acid, can be obtained by reducing the value 15,680 by the amount of hydrochloric acid (2.45%) corresponding to the amount of chloride shown in column 4 of Table I. This leads to a value of 15,300 for the molecular weight of air-dried lysozyme.

The water content of the air-dried crystals was determined by placing weighed amounts of the crystalline material into a 105° vacuum oven for twenty-four hours and determining the loss of weight. Several runs made on different days gave a spread between 8.4% and 9.6% with an average value of 9%. With this value for the water content the molecular weight of dry lysozyme can be calculated to be 13,900.

It is difficult to estimate the probable error of this determination, but it seems reasonable to assume, in spite of the corrections made, that the probable error does not exceed 4% or about 560 molecular weight units.

The value 13,900 is slightly lower than the lower limit (14,000) given by Oncley[7] based on his sedimentation–diffusion measurements. His limits were, however, based on an assumed range of 0.70–0.75 for the partial specific volumes of lysozyme. In any case the lower limit is within the estimated probable error range of the X-ray determination. Oncley's osmotic pressure value of 17,500 is somewhat higher than the X-ray value. This discrepancy may be due to the fact that the membrane used by Oncley was not completely impermeable to lysozyme.

Acknowledgments.—The authors are indebted to H. L. Fevold and Gordon Alderton for their kindness in furnishing us with the lysozyme chloride crystals used in this investigation.

Summary

Five degree oscillation photographs have been taken of air-dried tetragonal lysozyme chloride. The only systematic absences appear to be (h00) when $h \neq 2n$ and (0k0) when $k \neq 2n$. No (00l) reflections appear. Possible space groups are D_4^2—$P42_1$; D_4^4—$P4_12_1$; D_4^6—$P4_22_1$; and D_4^8—$P4_32_1$.

---

[6] The authors are indebted to L. M. White of this Laboratory for the microchemical analyses.

[7] J. L. Oncley, private communication to H. L. Fevold.

The tetragonal unit cell of air-dried lysozyme chloride grown at a *p*H of 4.5 has dimensions of a = 71.1 kX and c = 31.3 kX. There are eight molecules in the unit cell. The density of the crystals was measured by suspension in a mixture of toluene and ethylene bromide. The observed density has been corrected for adhering sodium chloride (1.27%) to give 1.305 ± 0.003 g./cc. at 27°. The corrected density has been used to calculate the weight per molecule in the unit cell. This value was then corrected for moisture (9%) and hydrochloric acid bound to the amino groups (2.45%) to give a value for the molecular weight of dry, chloride-free, lysozyme of 13,900 ± 600.

ALBANY, CALIF. RECEIVED OCTOBER 4, 1947

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

Compound Formation between 2,6-Lutidine and Polyhalogenated Methanes

BY CALVIN A. VANDERWERF, ARTHUR W. DAVIDSON AND CARL I. MICHAELIS

In phase equilibrium studies recently reported from this laboratory,[1] evidence was obtained for the existence of eight addition compounds of pyridine with various polyhalogenated methanes. Because the structure of all of these compounds could not be explained in terms of a single consistent theory, the present investigation of the systems consisting of 2,6-lutidine with each of these same polyhalogenated methanes was undertaken in the hope that further light might be shed upon the process of addition compound formation in such systems. Selection of 2,6-lutidine was suggested by the following considerations: (1) because of its electronic structure, its nitrogen atom would be expected to exhibit a greater tendency than that of pyridine to act as an electron donor; (2) because of the proximity of the two substituent groups to the nitrogen atom, steric factors might be expected to interfere with the coördination of several lutidine molecules about a single molecule of polyhalogenated methane.

Experimental[2]

Purification of Materials.—The 2,6-lutidine, obtained from the Reilly Tar and Chemical Corporation, was purified by repeated recrystallization of the hydrochloride from concentrated hydrochloric acid. The base was regenerated by means of concentrated sodium hydroxide solution, and, after separation from the aqueous layer, was dried over sodium hydroxide pellets for ten days. Fractional distillation through a five-foot packed column gave pure 2,6-lutidine, b. p. 142.5° at 738 mm., f. p. (from cooling curve) −5.5°. The purified material was stored in a dark bottle and was guarded against contact with moisture and carbon dioxide.

The chloroform, bromoform and carbon tetrachloride were dried over drierite, then fractionally distilled through the column referred to above. The physical constants observed for the pure compounds are as follows: for chloroform, b. p. 60.7° at 745 mm., f. p. (from cooling curve) −62.1°; for bromoform, b. p. 148.2° at 740 mm., f. p. (from cooling curve) 8.3°; for carbon tetrachloride, b. p. 76.1° at 741 mm., f. p. (from cooling curve) −21.8°.

Eastman Kodak Co. iodoform and bromoform were recrystallized twice from ethanol; the former melted at 121.1°, the latter at 90.9°.

Apparatus and Procedure.—The freezing point cell used in the determination of the temperature–composition diagrams was similar to that described in a previous publication from this Laboratory,[3] except that the cell was constructed in two parts joined to each other by means of a ground glass joint. This design makes possible the easy removal of the stirrer. All cooling curves were recorded directly by means of a Brown Electronik Strip Chart potentiometer which had been calibrated at the m. p. of ice, the b. p. of ammonia, and the sublimation point of solid carbon dioxide. Each freezing point was determined at least twice. Data obtained by this method are believed to be correct, even for the steeper portions of the freezing point curves, to 1.5°.

Results

The experimental data are shown in tabular and graphical form below. Compositions, as indicated, are given in mole %.

TABLE I

SYSTEM 2,6-LUTIDINE–CHLOROFORM

Mole % chloroform	Temp., °C.
Solid phase C_7H_9N	
0.0	− 5.5
5.75	− 8.9
8.10	−10.9
11.1	−11.9
13.4	−13.8
16.3	−15.1
18.4	−17.9
21.1	−20.0
23.4	−21.5
26.0	−24.5
28.2	−27.3
30.5	−30.0
36.2	−40.0
38.4	−44.5
40.4	−48.0
41.2	−49.0
42.4	−51.0
Solid phase $C_7H_9N \cdot CHCl_3$	
43.8	−51.5
44.3	−50.5
45.9	−49.5
48.7	−48.3
49.9	−48.3
52.1	−49.0
54.3	−49.1
57.2	−51.5
59.8	−53.8
62.8	−56.7
63.3	−57.3
66.9	−62.9
68.2	−64.3
72.9	−72.0
74.5	−74.5
75.9	−77.0
Solid phase $CHCl_3$	
76.5	−76.3
78.5	−74.0
83.0	−71.0
87.3	−67.2
91.4	−65.0
93.6	−63.2
95.6	−63.0
100.0	−62.1

A. As shown graphically in Fig. 1, curve A, 2,6-lutidine and chloroform form a single stable

---

(1) Davidson, VanderWerf and Boatright, THIS JOURNAL, **69**, 3045 (1947).

(2) Melting points corrected, boiling points uncorrected.

(3) Davidson, Sisler and Stoenner, THIS JOURNAL, **66**, 779 (1944).

compound, $C_7H_9N{\cdot}CHCl_3$, which melts congruently at −48.3°. The eutectics are: (a) 43.6 mole % chloroform, f. p. −51.6°, and (b) 75.7 mole % chloroform, f. p. −77.0°.

TABLE II

SYSTEM 2,6-LUTIDINE–BROMOFORM

Mole % bromoform	Temp., °C.
Solid phase C_7H_9N	
0.0	− 5.5
2.10	− 8.0
5.90	−10.1
11.3	−14.2
13.2	−15.9
16.8	−19.3
19.2	−21.5
21.1	−24.1
23.7	−27.0
26.2	−30.0
27.7	−30.9
29.3	−33.5
Solid phase $C_7H_9N{\cdot}CHBr_3$	
31.9	−30.5
33.3	−29.0
34.1	−27.9
35.8	−26.0
38.8	−23.9
42.6	−22.8
43.7	−22.3
45.9	−21.0
49.9	−21.0
50.5	−21.0
51.4	−21.5
54.8	−21.8
59.2	−23.8
62.2	−24.2
Solid phase $CHBr_3$	
64.9	−24.3
67.1	−21.0
69.9	−17.2
74.1	−13.7
76.5	−10.2
79.8	− 7.8
81.2	− 5.0
85.0	− 2.1
86.0	− 0.8
87.9	1.2
89.2	1.3
91.6	3.1
97.2	7.1
100.0	8.3

B. As indicated in Fig. 1, curve C, 2,6-lutidine and bromoform form a single stable compound, $C_7H_9N{\cdot}CHBr_3$, which melts congruently at −21.0°. The eutectics are: (a) 29.5 mole % bromoform, f. p. −33.9°, and (b) 64.2 mole % bromoform, f. p. −24.8°.

TABLE III

SYSTEM 2,6-LUTIDINE–IODOFORM

Mole % iodoform	Temp., °C.
Solid phase C_7H_9N	
0.0	− 5.5
1.78	− 8.0
7.45	−13.3
8.58	−11.9
10.3	−15.5
13.4	−17.0
14.6	−18.1
16.0	−18.9
16.6	−19.3
Solid phase $2C_7H_9N{\cdot}CHI_3$	
17.2	−17.5
18.5	− 8.4
18.9	− 8.0
19.7	− 6.3
20.8	−4.5
21.8	−1.0
22.3	−0.5
22.7	1.3
Solid phase CHI_3	
24.1	21.7
28.5	41.0
31.3	50.8
33.7	57.5
34.2	57.5
37.6	66.0
42.5	74.0
55.5	91.0
67.5	99.0
100.0	121.0

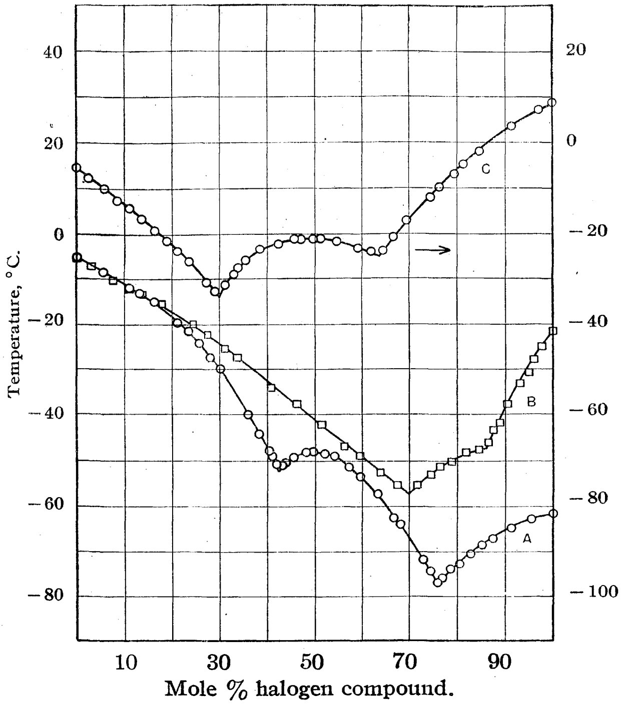


Fig. 1.—Systems 2,6-lutidine–polyhalogenated methanes: curve A, chloroform; curve B, carbon tetrachloride; curve C, bromoform (use temperature scale on right).

C. As represented in Fig. 2, curve B, 2,6-lutidine and iodoform form a single compound which undergoes transition into iodoform and solution at 2.0°. Inasmuch as the compound does not melt congruently, its composition is not definitely indicated, but from the course of the curve it appears

TABLE IV

SYSTEM 2,6-LUTIDINE–CARBON TETRACHLORIDE

Mole % carbon tetrachloride	Temp., °C.
Solid phase C_7H_9N	
0.0	− 5.5
2.74	− 7.5
7.40	−10.2
10.7	−12.2
13.5	−13.6
17.6	−15.8
20.6	−17.9
24.3	−20.0
27.4	−22.7
31.0	−25.5
33.8	−27.9
37.1	−30.0
38.7	−31.9
40.9	−34.0
42.8	−35.7
44.8	−37.0
46.2	−38.0
48.6	−40.0
51.7	−42.0
54.0	−45.3
56.3	−47.0
59.5	−49.0
61.9	−51.1
64.0	−52.0
66.8	−54.0
67.5	−55.3
Solid phase α-CCl_4	
72.0	−55.5
75.1	−53.2
76.7	−51.0
79.0	−51.0
82.2	−48.2
84.9	−47.5
Solid phase β-CCl_4	
87.0	−46.5
87.9	−43.2
89.4	−42.0
90.9	−37.5
93.6	−33.0
95.4	−31.1
96.5	−28.0
98.1	−25.2
100.0	−21.8

likely that it is $2C_7H_9N{\cdot}CHI_3$. Extrapolation indicates that the melting point of the compound would be about 7.5°. The eutectic is 16.8 mole % iodoform, f. p. −19.4°.

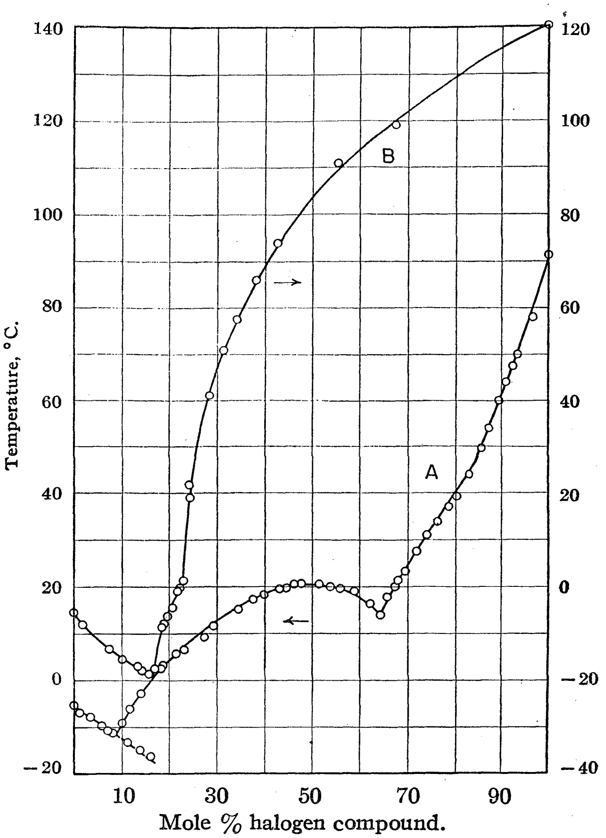


Fig. 2.—Curve A, system 2,6-lutidine–carbon tetrabromide (use temperature scale on left); curve B, system 2,6-lutidine–iodoform (use temperature scale on right).

D. As shown in Fig. 1, curve B, no compound formation occurs between 2,6-lutidine and carbon tetrachloride. The single eutectic is 70.4 mole % carbon tetrachloride, f. p. −57.0°. The distinct change in the slope of the curve at −46.5° results from the transition from the α- to the β-form of carbon tetrachloride.

E. As indicated in Fig. 2, curve A, 2,6-lutidine and carbon tetrabromide form a single stable compound, $C_7H_9N{\cdot}CBr_4$, which melts congruently at 20.7°. The eutectics are: (a) 8.3 mole % carbon tetrabromide, f. p. −11.3°, and (b) 64.5 mole % carbon tetrabromide, f. p. −11.3°, and (b) 64.5 mole % carbon tetrabromide, f. p. 13.9°. The change in the slope of the curve at 47° corresponds to the transition from the α- to the β-form of carbon tetrabromide at that temperature.

Discussion

In general, the number and complexity of the stable solid addition compounds between the polyhalogenated methanes and 2,6-lutidine is less than in the corresponding systems with pyridine, a fact which may probably be attributed to the steric factors effective in the 2,6-lutidine molecule. The fact that the compound of 2,6-lutidine with chloroform appears to be more stable than the corresponding compound of pyridine is noteworthy; in this case, the enhanced stability of the compound may be attributed to the greater tendency of the disubstituted base to act as an electron donor, resulting from the electron releasing effects of the two methyl groups.

TABLE V

SYSTEM 2,6-LUTIDINE–CARBON TETRABROMIDE

Mole % carbon tetrabromide	Temp., °C.	Mole % carbon tetrabromide	Temp., °C.
Solid phase C_7H_9N		47.8	20.6
0.0	− 5.5	50.8	20.1
1.35	− 6.9	51.4	20.7
3.61	− 7.8	53.8	20.2
6.00	− 9.9	56.0	19.8
7.33	−10.8	59.0	19.0
8.10	−11.3	62.2	16.3
		64.4	14.0
Solid phase $C_7H_9N{\cdot}CBr_4$		Solid phase α-CBr_4	
10.0	− 9.3	65.9	17.8
10.7	− 6.7	67.5	20.0
11.8	− 6.3	68.0	21.3
13.4	− 3.4	69.4	23.2
14.3	− 3.0	72.0	27.5
16.8	1.2	74.1	31.0
18.6	2.5	76.3	33.9
18.8	3.2	78.6	37.0
19.1	3.3	80.4	39.3
21.5	5.8	83.5	44.2
23.4	6.5	Solid phase β-CBr_4	
27.6	9.3	85.7	49.5
29.2	11.5	87.5	54.0
34.5	15.2	89.4	60.0
37.7	17.4	91.0	64.0
40.0	18.3	92.6	67.5
43.7	19.7	93.5	70.8
44.8	19.8	95.8	78.0
46.4	20.5	100.0	91.0

Summary

1. Temperature–composition data are presented for systems consisting of 2,6-lutidine with each of several polyhalogenated methanes.

2. It has been shown that chloroform, bromoform and carbon tetrabromide each form a 1:1 addition compound with 2,6-lutidine, and that a 2:1 addition compound is formed in the system 2,6-lutidine–iodoform.

3. The behavior of 2,6-lutidine toward the polyhalogenated methanes is compared with that of pyridine in similar systems.

LAWRENCE, KANSAS RECEIVED AUGUST 7, 1947

[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES OF THE AMERICAN CYANAMID COMPANY]

"Analytical Boundary" Method for the Determination of Transference Numbers

BY A. P. BRADY[1]

During the course of the investigation of solutions of colloidal electrolytes in this Laboratory, the need was felt for a fairly simple and rapid method for determining electrical mobilities to an accuracy of about 1%. It was desired to avoid the Hittorf method if possible, not only because of the time involved, but because of the difficulty in analyzing many of these solutions to an accuracy much better than 1%. The use of the moving boundary method with colloidal electrolytes usually involves a difficulty in the choice of a suitable following or "indicator" electrolyte for forming the boundary. The indicator must have a lower conductivity than the salt under investigation in the leading solution; further, the indicating ion must be slower than the leading ion in any possible mixture of the two solutions. The comparatively low conductivity of colloidal ions eliminates the use of simple electrolytes for indicators, and the possibility, or indeed probability, of interaction bars the use of another colloidal electrolyte. Hartley, *et al.*,[2,3] recognized this difficulty, and circumvented it in a study of certain cationic surface active agents by their "balanced boundary" method. Their method, although quite successful in this application, introduces a further complication in apparatus, since the boundary must be kept stationary by mechanical means. Moreover, because of the necessity of analysis *in situ*, the method is inapplicable in the many instances where multiple boundaries are formed.

The purpose of the present paper is to describe the theory and operation of a simpler cell in which, as in the "balanced boundary" method, the roles of the leading and indicating solutions are reversed. Experimental tests of the cell using simple electrolytes will be presented here, and applications to more complex systems given in the following paper.

The apparatus used is shown schematically in Fig. 1. The cell proper is a U tube divided into the two portions A and B by a sintered glass membrane (Pyrex medium grade). Compartment B contains the solution under investigation; the requirements for the solution in A will be referred to in more detail below. The electrode joined to compartment A is of the closed non-gassing type; that at the other leg of the U-tube may gas. The apparatus, called an "analytical boundary" cell for convenience, may be regarded as simply a means for combining the Hittorf and moving boundary methods. The procedure consists essentially of determining analytically the amount of the ion being studied in compartment A that has been transported electrically from compartment B through the boundary created by the membrane.

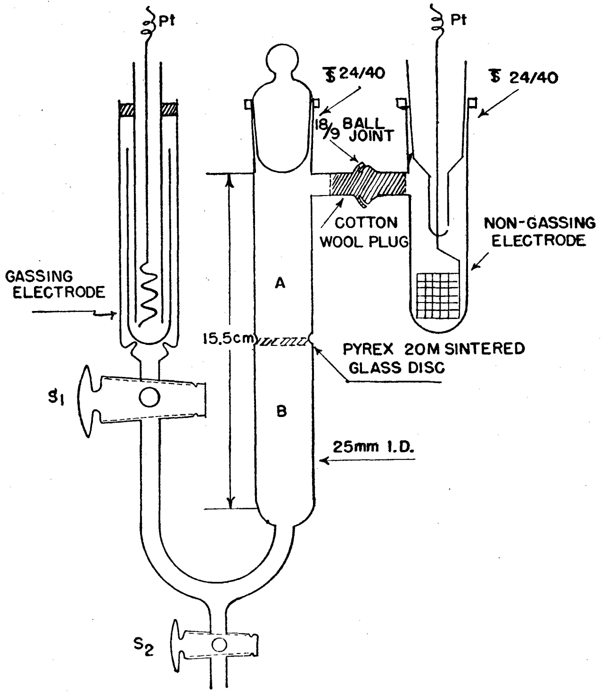


Fig. 1.—Analytical boundary apparatus: A, analytical compartment containing leading electrolyte; B, compartment containing solution under investigation; S_1, S_2, stopcocks.

The operation of the cell can most conveniently be examined from the standpoint of the moving boundary equations. Figure 2 is a diagrammatic representation of a moving boundary experiment. Originally AR and AS (at concentrations C_{AR} and C_{AS}, respectively) form a boundary at ab; after passage of current this boundary moves to cd. As a moving boundary experiment, the arrangement is designed to determine the transport number of S in AS. As an analytical boundary experiment, however, it will be used to determine that of R in AR.

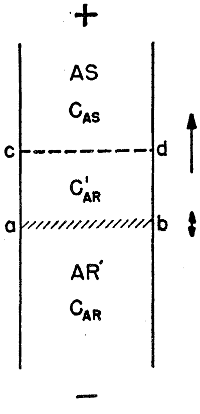


Fig. 2.—Moving boundary experiment.

After a quantity Q of electricity is passed through the solution, the volume V swept out by

---

[1] Present address: Stanford University, Department of Chemistry, Stanford University, Calif.

[2] Hartley, *Trans. Faraday Soc.*, **30**, 648 (1934).

[3] Drew and Hartley, *ibid.*, 653 (1934); Collie and Hartley, *ibid.*, 657 (1934).

the boundary cd is[4]

$$V = \frac{QT_{\mathrm{S}}}{FC_{\mathrm{AS}}} \tag{1}$$

where T_{S} denotes the transport number of S ion in AS. Equation (1) is the fundamental equation for determining the transport number of S by the moving boundary method. The concentration of AR behind the boundary is no longer the original C_{AR}, but an adjusted value, C'_{AR}, given by the Kohlrausch[5] conditions

$$\frac{T'_{\mathrm{R}}}{C'_{\mathrm{AR}}} = \frac{T_{\mathrm{S}}}{C_{\mathrm{AS}}} \tag{2}$$

where T'_{R} is the transport number of R at the indicator concentration, C'_{AR}. Substitution of equation (2) into equation (1) gives

$$C'_{\mathrm{AR}}V = Q\,T'_{\mathrm{R}}/F \tag{3}$$

Since in general $C'_{\mathrm{AR}} \neq C_{\mathrm{AR}}$, a slowly moving boundary will remain in the neighborhood of ab. Considering upward movement in Fig. 1 as positive, this boundary will sweep out a volume[4]

$$C' = \frac{Q(T_{\mathrm{R}} - T'_{\mathrm{R}})}{F(C_{\mathrm{AR}} - C'_{\mathrm{AR}})} \tag{4}$$

In the present instance, we are interested in the total quantity of R, M_{R}, that passes through the plane ab, since this is the quantity that will be determined. If the secondary boundary at ab is stationary or moves downward with time, evidently M_{R} is given by the left-hand side of equation (3); therefore

$$M_{\mathrm{R}} = QT'_{\mathrm{R}}/F \tag{5}$$

If, on the other hand, the secondary boundary moves upward with time, then $M_{\mathrm{R}} = C'_{\mathrm{AR}}V + (C_{\mathrm{AR}} - C'_{\mathrm{AR}})V'$, and from equations (3) and (4)

$$M_{\mathrm{R}} = QT_{\mathrm{R}}/F \tag{6}$$

Thus multiplying the amount of R passing through the plane ab by F/Q gives the transport number of the radical R at the initial or at the adjusted concentration, depending upon whether the secondary boundary moves upward or downward. In the applications to which this cell has so far been put there has been no ambiguity. If such a difficulty did arise, it would be necessary to determine the general shape of the T *vs.* C curve; by using a leading solution of known properties the value of C'_{AR} may be readily approximated from equation (2) and from equation (4) the decision made as to which concentration the observed transference number refers.

An experimental alternative that circumvents the above ambiguity and is convenient and easy to apply, especially in complex systems, is a radiotracer technique. In this method, the leading and unknown solutions are of identical composition, but the latter contains a radioactive isotope of the ion or ions under investigation. There are then no restrictions on the complexity of the system, and, since the "adjusted" concentration is automatically that of the original solution, no complications arise due to motions of secondary boundaries. This technique should find increasing applications as the larger supplies of radioactive elements from uranium piles become available.

The following comments concerning the analytical boundary cell are of importance. First of all, in the derivation of equations (5) and (6) for clarity the assumption was made that stable sharp boundaries are formed. This would require the fulfillment of definite conditions, namely, that the density increase from top to bottom of the cell and that the conductivity of C_{AS} be greater than that of C_{AR}. However, the above assumption is unnecessary since the equations may be derived in terms of the volume velocities past plane ab, and consequently the solution in compartment A does not have to satisfy such rigid requirements. For practical operation of the cell, however, it is necessary to insure that the material transported through the membrane will not be lost in the electrode compartment. Convectional instability is therefore to be avoided. Electrical stability is desirable but not necessary, although again, in order to minimize the possibility of losses the conductivity of the leading solution should not be much less than that of the unknown.

The radical R need not be a single species. However, if it is not, it will usually be necessary to neglect the motion of the secondary boundary, leading to the aforementioned uncertainty as to the exact concentration to which the transport number refers. The error so introduced is usually small. Again, the tracer method overcomes the difficulty.

It is obvious that the migration of foreign ions from either electrode to the neighborhood of the membrane will vitiate results. It is desirable, therefore, although not always necessary, to introduce a small amount of concentrated solution of the unknown around the gassing electrode; it will then be in a region of high conductivity and any hydrogen or hydroxide ion produced in the electrode will have less chance of getting over into compartment B. The baffle system at the gassing electrode is also an aid in this respect. The composition of the non-gassing electrode depends upon that of the leading solution in A and must be so chosen as to introduce no foreign ions into A by electrolytic migration.

Some of the early cells used by Hittorf[6] and by Steele[7] contained membranes. These were abandoned because such materials as fish bladder and gelatin obviously influenced results, either through electroendosmotic streaming or conductivity changes within the membrane. In the present apparatus endosmosis is prevented by the closed system above the membrane, and it is imperative that there be no leakage here. The pore diameter of the membrane is several microns, making the

---

[4] MacInnes and Longsworth, *Chem. Rev.*, **11**, 171 (1932).

[5] Kohlrausch, *Ann. Physik*, **62**, 209 (1897).

[6] Hittorf, *Z. physik. Chem.*, **39**, 613 (1901); **43**, 239 (1903).

[7] Steele, *ibid.*, **40**, 689 (1902).

TABLE I

TRANSFERENCE NUMBERS OF SOME SIMPLE ELECTROLYTES AT 25° BY THE ANALYTICAL BOUNDARY METHOD

Solution tested	Ion	Solution	Non-gassing electrode	Milliequiv. transported	Coulombs passed	T
0.1 N $AgNO_3$	Ag^+	0.1 N KNO_3	Pt/$Fe(NO_3)_3$	0.208	42.38	0.473
.01 N $AgNO_3$	Ag^+	.01 N KNO_3	Pt/$Fe(NO_3)_3$	.01892	3.892	.469
.1 N KBr	Br^-	.1 N KNO_3	Pt/$K_4Fe(CN)_6$	.2655	49.31	.519
.01 N KBr	Br^-	.1 N KNO_3	Pt/$K_4Fe(CN)_6$	.02356	4.274	.531
.01 N KBr	Br^-	.1 N KNO_3	Pt/$K_4Fe(CN)_6$	.02773	5.006	.527
.05 N NaCl[a]	Cl^-	.05 N NaCl	Pt/$Na_4Fe(CN)_6$	.1369	21.98	.601
.05 N NaCl[a]	Cl^-	.05 N NaCl	Pt/$Na_4Fe(CN)_6$	.1120	17.95	.602
.02 N NaCl[b]	Na^+	.02 N NaCl	Ag/AgCl	.0594	14.478	.396

[a] Radiotracer method; tagged with Br^{82}, see text. [b] Radiotracer method; tagged with Na^{22}.

existence of appreciable surface conductivity improbable. The possibility still exists, of course, but experiments with either uni-univalent electrolytes or solutions of surface active agents (to be presented in a following paper) give no indication of abnormal behavior.

As in the moving boundary method, a small correction in the observed values for the transport number must be made for volume changes above the original boundary during the course of electrolysis, in order to refer the movement to the water rather than the apparatus. The solutions reported here are sufficiently dilute for the correction to be within the experimental error, and it was consequently ignored.

Experimental

Materials.—Reagent grade chemicals were used throughout without further purification. The water used was de-ionized by ion exchange resins, and had a specific conductivity of 2 × 10^{-6} mho cm.$^{-1}$; this amounted in most cases to about 0.01% of that of the solution tested and never to more than 0.1%.

Radioactive sodium, Na^{22}, was obtained from a magnesium target which had been bombarded with deuterons in the University of California cyclotron. A chemical separation without sodium carrier was made by Mr. R. K. Madison of the Radioactivity Group of these Laboratories. Radiobromine, Br^{82}, was obtained with no carrier by the Szilard-Chalmers procedure(8) from C. P. ethyl bromide bombarded with neutrons from the Columbia University cyclotron. In preparing the tagged solutions, two aliquots of a stock solution were diluted to volume, in one case with a radioactive tracer solution and in the other with water.

Procedure.—The left-hand side of the U-tube, the region below the membrane, and the membrane itself are filled with the solution to be investigated. Compartment B may be rinsed by the use of stopcock S-2; stopcock S-1 is to prevent streaming through the membrane while compartment A is rinsed and filled with the leading solution.

The cell is placed in a thermostat and the desired voltage impressed across the electrodes from storage batteries. A milliammeter and voltmeter serve to check the approximate wattage; no extensive experiments have been made, but the apparatus works satisfactorily up to about 500 milliwatts. The current is read periodically with a Leeds and Northrup type K-2 potentiometer in terms of the voltage across a fixed series resistor. The duration of the experiment depends entirely upon the transference number of the ion under investigation; in the examples given in this paper a calculated movement of about a centimeter for the ion under investigation was found to be satisfactory—tripling this movement gave results several per cent. too low. With the arbitrary limit set on the wattage, this required thirty to ninety minutes, depending upon the concentration.

Analyses.—At the completion of a run the analytical compartment A was rinsed out, then the contents made up to a specified volume. Closing stopcock S-1 prevents streaming during this operation.

Silver and bromide ions were titrated conductometrically with potassium bromide and silver nitrate, respectively (precision *ca.* ±0.2%); the radioactive solutions were counted in a small glass jacketed Geiger counter tube(9) with a conventional amplifying and scaling circuit, and the total number of counts taken on a given sample was sufficient to make the probable counting error less than ±1%.

Results and Discussion

The results of a series of transport determinations in simple electrolytes using the analytical boundary method are given in Table I. The first example, potassium nitrate leading, silver nitrate following, from which T_{Ag^+} was determined, is a system forming a stable boundary. In the second example, potassium nitrate leading, potassium bromide following, from which T_{Br^-} was determined, the boundary is convectionally stable but unstable electrically.

The last three rows in Table I are examples of the radiotracer method. The second of these, in which Na^{22} is used to trace Na^+, is straightforward. In the first, Br^{82} is used to follow Cl^- in NaCl, this combination being adopted to test the general feasibility of using radiobromide to trace chloride ion. The radioisotopes Cl^{34} and Cl^{38} are of too short half life (thirty-three and thirty-seven minutes) for convenient use, and the long lived Cl^{36} (10^3 yr.) was not available to us. The observed migration of radiobromine was divided by the ratio of the equivalent conductivity of Br^- to that of Cl^- at infinite dilution to convert to chloride migration.

In Table II the analytical boundary results are compared with those obtained by the moving boundary(4) and the Hittorf(10) methods. The latter are older values and would be considerably improved by modern techniques, but only with a corresponding increase in manipulative and analytical difficulties. From the results in the table it

---

(8) Szilard and Chalmers, *Nature*, **134**, 462 (1934); Seaborg, *Chem. Rev.*, **27**, 260 (1941).

(9) Barnes and Salley, *Ind. Eng. Chem., Anal. Ed.*, **15**, 4 (1943).

(10) Landolt-Börnstein, "Tabellen," HWII, p. 1109.

can be seen that although the listed analytical boundary results are only accurate to about 2%, they are as accurate as a reasonably careful Hittorf determination (taking the moving boundary values as correct), and certainly far less tedious and analytically exacting. The accuracy could be improved by a careful purification of materials and by more precise analytical procedures, but is shown to be sufficient for the purposes for which the cell was designed. The substances listed in Table I were run, of course, only for test purposes, since the moving boundary method gives more accurate results just as quickly. In a following paper (with D. J. Salley), an application to colloidal electrolytes will be presented. It is also obvious that the method is applicable to the study of proteins, dyes (where colorimetric analysis may readily be used), and complex systems such as solutions of acid polymerized trimethylol melamine.

Table II

Comparison of Analytical Boundary Results with Other Methods

Solution	Concn.	Cation transference no. Analytical boundary	Moving boundary	Hittorf[a]
$AgNO_3$	0.1	0.473	0.468	0.474
	.01	.469	.465	.474
KBr	.1	.481	.485	...
	.01	.471	.483	.496
NaCl	.05	.399	.390	.396
	.02	.396	.389	.396

[a] These values are at 18°; the temperature correction is small but should tend to *raise* them.

Acknowledgment is due to cyclotron groups at the University of California and at Columbia University for radiotracers. In addition the writer wishes to express his gratitude to Drs. J. K. Dixon and D. J. Salley for advice and criticism, and to thank the Directors of this Laboratory for permission to publish these results.

Summary

1. The design and operation of a cell of simple construction for measuring transference numbers, embodying a combination of the Hittorf and moving boundary techniques, is described. Because of the interchange of the usual roles of the leading and indicator solutions as compared to the moving boundary method, the method is suited for electrolytes containing a colloidal ion.

2. Analytical requirements are much less exacting than in the Hittorf method, permitting a wide choice of methods (*e. g.*, radioactivity counts, conductometric titrations, and colorimetry).

3. In complex systems where the moving boundary results would be difficult or impossible to interpret, radiotracer techniques may be readily applied. Because of the reduced analytical requirements ordinary counting methods may be used.

4. Tests of the cell using solutions of simple electrolytes, employing both analytical and radiotracer methods, indicate an accuracy equivalent to that obtained in reasonably careful determinations by the Hittorf method.

Stamford, Conn. Received March 29, 1947

[Contribution from the Stamford Research Laboratories of the American Cyanamid Company]

The Self-diffusion Coefficients and Transference Numbers of the Small Ions in Colloidal Electrolytes

By A. P. Brady[1a] and D. J. Salley

Introduction

The fraction of small ions associated kinetically with the large aggregates in aqueous solutions of colloidal electrolytes is of general interest for the better understanding of these solutions. The "fraction bound" has been estimated for various colloidal systems from measurement of the thermodynamic properties of the solution, as by freezing point depression[1] or dew point lowering,[2] from the conductivity plus the transference number,[3,4] from e. m. f. measurements,[5,6,7] and from membrane equilibrium.[8] In addition specific methods have been used, such as measuring the *p*H of hexanolamine caprylate solutions containing excess hexanolamine,[9] and the increase of conductivity of lauryl sulfonic acid solutions when potassium nitrate is added.[10] Another general method that suggests itself is self-diffusion, but insofar as the authors are aware it has not yet been applied to this problem.

Any value of the fraction bound derived from experimental data must, of necessity, result from a series of assumptions. Because of this, the values obtained from any one of the above methods may be quite uncertain. This paper compares, under consistent assumptions, the fraction bound as obtained by three methods: self-diffusion, conductivity plus transport, and freezing point lowering.

(1a) Present address: Stanford University, Department of Chemistry, Stanford University, California.

(1b) McBain, Laing and Titley, *J. Chem. Soc.*, **115**, 1279 (1919).

(2) McBain and Salmon, This Journal, **42**, 426 (1920).

(3) McBain and Thomas, *J. Phys. Chem.*, **40**, 997 (1936).

(4) Hartley, Collie and Samis, *Trans. Faraday Soc.*, **32**, 785 (1936).

(5) Salmon, *J. Chem. Soc.*, **115**, 530 (1920).

(6) Lottermoser and Puschel, *Kolloid Z.*, **63**, 175 (1933).

(7) McBain and Betz, This Journal, **57**, 1909 (1935).

(8) Northrup and Kunitz, *J. Gen. Physiol.*, **11**, 481 (1928).

(9) Gonick, This Journal, **68**, 177 (1946).

(10) Walton, *ibid.*, **68**, 1182 (1946).

The experimental work comprised the determination for two cationic and two anionic agents of the self-diffusion constant and the transference number of the small ion, as well as the solution conductivities. The freezing point data used were taken from the literature.

A feature of the experiments was that radioactive isotopes were employed. In self-diffusion, isotopic tracers are of course required, and they are also of considerable aid in the rapid measurement of transference numbers in complex systems by the "analytical boundary" method described in the foregoing paper.[11] It is worthy of note that the tracer technique obviates errors which may arise if equilibria involving various micelle types are not fast compared to diffusion or electrical transport.

Experimental

Materials

Sodium 2-Ethylhexyl Sulfosuccinate (Aerosol OT).—Commercial "Aerosol OT 100%" (American Cyanamid Company) was used after vacuum drying at 110° for several hours.

Sodium Methyl Amyl Sulfosuccinate (Aerosol MA).—Dried commercial "Aerosol MA 100%" (American Cyanamid Company) was used. At low concentrations faintly hazy solutions were formed presumably because of the presence of a small amount (approximately 1%) of the corresponding maleic ester. Such solutions were cleared by passage through a bacteriological filter, in order to protect the membranes in the diffusion and transport cells. The filtration had no detectable effect upon the conductivity.

N-(Laurylcolaminoformylmethyl)-pyridinium Chloride (E-607).—Material supplied by the Emulsol Corporation was used directly.

Myristamidopropyldimethylbenzylammonium Chloride.—This is hereafter referred to as "Agent M," for purposes of abbreviation. A special preparation made at these Laboratories was employed. The only impurity detected (other than water) was 1.0% of the unbenzylated tertiary amine.

Radiotracers.—The anionic materials were tagged with either Na^{22} or Na^{24}. The former was obtained carrier free as described in the foregoing paper.[11] The latter was usually received as a solution of sodium chloride from Columbia University. In one series of runs, however, Aerosol OT solutions were bombarded directly with neutrons to produce the Na^{24}.

The chloride ion in the cationic agents was followed by Br^{82}, the latter being obtained carrier free from neutron-bombarded ethyl bromide. Radiobromine appears to serve well as a chloride tracer provided the results are corrected for its 3% higher mobility.[11]

Solutions.—The tagging of the various solutions was accomplished by adding the requisite amount of radioactive solution to one aliquot of a stock solution and an equal volume of water to another. The radioactive solutions used for tagging invariably contained extraneous electrolytes, and the amount present was estimated by conductivity or analysis. The specific activities were so high that the total amount of electrolyte introduced in the tagging operation was less than 0.1% of the final concentration. One exception to this is referred to below.

Procedure

Self-diffusion.—The cells used for self-diffusion were the sintered-glass membrane (Pyrex F) type similar to those described by McBain and Dawson.[12] To provide stirring, which is necessary because of lack of density gradients, each compartment contained a 1-cm. length of 1-cm. Pyrex tubing and the cells were rotated end-over-end at 3 r. p. m. A preliminary diffusion period of three to six hours was adopted to establish a steady state in the membrane, after which fresh solutions were substituted and diffusion allowed to proceed until 5 to 10% of the radioactivity had diffused. Determination of the cell constants was carried out with 0.1 *N* KCl, taking 1.595 sq. cm./day as the diffusion constant.[13] The diffusion results were calculated according to the usual logarithmic formula

$$KD = -\frac{1}{t}\log\left[1 - \frac{(1+F)C}{C_0}\right]$$

where K is the cell constant, D the diffusion constant, F the ratio of the volumes of the diffusate to diffusing compartments, t the duration of the experiment, C the concentration of the diffusate and C_0 the initial concentration of diffusing material. Concentration units cancel, so that radioactivity counts can be substituted directly.

Transference.—Transference numbers were determined by the "analytical boundary" method described in detail in the foregoing paper.[11] The present application involves the measurement of the amount of radioactivity transported electrically across the boundary created by the sintered glass membrane.

Conductivity.—A Leeds and Northrup 60-cycle bridge (Cat. no. 4866) and a dipping electrode were used. Results were good to about ±0.5%, no attempt being made to obtain highly precise data. Diffusion, transference, and conductivity experiments were made at 25 ± 0.01°.

Radioactivity Measurements.—This radioactive solutions were counted in a small glass-jacketed Geiger counter tube with a conventional amplifying and scaling circuit.[11] Sufficient counts were taken to make the probable counting error less than ±1%.

Results

Self-diffusion.—Self-diffusion results for sodium in Aerosol OT and in Aerosol MA, and for bromine in Agent M and in E-607 are given in Table I. Included are the data for the same ions in sodium chloride. The effect of micelle formation in lowering the rate of self-diffusion of the small ions is clearly evident from the data; this will be discussed quantitatively in a later section of this report.

TABLE I

SELF-DIFFUSION COEFFICIENTS OF SODIUM AND OF BROMIDE IONS

Substance	Tagging ion	Concentration *N*, mole/liter	Self-diffusion constant of tagging ion, *D*, sq. cm./day *a*	*b*	Av.
NaCl	Na^{24}	0.00296	1.20	1.20	1.20
		.0285	1.16	1.17	1.16
Aerosol MA	Na^{22}	.050	0.91	0.88	0.89
		.096	0.97	0.91	0.94
		.186	0.86	0.85	0.86
		.43	0.58	..	0.58
Aerosol OT	Na^{24}	.00293	1.19	1.21	1.20
		.0287	0.82	0.78	0.80
NaCl	Br^{82}	.050	1.63	1.62	1.62
E-607	Br^{82}	.0617	0.53	0.56	0.55
Agent M	Br^{82}	.0194	0.46	0.45	0.46

It may be noted that the self-diffusion coefficient of sodium ion in the dilute solutions of either

---

[11] Brady, THIS JOURNAL, **70**, 911 (1948).

[12] McBain and Dawson, *Proc. Roy. Soc.* (*London*), **148A**, 32 (1935).

[13] Gordon, *N. Y. Acad. Sci. Symposium*, Oct. 27–28 (1944).

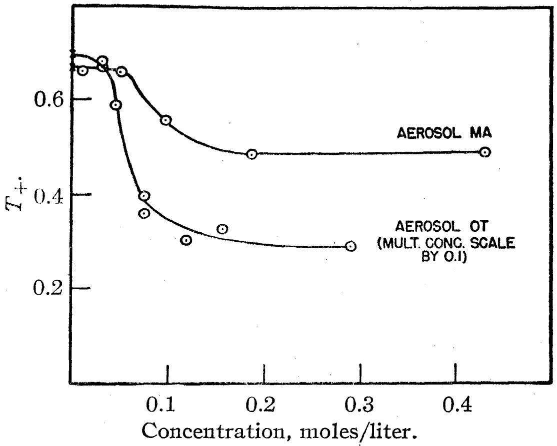


Fig. 1.—Cation transference numbers in Aerosol OT and in Aerosol MA solution.

Aerosol OT or sodium chloride, 1.20 sq. cm./day, is greater than the theoretical limiting value, 1.15 sq. cm./day. This probably arises because the method of calibration of the cells (diffusion of 0.1 *N* KCl into water) leads to density gradients, whereas no such gradients exist in this self-diffusion. Such differences may bring about a 5 to 10% change in the effective thickness of the membrane.[14] Since the self-diffusion will be employed entirely on a comparative basis, a calibration error of this sort will have no appreciable effect upon the conclusions drawn.

Conductivities.—The equivalent conductivities of the two Aerosols are included in Table II; these agree with the data of Haffner, Piccioni and Rosenblum[15] to within 1%. The critical concentrations appear to be about 0.005 *N* and 0.05 *N* for the OT and the MA, respectively. Extrapolation of the usual curves of conductivity *versus* square root of concentration leads to limiting conductivities of 72 and 75, which in turn give 22 and 25 as the limiting conductivities of the two Aerosol anions (using 50.1 for the Na ion).

Transference Numbers.—Table II also gives the mobilities and transference numbers at various concentrations. The specific conductivities are those of the tagged solution, which in most cases do not differ appreciably from those of the untagged. Special mention is required, however, for one series with Aerosol OT, where because of a miscalculation far too much tagging solution was added, and the extra electrolyte so introduced could not be neglected. About the only recourse under these circumstances is to assume that the extra electrolyte did not appreciably affect the mobility of the sodium ion, even though its transference number changed. The observed mobility and the conductivity of the untagged solution may then be employed in order to estimate the transference number in the absence of a foreign electrolyte. Because of the resulting uncertainty, however, a series was also run in which the Aerosol OT solutions were directly bombarded by neutrons to give Na^{24}; this procedure should introduce no foreign electrolyte. As is shown in Table II, results by both methods are in essential agreement.

Table II

Transference Numbers of Sodium and of Chloride Ions

Substance	Tagging ion	Concentration, *N*, mole/liter	Sp. cond. mho/cm. × 10^3	W, sq. cm./volt, sec. × 10^4	*T*	Λ^c
Aerosol MA	Na^{22}	0.0100	0.69	4.75	0.65	69
	Na^{22}	.0300	1.93	4.70	.68	64
	Na^{22}	.0498	3.04	4.18	.66	61
	Na^{22}	.0960	4.89	2.97	.56	51
	Na^{22}	.1863	7.81	2.12	.49	42
	Na^{22}	.430	16.83	1.98	.49	39
Aerosol OT	Na^{24a}	.00295	0.205	4.57	.66	69
	Na^{24b}	.00298	.231	4.73	.67	..
	Na^{24b}	.00447	.333	4.14	.59	68
	Na^{24a}	.00738	.485	2.47	.36	65
	Na^{24b}	.00745	.513	2.69	.40	..
	Na^{24a}	.0118	.731	1.97	.31	62
	Na^{22}	.0147	.873	1.99	.32	60
	Na^{22}	.0289	1.54	1.59	.29	53
E-607	Br^{82}	.0617	2.75	1.360	.30	..
Agent M	Br^{82}	.0194	0.727	0.0	.0	..

[a] Activity produced directly by neutron bombardment of the solutions. [b] Excess electrolyte, see text. [c] Derived from measurements on the untagged solutions.

The transference numbers of Aerosols MA and OT are plotted against concentration in Fig. 1. There is a sharp change in transference number in the neighborhood of the critical concentration.

Calculation of the Fraction of Small Ions Bound to the Micelles.—In order to utilize the foregoing data for calculating the fraction of small ions bound, a general model for the association is necessary. We shall assume that below the critical concentration the long chain ions have a concentration equal to the stoichiometric concentration of the solution; above the critical, large aggregates are formed by these ions, including varying amounts of small ions. The free monomeric ions will be assumed to behave roughly as they would in a univalent salt solution at the same total concentration. This is in accord with earlier data of others[7,16] obtained on similar systems.

Since the aggregate is assumed large, as a first approximation the concentration of monomeric long chain ions may be taken to change little with total concentration above the critical, in the range considered in this paper. Actually, since more long chain ions than small ions are included in the micelle, mass law predicts that at concentrations above the critical the concentration of monomeric long chain ions will decrease with increasing

---

(14) Moquin and Cathcart, This Journal, **57**, 1791 (1935).

(15) Haffner, Piccioni and Rosenblum, *J. Phys. Chem.*, **46**, 662 (1942).

(16) McBain and Searles, *J. Phys. Chem.*, **40**, 493 (1936).

total concentration. However, calculation of the rate of decrease on a reasonable model indicates that, in the concentration region where the influence of the single long chain ions is important in the equations to be developed, the inaccuracy of the above simple assumption is small compared to other uncertainties.

In the following equations the colloidal electrolyte will be considered to be anion active; for a cation active agent the signs of the subscripts are simply interchanged. Because of lack of detailed knowledge concerning the colloidal particles, all species must, of necessity, be lumped together and thought of as an "average" micelle. This effectively assumes that the mobility of the average bound small ion is the same as that of the average aggregate, which is, of course, not necessarily true.

Self-diffusion.—Denoting the diffusion constant of the average micelle by D_m, that of the free cations by D_+^0, and the measured net diffusion constant of the cations by D_+

$$D_+ C = D_+^0 C_+^0 + D_m C_+^B \qquad (1)$$

where C, C_+^0 and C_+^B are the total, free cation, and bound cation concentrations, respectively. Noting that $C_+^B + C_+^0 = C$, equation (1) transforms to

$$C_+^B/C = \frac{D_+^0 - D_+}{D_+^0 - D_m} \qquad (2)$$

Transference.—Letting W be the mobility in sq. cm./volt second, with subscripts and superscripts having the same meaning as before, the flux of the positive and negative ions across one square centimeter at a field strength of one volt/cm. is given by

$$\begin{aligned} CW_+ &= C_+^0 W_+^0 - C_+^B W_m \\ CW_- &= C_-^0 W_-^0 + C_-^B W_m \end{aligned} \qquad (3)$$

Equations (3) may be combined with the well known equations $W_i = \Lambda_i/F$, $T_+ + T_- = 1$, and $T_i = \Lambda_i/\Lambda$ (where Λ is the observed equivalent conductivity) and the material balance $C = C_+^0 + C_+^B = C_-^0 + C_-^B$. It follows that

$$C_+^B/C = 1 - \frac{\Lambda - (C_-/C)(T_+\Lambda + \Lambda_-^0)}{\Lambda_+^0 + (1 - T_+)\Lambda - (C_-^0/C)\Lambda^0} \qquad (4)$$

where $\Lambda^0 = (\Lambda_+^0 + \Lambda_-^0)$ is the hypothetical conductivity the solution would have if there were no micelle formation. Now, according to the assumption made above for the model, $C_-^0 \cong C_c$ at concentrations above the critical; consequently in applying equation (4) in subsequent calculations, this approximation will be used. It may be noted that at concentrations far above the critical, where $C_c/C \ll 1$, the above equation reduces to that derived and discussed by Molliet, Collie and Hartley.[17]

Freezing Point Depression.—Since it is supposed that the micelles are of sufficient size so that their contribution to the freezing point depression is negligible, the osmotic coefficient, g (the ratio of the observed to the theoretical freezing point lowering), may be considered to be the sum of two terms, the first arising from the free long chain ions, the second from free small ions

$$g = \frac{C_-^0 + C_+^0}{2C}$$

Again using the approximation that $C_-^0 \cong C_c$, along with the equation for the material balance

$$C_+^B/C = 1 - 2g + C_c/C \qquad (5)$$

Calculations.—The non-experimental quantities in equations (2), (4) and (5) are D_+^0, D_m, Λ_+^0 and Λ^0. Accordingly, the model must be used for their estimation.

The self-diffusion constants for the sodium ions, D_+^0, may be taken directly from the experiments on sodium chloride recorded in Table I, except in the case of Aerosol MA, which was studied in a higher concentration range. Since Jehle[18] has found that the self-diffusion coefficient of Na^+ in NaCl in the concentration region 0.05–0.5 N is nearly constant and about 8% lower than at infinite dilution, D_+^0 may be taken as 1.10 sq. cm./day throughout the range studied for the Aerosol MA.

There is no very good way to estimate the self-diffusion coefficient of the micelles, D_m. It is hoped to measure this in the near future for the sulfosuccinates using radiosulfur. One logical assumption is that the micelles binding small ions are so large that their diffusion constant can be neglected. Another, which is that employed here, is to extend the observation of Hartley and Runnicles[19] that the diffusion coefficients of some cationic agents swamped with salt roughly correspond to those of spheres with a radius equal to the length of the molecule. This leads to a D_m of 0.16 and 0.14 sq. cm./day for the micelles of Aerosols MA and OT, respectively, corresponding to lengths of 13 Å. and 15 Å. Those for E-607 and Agent M will be taken as 0.073 and 0.070, corresponding to 29 and 30 Å.

The electrical conductivities of the free monomeric ions, Λ_+^0 and Λ_-^0, will, according to the model, vary with concentration in the same proportion as the conductivity of sodium chloride solutions.

No correction will be applied to D_+^0, D_m, Λ_+^0 or Λ_-^0 for the viscosity increase of the solution. Such a viscosity correction would not greatly influence results for Aerosol OT and the cationic agents, but if applied to the results for Aerosol MA the self-diffusion of the sodium ion not only falls out of line with the other salts but becomes unreasonably high at the higher concentrations. This lack

---

[17] Molliet, Collie and Hartley, *Trans. Faraday Soc.*, **31**, 120 (1935).

[18] Jehle, Ph.D. Thesis, University of California, 1938.

[19] Hartley and Runnicles, *Proc. Roy. Soc.* (*London*), **168A**, 420 (1938).

of influence of solution viscosity on the mobility of the small ions is in harmony with McBain's observations on the conductivity of solutions of colloidal electrolytes.[20]

The critical concentration for micelles is also needed for utilization of the equations for the fraction of small ions bound. Table III lists this quantity for the surface active agents considered here, as determined by transference (Fig. 1), conductivity (Table II and Ref. 16), freezing point,[21,22] and surface tension.[23] The present self-diffusion data are too meager to be useful in this connection.

TABLE III

CRITICAL CONCENTRATION OF THE SURFACE ACTIVE AGENTS

Substance	Critical concn., N	Method
Aerosol MA	0.055	*a, b, c*
Aerosol OT	.0035	*a, c, d*
	.0055	*b*
Agent M	.0009	*d*
E-607	.005	*c*

[a] Transference numbers. [b] Conductivity. [c] Freezing point lowering. [d] Surface tension.

Table IV gives a comparison of the application of equations (2), (4), and (5) in estimating the fraction of small ions bound to the micelle. The osmotic coefficients for the Aerosols were taken from McBain and Bolduan,[21] that for E-607 from McBain and Brady.[22] The data of the table show that there is fair concordance among the three methods of measurement up to concentrations three to four times greater than the critical. This lends support not only to the model, but to the general validity of the self-diffusion or the transport approach to systems where the freezing point method is not applicable. (An exception to the general agreement is the self-diffusion run at the lowest concentration of Aerosol MA; this value is included because nothing could be found wrong with the experiment, but it can be seen even in Table I that it falls out of line.)

TABLE IV

COMPARISON OF PERCENTAGE OF SMALL IONS BOUND AS CALCULATED FROM SELF-DIFFUSION, TRANSPORT, AND FREEZING POINT

Substance	Concn., N	% Small ion bound Self-diff.	Trans.	F. P.
Aerosol MA	0.050	22 (?)	0	0
	.096	17	12	14
	.186	25	37	39
	.430	50	30	55
Aerosol OT	.0029	0	0	0
	.0045	..	15	11
	.0074	..	22	19
	.0118	..	29	30
	.0289	36	35	52[a]
Agent M	.0194	75	65	..
E-607	.0617	69	54	70

[a] Calculated from an extrapolated value of g obtained from a generalized curve for this compound.[22]

The results of the calculation according to equation (2) are relatively insensitive to values chosen for the self-diffusion coefficient of the micelles, D_m, since under any reasonable assumption, D_m should be small compared with D_0^+. If, for instance, zero had been assumed instead of 0.16 for D_m, then at 0.430 N Aerosol MA, the calculated per cent. bound would be 47 rather than 50. Results from Equation (4) are still less sensitive to variations in Λ_0^-, the equivalent conductivity of the monomeric long chain ions.

At the higher concentrations, the agreement in the calculated "fraction bound" becomes less satisfactory, especially between freezing point and transport results (at still higher concentrations than those studied here it is known[4] that such disparity becomes even greater). The disagreement could arise from a true difference in this quantity when the three different measurements are involved; thus surface conductivity on lamellar micelles of high surface area would give a lower "fraction bound" for diffusional or electrical transport processes than that derived from osmotic measurements. Another cause for disagreement lies in the assumption of an "average" micelle, since the presence of some "ionic" micelles, proposed by McBain a number of years ago,[2] would lead to an apparently lower "fraction bound" from the transport than from the diffusion and freezing point methods.

The inclusion of small ions in the colloidal particle is a logical consequence of the electrostatic effects of aggregation. The juxtaposition of the like charges of the end groups at the water-micelle interface would disrupt the micelle unless a large number of small ions of opposite charge are drawn in to neutralize partially what would otherwise be an excessive electrostatic potential. In the interior of the lamellar micelles indicated by X-ray diffraction studies,[24] this effect will be even more pronounced, so that there should be virtually no osmotically active small ions arising from this region. Because of the masking effect of the small ions, osmotic data from freezing points consequently give no direct idea of the size of the micelle, except in that it is fairly large.

A further consideration of the question of bound ion, however, offers an opportunity for indirect comparison between certain colloidal electrolytes. The values for the fraction bound given in Table IV are based on total long chain ion, micellar plus monomeric. In order to determine the amount bound per mole of micellar ion, use can be made of the probability that in the range considered the concentration of monomeric long

---

(20) Laing and McBain, *Trans. Faraday Soc.*, **117**, 1506 (1920).

(21) McBain and Bolduan, *J. Phys. Chem.*, **47**, 94 (1943).

(22) McBain and Brady, THIS JOURNAL, **65**, 2072 (1943).

(23) Unpublished work in this Laboratory.

(24) Harkins, Mattoon and Corrin, THIS JOURNAL, **68**, 220 (1946), and references therein.

chain ions changes little with total concentration above the critical. The desired quantity is then $\mathrm{d}C_+^{\mathrm{B}}/\mathrm{d}C$, the number of small ions bound per mole of colloidal electrolyte added to an infinite amount of solution. From equation (5)

$$\frac{\mathrm{d}C_+^{\mathrm{B}}}{\mathrm{d}C} = 1 - 2\,\frac{\mathrm{d}(gC)}{\mathrm{d}C} \qquad (6)$$

Figure 2 shows a plot of gC *vs.* C for Aerosols MA and OT, and, for comparison potassium laurate.[21,25] It can be seen that slightly above the critical concentration straight lines result, the slopes of which provide values for $\mathrm{d}(gC)/\mathrm{d}C$ in equation (6). The slopes for the Aerosol-type agents are about 0.16; hence, $\mathrm{d}C_+^{\mathrm{B}}/\mathrm{d}C = 0.68$, and consequently for each hundred moles of Aerosol added 68 moles of sodium are included in the micelles. For potassium laurate, on the other hand, $\mathrm{d}C_+^{\mathrm{B}}/\mathrm{d}C = 0.86$. Since nearly all of the potassium is included, this suggests much larger micelles for this substance, although possibly the structure of the micelles may also play a role. This general difference exists between the branched chain salts, to which class most of the efficient wetting agents belong, and the straight chain salts, among which are found the more efficient solubilizing and emulsifying agents.

Acknowledgment.—The authors wish to thank the cyclotron groups at Columbia University and the University of California for the supply of radiotracers. Also, we wish to express our indebtedness to Dr. J. K. Dixon for valuable advice and criticism, and to the Directors of these Laboratories for permission to publish these results.

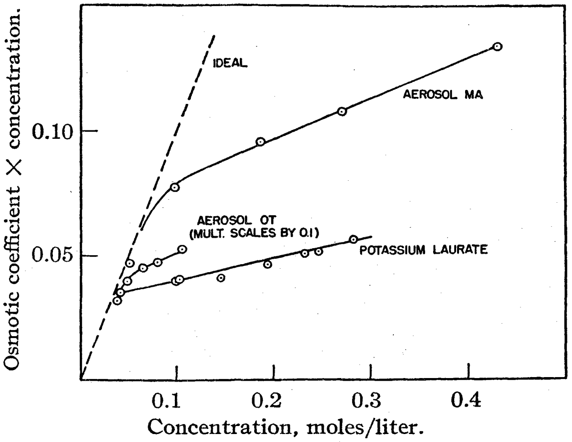


Fig. 2.—Osmotic coefficient times concentration *vs.* concentration for some colloidal electrolytes.

Summary

1. The transference numbers and self-diffusion coefficients for two anionic and two cationic surface active agents were determined using radiotracer techniques.

2. Utilizing the present results and freezing point data extant in the literature, the fraction of the small ions bound to the colloidal aggregates was calculated under consistent assumptions. The values calculated from the three types of measurements agreed well with one another up to several times the critical concentration for micelles. Possible causes for disagreement among the three types of measurements at higher concentrations were discussed.

3. The relationship of the extent of binding to the structure and size of the micelles was briefly considered.

STAMFORD, CONN. RECEIVED MARCH 29, 1947

[25] Brady, Thesis, Stanford University, 1944, and unpublished work.

[CONTRIBUTION FROM U. S. NAVAL RESEARCH LABORATORY]

Liquid Immiscibility in the System H_2O–Na_2O–SiO_2

BY O. F. TUTTLE[1] AND I. I. FRIEDMAN

Introduction

The dwindling supply of natural quartz for piezoelectric uses, together with the remarkable success attained in growing other crystals for a variety of uses, has stimulated interest on the part of the Armed Forces in the production of synthetic quartz. This work on phase equilibria in a portion of the ternary system H_2O–Na_2O–SiO_2 is a result of efforts to find a commercially feasible method for growing quartz crystals.

The data presented here are incomplete, but publication at this time seems advisable because of the theoretical and practical value of the information. Liquid immiscibility has been observed and investigated in the region $Na_2Si_2O_5$–SiO_2–H_2O. The 250, 300 and 350° isotherms have been worked out at the vapor pressures of the compositions investigated.

Preparation of Materials

All mixtures used in this work were made from a stock solution of sodium hydroxide and quartz or silica glass. The solution was prepared by saturating distilled water with reagent grade sodium hydroxide at 80°. The sodium carbonate precipitated was allowed to settle and the solution decanted through glass wool. The saturated solution was then diluted to approximately 20 *N* and stored in a wax-lined bottle. The composition was determined by titrating a weighed volume against a standard solution of sulfuric acid. The resulting solution contained 388 g. of sodium oxide per 1000 g. and had a specific gravity

---

[1] Present address: Geophysical Laboratory, Carnegie Institution of Washington, Washington, D. C.

of 1.566 at 25°. After one year, the composition was again determined by titrating with sulfuric acid and was found to be unchanged. A gravimetric check of the sodium oxide and silicon dioxide content gave a sodium oxide content of 386 ± 2 g. per 1000 g. and a silicon dioxide content of less than 0.1%.

Quartz oscillator plates of various sizes were used for all solubility experiments. The rate of solubility was determined using slabs of quartz cut and ground to uniform size. The variation in area of these blocks was less than 0.5%.

Clear silica glass rods were used for all other experiments. The rods were crushed in a diamond mortar and sieved. The material passing the 100 mesh, but not the 250 mesh screen was used after boiling in concentrated hydrochloric acid, washing and igniting at 800° in platinum crucibles. A 0.5 g. sample gave less than 0.0001 g. of residue on treatment with sulfuric acid and hydrogen fluoride.

Analytical Methods

The composition of the two immiscible liquids was determined by chemical analysis. The water content was determined in platinum crucibles by the loss of weight on ignition at bright red heat. As both liquid phases were readily soluble in water, the silicon dioxide was determined by precipitating with hydrochloric acid and igniting as silicon dioxide. It was found necessary to use two precipitations. Evaporation of the filtrate from the silicon dioxide precipitations gave the sodium oxide content as sodium chloride. The sodium chloride was heated to constant weight at 250°.

Experimental Methods

As the vapor pressures of the compositions investigated are of the order of magnitude of the vapor pressure of water at the temperatures employed (250, 300, 350°), it was necessary to use a container that was capable of withstanding considerable pressure. A bomb (Fig. 1) described by Morey and Ingerson[2] was found to be satisfactory. For part of the work it was found necessary to modify the seal slightly and to line the chamber by plating with gold (0.01 in.). The seal on the gold-plated bombs is illustrated in Fig. 2. The silver disc welded to the seat during the experiments, and on opening it was necessary to cut out the center of the disc, leaving a silver ring on the shoulder of the pressure chamber. In subsequent runs the silver continued to weld to the previous silver rings and it was necessary to dissolve the excess silver from the shoulder after 10 or 20 runs. The silver disc seal was also used in unlined bombs for much of the work, as it tended to prevent leaking during quenching.

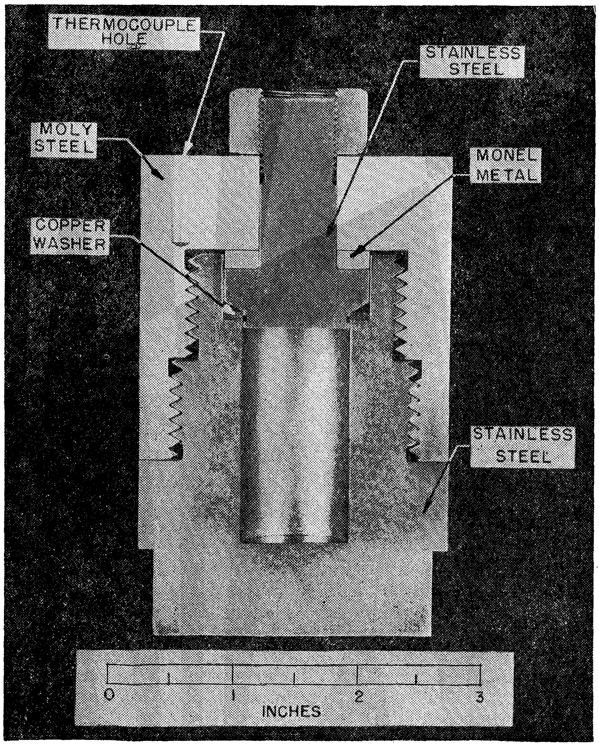


Fig. 1.—Cross-section of bomb used for this work.

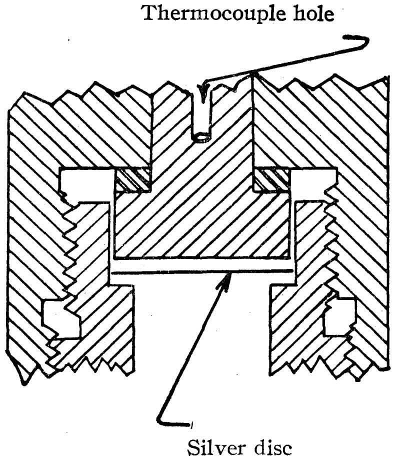


Fig. 2.—Cross-section of a portion of bomb showing construction when used with a silver disc as a seal.

The charges were stirred to hasten equilibrium by rocking the furnaces throughout the experiments (Fig. 3). The cylindrical resistance furnaces were oscillated 60° at 15 cycles per minute about an axis normal to the long axis of the bombs. Furnace temperatures were set manually by regulating the input voltages to the wire-wound heating element by means of a variac. Line voltage variations were kept to a minimum by a constant voltage transformer. It was possible to maintain temperatures at the thermocouple within ±2° by this method, but variations in the gradients between the thermocouple and charge in the different bombs used leads to an estimated uncertainty of ±5°. Temperatures were continually recorded by a Brown Electronik Strip Chart recorder using iron–constantan thermoelements.

Quartz Solubility Determinations.—The solubility of quartz in sodium hydroxide solution was used to establish the boundary of the quartz field. A weighed block of quartz was placed in an 18-cc. bomb together with 10 cc. of a sodium hydroxide solution of known composition, and the bomb was sealed. The bombs were then placed in the rocking furnaces at a predetermined temperature and allowed to attain equilibrium (thirty-six to one-hundred hours, depending upon temperature and composition), after which they were quickly removed and quenched under the cold water tap. The bomb and contents cooled to 100° within forty-five seconds and to room temperature in ninety seconds. The bombs were then opened and the quartz plate removed, washed and reweighed.

The composition of the solution in many of these runs passed through the stability field of sodium disilicate as the silica was being dissolved from the quartz plate; hence, if the length of run was insufficient to reach equilibrium, crystals of sodium disilicate were present on quenching.

Hydrothermal Quenching Method.—Equilibrium relations were studied by determining, at various constant

---

[2] G. W. Morey and Earl Ingerson, *Am. Mineral.*, **22**, 1121–1122 (1937).

temperatures, the presence or absence of crystalline and liquid phases on changing the composition of a series of sodium hydroxide–water solutions varying in composition from 1.5 to 38.8% sodium hydroxide, by adding different amounts of silica. A weighed amount of silica glass was placed in a bomb and 10 cc. of sodium hydroxide solution of known composition added. The bombs were heated, quenched, and examined as in the solubility determinations. All crystalline phases were examined and identified with a petrographic microscope.

The method can be illustrated by an example as follows: To 10 cc. of a solution containing 5.8% sodium oxide and 94.2% water at 300°

0.22 g. silica—one liquid, no crystalline phase
0.33 g. silica—one liquid plus disilicate crystals
1.35 g. silica—two liquids plus disilicate crystals
1.50 g. silica—two liquids no crystalline phase
1.90 g. silica—two liquids plus quartz crystals

Thus it can be seen that, by varying the amount of silica above and below that at which a new phase appears, the limits between which the phase appears can be fixed. These are, then, points on fusion or solubility surfaces of the phases in question.

One disadvantage of the method is that the pressures are not known and cannot be calculated with any reasonable degree of accuracy except in compositions approaching pure water. However, as there is only one pressure at which equilibrium between any of the phases can exist for a given temperature and composition, the results are useful without this information. The data represent what is usually called the condensed system, that is, the solid–liquid relations at the vapor pressure of the system.

Morey and Fenner[3] have discussed in considerable detail two sources of error in the hydrothermal quenching method as used in working out the system H_2O–K_2O–SiO_2. The first source of error described concerns the possibility that the composition of the quenched glass does not represent the composition of the liquid. This error is negligible in the present work because the composition of the liquid or liquids at the liquidus temperatures *is the composition placed in the bomb* with the exception of the amount lost to the vapor phase. This error would increase, then, as the density and amount of the vapor phase increased. Since the density of the vapor increases with pressure, it seems reasonable to assume that this factor would be greatest for compositions approaching water because the vapor pressure at constant temperature for the compositions investigated would be in all cases less than for water. The amount of vapor phase is greatest at the 300° isotherm since 10 cc. of liquid was placed in the 18 cc. bomb for all runs. For water, the amounts in the liquid and vapor phases would be

at 250° 9.85 g. in liquid, 0.12 g. in vapor
300° 9.77 g. in liquid, 0.20 g. in vapor
350° 9.89 g. in liquid, 0.08 g. in vapor

It thus appears to be a reasonable assumption that the greatest error that would arise would be less than 2% of the composition placed in the bomb.

The second source of error in the quenching technique is in the certainty that the quenched phases have not changed composition during the quench. This has been discussed by Morey and Fenner[4] in considerable detail and the possibility of error in this respect seems very remote.

A third error is in being certain that equilibrium conditions have been attained. This possibility was repeatedly checked by making successive runs with increasing time. Consistent results over a wide range of compositions at different temperatures add to the certainty that equilibrium was attained.

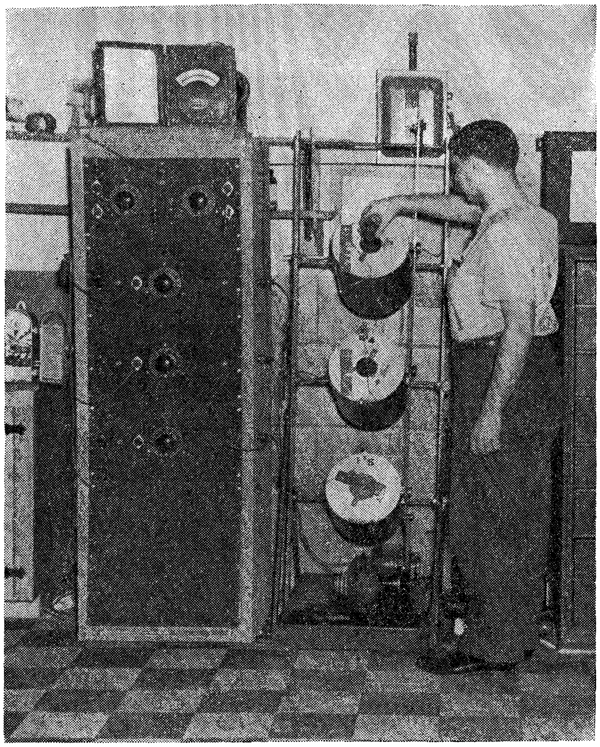


Fig. 3.—Rocking furnaces used for stirring charges at elevated temperatures and pressures.

Results

Isothermal Polybaric Equilibrium Relations.—Table I is a summary of the experiments carried

TABLE I

SiO_2, %	Na_2O, %	H_2O, %	Duration of run, hr.	Temp., °C.	Equilibrium phases
					250° Isotherm
					Quartz Solubility Runs
1.4	0.98	97.6	65	253	One liquid
2.4	1.5	96.1	112	248	One liquid
3.3	1.9	94.8	65	253	One liquid
7.5	3.5	89.0	112	251	One liquid
9.8	4.4	85.8	67	247	One liquid
10.5	4.4	85.1	147	247	Small amt. heavy phase
12.6	5.2	82.2	89	251	Small amt. heavy phase
14.3	5.9	79.8	112	248	Approx. 2 ml. heavy phase
16.5	6.2	77.3	118	251	Two liquids
20.2	7.6	72.2	147	247	Two liquids
28.3	10.7	62.0	89	247	Two liquids
					Other Runs
7.6	4.4	88.0	47	251	One liquid
8.1	4.4	87.5	47	252	Approx. 0.1 ml. heavy phase
8.6	4.4	87.0	47	251	Approx. 0.5 ml. heavy phase
5.0	5.4	89.6	18	248	One liquid
8.5	5.2	86.3	18	248	Approx. 1 ml. heavy phase

---

[3] G. W. Morey and C. N. Fenner, THIS JOURNAL, **39**, 1183–1187 (1917).

[4] Ref. 3, p. 1187.

TABLE I (*Continued*)

SiO_2, %	Na_2O, %	H_2O, %	Duration of run hr.	Temp., °C.	Equilibrium phases
8.3	7.1	84.6	98	250	One liquid
9.5	7.0	83.5	98	250	One liquid
23.1	15.2	61.5	72	246	One liquid
25.4	14.8	59.8	72	246	One liquid
27.9	14.3	57.8	18	253	Two liquids
30.3	13.8	55.9	20	250	All heavy phase
32.1	13.4	54.5	22	250	Two liquids
33.9	13.0	53.1	71	248	Two liquids
32.5	18.0	49.5	19	245	One liquid glycerol consist. n_D 1.436
38.6	16.3	45.1	19	250	Approx. 3 ml. liquid, n_D 1.391, heavy phase n_D 1.472
17.6	24.8	57.6	19	250	One liquid
24.3	22.8	52.9	19	252	One liquid, Na_2SiO_3
31.7	20.6	47.7	19	250	One liquid n_D 1.448, $Na_2Si_2O_5$
40.9	17.8	41.3	23	250	No thin phase, $Na_2Si_2O_5$
48.3	18.0	33.7	132	252	No thin phase, $Na_2Si_2O_5$ and quartz
50.9	17.2	31.3	132	247	No thin phase, quartz
48.9	19.8	31.3	132	247	No thin phase, $Na_2Si_2O_5$, and quartz
300° Isotherm Quartz Solubility Runs					
1.6	0.98	97.4	44	298	One liquid
4.2	1.9	93.9	44	298	Small amt. heavy phase
11.3	4.3	84.4	43	294	Two liquids
13.7	5.1	81.2	65	294	Two liquids
17.6	6.4	76.0	43	294	Two liquids
19.6	7.1	73.3	88	292	Two liquids
21.2	7.5	71.3	72	300	Two liquids
21.4	7.5	71.1	16	300	Two liquids
23.0	8.3	68.7	114	297	Two liquids
26.5	9.4	64.1	88	295	Two liquids
29.8	10.4	59.8	88	295	Two liquids
Other Runs					
2.0	2.8	95.2	17	299	One liquid, very small amt. $Na_2Si_2O_5$
3.0	2.8	94.2	17	297	One liquid, small amt. $Na_2Si_2O_5$
5.3	2.7	92.0	17	299	Approx. 0.1 ml. heavy phase
2.0	3.7	94.3	16	299	One liquid
3.0	3.7	93.3	17	297	One liquid, some $Na_2Si_2O_5$
4.0	3.6	92.4	19	298	One liquid, some $Na_2Si_2O_5$
6.0	3.6	90.4	19	298	Approx. 0.5 ml. heavy phase—$Na_2Si_2O_5$
7.6	3.8	88.6	40	299	Approx. 0.1 ml. heavy phase—small amt. $Na_2Si_2O_5$
8.0	3.8	88.2	40	299	Approx. 0.1 ml. heavy phase—small amt. $Na_2Si_2O_5$
8.7	3.8	87.5	115	302	Approx. 0.1 ml. heavy phase
2.0	5.6	92.4	19	302	One liquid
3.0	5.4	91.6	16	300	One liquid
4.0	5.4	90.6	18	300	One liquid, $Na_2Si_2O_5$
8.1	5.2	86.7	19	305	One liquid, $Na_2Si_2O_5$
11.1	5.0	83.9	19	303	Two liquids, some $Na_2Si_2O_5$
14.9	4.8	80.3	19	305	Two liquids, quartz
17.1	8.0	74.9	16	302	Two liquids, some $Na_2Si_2O_5$
19.1	7.8	73.1	16	300	Two liquids, some $Na_2Si_2O_5$
33.0	13.3	53.7	20	296	Two liquids, very small amt. $Na_2Si_2O_5$
33.9	13.0	53.1	49	300	Two liquids
35.1	12.8	52.1	66	298	Two liquids
36.3	12.6	51.1	66	298	One liquid, small amt. quartz
350° Isotherm Quartz Solubility Runs					
2.5	0.97	96.5	44	347	One liquid
5.3	1.9	92.8	44	347	Two liquids
7.5	2.5	90.0	42	353	Two liquids
9.9	3.5	86.6	71	345	Two liquids
12.5	4.3	83.2	162	350	Two liquids
14.7	5.0	80.3	71	345	Two liquids
19.0	6.3	74.7	55	350	Two liquids
22.3	7.4	70.3	118	345	Two liquids
24.2	8.2	67.6	65	350	Two liquids
25.9	8.8	65.3	118	345	Two liquids
27.0	9.3	63.7	56	350	Two liquids
24.0	9.7	66.3	48	353	Two liquids, $Na_2Si_2O_5$
Other Runs					
1.5	1.5	97.0	17	352	One liquid, some $Na_2Si_2O_5$
3.0	1.5	95.5	16	350	One liquid, small amt. $Na_2Si_2O_5$
3.5	1.4	95.1	20	350	Approx. 0.1 ml. heavy phase
1.0	3.8	95.2	17	352	One liquid
2.0	3.7	94.3	16	348	One liquid, small amt. $Na_2Si_2O_5$
4.0	3.6	92.4	19	347	One liquid, small amt. $Na_2Si_2O_5$
7.1	3.6	89.3	19	350	One liquid, $Na_2Si_2O_5$
13.2	3.3	83.5	21	353	Two liquids, quartz
12.6	4.5	82.9	19	348	Two liquids
1.4	5.5	93.1	17	346	One liquid
2.6	5.5	91.9	17	348	One liquid
4.0	5.5	90.5	19	349	One liquid, small amt. $Na_2Si_2O_5$
5.1	5.4	89.5	17	351	One liquid, $Na_2Si_2O_5$
7.7	5.2	87.1	17	347	One liquid, $Na_2Si_2O_5$
12.5	5.1	82.4	21	343	Small amt. heavy phase, some $Na_2Si_2O_5$
12.0	6.1	81.9	17	350	Two liquids, $Na_2Si_2O_5$
18.4	6.3	75.3	19	349	Two liquids
11.1	7.7	81.2	17	355	One liquid, $Na_2Si_2O_5$
17.1	7.9	75.0	67	346	Two liquids, $Na_2Si_2O_5$
25.6	8.7	65.7	18	355	Two liquids
10.2	9.6	80.2	17	348	One liquid, $Na_2Si_2O_5$
16.0	9.7	74.3	67	352	Two liquids, $Na_2Si_2O_5$
20.0	10.0	70.0	21	345	Two liquids, $Na_2Si_2O_5$

TABLE I (*Concluded*)

SiO_2, %	Na_2O, %	H_2O, %	Duration of run, hr.	Temp., °C.	Equilibrium phases
21.9	9.8	68.3	21	350	Two-liquids, $Na_2Si_2O_5$
25.3	9.4	65.3	19	357	Two liquids, $Na_2Si_2O_5$
14.8	12.4	72.8	67	350	One liquid, $Na_2Si_2O_5$
17.2	12.1	70.7	21	348	One liquid, $Na_2Si_2O_5$
29.8	10.3	59.9	19	343	Two liquids, small amt. quartz
30.9	10.1	59.0	18	350	Two liquids, quartz
34.2	13.1	52.7	41	350	Two liquids, $Na_2Si_2O_5$
36.1	12.6	51.3	64	347	Two liquids
37.8	12.3	49.9	41	353	Two liquids, quartz
50.9	19.0	30.1	40	353	Two liquids, $Na_2Si_2O_5$, quartz
55.0	17.4	27.6	40	353	Two liquids, quartz

out to determine the equilibrium conditions for the 250, 300, and 350° isotherms. The three isothermal sections are shown graphically in Figs. 4, 5, and 6. Compositions investigated are shown by small circles.

Equilibrium relations can perhaps best be illustrated by discussing, in some detail, the 250 and 350° isothermal sections. (The 300° and 350° are essentially alike.)

At 250° (Fig. 4) the area investigated is divided into two principal regions by the complicated curve H_2O–A–B–C–D–E–F. All compositions to the left of the curve are unsaturated at 250°, and all mixtures to the right of the curve consist of two liquids or of one liquid and one or more crystalline phases. The composition of all liquids that can coexist with crystalline phases is represented by the curve itself with the exception of the portion A–B–C. Mixtures in the area A–C–B consist of two liquids whose compositions vary along A–B and C–B. All other mixtures are partly crystalline at 250°, with the exception of compositions along the SiO_2–Na_2O side of the diagram which are completely crystalline at 250°.

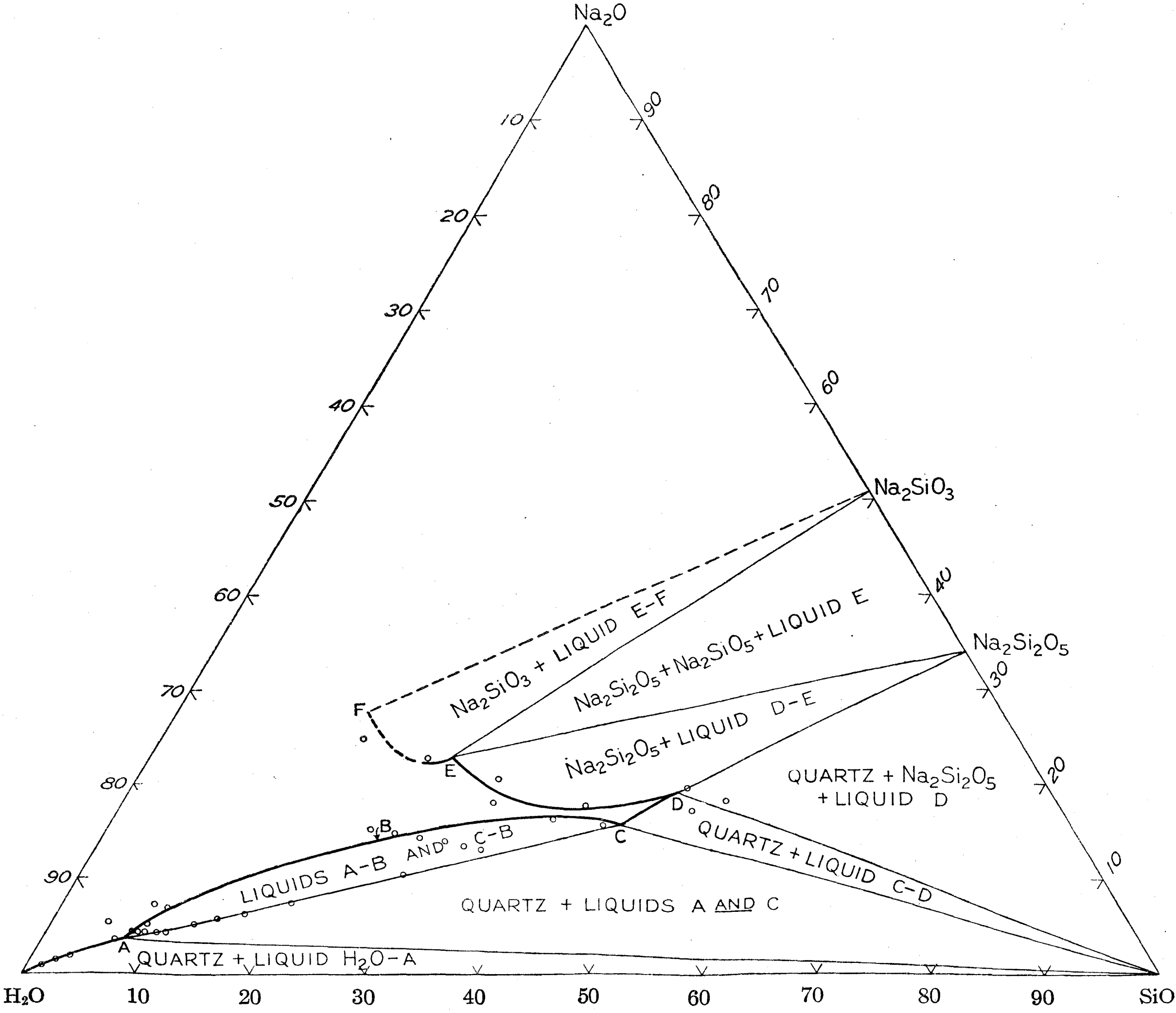


Fig. 4.—Polybaric saturation relations at 250° in the system H_2O–Na_2O–SiO_2.

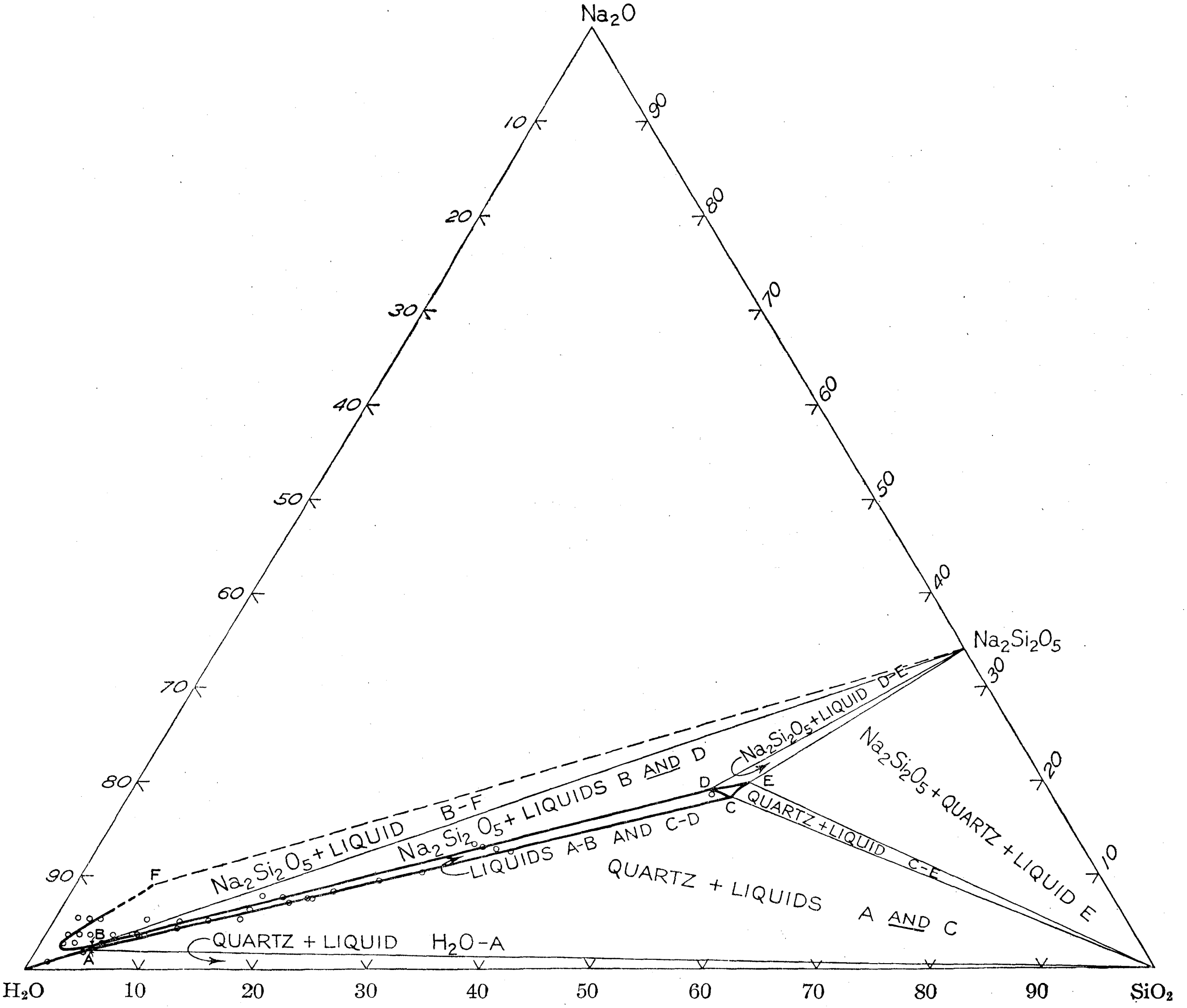


Fig. 5.—Polybaric saturation relations at 300° in the system H_2O–Na_2O–SiO_2.

All mixtures in the area H_2O–A–SiO_2 consist of one crystalline phase (quartz) and one liquid whose composition lies along the curve H_2O–A. Compositions in the triangle A–C–SiO_2 consist of quartz and two liquids A and C. The remainder of the diagram is largely self-explanatory and it seems unnecessary to describe each stability field separately.

The saturation relations at 350° are illustrated in Fig. 6. The relations here are similar to those at 250° with the exception that the $Na_2Si_2O_5$ stability field intersects the immiscible area. All mixtures, then, lying in the area A,B,D,C consist of two liquids A–B and C–D. Compositions in the triangle A–C–SiO_2 consist of quartz and two liquids A and C as at 250° and compositions in the triangle B–D–$Na_2Si_2O_5$ consist of $Na_2Si_2O_5$ crystals and two liquids B and D. The small area C–D–E represents a region consisting of one liquid only and was not realized experimentally; but from theoretical considerations such a relation appears necessary.

The Binary System $Na_2Si_2O_5$–H_2O.—A portion of this system has been studied by Morey and Ingerson.[5] They worked out the pressure–temperature relations at saturation from the melting point of $Na_2Si_2O_5$ (874°) down to 730° and 2000 lb./sq. in.[2] This portion of the system is apparently binary.

At 250° (Fig. 4) the system is binary in part, but where the $Na_2Si_2O_5$–H_2O join intersects the immiscible field, the two liquids formed do not lie on the join, hence the system is not binary from this point to A. From H_2O to point A, quartz crystallizes from $Na_2Si_2O_5$–H_2O mixtures and therefore this part of the system is not binary. There is some uncertainty as to whether or not the system is binary at 300 and 350° because the precision with which point B (Figs. 5 and 6) is located does not permit a decision as to whether $Na_2Si_2O_5$ will form two liquids or one. If two liquids are formed the system will not be binary, as the com-

---

(5) G. W. Morey and Earl Ingerson, *Am. J. Sci.*, [5] **35A**, 217–225 (1938).

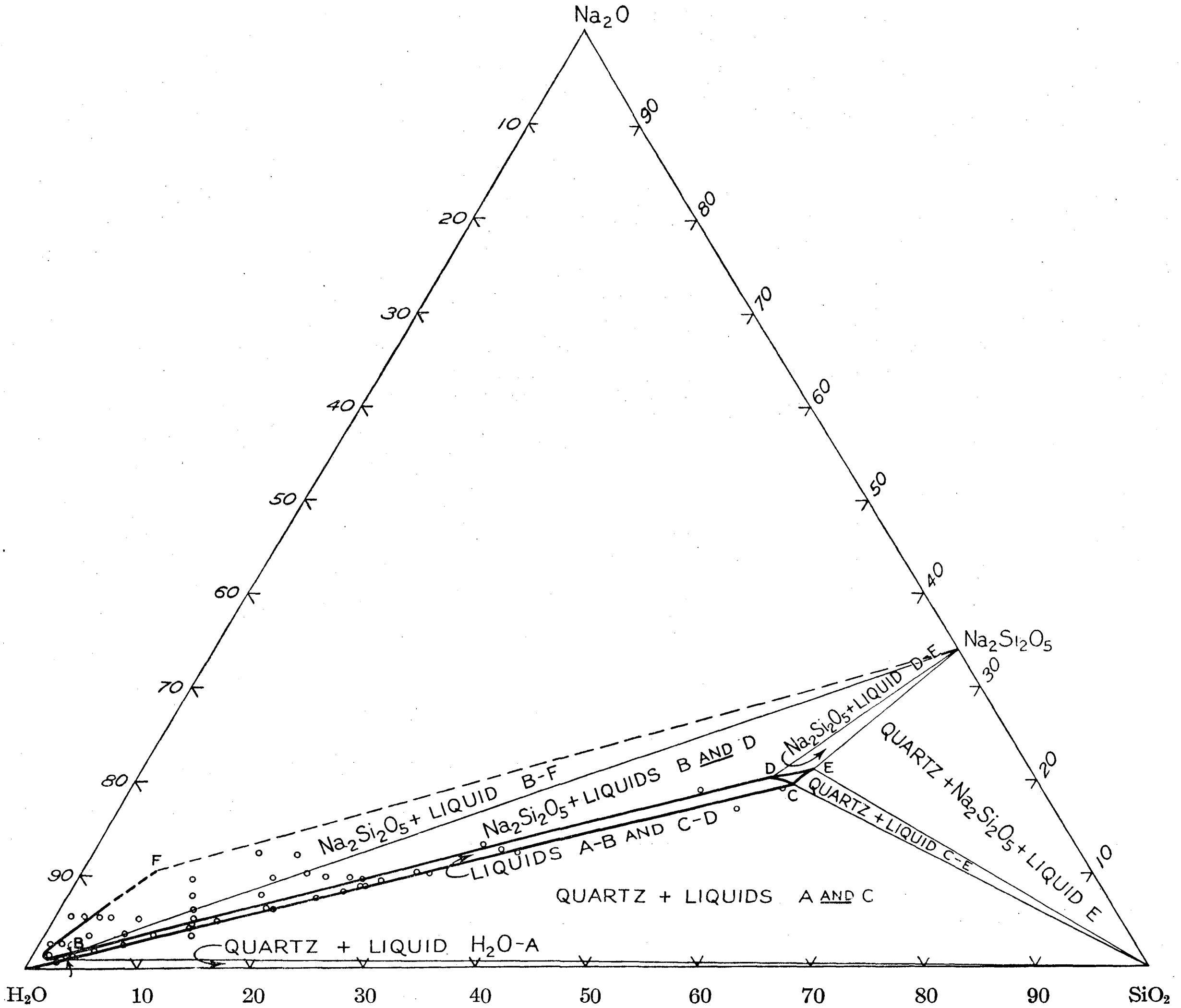


Fig. 6.—Polybaric saturation relations at 350° in the system H_2O–Na_2O–SiO_2.

position of the heavy liquid will not lie on the $Na_2Si_2O_5$–H_2O join. At 300° it is probable that the quartz field crosses the $Na_2Si_2O_5$–H_2O join at low $Na_2Si_2O_5$ concentrations, in which case this portion of the system will not be binary.

Liquid Immiscibility.—Many of the quartz solubility runs were characterized by the presence of a clear water-soluble glass together with a thin liquid upon quenching and opening. The amount of glass increased as the Na_2O concentration was increased. The glass was shown to be a liquid at the temperature of the experiment by quenching the bomb in different positions and observing that the glass always occupied the lowest point in the bomb.

The presence of a small amount of glass, which represented a liquid phase containing 30 to 40% H_2O, in a run whose total composition was 90% water, established the fact that two liquids must coexist at the temperature of the experiment. The question arises, is it possible that the glass represents a liquid phase and the thin liquid the vapor phase? A simple calculation shows that at 350°, for example, less than 1% of the volume of the 18-cc. bomb could be occupied by the vapor phase and the thin phase present on quenching may occupy as much as *8 or 9 cc. at room temperature*. It is obvious, then, that the thin phase represents a liquid phase at the temperature of the experiment plus a small amount of material that was in the vapor phase.

Character of the Heavy Phase.—Quartz solubility determinations at 250° yielded a glass whose composition is represented by point C (Fig. 4). This glass has a hardness of about 2.5 and is readily soluble in water. At 300° the glass had a composition shown by point C (Fig. 5) and is noticeably harder and less soluble than the 250° glass. The 350° glass is very brittle, has a hardness of approximately 5, and is slowly soluble in water (C, Fig. 6). As the composition of the heavy phase approached the critical point (B,

Fig. 4), the viscosity of the quenched material changed continuously from a glass at C to a liquid with the approximate consistency of SAE 20 lubricating oil.

Table II is a summary of analyses of the two phases, together with the original composition. The composition of the two immiscible liquids cannot be determined with great accuracy without elaborate equipment for sampling under the pressure–temperature conditions encountered. However, the heavy phase quenches readily to a glass which, with some caution, can be sampled with little or no contamination from the light phase, but the latter cannot be sampled nearly so accurately because of contamination from the condensed vapor phase and solution of some of the heavy phase.

TABLE II

Temp., °C.	Initial composition, %			Composition of light phase, %			Composition of heavy phase, %		
	SiO_2	Na_2O	H_2O	SiO_2	Na_2O	H_2O	SiO_2	Na_2O	H_2O
250	33.9	13.0	53.1	21.8	9.0	69.2	45.5	17.5	37.0
300	35.1	12.9	52.0	17.2	6.7	76.1	51.0	18.0	31.0
350	36.1	12.6	51.3	12.1	4.5	83.4	55.4	20.1	24.5

The analysis of the heavy phase was used in locating the boundary of the immiscible area on the high silica end of the region. The boundary of the immiscible area in the low silica region was defined by allowing the bombs to remain inverted in the furnace a few minutes prior to removal, and quenching in the inverted position for forty-five seconds, after which the bombs were turned right side up and opened. The heavy phase collects on the silver washer, and amounts as small as 0.05 g. of the glass can easily be detected.

The Immiscible Region.—In the three-dimensional temperature–composition prism the region of liquid immiscibility in a ternary system in which there is no solubility gap in the liquid phases of the binary systems has the shape of a spheroid when it is not intersected by the stability field of a crystalline phase. Theoretically, this spheroid may be cut off by the stability fields of crystalline phases in almost any manner. In most examples the lower portion of the spheroid is intersected by one or more stability fields of crystalline phases. The present system is unusual in that the upper portion of the spheroid is apparently cut off by stability fields of $Na_2Si_2O_5$ and quartz. Immiscibility has not been found in several runs at 200°, hence the lower consolute point on the immiscibility spheroid is probably between 200 and 250°. The upper extent of the immiscible region has not been reached.

Acknowledgment.—This work was undertaken on the basis of preliminary experiments done at the Geophysical Laboratory by Dr. G. W. Morey and O. F. Tuttle.

Summary

A portion of the system Na_2O–SiO_2–H_2O was investigated. Equilibrium relations were determined at 250, 300 and 350°. The system possesses liquid immiscibility with a lower consolute temperature between 200 and 250°. The immiscible region is intersected at 250° by the quartz stability field, and at 300 and 350° by the stability fields of quartz and $Na_2Si_2O_5$.

WASHINGTON 20, D. C. RECEIVED JUNE 13, 1947

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Methanolysis of 3,4-Epoxy-1-butene

BY PAUL D. BARTLETT AND SIDNEY D. ROSS[1]

Introduction

Kadesch[2] reported that the allylic epoxide, 3,4-epoxy-1-butene, was attacked by methanol at the primary position in the presence of sodium methoxide and at the secondary position in the presence of sulfuric acid. In an attempt to prepare the resulting isomeric ether–alcohols we repeatedly obtained products from both acid and alkaline treatments yielding the same 3,5-dinitrobenzoate (m. p. 75.5–76°). Furthermore, the yield of this derivative was highest in the case of the acid-catalyzed methanolysis from which Kadesch reported only a 3,5-dinitrobenzoate melting at 107–109°. As a result of these discrepancies we have made a more careful study of the reaction than was at first intended, with the following conclusions: The product of the acid-catalyzed methanolysis is the primary alcohol 2-methoxy-3-buten-1-ol (II) as reported by Kadesch, although its 3,5-dinitrobenzoate melts at 75.5–76° and not at 107–109°. The alcohol is accompanied by a small amount of crotonaldehyde and by a larger amount of a dimolecular product, probably the 2-erythryl ether of 2-methoxy-3-buten-1-ol (VIII). The low-boiling product of the base-catalyzed methanolysis is a mixture of II and 1-methoxy-3-buten-2-ol (I) which could not be separated and from which only the 3,5-dinitrobenzoate of II could be crystallized. We obtained neither the dinitrobenzoate of I nor any compound resembling the dinitrobenzoate of Kadesch melting at 107–109°. Our results and their relation to the results of Kadesch are summarized in the flow sheet and in Table I.

Discussion of Results

Kadesch[2] has given an able discussion of the

---

[1] Pittsburgh Plate Glass Fellow, 1945–1946.

[2] Kadesch, THIS JOURNAL, **68**, 41 (1946).

TABLE I

COMPARISON OF PRESENT RESULTS (B. & R.) WITH THOSE OF KADESCH (K.) ON METHANOLYSIS OF 3,4-EPOXY-1-BUTENE

Reagent	Mole % and investigator	Structure assigned to product	M. p. of 3,5-dinitrobenzoate, °C.	Method of structure proof
H_2SO_4 in CH_3OH	0.16 (K.)	II	107–109	Oxidation to $CH_3OCH(COOH)_2$
	1–5 (B. & R.)	II	75.5–76	Hydrogenation to
		VIII $CH_3CH{=}CHCHO$		$\mathrm{III} \xrightarrow{\text{ox.}} \mathrm{V} \begin{smallmatrix} \nearrow \mathrm{VI} \\ \searrow \mathrm{VII} \end{smallmatrix}$
$NaOCH_3$ in CH_3OH	1.4–2.1 (K.)	I	72	Comparison with results of Petrov.[2a]
	2.3 (B. & R.)	II	75.5–76	
		I	.....	Hydrogenation to $\mathrm{IX} \xrightarrow{\text{ox.}} \mathrm{X}$

mechanisms of the opening of the epoxide ring which might be expected under acidic and basic conditions. This author points out that the S_N1 mechanism, favored by acidic conditions, should involve cleavage of the allylic, secondary C-O bond rather than that of the non-allylic, primary C-O bond. Our results are in entire accord with this interpretation of the acidic mechanism although we, like Kadesch, have not carried out kinetic or quantitative studies of the reaction. With regard to the alkaline methanolysis, Kadesch cites previous reasons for believing that the mechanism of this reaction is of the S_N2 type, in view of which it was not surprising to find apparently exclusive opening of the expoxide ring at the primary position. The recent results of Chitwood and Freure[3] on the alcoholysis of propylene oxide provide further examples of the occurrence of attack by alkoxide ion exclusively at the primary position in a saturated epoxide. Our observation that the alkaline methanolysis of 3,4-epoxy-1-butene leads to a mixture of the primary and secondary methyl ethers raises the question: is the attack at the secondary position due to the appearance of the S_N1 mechanism even in alkaline solution, or does the allylic character of the secondary position make it susceptible to S_N2 attack in competition with the primary position?

An experiment for which we are indebted to Dr. Harry F. Herbrandson seems to settle this question in favor of the S_N2 mechanism in the case of both products of the alkaline cleavage. Methanolysis of the oxide by a concentration of sodium methoxide more than seven times that used previously by us led to essentially the same proportion of the isomers in the product. Had the attack on the primary position involved direct participation of the methoxide ion and the attack on the secondary position not, this experiment should have given seven times the ratio of I to II previously observed. It is, of course, well recognized that allylic character can enhance the reactivity of halides in direct bimolecular displacement reactions as well as in reactions of the S_N1 type.[4] This can be regarded as a lowering of the energy of the transition state through allylic resonance.

A factor limiting the interpretation of the relative amounts in which isomers are isolated in this reaction should perhaps be pointed out.[5] If our interpretation of the higher-boiling material is correct, the primary alcohol II is much more likely to be converted into such material than is the secondary alcohol I, and the ratio of (II)/(I) isolated will be smaller than the ratio of reactivities at carbon atoms 3 and 4 whenever higher-boiling products are also present.

Experimental Details

Methanolysis of 3,4-Epoxy-1-butene with 1 mole per cent. Sulfuric Acid.—To methanol (192.2 g. (6 moles) dried over magnesium methoxide, b. p. 64.6°, $n^{25}D$ 1.3279) and sulfuric acid (1.92 g. (0.02 mole) Merck reagent grade; sp. gr. 1.84) in a three-neck flask, fitted with a mechanical stirrer and reflux condenser and heated to reflux, was added over a ninety-minute period 120 g. (2 moles) of 3,4-epoxy-1-butene. This epoxide was obtained from the Columbia Chemical Division of the Pittsburgh Plate Glass Co. and redistilled through a Lecky-Ewell type column rated at sixty theoretical plates. The oxide had b.p. 67°, $n^{23}D$ 1.4151. Boiling was continued for two hours after the addition, ten grams of potassium carbonate was added and the mixture was stirred at room temperature for one-half hour. The total reaction mixture was then distilled through the column used in purifying the 3,4-epoxy-1-butene. The following fractions were obtained:

Fraction	Pressure, mm.	B. p., °C.	Wt., grams	$n^{25}D$
1	760	64.6	131	1.3280
2	55	to 65	1.5	1.3829
3	55	65–69	4.5	1.4250
4	55	69–71	10.5	1.4280
5	55	71	17.5	1.4280
6 (Trap)			6.5	1.3849
7	55	71	11.0	1.4280
8	55	69	42.5	1.4280
9	55	69	7.0	1.4278
Combined higher boiling fractions			59.5	

Fraction 1 above is recovered methanol, fractions 2, 3 and 6 are intermediate fractions and fractions 4, 5, 7, 8 and 9 are 2-methoxy-3-buten-1-ol, II. Fraction 7 was analyzed.

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.68; H, 9.85. Found: C, 59.13; H, 9.99.

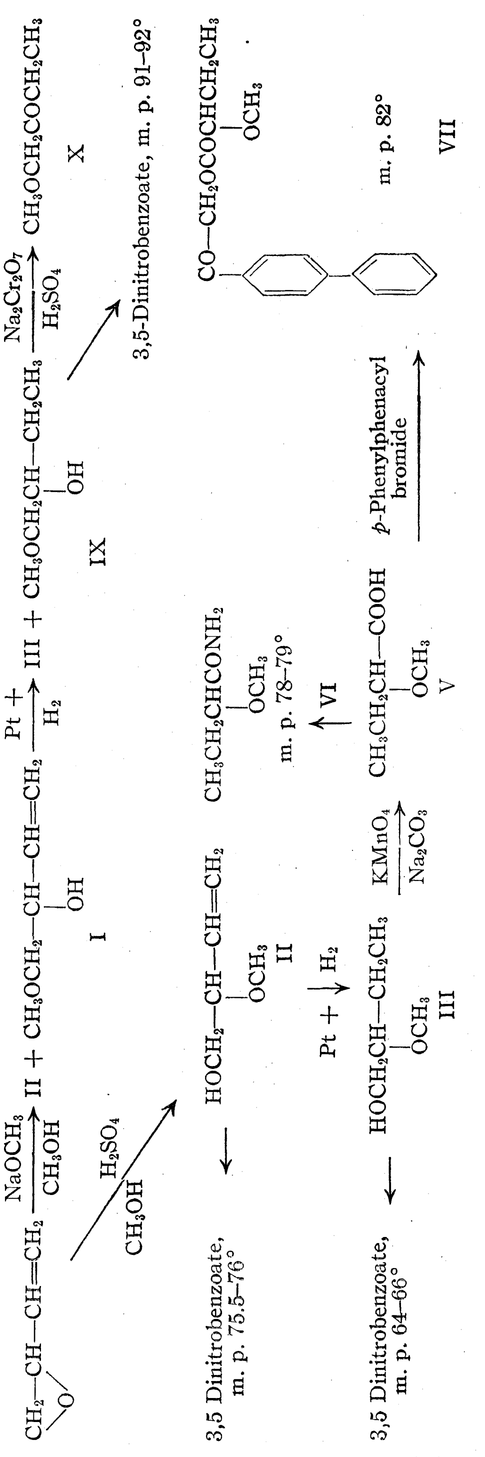
Detection of Crotonaldehyde.—A little of fraction 6 was treated with 2,4-dinitrophenylhydrazine in alcohol. A

(2a) Petrov, *J. Gen. Chem.* (*USSR*), **8**, 131 (1938).

(3) Chitwood and Freure, THIS JOURNAL, **68**, 680 (1946).

(4) For example, in the bimolecular reaction between chlorides and potassium iodide in acetone at 50°, allyl chloride is 79 times as reactive as *n*-butyl chloride (Conant, Kirner and Hussey, THIS JOURNAL, **47**, 488 (1925)).

(5) For this point we are indebted to Dr. X, a colleague of Referee 5.



drop of concentrated hydrochloric acid was added and the mixture was warmed on the steam-bath. On cooling the hydrazone crystallized. The melting point after crystallization from ethanol–acetic acid was 188–189°. The melting point of a mixture with an authentic sample of the 2,4-dinitrophenylhydrazone of crotonaldehyde showed no depression.

Preparation of the 3,5-Dinitrobenzoate of II.—Fractions 4, 7 and 9 were converted to the 3,5-dinitrobenzoate by heating 0.92 g. of 3,5-dinitrobenzoyl chloride with 0.31 g. of the alcohol in 10 cc. of benzene containing 0.40 g. of pyridine. All three fractions gave quantitative yields of crude ester. On recrystallization from alcohol–water they gave, respectively, 83.5, 89 and 78% yields of the pure ester melting at 75.5–76°.

Anal. Calcd. for $C_{12}H_{12}O_7N_2$: C, 48.65; H, 4.08. Found: C, 48.82; H, 3.95.

Methanolysis of 3,4-Epoxy-1-butene with 5 mole per cent. Sulfuric Acid.—A procedure similar to that in the 1 mole per cent. acid run gave 113.5 g. of recovered methanol, 22.5 g. of intermediate fraction, 62.5 g. of 2-methoxy-3-buten-1-ol, II and 68 g. of higher boiling material.

The High-Boiling Product, VIII.—Repeated fractionation of the combined higher boiling fractions from the two acid-catalyzed reactions above gave finally 15.0 g. of a viscous, colorless liquid boiling constantly at 112° at 23 mm. and having n^{25}_{D} 1.4520. The product shows one active hydrogen in the Grignard machine and has been assigned structure VIII.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 63.27, 63.59; H, 9.47, 9.54.

Treatment of 2-methoxy-3-buten-1-ol, II (47 g., 0.46 mole), with 3,4-epoxy-1-butene (18 g., 0.3 mole) in the presence of a small pellet of sodium followed by warming for three and one-half hours on the steam-bath gave on distillation 22 g. of a colorless liquid having b. p. 113° at 21 mm. and n^{25}_{D} 1.4510. This product, too, shows one active hydrogen in the Grignard machine, but analogy with the base-catalyzed methanolysis of the oxide points to its being a mixture of isomers rather than a single substance.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 63.31, 63.46; H, 9.68, 9.46.

Hydrogenation of 2-Methoxy-3-buten-1-ol, II.—2-Methoxy-3-buten-1-ol, II (30.6 g., 0.3 mole), in 100 cc. of absolute ethanol was hydrogenated over 0.2 g. of Adams catalyst. Hydrogen was rapidly taken up while the gage showed a drop in pressure of 25.5 lb. The catalyst was filtered off and the product was distilled giving 27 g. of 2-methoxy-1-butanol, III, which boiled at 60–63° at 25 mm. and had n^{25}_{D} 1.4130. A small portion, redistilled through a one-foot Vigreux column for analysis, had b. p. 147.2° and n^{25}_{D} 1.4138.

Anal. Calcd. for $C_5H_{12}O_2$: C, 57.61; H, 11.62. Found: C, 58.43; H, 11.91.

Preparation of the 3,5-dinitrobenzoate as previously described for II gave a quantitative yield of crude ester and a 66% yield of purified 3,5-dinitrobenzoate, m. p. 64–66°.

Anal. Calcd. for $C_{12}H_{14}O_7N_2$: C, 48.32; H, 4.73. Found: C, 48.66; H, 4.81.

Oxidation of 2-Methoxy-1-butanol, III.—2-Methoxy-1-butanol III (10 g., 0.96 mole), in 30 cc. of water containing 3 g. of sodium carbonate was placed in a three-neck flask fitted with a mechanical stirrer and cooled in an ice-bath. Potassium permanganate (19.8 g., 1.25 mole) in 600 cc. of water was added gradually with stirring. The mixture was stirred an additional six hours with cooling and finally left standing over-night at room temperature. The manganese dioxide was filtered off and the aqueous solution was concentrated *in vacuo* to a volume of 50 cc. It was then extracted continuously with ether. The ether extract was dried over magnesium sulfate and distilled yielding 1.5 g. of crude 2-methoxybutyric acid, V, b. p. 90–107° at 25 mm.

Preparation of 2-Methoxybutyramide, VI.—The acid, V, (0.5 g.) was refluxed with thionyl chloride for thirty minutes, the excess thionyl chloride was removed and 5 cc. of concentrated ammonia was added. The aqueous solution was extracted continuously with ether. The ether extract was dried and the ether was then removed yielding a viscous brown oil. The oil was extracted with boiling water. The aqueous extract was decolorized with Norite and the water was removed *in vacuo*. This gave the crude amide, VI, melting at 69–75°.[6] Several crystallizations from a mixture of benzene, petroleum ether and methanol

---

[6] Duvillier, *Ann. chim.*, [5] **17**, 548 (1879).

raised the melting point to 78–79°. On admixture with acetamide (m. p. 81° pure) the melting point was depressed to 40–65°. Mixing with propionamide (m. p. 79–80° pure) resulted in an oil.

Preparation of the *p*-Phenylphenacyl Ester, VII.—The acid V (0.5 g.), in 3 cc. of water was just neutralized with 10% sodium hydroxide. It was then made acid with a few more drops of V. Ethanol (8 cc.) and *p*-phenylphenacyl bromide (0.5 g.) were added, and the mixture was refluxed for one hour. This gave a crude product which after two crystallizations from methanol weighed 0.5 g. and melted at 82° alone and when mixed with a synthetic specimen made from 2-methoxybutyric acid obtained by the methanolysis of 2-bromobutyric acid.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.81; H, 6.63.

Base-catalyzed Methanolysis of 3,4-Epoxy-1-butene.—To methanol (192.2 g., 6 moles, dried over magnesium methoxide, b. p. 64.6°, $n^{25}D$ 1.3279) and sodium (3.2 g., 0.14 mole) heated to reflux was added dropwise 3,4-epoxy-1-butene (120 g., 1.7 moles, b. p. 67°, $n^{25}D$ 1.4151). The mixture was heated under reflux for four hours after the addition and then left standing overnight. Seven cc. of acetic acid was added to decompose the sodium methoxide and the total reaction mixture was distilled in a Lecky–Ewell type still rated at sixty theoretical plates. The following fractions were obtained.

Fraction	Pressure, mm.	B. p., °C.	Wt., grams	$n^{25}D$
1	760	64.1	124.5	1.3280
2	55	50–70	6.5	1.4222
3	55	70–71	7.0	1.4261
4	55	70–71	9	1.4281
5	55	70–71	19	1.4290
6	55	71	7.0	1.4290
7	55	71	9.7	1.4291
8	55	71	6.5	1.4283
9	55	71	18.0	1.4265
Combined higher boiling fractions			47.9	

Fraction 1 above is recovered methanol, fractions 2 and 3 are intermediate fractions and fractions 3–8 contain mixtures of 3-methoxy-3-buten-1-ol, II, and 1-methoxy-3-buten-2-ol, I.

Preparation of the 3,5-Dinitrobenzoate of the Base-catalyzed-Product.—3,5-Dinitrobenzoates were prepared from fractions 4 and 8 as previously described for the acid-catalyzed product. Fraction 1 gave only an 11% yield of the ester (m. p. 73–75°) whereas fraction 8 gave a 39% yield of the same derivative. No other solid 3,5-dinitrobenzoate could be isolated from either reaction mixture.

Hydrogenation of the Base-catalyzed Product.—Fractions 3–8 of the base catalyzed product above were combined and 30.6 g. (0.3 mole) was hydrogenated over 0.2 g. of Adams catalyst in 100 cc. of ethanol. The hydrogen pressure dropped by 28 lb. On distillation the following fractions were obtained.

Fraction	Pressure, mm.	B. p., °C.	Wt., grams	$n^{25}D$
1	85	73–75	8.5	1.4106
2	85	75–76	6.0	1.4110
3	30	to 60°	1.5	1.4129
4	30	60–62.5	4.0	1.4135

Fraction 1 above gave a 78% yield of a 3,5-dinitrobenzoate melting at 91.5–92°. This is the 3,5-dinitrobenzoate of 1-methoxy-2-butanol, IX.

Anal. Calcd. for $C_{12}H_{14}O_7N_2$: C, 48.32; H, 4.73. Found: C, 48.39; H, 4.50.

Fraction 4 above gave a 44% yield of the 3,5-dinitrobenzoate of 2-methoxy-1-butanol, III, m. p. 64–66°, showing no depression on mixture with the previously obtained sample.

Oxidation of 1-Methoxy-2-butanol, IX.—To a stirred mixture of sodium dichromate monohydrate (15.8 g., 0.053 mole) and sulfuric acid (12.6 g., 0.129 mole) in 75.5 cc. of water was slowly added 1-methoxy-2-butanol, IX (fraction 1 above, 8 g., 0.077 mole). The reaction mixture was surrounded with an ice-bath and the temperature was not permitted to rise above 50° during the addition. The reaction mixture was permitted to come to room temperature and then steam distilled. The steam distillate was extracted continuously with ether. The ether extract was dried and distilled yielding 3 g. of 1-methoxy-2-butanone, X, b. p. 132–135°, $n^{25}D$ 1.4068 (reported, b. p. 133–133.6°, $n^{20}D$ 1.4063).[7]

The ketone gave a 2,4-dinitrophenylhydrazone which after several crystallizations from acetic acid melted at 193.2–194° (reported, 198–198.5°).[8]

Summary

The addition of methanol to 3,4-epoxy-1-butene in the presence of sulfuric acid produced predominantly 2-methoxy-3-buten-1-ol. Small amounts of crotonaldehyde and a higher boiling product resulting from the attack of 2-methoxy-3-buten-1-ol on 3,4-epoxy-1-butene were also obtained.

With sodium methoxide as catalyst the predominant product was 1-methoxy-3-buten-2-ol, but some 2-methoxy-3-buten-1-ol was also obtained.

The mechanisms of these reactions have been discussed.

CAMBRIDGE, MASSACHUSETTS RECEIVED JULY 24, 1947

---

[7] Henze and Rigler, THIS JOURNAL, **56**, 1350 (1934).

[8] Maruyama, *Sci. Papers inst. Phys. Chem. Research* (*Tokyo*), **20**, 53 (1933); *C. A.*, **27**, 1863 (1933).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF POLAROID CORPORATION]

Polarographic Studies on Aliphatic Polyene Aldehydes

BY MELVIN FIELDS AND ELKAN R. BLOUT

The polarographic behavior of polyene aldehydes is of interest in connection with other research in progress in this Laboratory.[1,2] Several investigators have studied the polarographic behavior of compounds containing one or two aliphatic carbon–carbon double bonds conjugated with a carbonyl group,[3,4,5] but polarographic data for the more highly unsaturated ketones or aldehydes have not been reported.

In this paper we are reporting the results of work on the behavior at the dropping mercury electrode of unsaturated aldehydes of the type I

$$CH_3—(CH{=}CH)_x—CHO \qquad \text{I}$$

where x equals 1, 2, 3, 4 and 5. We were particularly interested in determining the effect of increasing chain length on the number, relative heights and half-wave potentials of the polarographic waves. In addition, we have studied the effect of *p*H on the polarographic characteristics of each compound. We have also calculated from the Ilkovic equation the diffusion coefficients of these polyenic aldehydes.

Experimental

Preparation of Aliphatic Polyene Aldehydes.—These compounds were prepared and purified by the procedures described or referred to in a previous paper.[1] The samples used for the polarographic measurements were of the same purity as those used for spectral measurements.

Instrument and Cells.—Polarographic measurements were made using a simple manual apparatus similar to the one described by Lingane and Kolthoff.[6] The usual H-type polarographic cell with a saturated calomel reference electrode was used. At a pressure of 65.0 cm. the capillary had a drop time of 3.5 seconds and an *m*-value of 1.908 mg. of mercury per second measured on open circuit in 50% aqueous dioxane solution tenth molar in potassium chloride.

Buffers.—The compositions of the stock buffer solutions which were prepared are listed below; when diluted with an equal volume of water or of dioxane they covered the indicated *p*H values as determined by measurement with a glass electrode.[7]

Stock buffer	Components	*p*H Range of buffer dil. with H_2O	*p*H Range of buffer dil. with $C_4H_8O_2$
A	0.2 *M* NaOAc–HCl	1.2–3.2	1.1–4.4
B	0.2 *M* NaOAc–HOAc	3.9–5.8	5.3–7.2
C	0.2 *M* NaOH–NH_4Cl	8.6–10.5	8.4–10.4

Polarographic measurements on the polyene aldehydes were made in 50% aqueous dioxane solutions prepared by dilution of the stock buffer solutions with dioxane purified as previously described.[1] The *p*H values mentioned throughout the rest of this discussion refer to the solutions 50% in dioxane and are uncorrected for the non-aqueous solution error of the glass electrode.[8] For that reason they are nominal values only.

For comparison of the polarographic behavior of members of this series it was desirable to use solutions of approximately the same concentration of supporting electrolyte throughout. The solubility characteristics of this series of aldehydes led to the choice of the particular solvent and buffer solutions used. Since the higher members of the series, particularly 2,4,6,8,10-dodecapentaenal, are only slightly soluble even in 50% aqueous dioxane solution, it was necessary in some cases to employ a solution whose buffer capacity is less than that desirable for polarographic work. The complications which this factor introduces in the interpretation of some of our data will be discussed in the sequel.

Procedure.—Because the aliphatic polyene aldehydes are relatively unstable the stock solutions of the compounds in dioxane were not allowed to stand more than three hours before measurement. The solutions of the aldehydes in the appropriate buffers were deaerated in the usual manner for twenty to thirty minutes with nitrogen purified by passage through a tube filled with freshly-reduced copper filings maintained at 450–500°. All potentials were measured against a saturated calomel electrode (S. C. E.) and the values recorded in this paper have been corrected for the *iR* drops of the solutions. Diffusion currents were corrected for the residual current of the supporting electrolyte. Measurements were made at 25 ± 0.5°.

Results and Discussion

The characteristics of the polarographic curves of the unsaturated aldehydes in acid, essentially neutral, and basic solutions may be seen in Figs. 1 to 5. Each of the compounds studied shows at least one well-defined wave in the *p*H range of 1 to 11. In addition a second polarographic wave of approximately the same height as the first is observed for each compound over a more limited *p*H range. The initial appearance of the second wave occurs at progressively lower *p*H values as the number of double bonds is increased. Although the first wave of each substance is well defined over the *p*H range investigated, the second tends to become less distinct in the most alkaline solutions.

As can be seen from Table I the values of the ratio $i_d/Cm^{2/3}t^{1/6}$ of the first wave are essentially independent of *p*H for all the unsaturated aldehydes. Moreover, the average value of this ratio is, to a first approximation, unaffected by the number of carbon–carbon double bonds conjugated with the carbonyl group; the slight de-

---

[1] Blout and Fields, THIS JOURNAL, **70**, 189 (1948).

[2] Blout, Fields and Karplus, *ibid.*, **70**, 194 (1948).

[3] Adkins and Cox, *ibid.*, **60**, 1151 (1938), report the polarographic reduction of crotonaldehyde, benzalacetone, cinnamalacetophenone, dibenzalacetone and several other unsaturated carbonyl compounds in tetramethylammonium hydroxide solution and in ammonium chloride solution.

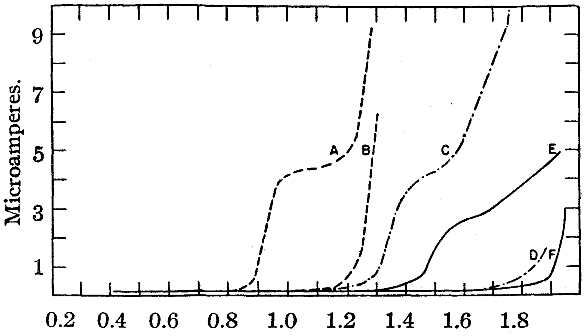
[4] Semerano and Chisini, *Gazz. chim. ital.*, **66**, 510 (1936).

[5] Schwaer, *Collection Czechoslov. Chem. Commun.*, **7**, 326 (1935), found that α,β unsaturated acids of the maleic acid type were reducible in 1 *N* hydrochloric acid solution. Whereas sorbic acid was reducible in alkaline solution at a highly negative potential, crotonic and itaconic acids could not be reduced before the decomposition of the supporting electrolyte occurred.

[6] Lingane and Kolthoff, THIS JOURNAL, **61**, 825 (1939).

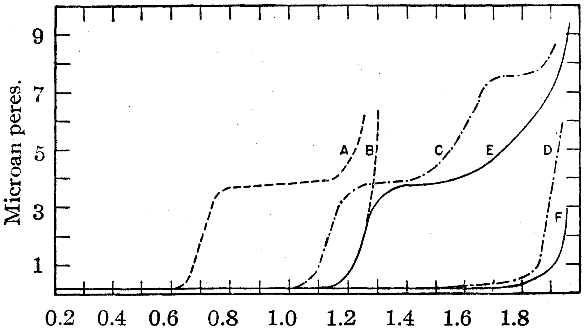
[7] Coleman Electric Company, Model 3A Electrometer.

[8] Dole, "The Glass Electrode," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 139.



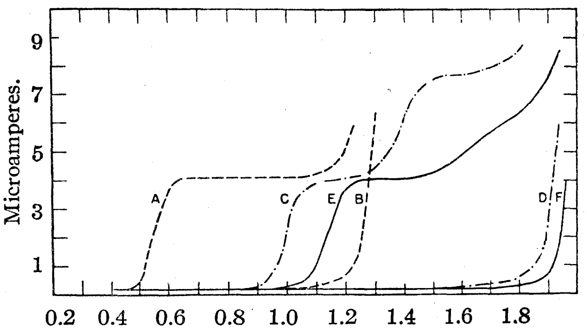
Potential of dropping mercury electrode *vs.* S. C. E., volts.

Fig. 1.—Polarograms of crotonaldehyde in buffered 50% aqueous dioxane solutions: A, *p*H 1.3, concentration 1.38 × 10^{-3} *M;* B, *p*H 1.3, solvent blank; C, *p*H 8.3, concentration 1.44 × 10^{-3} *M;* D, *p*H 8.3, solvent blank; E, *p*H 10.4, concentration 0.84 × 10^{-3} *M;* F, *p*H 10.4, solvent blank.



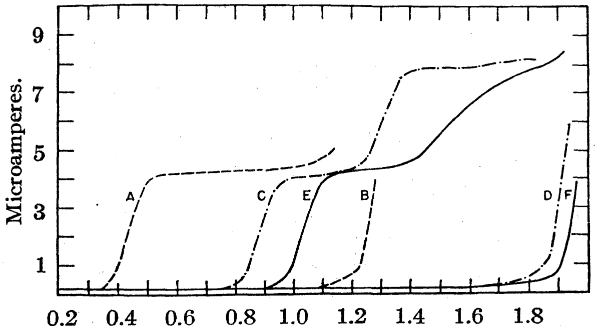
Potential of dropping mercury electrode *vs.* S. C. E., volts.

Fig. 2.—Polarograms of 2,4-hexadienal in buffered 50% aqueous dioxane solutions: A, *p*H 1.3, concentration 1.32 × 10^{-3} *M;* B, *p*H 1.3, solvent blank; C, *p*H 8.3, concentration 1.29 × 10^{-3} *M;* D, *p*H 8.3, solvent blank; E, *p*H 10.4, concentration 1.43 × 10^{-3} *M;* F, *p*H 10.4, solvent blank.



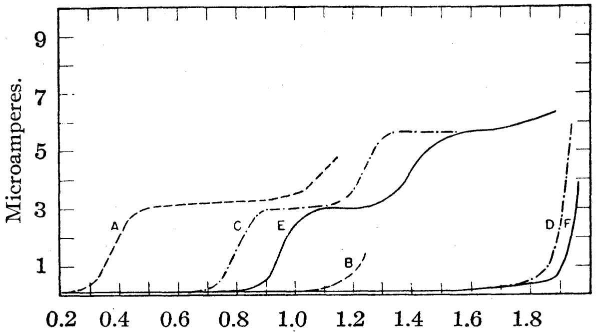
Potential of dropping mercury electrode *vs.* S. C. E., volts.

Fig. 3.—Polarograms of 2,4,6-octatrienal in buffered 50% aqueous dioxane solutions: A, *p*H 1.3, concentration 1.42 × 10^{-3} *M;* B, *p*H 1.3, solvent blank; C, *p*H 8.3, concentration 1.44 × 10^{-3} *M;* D, *p*H 8.3, solvent blank; E, *p*H 10.4, concentration 1.44 × 10^{-3} *M;* F, *p*H 10.4, solvent blank.



Potential of dropping mercury electrode *vs.* S. C. E., volts.

Fig. 4.—Polarograms of 2,4,6,8-decatetraenal in buffered 50% aqueous dioxane solutions: A, *p*H 1.3, concentration 1.70 × 10^{-3} *M;* B, *p*H 1.3, solvent blank; C, *p*H 8.4, concentration 1.62 × 10^{-3} *M;* D, *p*H 8.4, solvent blank; E, *p*H 10.4, concentration 1.68 × 10^{-3} *M;* F, *p*H 10.4, solvent blank.



Potential of dropping mercury electrode *vs.* S. C. E., volts.

Fig. 5.—Polarograms of 2,4,6,8,10-dodecapentaenal in buffered 50% aqueous dioxane solutions: A, *p*H 1.3, concentration 1.28 × 10^{-3} *M;* B, *p*H 1.3, solvent blank; C, *p*H 8.4, concentration 1.08 × 10^{-3} *M;* D, *p*H 8.4, solvent blank; E, *p*H 10.3, concentration 1.19 × 10^{-3} *M;* F, *p*H 10.3, solvent blank.

crease in these ratios with increasing molecular weight probably arises from diminished diffusion coefficients rather than a change in the electron requirements of the waves. Furthermore, the near equivalence of the $i_d/Cm^{2/3}t^{1/6}$ ratios for the first and second waves of each compound except crotonaldehyde makes it probable that the *n*-values of the two waves are identical. The variations in the diffusion current for the first wave of crotonaldehyde are probably to be attributed to losses of varying quantities of this volatile compound during deaeration with nitrogen. Since the second wave of crotonaldehyde does not attain its limiting value before decomposition of the supporting electrolyte occurs, accurate measurement of its diffusion current and half-wave potential is difficult. The $i_d/Cm^{2/3}t^{1/6}$ ratios for 2,4-hexadienal are somewhat lower than might be expected from the values of the ratios for the higher members of the series; this may arise from the greater instability of this compound as compared with the more highly conjugated aldehydes.

In Fig. 6 we have plotted for the polyene alde-

TABLE I

	Crotonaldehyde										
pH	1.3	2.3	3.1	4.2	5.2	6.3	7.2	8.3	9.2	10.4	11.1
$i_d/Cm^{2/3}t^{1/6}$	1.58	1.51	1.52	1.29	1.16	1.61	1.61	1.63	1.48	1.61	1.45
	2,4-Hexadienal										
pH	1.3	2.1	3.1	4.3	5.2	6.3	7.2	8.3	9.1	10.4	11.3
$i_d/Cm^{2/3}t^{1/6}$	1.43	1.46	1.35	1.35	1.35	1.38	1.34	1.48 (1.52)[a]	1.43 (1.57)	1.35	1.37 (0.21)
	2,4,6-Octatrienal										
pH	1.3	2.4	3.3	4.1	5.2	6.3	7.2	8.3	9.2	10.4	11.0
$i_d/Cm^{2/3}t^{1/6}$	1.45	1.40	1.42	1.38	1.39	1.40 (1.09)	1.46 (1.12)	1.42 (1.33)	1.42 (1.25)	1.45	1.48
	2,4,6,8-Decatetraenal										
pH	1.3	2.3	3.4	4.2	5.2	6.3	7.0	8.4	9.3	10.4	11.0
$i_d/Cm^{2/3}t^{1/6}$	1.29	1.33	1.34	1.28	1.30	1.29 (1.20)	1.30 (1.09)	1.28 (1.20)	1.29 (1.24)	1.33 (1.09)	1.30 (1.07)
	2,4,6,8,10-Dodecapentaenal										
pH	1.3	2.3	3.1	4.1	5.1	6.0	7.0	8.4	9.3	10.3	
$i_d/Cm^{2/3}t^{1/6}$	1.25	1.22	1.22	1.30 (0.94)	1.20 (1.08)	1.26 (1.14)	1.31 (1.14)	1.34 (1.38)	1.33 (1.36)	1.29 (1.25)	

[a] The values in parentheses refer to the second wave.

hydes the half-wave potentials of the first wave $(E_{\frac{1}{2}})_1$ and of the second wave $(E_{\frac{1}{2}})_2$ for several pH values as a function of the number of carbon–carbon double bonds. The addition of another C=C to an aliphatic polyene aldehyde with x double bonds causes a shift in $(E_{\frac{1}{2}})_1$ toward less negative potentials; that is, the ease of reduction increases with the number of double bonds conjugated with the carbonyl group. It is noted, however, that the increment per double bond decreases as the chain is lengthened.[9] Thus, while the $(E_{\frac{1}{2}})_1$ values for 2,4-hexadienal are on the average 0.23 volt more positive than those for crotonaldehyde, the $(E_{\frac{1}{2}})_1$ values for 2,4,6,8,10-dodecapentaenal are on the average only 0.07 volt more positive than those for 2,4,6,8-decatetraenal.

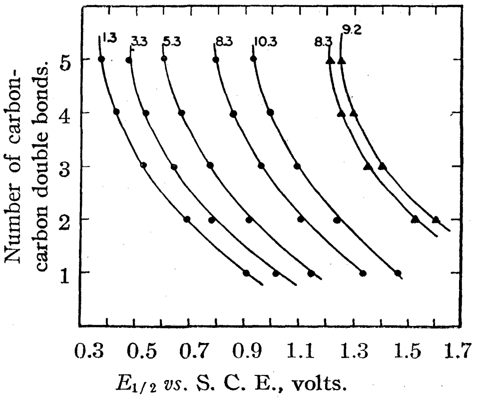
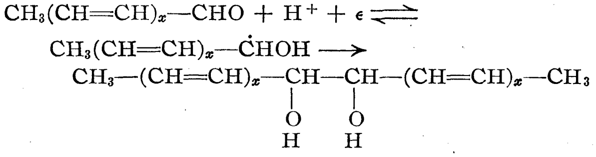


Fig. 6.—Half-wave potentials *vs.* number of carbon–carbon double bonds: —●—●—, first wave —▲—▲—, second wave. The number beside each curve refers to the pH at which measurements were made.

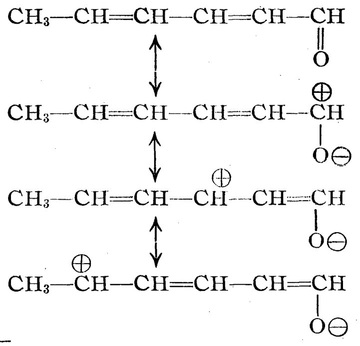
A plausible explanation for the direction of the shift of $(E_{\frac{1}{2}})_1$ with x can be given if we assume that in the reaction which produces the first polarographic wave the electrode-active species are the aldehyde (I) and the conjugate acid (II) of the radical-ion formed by a one-electron reduction of the parent substance.[10] The formation of the radical II may be followed by its dimerization to produce, perhaps, the unsaturated glycol III. Although dimerization of the initially-formed radicals makes the over-all electrode reaction an irreversible process, the step involving electron transfer may very well be a reversible one. The significance of the half-wave potentials for systems of this type is the same as for reversible ones.



$$CH_3(CH{=}CH)_x{-}CHO + H^+ + \epsilon \rightleftharpoons$$
$$CH_3(CH{=}CH)_x{-}\dot{C}HOH \longrightarrow$$
$$CH_3{-}(CH{=}CH)_x{-}\underset{\underset{H}{O}}{CH}{-}\underset{\underset{H}{O}}{CH}{-}(CH{=}CH)_x{-}CH_3$$

I II III

Since the nature of the electrode and other experimental conditions remained constant throughout, on the basis of the foregoing assumptions the change in the $(E_{\frac{1}{2}})_1$ values at constant pH affords a measure of the change in the relative stabilities



$$CH_3{-}CH{=}CH{-}CH{=}CH{-}\underset{\underset{O}{\|}}{CH} \qquad IV$$
$$\updownarrow$$
$$CH_3{-}CH{=}CH{-}CH{=}CH{-}\overset{\oplus}{\underset{O^{\ominus}}{CH}} \qquad V$$
$$\updownarrow$$
$$CH_3{-}CH{=}CH{-}\overset{\oplus}{CH}{-}CH{=}\underset{O^{\ominus}}{CH} \qquad VI$$
$$\updownarrow$$
$$CH_3{-}\overset{\oplus}{CH}{-}CH{=}CH{-}CH{=}\underset{O^{\ominus}}{CH} \qquad VII$$

---

(9) This effect is similar to that observed in the ultraviolet and infra-red spectra of these compounds where the shift in the position of at least one of the absorption maxima seems to become smaller as the length of the conjugated system is increased.[1,2]

(10) The bimolecular reductions of carbonyl compounds are well known. Familiar examples which may be mentioned are the electrolytic reduction of anisaldehyde to a mixture of the pinacols, hydroanisoin and iso-hydroanisoin,[a] the reduction of crotonaldehyde and cinnamaldehyde with zinc-copper couple to dipropenyl glycol[b] and hydrocinnamoin,[c] respectively, and the reduction of aromatic and unsaturated aldehydes with vanadous salts to the corresponding pinacols.[d] (*a*) Law, *J. Chem. Soc.*, **89**, 1512 (1906). (*b*) Young, Levanas and Jasaitis, THIS JOURNAL, **58**, 2274 (1936). (*c*) Kuhn and Winterstein, *Ber.*, **60**, 432 (1927). (*d*) Conant and Cutter, THIS JOURNAL, **48**, 1016 (1926).

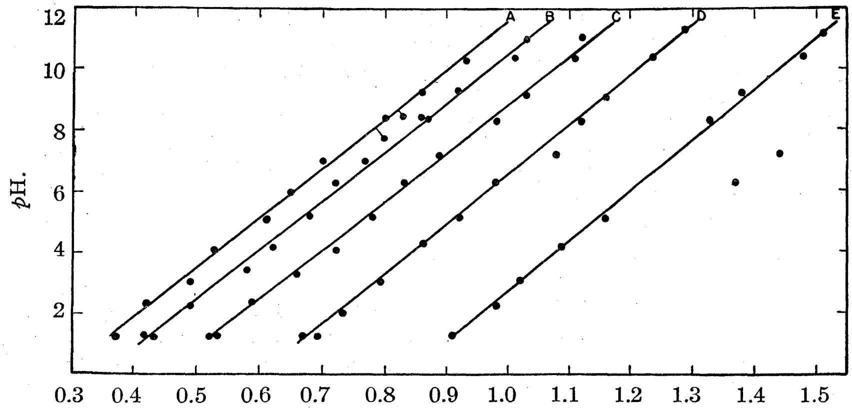
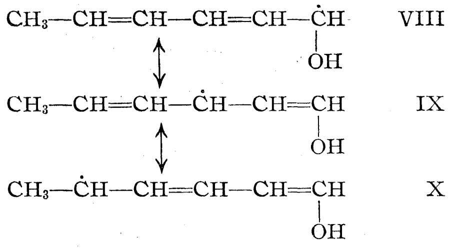


Fig. 7.—Half-wave potential of first wave *vs.* *p*H for: A, 2,4,6,8,10-dodecapentaenal; B, 2,4,6,8-decatetraenal; C, 2,4,6-octatrienal; D, 2,4-hexadienal; E, crotonaldehyde.

of the aldehyde and its related free radical on going from one member of the series to the next.

An aliphatic polyene aldehyde such as 2,4-hexadienal may be represented as a hybrid of the classical form, IV, and ionic forms such as V through VII.

On the other hand, the major contributing forms of the corresponding free radical, structures VIII-X, all contain the same number of the same kinds of bonds, do not involve charge separation and are probably of approximately equal energy. The resonance energy of the radical, therefore, is probably greater than that of its related aldehyde.



$$\mathrm{CH_3{-}CH{=}CH{-}CH{=}CH{-}\underset{\substack{|\\ OH}}{\dot{C}H}} \qquad \mathrm{VIII}$$

$$\updownarrow$$

$$\mathrm{CH_3{-}CH{=}CH{-}\dot{C}H{-}CH{=}\underset{\substack{|\\ OH}}{CH}} \qquad \mathrm{IX}$$

$$\updownarrow$$

$$\mathrm{CH_3{-}\dot{C}H{-}CH{=}CH{-}CH{=}\underset{\substack{|\\ OH}}{CH}} \qquad \mathrm{X}$$

While the resonance energy of a polyene aldehyde as well as that of the corresponding radical would be expected to increase with the length of the conjugated system, each additional double bond should lead to a relatively greater stabilizaton of the radical than of the aldehyde. This factor would account for the direction of the shift. The decrease in the magnitude of the change in $(E_{\frac{1}{2}})_1$ per double bond noted for the higher members of the series can be correlated with the fact that as x is increased each additional double bond produces a proportionately smaller increase in the number of equivalent forms contributing to the structure of the aldehyde and the free radical and, thus, probably also a smaller change in the relative stabilities of the aldehyde and its reduction product.

For the five polyene aldehydes studied $(E_{\frac{1}{2}})_1$ is an approximately linear function of *p*H (Fig. 7); in each case a unit increase in *p*H shifts the half-wave potential to more negative values by 0.06 volt. In the measured *p*H range 6–8 two points on the crotonaldehyde curve and one on the hexadienal curve deviate markedly from the straight lines which fit all the remaining data. Although the buffer capacity of the *p*H 6 and especially the *p*H 7 supporting electrolytes are quite low, it appears unlikely that the deviations of the half-wave potentials of crotonaldehyde and hexadienal arise from this cause. No such pronounced deviations in this *p*H region are observed for the other (more stable) compounds which were studied at approximately the same concentrations and in solutions of the same compositions. For a thermodynamically reversible reaction such a dependence of $E_{\frac{1}{2}}$ would indicate that the reduction product differed from its oxidized form by one hydrogen atom. It is interesting to note that in the electrode reactions under consideration the variation of $(E_{\frac{1}{2}})_1$ with *p*H conforms closely to that anticipated for the reversible case.

The second half-wave potential, like the first, shifts toward less negative values as the number of double bonds is increased (Fig. 8). The increment of $(E_{\frac{1}{2}})_2$ for those members of the series which show a well-defined second wave decreases with increasing chain length in much the same manner as observed with $(E_{\frac{1}{2}})_1$.

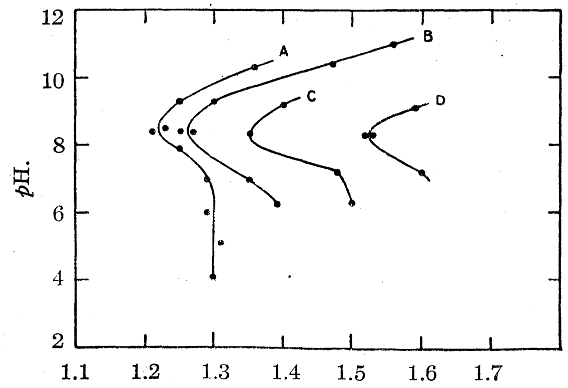


Fig. 8.—Half-wave potential of second wave *vs.* *p*H for: A, 2,4,6,8,10-dodecapentaenal; B, 2,4,6,8,-decatetraenal; C, 2,4,6-octatrienal; D, 2,4-hexadienal.

The second wave is well defined in most cases only in solutions more alkaline than *p*H 6; generally, in acid solutions this wave merges with or is obscured by that due to decomposition of the supporting electrolyte. For 2,4,6,8,10-dodecapentaenal a distinct second wave is obtained over the pH range of 4 to 10 and in acid solutions $(E_{1/2})_2$ seems to be independent of pH. In all the compounds studied the plot of $(E_{1/2})_2$ *vs.* pH shows a minimum in the region of pH 8. A possible explanation for this unusual behavior may be the low buffer capacity of some of the supporting electrolytes used. Further work on this point is now in progress.

Calculation of Diffusion Coefficients.—The diffusion coefficient, D, of a substance which undergoes oxidation or reduction at the dropping mercury electrode can be calculated from the Ilkovic equation[11] $i_d = 605nD^{1/2}Cm^{2/3}t^{1/6}$. We have calculated the diffusion coefficients of each of the five unsaturated aldehydes investigated using the average values of the diffusion currents for the first and second waves and assuming that each wave corresponds to a one-electron reduction. The values found are listed in Table II.

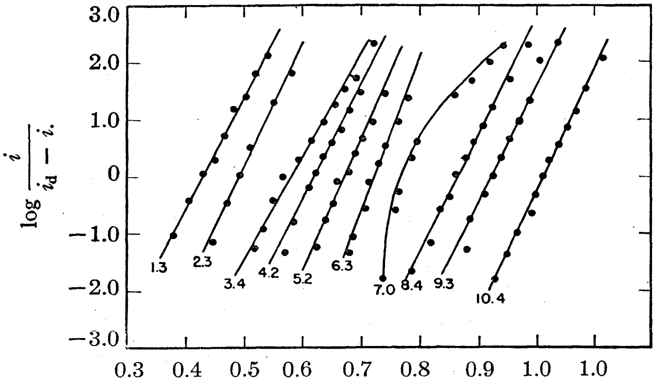


Fig. 9.—Plots of log $i/(i_d - i)$ *vs.* potential of the dropping mercury electrode for 2,4,6,8-decatetraenal. The number beside each curve refers to the pH at which measurements were made.

TABLE II

Compound	D (cm.² sec.⁻¹)
Crotonaldehyde	6.1×10^{-6}
2,4-Hexadienal	5.3×10^{-6}
2,4,6-Octatrienal	5.1×10^{-6}
2,4,6,8-Decatetraenal	4.3×10^{-6}
2,4,6,8,10-Dodecapentaenal	4.2×10^{-6}

In all cases the drop time used in these calculations was measured at the same potential as the diffusion current. The diffusion coefficient recorded above for crotonaldehyde is probably somewhat below the actual value because the loss of this rather volatile aldehyde during deaeration results in a decrease in the actual concentration of the material below the original value. This loss of aldehyde results in a lower diffusion current and hence a lower diffusion coefficient. All the higher aldehydes have sufficiently low vapor pressures so that the error from this source is probably negligible. The value of the diffusion coefficient of 2,4-hexadienal is probably low, possibly as a result of some decomposition of this relatively unstable compound during deaeration and measurement.

Reversibility of Electrode Reactions.—For a reversible reaction at a constant pH at 25° the potential of the dropping mercury electrode is related to the current at any point on the polarographic wave by the equation

$$E_{\text{d.e.}} = E_{1/2} - \frac{0.059}{n} \log \frac{i}{i_d - i}$$

If log $i/(i_d - i)$ is plotted as a function of $E_{\text{d.e.}}$, a straight line is obtained from the slope of which the number of electrons involved in the electrode reaction can be calculated. It is observed experimentally that many irreversible reactions obey the related equation

$$E_{\text{d.e.}} = E_{1/2} - \frac{0.059}{\alpha} \log \frac{i}{i_d - i}$$

and also yield linear plots of log $i/i_d - i)$ *vs.* $E_{\text{d.e.}}$ In these cases, α is not necessarily an integer and may even be less than 1. An exact interpretation of the polarographic waves obtained in such cases has not yet been presented.

We have plotted for the first polarographic wave of each of the five unsaturated aldehydes log $i/(i_d - i)$ as a function of $E_{\text{d.e.}}$ and have found approximately linear relationships at many of the pH values examined. The curves shown in Fig. 9 for 2,4,6,8-decatetraenal are typical of those obtained for the other members of the series. Table III lists the values calculated from the slopes of the straight lines mentioned above or from the slopes of the tangents to the curves at the half-wave potentials.

TABLE III

	Crotonaldehyde									
pH	1.3	2.3	3.1	4.2	5.2					
α	1.7	1.8	1.3	1.2	1.1					
	2,4-Hexadienal									
pH	1.3	2.1	3.1	4.3	5.2	8.3	9.1	10.4		
α	1.4	1.8	1.4	1.5	1.2	1.2	1.3	1.0		
	2,4,6-Octatrienal									
pH	1.3	2.4	3.3	4.1	5.2	6.3	8.3	9.2	10.4	
α	2.0	1.7	1.3	1.4	1.6	1.7	1.1	1.6	1.1	
	2,4,6,8-Decatetraenal									
pH	1.3	2.3	3.4	4.2	5.2	6.3	7.0	8.4	9.3	10.4
α	1.2	1.3	1.0	1.1	1.3	1.6	1.6	1.2	1.2	1.2
	2,4,6,8,10-Dodecapentaenal									
pH	1.3	2.3	3.1	4.1	5.1	6.0	7.0	8.4	9.3	10.3
α	1.4	0.9	0.9	0.8	1.1	1.1	1.2	1.2	1.2	1.0

The deviation from linearity of the curve for 2,4,6,8-decatetraenal at pH 7 quite probably arises from the low buffer capacity of this supporting electrolyte. Some of the high α-values may also be due to this cause or to a degree of irreversibility in the electrode reaction.

Although the relationship between $E_{\text{d.e.}}$ and

---

[11] Kolthoff and Lingane, "Polarography," Interscience Publishers, New York, N. Y., 1941, p. 30.

$\log i/(i_d - i)$ affords a convenient and reliable means of determining the n-values of reversible electrode reactions, other methods are generally used when dealing with irreversible reactions. The Ilkovic equation can be used to calculate the n-values of irreversible as well as reversible electrode reactions, but the paucity of diffusion coefficient data severely limits the usefulness of this procedure. Coulometric measurements afford the most reliable means of determining n- values in irreversible reactions.[12] Such measurements for the aliphatic polyene aldehydes will be reported in a later paper.

Acknowledgment.—We wish to express our appreciation to Mr. Marshall Kane, who assisted in the preparation and measurement of many of these compounds.

Summary

The polarographic behavior of aliphatic polyene aldehydes has been examined in buffered 50% dioxane solution over the *p*H range 1 to 11. The variations in half-wave potentials and the $i_d/Cm^{2/3}t^{1/6}$ ratios have been examined as functions of *p*H and the number of double bonds in the molecule.

CAMBRIDGE 39, MASSACHUSETTS

RECEIVED APRIL 26, 1947

---

[12] Lingane, THIS JOURNAL, **67**, 1916 (1945).

[CONTRIBUTION FROM THE ATLANTIC REFINING CO.]

The Isolation and Physical Properties of the Diisopropylbenzenes

BY F. W. MELPOLDER, J. E. WOODBRIDGE AND C. E. HEADINGTON

Introduction

The physical properties of the isomeric diisopropylbenzenes reported in the literature are fragmentary and the wide variations in these values indicate that only incomplete separations of the isomers have previously been accomplished.[1–7] Newton,[8] however, isolated meta and para diisopropylbenzene by distillation from a propylated benzene which apparently contained none of the ortho isomer. The physical properties reported by him for the two isomers are in substantial agreement with those found by the authors in the work to be described (Table I).

TABLE I

PHYSICAL PROPERTIES OF THE ISOMERIC DIISOPROPYLBENZENES

Property		Found by this study			Found by Newton[8]	
		Ortho	Meta	Para	Meta	Para
Purity, mole %		99.6	99.6	99.8		
Melting point, °C.		−56.68	−63.13	−17.07		
Cryoscopic constant, mole frac./°C.		0.0221	0.0285	0.0292		
Boiling point, °C.	760 mm.	203.75	203.18	210.37	203.0	210.3
	300 mm.	168.33	167.83	174.4	168.9[b]	174.4[b]
	100 mm.	133.9	133.4	139.3		
	50 mm.	115.4	114.9	120.2		
Antoine constants[a]	A	6.9800	6.9805	7.0667	7.1710[b]	7.0726[b]
	B	1619.5	1616.6	1711.9	1766.4[b]	1709.2[b]
	C	191.33	191.15	198.59	207.40[b]	197.51[b]
Refractive index	20°	1.49603	1.48883	1.48983	1.4884	1.4895
	25°	1.49373	1.48748	1.48758		
Specific dispersion 25°		157	155	157		
Density, g./ml. 20°		0.87007	0.85593	0.85676	0.8566	0.8571
Molecular weight		161.93	161.38	162.67		
Carbon–hydrogen ratio		7.96	7.92	7.91		

[a] Antoine equation, $\log_{10} P = A - B/(C + t)$, P = pressure, mm. t = boiling point, °C. [b] Calculated from data of Newton.

In this work the isolation of substantially pure ortho, meta, and para diisopropylbenzenes from benzene–propylene alkylate was accomplished by a combination of distillation, fractional crystallization, adsorption, sulfonation, and hydrolysis. Precise physical properties as well as ultraviolet, infrared and mass spectra are reported on each of the isomers.

Initial Separation.—The source of these compounds was a high boiling by-product fraction, b. p. 200–215°, produced by a commercial process for making cumene wherein benzene is alkylated with propylene over U. O. P. phosphoric acid catalyst. To roughly determine the distribution of the isomeric diisopropylbenzenes in the mixture a 700-cc. volume was fractionally distilled through a 100-plate Heligrid column into 5% cuts. Although the distillation curve (Fig. 1) exhibits only two boiling point flats, the refractive index curve indicates that at least two distinct compounds are present in fraction I, b. p. 203–204°, and one in fraction II, b. p. 210–211°. Inspection of the refractive indices and ultraviolet spectra indicated that the material present in fraction I contained a major amount of meta diisopropylbenzene and a minor concentration of the ortho isomer, while fraction II, comprising nearly half of the crude mixture, was largely para isomer. The next step was therefore to distil 15 liters of the charge stock into two fractions, one boiling at 203–204° and the other at 210–211°.

Separation of *o*- from *m*-Diisopropylbenzene.—It was found that repeated high efficiency distillations of the 203–204°, material resulted in only a partial separation of ortho and meta isomers. The best distillate fraction of ortho isomer froze to a viscous partially crystalline mass at −80° whereas the meta isomer fraction crystallized with some difficulty at −72°.

Since *m*-xylene was successfully purified by Mair, Termini, Willingham and Rossini[9] by the selective sul-

---

(1) V. N. Ipatieff, B. B. Corson and H. Pines, THIS JOURNAL, **58**, 919 (1936).

(2) V. N. Ipatieff and H. Pines, *ibid.*, **59**, 56 (1937).

(3) T. U. Ju, C. E. Wood and F. H. Gorner, *J. Inst. Petr.*, **28**, 159 (1942).

(4) J. F. McKenna and F. J. Sowa, THIS JOURNAL, **59**, 470 (1937).

(5) S. J. Slanina, F. J. Sowa and J. A. Nieuwland, *ibid.*, **57**, 1547 (1935).

(6) D. R. Stull, *Ind. Eng. Chem.*, **39**, 517 (1947).

(7) Uhlhorn, *Ber.*, **23**, 3142 (1890).

(8) A. Newton, THIS JOURNAL, **65**, 320 (1943).

(9) B. J. Mair, D. J. Termini, C. B. Willingham and F. D. Rossini, *J. Res. Nat. Bur. Stds.*, **37**, 229 (1946).

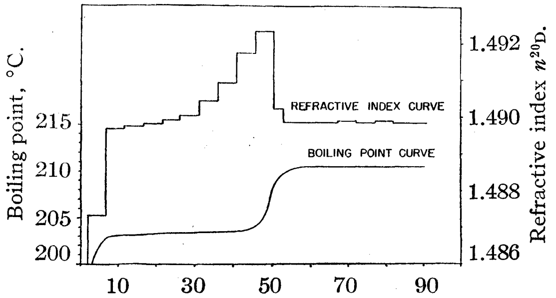


Fig. 1.—Distillation of the crude diisopropylbenzene mixture.

fonation and hydrolysis of a meta and para xylene mixture, the same technique was applied to this separation. A small quantity of ortho–meta-diisopropylbenzene mixture was sulfonated at room temperature with 105% H_2SO_4, the reaction reaching completion in about half an hour. The mixture was diluted with ice and then steam distilled at elevated temperatures. A small amount of unreacted hydrocarbon distilled over at 120°, but no appreciable hydrolysis occurred until a temperature of 135° was reached. At this point there was collected a large fraction of nearly pure meta as evidenced by the low refractive index, n^{20}D 1.4890, and high freezing point, −64°. As the temperature of the hydrolysis was raised the concentration of ortho in the distillate gradually increased to a maximum at 160°. A graph showing the progress of the hydrolysis (Fig. 2) is indicative of the sharpness of the separation of the ortho and meta isomers. In view of the separation obtained, 4 liters of 203–204° material were similarly treated. To further purify the meta isomer, the fraction which hydrolyzed at 135° was resulfonated and hydrolyzed. Similar treatment of the fractions which hydrolyzed at 160°, however, failed to enrich the ortho isomer.

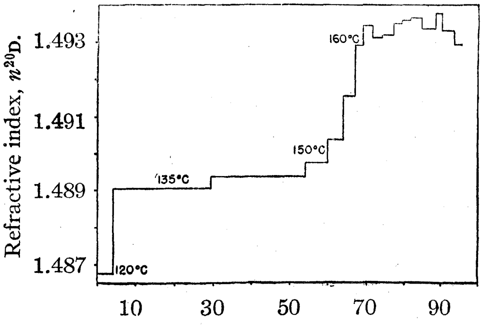


Fig. 2.—Hydrolysis of *o*–*m*-diisopropylbenzene sulfonic acids.

Isolation of *o*-Diisopropylbenzene.—The hydrolyzed ortho isomer fraction was washed with caustic solution and water and then distilled in a 100-plate column. A 150 cc. middle fraction, n^{20}D 1.4955, f. p. −60°, was collected. A time–temperature melting test[10] showed this fraction to be only about 90% pure.

A new technique for purification of compounds by silica gel adsorption was recently reported by Hirschler and Amon[11] wherein it is possible to adsorb preferentially small concentrations of impurities having adsorbabilities similar to that of the major component at higher concentrations. In accordance with this the 150-cc. distillate fraction was percolated several times through an 11-mm. i. d. column packed with fine silica gel as recommended by Mair.[12] The total length of column utilized was equivalent to about 30 feet. The first 17 cc. of percolate, n^{20}D 1.4960, f. p. −57°, was found to be 99.6% pure by the time–temperature melting test.

Isolation of *m*-Diisopropylbenzene.—After washing and drying, the meta isomer fraction was distilled in a 100-plate column at high reflux ratio. About 500 cc. of distillate was collected, n^{20}D 1.4888, f. p. −63°. A time–temperature melting test indicated that this material was also 99.6% pure.

Isolation of *p*-Diisopropylbenzene.—The fraction boiling at 210–211° was subjected to an 80-plate distillation. A volume of 3 liters of para isomer concentrate was collected which was estimated from a freezing test to be about 90% pure. A second distillation failed to increase the purity of this material. It formed large crystals from a non-viscous solution at approximately −20°, the symmetry of the para molecule accounting for the high freezing point.

Three liters of para isomer concentrate were therefore fractionally crystallized in four stages. Batches up to 500 cc. each were slowly crystallized with constant stirring in a partially evacuated Dewar type vessel immersed in a Dry Ice-bath. The slush was then transferred to a precooled basket centrifuge inside a large Dewar and the contents spun until the crystals were dry. By properly blending the crystalline and mother liquor fractions from the various stages more than half of the para isomer fraction was isolated as best crystals, f. p. −17°. The purity of the final product was found to be 99.8% by the melting point test.

Physical Properties.—Precise physical properties (Table I) were determined for each isomer by the following methods:

1. Purities were determined by the time–temperature freezing and melting point procedure described by Glasgow, Streiff and Rossini.[10] Since time–temperature freezing tests were found to be unsuitable due to the existence of non-equilibrium conditions between solid and liquid phases, purities were calculated from time–temperature melting curves.

A special melting point apparatus was constructed to accommodate the small quantity of pure ortho isomer fraction. A glass liner was placed in the conventional apparatus in order to reduce the required sample volume to 5 cc. A stirrer was then constructed from piano wire in spiral form, slightly larger in diameter than the platinum resistance thermometer. The accuracy of this apparatus was checked by comparing the melting point of a 50-cc. sample of meta isomer measured in the larger apparatus and a 5-cc. sample of the same material in the modified tube. The difference in melting point was 0.02° and no significant change was noted in the shape of the time–temperature curves.

2. Cryoscopic constants were determined by adding a known quantity of impurity to each pure isomer and measuring the corresponding melting point depression. *m*-Diisopropylbenzene was added to the ortho isomer, *m*-methylethylbenzene to the meta isomer, and *p*-methylethylbenzene to the para isomer.

3. To check the relative concentrations of the isomers in the original starting mixture the cryoscopic method of Streiff and Rossini[13] was employed. This was done by adding a measured amount of the crude diisopropylbenzene mixture to each isomer and finding the resultant melting point depression. These tests revealed that the 200 to 215° alkylate fraction contained 6% ortho, 36% meta and 42% para diisopropylbenzene.

4. Boiling points were determined in a Cottrell type ebulliometer and temperatures were measured to 0.002° with the same platinum resistance thermometer used in

---

[10] A. R. Glasgow, A. J. Streiff and F. D. Rossini, *J. Research Nat. B. Stds.*, **35**, 355 (1945).

[11] A. E. Hirschler and S. Amon, *Ind. Eng. Chem.*, **39**, 1585 (1947).

[12] B. J. Mair, *J. Res. Nat. Bur. Stds.*, **34**, 435 (1945).

[13] A. J. Streiff and F. D. Rossini, *J. Research Nat. Bur. Stds.*, **39**, 303 (1947).

TABLE II

WAVE LENGTHS, FREQUENCIES AND INTENSITIES OF INFRARED ABSORPTION MAXIMA OF THE DIISOPROPYLBENZENES

λ(μ)	ν(cm.$^{-1}$)	Intensities	λ(μ)	ν(cm.$^{-1}$)	Intensities
o-Diisopropylbenzene					
3.38	2959	10	8.58	1166	3
3.66	2732	2s	8.77	1140	2
5.18	1931	1s	9.04	1106	6
5.24	1908	1	9.32	1073	9
5.33	1876	0s	9.55	1047	5
5.47	1828	1	9.70	1031	9
5.56	1799	1	10.04	996	0
5.77	1733	0s	10.25	976	1
5.91	1692	1	10.39	962	1s
6.27	1595	3	10.61	943	4
6.72	1488	10	10.83	923	2
6.84	1462	10	11.17	895	3
7.23	1383	8	11.33	883	1s
7.32	1366	8	11.54	867	1
7.66	1305	3	12.38	808	0s
7.81	1280	4	13.23	756	10s
7.90	1266	5	13.26	754	10
8.17	1224	4	13.29	752	10s
8.44	1185	4	14.26	701	3
m-Diisopropylbenzene					
3.40	2941	10	8.42	1188	6
3.65	2740	2s	8.54	1171	3
3.86	2591	1	8.73	1145	1
5.20	1923	1	9.06	1104	5
5.39	1855	1	9.23	1083	6
5.63	1776	2	9.52	1050	8
5.93	1686	2	10.04	996	1
6.26	1597	9	10.35	966	1
6.53	1531	1	10.48	954	1
6.73	1486	10	10.82	924	7
6.88	1453	10	11.23	890	8
6.93	1443	10s	12.34	810	4s
7.25	1379	8	12.61	793	10
7.34	1362	8	14.23	703	10
7.61	1314	7	14.82	675	1s
7.88	1269	4	15.02	666	1
p-Diisopropylbenzene					
3.40	2941	10	8.11	1233	1s
5.28	1894	2	8.25	1212	2
5.62	1779	1	8.41	1189	1
5.74	1742	0s	8.72	1147	5
6.04	1656	3	9.08	1101	6
6.11	1637	0s	9.35	1070	8
6.42	1558	1s	9.52	1050	8
6.62	1511	9	9.84	1016	7
6.85	1460	10	10.41	961	2
7.05	1418	9	10.64	940	1
7.12	1404	8	10.84	923	3
7.25	1379	8	11.22	891	3
7.35	1361	8	11.50	870	1s
7.52	1330	6	12.05	830	10
7.70	1299	6	12.50	800	1s
7.83	1277	5	12.86	778	1
			13.11	763	1s

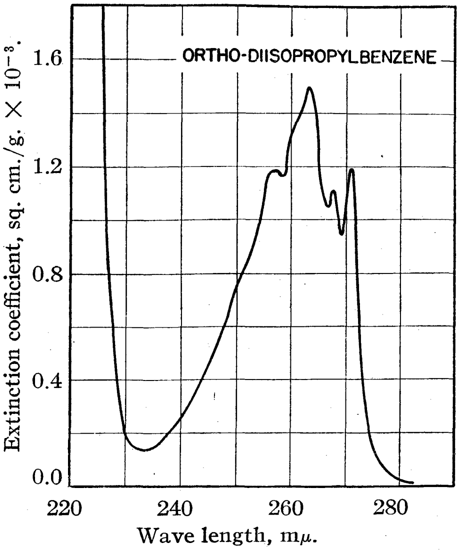


Fig. 3.—Ultraviolet spectrum of *o*-diisopropylbenzene.

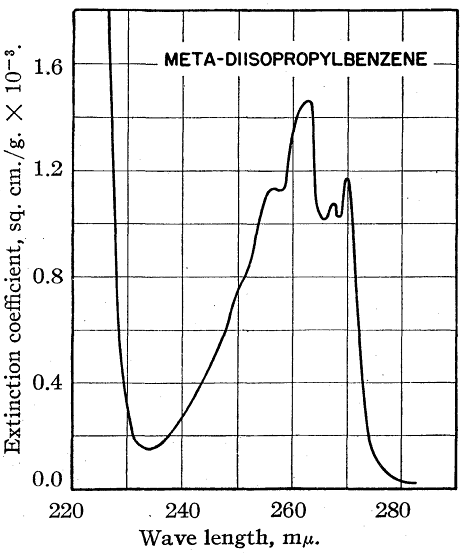


Fig. 4.—Ultraviolet spectrum of *m*-diisopropylbenzene.

the melting point tests. The pressure was regulated by a manostat system to ± 0.5 mm. Pressures were read on an open arm mercury manometer and corrected for barometric fluctuations. Boiling point measurements were made at the pressures 760, 300, 100 and 50 mm. and the data were fitted to the Antoine equation to permit calculation of boiling points at intermediate pressures.

5. Refractive indices were measured with a Bausch and Lomb precision refractometer at 20 and 25 ± 0.05°. A sodium lamp and filter provided the source of 5890 A. light. The accuracy of the refractive index values is believed to be ±0.0001.

6. Specific dispersions were determined with the Bausch and Lomb refractometer at 25° using the hydrogen 4860 and 6570 Å. lines.

7. Densities were measured at 20° in a 10-cc. pycnometer described by Lipkin, Davison, Harvey and Kurtz.[14] The temperature of the thermostat was automatically controlled by an electronic regulator at 20.00 ± 0.01°.

---

(14) M. R. Lipkin, J. A. Davison, W. T. Harvey and S. S. Kurtz, *Ind. Eng. Chem., Anal. Ed.*, **16**, 55 (1944).

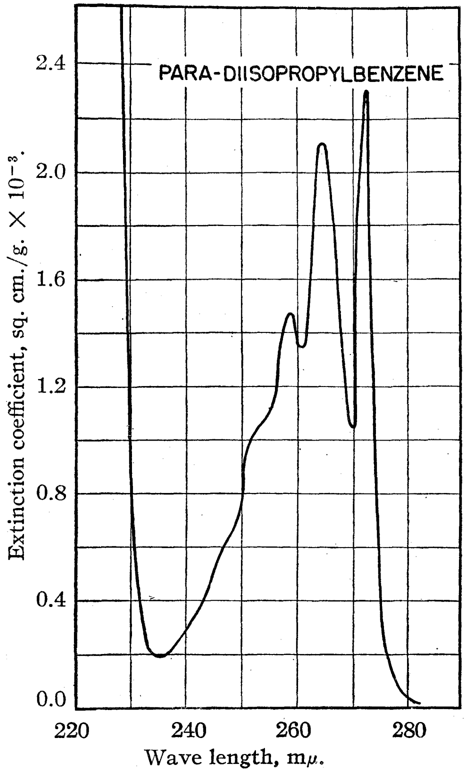


Fig. 5.—Ultraviolet spectrum of *p*-diisopropylbenzene.

The accuracy of these measurements by comparison with other pure compounds was better than ±0.0001 g./ml.

8. Molecular weights were determined for each isomer by observing the freezing point depression in benzene at several concentrations. Good agreement was found between the calculated molecular weights at different concentrations, indicating that the ideal solution laws apply.

9. Carbon–hydrogen ratios were found by the usual combustion method. Based on results of other known samples the accuracy is within ±0.5%.

10. A structure analysis of each isomer was made by oxidation of the side chains to the corresponding phthalic acids, and preparation of derivatives. Of particular interest was the resistance of the ortho isomer to oxidation. Both chromic acid and permanganate solution at 100° gave little conversion, but vapor phase oxidation over vanadium oxide catalyst at 350° gave a good yield of orthophthalic acid. The meta and para isomers were readily oxidized with chromic acid at 100°. The following derivatives were prepared; phthalanil from orthophthalic acid, dimethyl isophthalate from isophthalic acid, and dimethyl terephthalate from terephthalic acid. Melting points of these derivatives checked those appearing in the literature thereby verifying the structure of the isomers.

Absorption and Mass Spectra.—Ultraviolet absorption spectra of the isomers were obtained with a Beckman spectrophotometer. The curves showing the extinction coefficients, sq. cm./g., at various wave lengths are shown in Figs. 3, 4 and 5. The extinction coefficient k is defined as $k = E/cd$ where E = optical density, c = concentration g./cc. and d = cell length. It will be observed that distinctive and characteristic peaks appear at 264 and 272 mμ for the para isomer, but that the ortho and meta spectra are not readily distinguishable.

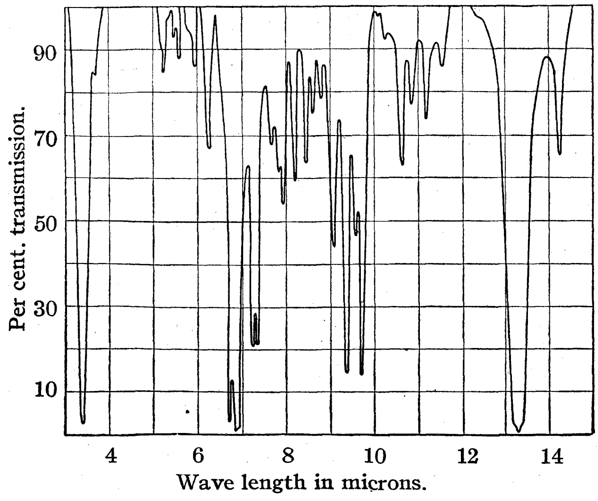


Fig. 6.—Infrared spectrum of *o*-diisopropylbenzene measured at 25°, 0.051 mm. cell length.

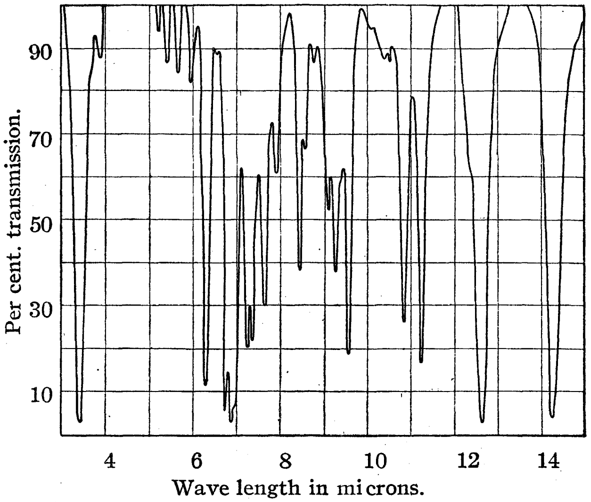


Fig. 7.—Infrared spectrum of *m*-diisopropylbenzene measured at 25°, 0.051 mm. cell length.

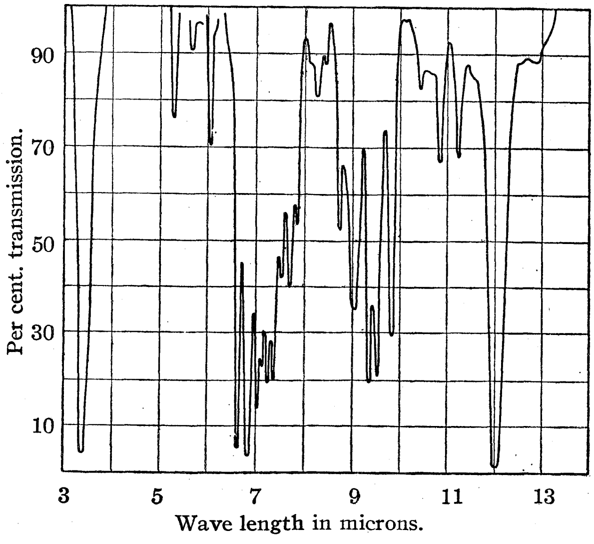


Fig. 8.—Infrared spectrum of *p*-diisopropylbenzene measured at 25°, 0.051 mm. cell length.

Infrared spectrograms of the isomers were determined on a Perkin-Elmer Infrared Spectrometer, Model 12A. These spectra (Figs. 6, 7, 8, and Table II) are seen to confirm the proof of structure by chemical means, the strong absorption bands characteristic of ortho occurring at 13.3 microns, of meta at 12.6 and 14.2 microns, and para at 12.0 microns. The isopropyl group is evident from the doublet in the region of 7.3 microns.

The mass spectra of the isomers, obtained on a Consolidated Engineering instrument, are shown in Table III. As would be expected no significant differences are seen in the mass spectra of the individual isomers.

TABLE III

MASS SPECTRA OF THE ISOMERIC DIISOPROPYLBENZENES

Mass	*o*-Diisopropylbenzene	*m*-Diisopropylbenzene	*p*-Diisopropyl benzene	*n*-Butane
27	31.4	44.9	38.0	
28	5.34	3.29	5.57	275
29	14.5	9.15	7.60	346
39	23.5	22.3	21.5	124
40	2.48	3.81	2.32	
41	51.8	48.8	41.8	239
42	2.82	2.45	2.58	102
43	23.1	85.6	59.5	826
44	0.80	3.01	1.97	
51	13.7	12.8	12.2	
52	3.88	3.79	3.49	
53	8.25	7.48	7.58	
58	4.08	0.75	1.61	100.0
63	7.03	7.36	6.01	
64	7.67	5.65	5.12	
65	15.3	12.3	10.9	
66	6.87	11.3	5.87	
77	23.0	24.3	22.7	
78	8.13	8.92	8.32	
79	20.2	15.1	13.0	
91	82.1	64.6	59.7	
92	6.67	5.34	4.92	
95–98[a]	4.75	0.64	0.56	
103	10.8	13.8	12.8	
104	4.48	5.79	6.06	
105	32.2	64.7	51.0	
106	2.72	5.01	4.18	
115	25.1	14.9	14.8	
116	11.1	7.79	9.03	
117	18.4	8.85	25.6	
118	4.28	3.72	5.31	
119	115	111	96.6	
120	8.96	10.4	8.20	
131	14.6	10.4	18.3	
132	2.1	2.4	13.5	
147	281	283	342	
162	100.0	100.0	100.0	
Sensitivity	23.0	22.0	23.3	4.73

[a] Metastable peak.

Acknowledgment.—Acknowledgment is hereby made to Barton Zieber for the infrared spectra and to C. W. Warfield for much of the laboratory manipulation.

Summary

The isolation of the three isomeric diisopropylbenzenes from a high boiling propylene-benzene alkylate is described. The most important physical properties and the relative concentrations of the isomers in the alkylate are listed. Infrared, ultraviolet, and mass spectra also are given, the former confirming the chemical evidence of the structure of the compounds isolated.

PHILADELPHIA, PA. RECEIVED JUNE 7, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Thermodynamics of Metallo-protein Combinations. Copper with Bovine Serum Albumin

BY IRVING M. KLOTZ AND HENRY G. CURME

The importance of metal ion–protein complexes in biological systems has long been recognized, and numerous studies have been made of the extent of combination of such cations with proteins.[1,2,3] Unfortunately most of these investigations have utilized protein preparations of questionable homogeneity and have correlated their quantitative data in terms of equations which are essentially empirical in nature. With the recent availability of crystallized plasma proteins[4] it has seemed opportune to make a careful quantitative study of metal complexes with pure proteins and to treat the data obtained in terms of relations similar to those used in describing the multiple equilibria between proteins and organic anions.[5]

Experimental

Apparatus.—The extent of binding of cupric ions by bovine serum albumin was measured by the equilibrium dialysis technique described previously.[5] However, the apparatus was modified slightly so that a bead could be suspended by a glass thread within the bag containing the protein solution. With the bead to facilitate stirring within the bag and with a mechanical shaker to agitate the outside solution, the time for the attainment of equilibrium was reduced materially.

Time Required to Attain Equilibrium.—With the modified apparatus the dialysis tubes reached equilibrium in

---

(1) J. H. Northrup and M. Kunitz, *J. Gen. Physiol.*, **7**, 25 (1924); **9**, 351 (1925); **11**, 481 (1928).

(2) D. M. Greenberg, in M. L. Anson and J. T. Edsall, "Advances in Protein Chemistry," Volume I, Academic Press, New York, N. Y., 1944, pp. 121–151.

(3) C. L. A. Schmidt, "The Chemistry of the Amino Acids and Proteins," Charles C. Thomas, Springfield, Ill., 1945, pp. 293–296, 746–762, 1091–1092, 1213–1214.

(4) E. J. Cohn, J. L. Oncley, L. E. Strong, W. L. Hughes, Jr., and S. H. Armstrong, Jr., *J. Clin. Invest.*, **23**, 417 (1944).

(5) I. M. Klotz, F. M. Walker and R. B. Pivan, THIS JOURNAL, **68**, 1486 (1946); **69**, 1609 (1947).

less than six hours. This was true whether protein solution or buffer was inside the bag, as is illustrated by the data in Table I. For the work carried out at 25° this shaking method was used, therefore. For the studies at 0° the dialysis tubes were maintained in an ice-water-bath, with occasional shaking by hand, for a period of seventy-two hours. In both cases, temperatures were maintained within ±0.05°.

TABLE I

TIME REQUIRED TO ATTAIN EQUILIBRIUM

Time in hours	Free Cu^{++} in blank bag	Free Cu^{++} in protein bag
0	0.0048	0.0048
6	.00282	.00195
10	.00282	.00195
22	.00283	.00195

Analytical Methods.—Analyses for cupric-ion concentrations were made by one of two methods, depending on the concentration range under investigation. In solutions of 0.001 to 0.01 molar the triethanolamine method of Yoe and Barton[6] was used. Two ml. of a 25% solution of triethanolamine in water was added to 10 ml. of the cupric ion solutions in acetate buffer and the absorption of light at 6460 Å. was measured with a Beckman spectrophotometer. In the dilute region of cupric ion concentrations, *i. e.* below 0.001 molar, the absorption of ultraviolet light by the cupric ions themselves was used to determine the concentration of cations.

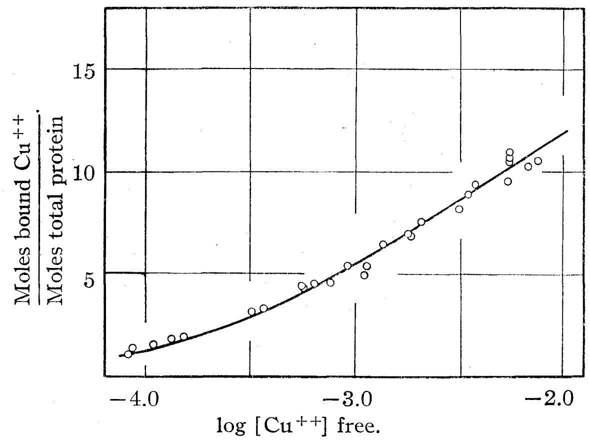


Fig. 1.—Binding of cupric ions by bovine serum albumin at 0°; *p*H of 4.83 at 25°.

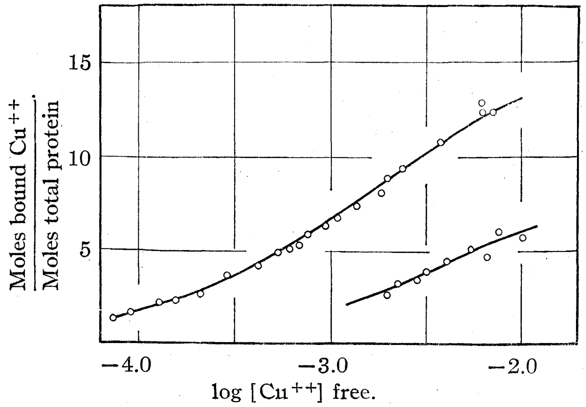


Fig. 2.—Binding of cupric ions by bovine serum albumin at 25°: upper curve at *p*H 4.83; lower curve at *p*H 4.00.

Materials.—Bovine serum albumin was Armour crystallized product. Corrections for water content were made by heating a small sample in an oven at 110° until constant weight was attained. Solutions of approximately 2% protein content were used. The copper salts employed were of analytical reagent grade and were used without further purification. Triethanolamine was an Eastman product.

The buffer solution used for the experiments near *p*H 5 was composed of 0.0357 molar acetic acid and 0.0643 molar sodium acetate. The same concentration of sodium acetate was used in the buffer of *p*H 4 but the acetic acid was increased to 0.2455 molar. The same concentration of acetate was used at both *p*H's in order to keep the ionic strengths equal in both solutions.

Results and Calculations

The extent of binding of cupric ions by bovine serum albumin has been calculated from the difference in the concentrations of free copper in a control tube containing buffer inside the bag and one containing protein. The details of such a calculation have been outlined previously.[5] The degree of binding has been represented in graphs of the average number of bound ions per molecule of protein versus the logarithm of the concentration of the free cupric ion, as is illustrated in Figs. 1 and 2. It is immediately evident, as has been observed previously for organic anions,[5] that the bovine albumin molecule is capable of binding many cupric ions even at relatively low concentrations of free copper.

Reversible Nature of the Binding.—Before considering the application of the laws of equilibirum to these observations it has seemed desirable to establish the reversible nature of the process under examination. To settle this point the experiment outlined in Table II was carried out. The dialysis bag was removed from a solution in which equilibrium had been attained between protein and free Cu^{++} at a final concentration of 9.18×10^{-4} *M*. This bag, containing an average of 6.30 bound ions per molecule of protein, was then placed in a solution of pure buffer and the bound copper allowed to dialyze out until a second equilibrium was established. From the volumes of the solutions used, and the concentration of free Cu^{++} at the end of the second equilibrium, it was possible to determine the average number of bound ions under the new conditions. This observed value, 4.39, is in excellent agreement with that of 4.60 which may be read from Fig. 2. The binding of Cu^{++} by bovine albumin thus seems to be a reversible process.

TABLE II

REVERSIBILITY OF BINDING

	First equilibrium	Second equilibrium
Free Cu^{++}, *M*	9.18×10^{-4}	4.98×10^{-4}
Number of bound ions per molecule of protein	6.30	4.39 (observed) 4.60 (from graph)

Method of Representation of the Data.—Under these circumstances it is permissible to

---

[6] J. H. Yoe and C. J. Barton, *Ind. Eng. Chem., Anal. Ed.*, **12**, 456 (1940).

represent the series of equilibria involved by equations of the form

$$\mathrm{PCu}_{i-1} + \mathrm{Cu}^{++} = \mathrm{PCu}_i \qquad (1)$$

where PCu_{i-1} and PCu_i represent protein–copper complexes with $i-1$ and i cupric ions, respectively. The number i may vary from 1 to n, the maximum number of bound cations. The moles of bound cation per mole of total protein, represented by r, would be obtained from the expression

$$r = \frac{\sum\limits_{i=1}^{n} i \left(\prod\limits_{j=1}^{i} k_j \right) (\mathrm{Cu}^{++})^i}{1 + \sum\limits_{i=1}^{n} \left(\prod\limits_{j=1}^{i} k_j \right) (\mathrm{Cu}^{++})^i} \qquad (2)$$

where the k's represent the equilibrium constants corresponding to each of the reactions of (1). Thus the calculation of the moles of bound ion per mole of total protein depends on a knowledge of these n equilibrium constants.

For the ideal situation, based on a model of a spherical protein molecule and assuming the absence of electrostatic interactions between successively bound ions, the equilibrium constants bear a simple relation to each other, given by the equation

$$k_i = \frac{n - (i - 1)}{i}\, k \qquad (3)$$

in which k is an intrinsic constant which depends on the nature of the protein and of the ion which is bound. When equation (3) is applicable, equation (2) may be simplified appreciably and the binding data may be correlated by the linear expression

$$\frac{1}{r} = \frac{1}{kn} \frac{1}{(\mathrm{Cu}^{++})} + \frac{1}{n} \qquad (4)$$

It has been shown previously[7] that the binding of calcium ions by casein may be represented adequately by an equation of the form of (4). For complexes between copper and bovine albumin, however, this linear expression has been found not to fit the observed data.

In similar circumstances in studies of the binding of organic anions by proteins,[5] deviations from the simple statistical relation have been attributed to electrostatic interactions between successively bound ions and have been accounted for quantitatively by assuming that they may be estimated from the equations of the simple Debye–Hückel theory. Thus successive equilibrium constants have been related to each other by the equation[5]

$$RT \ln (k_{i-1}/k_i) = RT \ln \left[\frac{n - (i - 2)}{n - (i - 1)} \frac{i}{i - 1} \right] + \frac{Nz^2e^2}{D} \left(\frac{1}{b} - \frac{\kappa}{1 + \kappa a} \right) \qquad (5)$$

with the second term representing the electrostatic factor. An attempt has been made to use this equation to correlate the data on copper complexes also. For this purpose, a value of 3 Å. was used for the radius of the aqueous cupric ion[8] and 30 Å. for the serum albumin molecule. With these parameters, values of $\Delta F_{\mathrm{elect.}}$, the second term in equation(5), were found to be 169 and 186 calories per mole at 0° and 25°, respectively, for free copper concentrations below about 0.001 molar.

Using such values for the electrostatic-interaction term, wide deviations were obtained between calculated and observed values of r. Excellent agreement between calculated and observed binding curves (Figs. 1 and 2) was obtained, however, when $\Delta F_{\mathrm{elect.}}$, was reduced arbitrarily to 60 calories/mole at both temperatures. The possible significance of this discrepancy between the theoretical and empirical values of $\Delta F_{\mathrm{elect.}}$ will be discussed shortly.

Using 60 calories/mole for $\Delta F_{\mathrm{elect.}}$ and 16 for n, one can calculate the free energy of formation of each protein-cation complex from its predecessor. These free energies, together with the entropies and enthalpies which may be derived therefrom by standard thermodynamic procedures, have been summarized in Table III. Strictly speaking these thermodynamic values refer only to solutions with copper concentrations not exceeding 0.001 molar. Above this concentration the cupric salts contribute appreciably to the ionic strength of the solution and hence change $\Delta F_{\mathrm{elect.}}$ slightly. For most purposes, however, the slight discrepancies may be neglected.

TABLE III

THERMODYNAMICS OF BINDING OF Cu^{++} BY BOVINE SERUM ALBUMIN

pH 4.83 at 25°; $\mathrm{PCu}_{i-1} + \mathrm{Cu}^{++} = \mathrm{PCu}_i$

	ΔF^0 at 0°, cal./mole	ΔF^0 at 25°, cal./mole	ΔS^0 cal./mole/ deg.	ΔH^0 cal./mole
1	−5179	−5908	29.2	2780
2	−4708	−5399	27.6	2840
3	−4391	−5058	26.7	2900
4	−4135	−4784	26.0	2960
5	−3910	−4544	25.4	3020
6	−3704	−4325	24.8	3080
7	−3509	−4117	24.3	3140
8	−3319	−3915	23.8	3200
9	−3131	−3715	23.4	3260
10	−2941	−3513	22.9	3320
11	−2746	−3305	22.4	3380
12	−2540	−3086	21.8	3440
13	−2315	−2846	21.2	3500
14	−2059	−2572	20.5	3560
15	−1742	−2231	19.6	3620
16	−1271	−1722	18.0	3680

These free energy quantities may be correlated also in the form of the equations

$$\text{At } 0°\text{:}\ \Delta F^0{}_i = -5179 + \sum_{j=2}^{j=i} RT \ln \frac{n - (j - 2)}{n - (j - 1)} \frac{j}{j - 1} + (i - 1)\phi_{\mathrm{elect.}} \qquad (6)$$

---

(7) I. M. Klotz, *Arch. Biochem.*, **9**, 109 (1946).

(8) J. Kielland, THIS JOURNAL, **59**, 1675 (1937).

$$\text{At } 25°: \Delta F^0_i = -5908 + \sum_{j=2}^{j=i} RT \ln \frac{n-(j-2)}{n-(j-1)} \frac{j}{j-1} + (i-1)\phi_{\text{elect.}} \quad (7)$$

where $\phi_{\text{elect.}}$ is taken as 60 calories/mole at each temperature. From these equations it is possible to deduce the following expressions for the entropy and enthalpy changes

$$\Delta S^0_i = 29.2 - \sum_{j=2}^{j=i} R \ln \frac{n-(j-2)}{n-(j-1)} \frac{j}{j-1} \quad (8)$$

$$\Delta H^0_i = 2780 + (i-1)\phi_{\text{elect.}} \quad (9)$$

It should be pointed out that in the general case the equations for ΔS^0_i and ΔH^0_i would also contain a term involving the factor $\partial\phi_{\text{elect.}}/\partial T$. However, in the present situation the data can be represented adequately with the same value of $\phi_{\text{elect.}}$ at both temperatures so the temperature coefficient of the electrostatic term vanishes.

Effect of *p*H on Binding.—Since the *p*H dependence of the binding ability reflects on the nature of the groups involved in the bond, a few experiments were carried out at a *p*H of 4.0. These data are compared in Fig. 2 with the corresponding results at *p*H 4.8 at the same temperature. It is immediately evident that the maximum number of binding groups has been decreased substantially in solutions of higher acidity.

Discussion

Thermodynamics of the Complex-formation.—Both the table and equations showing the dependence of ΔF^0 on i illustrate the general trend downward in stabilization energy as the number of bound ions increases. The equations (6) and (7), in addition, show explicitly the basic sources of this trend—the contributions of the statistical and electrostatic terms, respectively, to the free-energy change. In the same connection it is of interest to note that the expression for the entropy, equation (8), contains the statistical term and lacks the electrostatic one, whereas the expression for the enthalpy, equation (9), includes an electrostatic contribution but no statistical one. Thus if no electrostatic interactions were involved, the enthalpy change, ΔH^0_i, would be the same for each successive complex.

It is also of interest to note that it is $T\Delta S$ term which supplies the necessary energy to make ΔF negative in the binding process. Thus from Table III it is evident that with positive values for the heat of binding, complex-formation between albumin and cupric ions would not be favored, were it not for the relatively large values of ΔS. The magnitude of the entropy changes probably indicates that the transfer of a Cu^{++} ion from the solvent to the protein molecule is accompanied by the release of several "frozen" water molecules and acetate ions.

Magnitude of the Electrostatic Effect.—It has been mentioned above that a value of 60 calories has been used for $\phi_{\text{elect.}}$ rather than 186 calories as would be expected from available molecular parameters and the electrostatic portion of equation (5). The basis of this large discrepancy is not clear. One source might be the use of a spherical model for the protein molecule instead of an ellipsoidal one. To estimate the magnitude of this difference, a calculation has been made of the electrostatic charging energy (at infinite dilution) of an ellipsoid of revolution with a major axis[4] of 150 Å. and a minor axis of 38 Å., and the value obtained has been compared with that of a sphere with a diameter of 60 Å. Though both these models encompass the same volume, the charging energy of the ellipsoid is 84% that of the sphere. The use of an ellipsoidal model, therefore, would change $\phi_{\text{elect.}}$ in the correct direction. Nevertheless, the extent of the decrease is not nearly sufficient to account for the observed drop from 186 to 60, or down to almost 30% of the spherical value.

It should be mentioned, of course, that the use of the Debye–Hückel expression to obtain the electrostatic portion in equation (5) is not really justified from a molecular point of view, for the protein molecule has discrete charges distributed along its surface as well as in its interior. In the absence of detailed information on the distribution of these charges it would be difficult to derive any convenient expression for further approximation of the electrostatic effect. Nevertheless, in connection with calculations at higher copper concentrations, where the cupric ions make an appreciable contribution to the ionic strength, it has been found convenient to use the Debye–Hückel expression and to take account of its inadequacy by increasing the magnitude of the dielectric constant to 350. This is a procedure similar to that used by Kirkwood and Westheimer,[9] though we do not have a corresponding theoretical justification. Using this higher "effective" dielectric constant at higher copper concentrations (above 10^{-3} *M*) one finds good agreement between the observed and calculated values of the extent of binding. Nevertheless, this agreement cannot be used to validate the approach because the binding equations are not sufficiently sensitive to small changes in the electrostatic contribution.

Nature of the Cation–Protein Bond.—The decrease in extent of binding at *p*H 4.0 as compared to that observed at *p*H 4.8 (Fig. 2) indicates that anionic carboxylate groups on the protein molecule are involved in bond formation with the cation. Such behavior would be in line with the many observations of complex-formation between cupric ions and carboxylic acids, including amino acids,[10] where similar *p*H dependence has been found. That the cation–protein linkage is through the carboxyl group is indicated also by the absorption spectrum of cu-

---

[9] J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506 (1938).

[10] H. Borsook and K. V. Thimann, *J. Biol. Chem.*, **98**, 671 (1932).

pric ions in albumin solutions (Fig. 3).[11] As has been pointed out by Borsook and Thimann,[10] in their work on amino acid complexes of copper, the absorption peak remains in the near infrared in complexes bound through the carboxylate substituent and moves toward shorter wave lengths when Cu–N bonds are formed. The absorption peak of cupric ions in the presence of protein is substantially in the same region as in copper chloride or copper sulfate solutions.

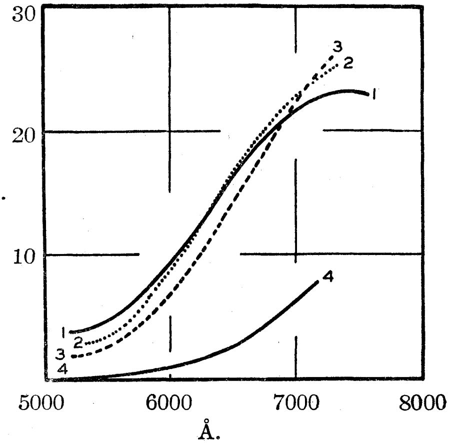


Fig. 3.—Absorption spectra of some copper complexes: 1, cupric ions with 2% bovine serum albumin at pH 4.23; 2, copper acetate in alcohol[10]; 3, cupric ions with glycine[10]; 4, cupric chloride pH 4.66.

Despite these indications of the importance of the carboxyl group in binding the cation, there is no agreement between the maximum number of bound copper ions (16) and the number of aspartyl (56) and glutamyl (80) residues in bovine serum albumin.[12] A similar lack of correspondence with the content of basic amino acids has been found in investigations of the binding of anions by bovine albumin.[5] It seems apparent once again that the primary focus of binding on the protein, the carboxyl group in Cu^{++} binding, must be in suitable juxtaposition with other substituents or residues before a stable complex can be formed.

Acknowledgment.—These investigations were carried out with the aid of a grant from the Office of Naval Research. The authors are indebted also to Professor George Scatchard of the Massachusetts Institute of Technology for several suggestions on improving the treatment of the data.

Summary

1. Measurements have been made of the binding of cupric ions by bovine serum albumin at a pH of 4.8 and at temperatures of 0° and 25°, respectively.

2. The results obtained have been correlated in terms of equations derived from statistical and electrostatic considerations. Free energies, entropies and enthalpies have been calculated for the multiple equilibria involved.

3. The decrease in binding with decrease in pH, as well as the character of the absorption spectrum of the copper–albumin complex, indicates the importance of carboxyl groups on the protein in the bond with the cation.

EVANSTON, ILLINOIS RECEIVED OCTOBER 24, 1947

---

[11] We are indebted to Miss Jean Urquhart for recording the spectrum of the copper–protein complex.

[12] E. Brand, *Annals N. Y. Acad. Science*, **47**, 187 (1946). Only 37 glutamic acid residues are listed as free.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Binding of Some Sulfonamides by Bovine Serum Albumin

BY IRVING M. KLOTZ AND F. MARIAN WALKER

Numerous studies have been made of the binding of sulfonamides by plasma.[1-3] From a pharmacological point of view it has been emphasized, particularly by Davis,[1] that the distribution of sulfonamides in various body fluids is strongly dependent on the extent of their binding by proteins. Similarly in connection with their chemotherapeutic properties, it has been pointed out that the antibacterial activity of these compounds parallels their adsorbability by plasma,[1] as well as by microörganisms.[4]

Davis[1] has demonstrated that it is the albumin fraction of plasma which is primarily responsible for the binding properties. Nevertheless, no investigations have been made of the formation of complexes between sulfonamides and crystallized serum albumin. Such a study with purified serum protein would be highly desirable, particularly since it would then be possible to apply a physicochemical analysis,[5] to the binding data and thereby to correlate the energy of binding with structural features in the drugs.

Experimental

Reagents.—Crystallized bovine serum albumin was obtained from Armour and Company. As in previous work,[5] corrections for water content were made by heating a

---

[1] B. D. Davis, *J. Clin. Invest.*, **22**, 753 (1943).

[2] D. R. Gilligan, *J. Pharmacol.*, **79**, 320 (1943).

[3] S. H. Fisher, L. Troast, A. Waterhouse and J. A. Shannon, *J. Pharmacol.*, **79**, 373 (1943).

[4] E. Havinga, H. W. Julius, H. Veldstra and K. C. Winkler, "Modern Development of Chemotherapy," Elsevier Publishing Co., Inc., New York, N. Y., 1946, pp. 45–49.

[5] I. M. Klotz, F. M. Walker and R. B. Pivan, THIS JOURNAL, **68**, 1486 (1946).

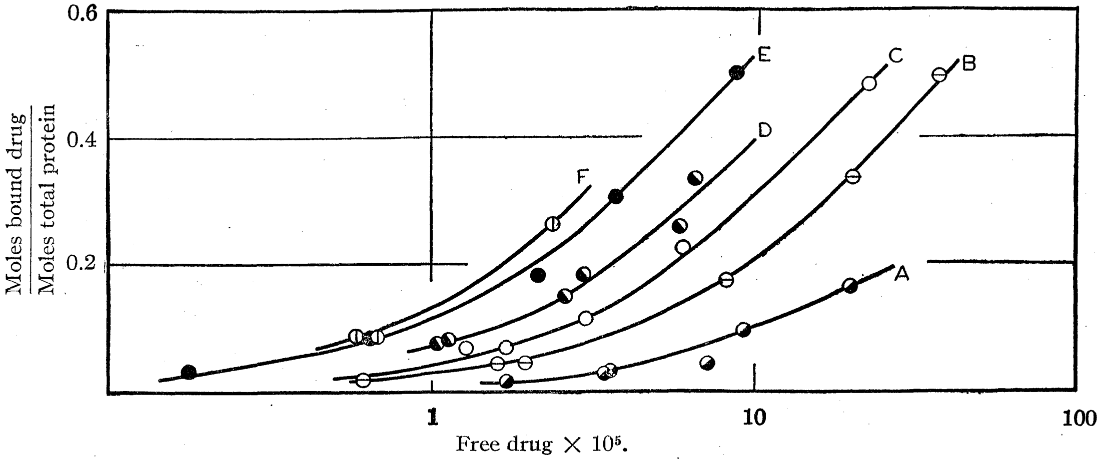


Fig. 1.—Binding of sulfonamides by bovine serum albumin in a phosphate buffer at *p*H 7.6 and 5°: A, sulfanilamide; B, sulfapyridine; C, N^1-acetylsulfanilamide; D, 5-sulfanilamido-3-methyl-isoxazole; E, 2-sulfanilamido-5-chloropyridine; F, N^1-benzoylsulfanilamide.

small sample in an oven at 110° until constant weight was attained.

Samples of the sulfonamides were kindly supplied by Drs. R. O. Roblin, Jr., and P. H. Bell of the American Cyanamid Company.

Dialysis Experiments.—The general procedure was the same as that described in earlier work.[5] Cellophane bags, prepared from commercial sausage casing, were filled with a measured amount of the protein solution of approximately 4% concentration. The bags were immersed in a solution of the sulfonamide and allowed seventy-two hours in a cold room (*ca.* 5°) for the attainment of equilibrium. For each sulfonamide concentration a control tube was also prepared which differed from the primary tube only in that the former contained buffer rather than a protein solution inside the bag.

Upon the attainment of equilibrium the sulfonamide concentrations *outside* the bags in the primary and control tubes, respectively, were analyzed. Though the compounds under investigation have no color, the absorption of ultraviolet light[6,7] may be used as an analytical method. These absorption measurements were made with a Beckman spectrophotometer using silica cells of 1 cm. thickness. The wave length of the maximum absorption of the compound was used in the analysis of the particular sulfonamide under investigation.

The calculation of the amount of bound sulfonamide per mole of total protein is essentially the same as in the example described in previous work.[5] In this investigation, however, the concentration of protein was much higher than in previous studies and hence the Donnan effect must be considered. An examination of the literature[8] reveals that the Donnan effect for serum, containing about 7% protein, would produce a ratio of monovalent anion concentrations outside and inside the bag, respectively, of about 1.02. Since the ratio is approximately proportional to the concentration of protein[8] the Donnan effect in the experiments described in this paper should produce a sulfonamide anion concentration outside the bag about 1% greater than inside.

This 1% Donnan correction on the anion concentrations would be completely negligible in the experiments with sulfanilamide and sulfapyridine, for only a small fraction of either of these compounds would be in the ionized form at the *p*H's used (7.6). For the other sulfonamides, the correction has been made though it is actually within experimental error.

In these experiments it was difficult to reproduce binding values to better than about 5%, perhaps because of very minute leakages from the bag containing the protein. While such leakages would not significantly affect the quantity of protein within the bag, it might introduce appreciable errors in the ultraviolet-absorption readings because bovine serum albumin has a strong peak in the neighborhood of those for the sulfonamides. Thus with a specific extinction coefficient, $E^{1\%}_{1\,\text{cm.}}$, of about 5 near 2800 Å.[9] the loss of as little as 0.004% protein from the liquid inside the bag (10 cc.) to that outside (20 cc.) would produce an increase in optical density of about 0.01 and hence an error of 1 to 5% in the readings (generally in the range of 0.2 to 0.8).

Results and Discussion

The binding data for six sulfonamides are summarized in Fig. 1. The method of presentation, average number of moles of bound drug per mole of total protein, *r*, *versus* the logarithm of the concentration of the free drug, log (A), is that most convenient for comparative studies of binding ability and for theoretical analysis in terms of the principles of mass action.

The equilibrium constants for the formation of the respective sulfonamide complexes may be calculated by methods previously described.[5] As is evident from Fig. 1, the average number of bound drug molecules per protein molecule does not exceed 1 over the region investigated. For purposes of comparison, then, it is sufficient to calculate k_1, the equilibrium constant for the formation of the first complex in each case. The statistical relation described previously (Equation (4) in reference (5))

$$k_i = \frac{n - (i - 1)}{i} k \qquad (1)$$

may be reduced to

$$k_1 = nk \qquad (2)$$

for the first equilibrium constant. Since the concentration of higher complexes must be small,

---

(6) J. M. Vandenbelt and L. Doub, This Journal, **66**, 1633 (1944).

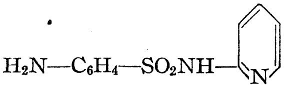
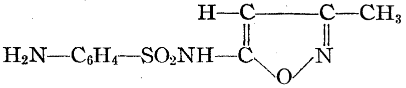
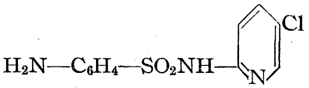
(7) I. M. Klotz and D. M. Gruen, *ibid.*, **67**, 843 (1945).

(8) F. C. McLean and A. B. Hastings, *J. Biol. Chem.*, **108**, 285 (1935).

(9) A. B. Lerner and C. P. Barnum, *Arch. Biochem.*, **11**, 505 (1946).

TABLE I

COMPLEX FORMATION AND RELATED PROPERTIES FOR SOME SULFONAMIDES

Compound	Formula	pK_a[10]	Per cent. in anionic state	Association[a] constant, k_1	ΔF_1^0 cal./mole
Sulfanilamide	$H_2N—C_6H_4—SO_2NH_2$	10.43	0.2	0.89×10^3	3740
Sulfapyridine		8.43	14	2.5×10^3	4320
N¹-Acetylsulfanilamide	$H_2N—C_6H_4—SO_2NHCOCH_3$	5.38	99	4.2×10^3	4600
5-Sulfanilamido-3-methyl isoxazole		4.2	100	7.8×10^3	4950
2-Sulfanilamido-5-chloropyridine		(7.15)[b]	80	13×10^3	5230
N¹-Benzoylsulfanilamide	$H_2N—C_6H_4—SO_2NHCOC_6H_5$	4.57	100	16×10^3	5350

[a] The buffer solution was at a pH of 7.6, and at a temperature of 5°. [b] The value for 2-sulfanilamido-5-bromopyridine has been used since data for the chloro compound are lacking.

electrostatic factors may be neglected, and the expression

$$\frac{1}{r} = \frac{1}{nk}\frac{1}{(A)} + \frac{1}{n} \qquad (3)$$

may be used as a reasonable approximation to the binding data. Thus from the slope of a graph of moles total protein per mole bound drug, $1/r$, *versus* the reciprocal of the concentration of free drug, $1/A$, one may evaluate the product nk for use in equation (2) in determining k_1. These slopes have been evaluated for the six drugs investigated and the equilibrium constants and free energy changes calculated for the association reaction

$$P + S = PS \qquad (4)$$

where P represents the protein molecule and S the sulfonamide. The results, together with acidity constants, pK_a's, taken from Bell and Roblin[10] have been assembled in Table I.

It is evident from these calculations that the binding energy increases with decreasing pK_a in the first three compounds in the table. This behavior is undoubtedly an expression of the increased concentration of anions as the pK_a decreases. That anions combine more strongly with proteins than do the corresponding non-ionized acids has been evident from other work.[11] That the sulfonamide ion is also the active species in bacteriostasis has been suggested previously.[12,13]

The difference in binding energy between sulfapyridine and 2-sulfanilamido-5-chloropyridine also seems attributable to the difference in anion concentration. If one takes into account the 5.7-fold higher anion concentration of the latter compound, it is evident that its binding energy should be approximately 960 calories (RT ln 5.7) higher than that of sulfapyridine. The observed difference in binding energy is 910 calories.

On the other hand in comparing the binding energies of N¹-acetylsulfanilamide and N¹-benzoylsulfanilamide, for which the anion concentrations in solutions of pH 7.6 are substantially identical, it is evident that another factor must enter. It seems likely that the additional stabilization energy of 750 calories for the albumin complex with benzoylsulfanilamide may be attributed to the stronger van der Waals forces which would be obtained with a phenyl group as compared to a methyl group. A similar effect has been noted by Gilbert[14] in studies of adsorption by wool where the phenyl group contributes about 1340 calories to the free energy change for the process, and the methyl group approximately 640 calories, a difference of 700 calories.

The relatively low binding energy for the isoxazole, as compared with the chloropyridine, for example, may be due to two factors. The van der Waals energy of the former is probably smaller because the number of atoms (excluding hydrogens) in it is fewer. Furthermore, the lower pK_a of the isoxazole would tend to reduce its ability to combine with the protein, if one adopts the Lewis generalized acidity concept discussed previously.[15] The loss in binding energy with decreasing pK_a in the sulfonamides seems to be small, however. If one corrects the binding energy of the chloropyridine to 100% anion concentration by adding RT ln (100/80) (130 calories), the difference between its ΔF_1^0 and that for the isoxazole is still only 400 calories for a change of 3 units in pK_a.

These investigations were supported by grants from the Lederle Laboratories Division of the American Cyanamid Company and from the Office of Naval Research.

---

(10) P. H. Bell and R. O. Roblin, Jr., THIS JOURNAL, **64**, 2905 (1942).

(11) I. M. Klotz, *ibid.*, **68**, 2299 (1946).

(12) C. L. Fox, Jr., and H. M. Rose, *Proc. Soc. Exp. Biol. Med.*, **50**, 142 (1942).

(13) F. C. Schmelkes, O. Wyss, N. C. Ludwig and F. B. Strandskov, *ibid.*, **50**, 145 (1942).

(14) Quoted by E. K. Rideal, *Trans. Faraday Soc.*, **39**, 368 (1943).

(15) I. M. Klotz, *Science*, **98**, 62 (1943).

Summary

Quantitative measurements have been made of the binding of sulfanilamide, sulfapyridine, N^1-acetylsulfanilamide, 5-sulfanilamido-3-methylisoxazole, 5-sulfanilamido-5-chloropyridine and N^1-benzoylsulfanilamide, respectively, by crystallized bovine serum albumin. Binding energies have been calculated and have been correlated with the structures of the compounds.

EVANSTON, ILLINOIS RECEIVED NOVEMBER 1, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

The Synthesis of Some Cyclopropane and Spirane Hydrocarbons[1]

BY R. W. SHORTRIDGE, R. A. CRAIG, K. W. GREENLEE, J. M. DERFER AND C. E. BOORD

This paper describes an extension of the Gustavson method[2,3,4] for the synthesis of cyclopropane and its derivatives. Three 1,1-dialkylcyclopropanes have been prepared; two of these compounds are new, and improved physical properties were determined for the third. The method has been applied to the preparation of spiranes containing a cyclopropane ring and provides an easy, straightforward way of producing this type of hydrocarbon in quantity and in a good state of purity. Cleavage of the cyclopropane ring by hydrogen has been investigated.

1,1-Dimethylcyclopropane has been produced from *sym*-dibromoneopentane most recently by Whitmore[5] and his co-workers. Isobutyraldehyde was condensed with formaldehyde in the presence of potassium hydroxide to obtain 2,2-dimethyl-1,3-propanediol which was converted to the corresponding dibromide by the action of phosphorus tribromide; the cyclization was accomplished with zinc in molten acetamide (Hass–McBee[6] procedure). In the present work the intermediates were synthesized by the same series of reactions, but the dibromide was cyclized by zinc in aqueous ethanol. The hydrocarbon was obtained in 96% yield (based on distilled dibromide), and it froze over a 0.4° range; physical properties were determined on a center fraction from the distillation of this product at about 10-plate efficiency.[7]

1,1-Diethylcyclopropane and 1-ethyl-1-butylcyclopropane were prepared by an analogous series of reactions. The yields from the dibromides were 92 and 94%, respectively; as in the case of 1,1-dimethylcyclopropane, the initial product was of high purity.[8] These two compounds have not been described previously.

TABLE I

		B. p., °C. (760 mm.)	F. p., °C.	d^{20}_4	n^{20}_D
1,1-Dimethyl cyclopropane	This work	20.63	−108.96	0.6589	1.3668
	Whitmore[5]	19.9	−108.4 to −107.3	....	....
1,1-Diethylcyclopropane		88.67	−105.91	.7318	1.4042
1-Ethyl-1-butylcyclopropane		140.41	−102.68	.7559	1.4183

Few spiranes have been synthesized. In all reported preparations where closure of the second ring was not the final step, the over-all yields have been no more than a few per cent. Recently spiropentane has been identified as a product from the reaction of pentaerythrityl tetrabromide with zinc[9,10] the yield being in the neighborhood of 25% based on the tetrabromide; this is the highest yield reported for any spirane. We have applied the Gustavson reaction to the preparation of spiro(2.5)octane and 4-methylspiro(2.5)octane. This work provides a general method for the preparation of spiranes containing a cyclopropane ring and is limited only by the availability of cyclic aldehydes which contain the desired configuration and which will undergo the methylol reaction to yield *gem*-dicarbinols. The yields are good.

Spiro(2.5)octane was prepared in the following way: 3-Cyclohexene-1-carboxaldehyde was prepared by condensing acrolein with butadiene (Diels–Alder). The adduct, an unsaturated alde-

---

[1] The material in this paper is taken from three sources: (a) From the dissertation submitted by R. W. Shortridge to the Graduate School of the Ohio State University in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in 1943; present address: Midwest Research Institute, Kansas City, Missouri. This portion of the material was presented before the Organic Division at the April, 1944, meeting of the American Chemical Society. (b) From a thesis submitted by R. A. Craig to the Graduate School of The Ohio State University in partial fulfillment of the requirements for the Degree of Master of Science; present address: The Ohio State University. This portion of the material was presented before the Organic Division at the April, 1946, meeting of the American Chemical Society. (c) From the experimental work of the American Petroleum Institute Research Project 45 which is administered by The Ohio State University Research Foundation.

[2] Gustavson, *J. prakt. Chem.*, **36**, 300 (1887).

[3] Gustavson and Popper, *J. prakt. Chem.*, **58**, 458 (1898).

[4] This reaction has been called the Freund reaction on occasion. However, reference to the original literature shows that although Freund (*Monatsh.*, **2**, 642 (1881)) was the first to make cyclopropane itself, he used an extension of the Wurtz reaction, and therefore had no claim to the method of ring closure which employs zinc in the presence of protonic solvent. This method was first reported by Gustavson[2] in 1887 by a paper entitled: "Concerning a New Method of Preparation of Trimethylene." Gustavson and Popper[4] extended this method to the preparation of substituted cyclopropanes.

[5] Whitmore, Popkin, Bernstein and Wilkins, THIS JOURNAL, **63**, 124 (1941).

[6] Hass, McBee, Hinds and Glusenkamp, *Ind. Eng. Chem.*, **28**, 1178 (1936).

[7] All plate ratings given in this paper represent estimates of column efficiency under actual operating conditions.

[8] Using this method, the American Petroleum Institute Research Project No. 45 has prepared four liters of 1,1-dimethylcyclopropane and five liters of 1,1-diethylcyclopropane, both in a state of high purity.

[9] Murray and Stevenson, THIS JOURNAL, **66**, 812 (1944).

[10] Slabey, *ibid.*, **68**, 1335 1(946).

hyde, reacted with formaldehyde to yield 4,4-bis-(hydroxymethyl)-1-cyclohexene which was hydrogenated catalytically to the corresponding saturated diol. Treatment of the diol with phosphorus tribromide gave 1,1-bis-(bromomethyl)-cyclohexane. Cyclization of the dibromide with zinc in ethanol produced spiro(2.5)octane in 91% yield. On distillation at about 25-plate efficiency, 71% of this material had a boiling range of 0.1° and a refractive index range of 0.0007; 51% had a constant boiling point and refractive index. The sample did not absorb bromine from carbon tetrachloride solution, and its time–temperature freezing curve showed it to be of high purity. Physical properties were determined on the constant index material.

4-Methylspiro(2.5)octane was made by the same series of reaction, starting with crotonaldehyde and butadiene. The yield of crude spirane was 89% from the dibromide; distillation at about ten-plate efficiency reduced this yield to 58% having a refractive index range of 0.0002. A good time–temperature freezing curve could not be obtained for this material, even after redistillation at about 25-plate efficiency and fractional crystallization. The physical properties listed were determined on the sample after recrystallization, and the material appeared to freeze over a range of about 5°. Since the ring closure reaction on di-primary halides gives high purity products consistently, it does not seem logical that in this case rearrangement occurred with the formation of an inseparable impurity; it is believed that the cryoscopic behavior can be attributed to a low heat of fusion for this spirane.

TABLE II

	B. p., °C. (760 mm.)	F. p., °C.	d^{20}_4	n^{20}_4
Spiro(2.5)octane	125.5	−86.2	0.8282	1.4476
4-Methylspiro(2.5)-octane	149.0	−53.6	.8386	1.4529

The stability of the cyclopropane ring is greatly affected by the nature and position of substituted groups. Willstätter and Bruce[11] found that cyclopropane, itself, is converted to propane at 80° by hydrogen over a nickel catalyst. Both Whitmore[12] and Fuson[13] state that alkyl-substituted cyclopropanes usually undergo ring opening more easily than does the parent substance. Studies on certain alkylcyclopropanes by other workers[14] indicate that temperatures of 150–170° are necessary to effect rupture of the ring.

In the present work hydrogenation studies have been carried out on three compounds containing the cyclopropane ring. No reaction occurred when an attempt was made to treat 1,1-diethylcyclopropane with hydrogen over platinum oxide catalyst at 60° and 40 p. s. i.; likewise, no reaction occurred when a palladium on calcium carbonate catalyst was used under these conditions. When the hydrocarbon was diluted with 60% of its volume of absolute ethanol, absorption of hydrogen did not occur even at 195° and 2400 p. s. i. over nickel on kieselguhr catalyst (Universal Oil Products). Successful hydrogenation of 1,1-diethylcyclopropane was accomplished in the absence of a solvent at 180° and 2000 p. s. i. over the nickel catalyst. Distillation of the hydrogenated product at about 10-plate efficiency gave 20% as headings and tailings (decomposition products and unchanged 1,1-diethylcyclopropane) and 80% of material (3° boiling range) which was identified as 3,3-dimethylpentane by inspection of the distillation curves (b. p. and $n^{20}\text{D}$). The boiling point range may be attributed to the presence of unchanged 1,1-diethylcyclopropane which boils only 2.5° higher than 3,3-dimethylpentane. No evidence was found for the presence of the other possible hydrogenation product, 3-ethylpentane.

Spiro(2.5)octane was hydrogenated successfully in the absence of a solvent over the nickel catalyst at 155° and 1900 p. s. i.; the theoretical amount of hydrogen was absorbed. Distillation of the hydrogenated product at about 25-plate efficiency gave 9% headings and tailings (decomposition products and unchanged spirane) and 91% of material (0.5° boiling range) which was identified as 1,1-dimethylcyclohexane on the basis of the physical properties of a heart cut (b. p. 119.65° (760 mm.), f. p. −34.02°, d^{20}_4 0.7809, $n^{20}\text{D}$ 1.4291). No evidence was found for the presence of the other possible hydrogenation product, ethylcyclohexane.

4-Methylspiro(2.5)octane was hydrogenated under the same conditions as spiro(2.5)octane. The single hydrogenation product found was tentatively identified as 1,1,2-trimethylcyclohexane, a new compound, and it had the following physical properties: b. p. 145.2° (760 mm.), f. p. −29.2°, d^{20}_4 0.7986, $n^{20}\text{D}$ 1.4385. A good freezing curve could not be obtained for this product, the general contour being the same as that for the original unhydrogenated spirane. 1,1,2-Trimethylcyclohexane, prepared at a later date[15] by a different method, and believed to be of good purity, had physical properties which agreed well with those of the product prepared by the hydrogenation of 4-methylspiro(2.5)octane. It exhibited the same peculiar cryoscopic behavior and was found to have a low heat of fusion and an unusually high freezing point depression on addition of *n*-heptane as impurity. This suggests that the original 4-methylspiro(2.5)octane was of good purity.

These studies indicate that when a *gem*-dialkylcyclopropane, or a spirane containing a cyclo-

---

(11) Willstätter and Bruce, *Ber.*, **40**, 4456 (1907).

(12) Whitmore, "Organic Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1947, p. 623.

(13) Fuson, Chapter in Gilman's "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 101.

(14) (a) Kishner, *J. Russ. Phys.-Chem. Soc.*, **44**, 169 (1912); **45**, 987 (1913). (b) Rosanoff, *ibid.*, **48**, 168 (1916). (c) Zelinsky, *Ber.*, **40**, 4743 (1907); **46**, 1466 (1913).

(15) Unpublished data of George L. Evans of this Laboratory.

propane ring, is hydrogenated under the conditions described above, rupture of the cyclopropane ring occurs almost exclusively at the bond opposite the *gem*-disubstituted carbon atom. Thus, hydrogenation under controlled conditions can provide an easy, reliable method for proving the structure of these types of compounds, and in some cases it may prove to be a good preparative reaction for synthesizing *gem*-dimethylcycloalkanes with rings containing more than three carbon atoms. Since ring cleavage requires rather severe conditions (especially in the presence of a solvent), it appears that alkylcyclopropanes can be produced from cyclopropylolefins by preferential hydrogenation of the carbon-carbon double bond.

Experimental

Preparation of 2,2-Dimethyl-1,3-propanediol.—This diol was prepared from isobutyraldehyde and formaldehyde by the procedure of Whitmore and his co-workers,[5] except that stirring of the reaction mixture was maintained during the dropwise addition of the alcohol solution of the reactants. Sodium hydroxide could be substituted for potassium hydroxide with little sacrifice in yield. After a twenty-four hour reflux period the reaction mixture was stripped of alcohol, and the residue was subjected to continuous ether extraction. After removal of the ether, the crude product was distilled from a Claisen flask at atmospheric pressure to obtain a 76% yield of the diol boiling at 176–205°. The bulk of the product was collected at about 200°; it melted at 130°.

Preparation of 1,3-Dibromo-2,2-dimethylpropane.—This compound was prepared from 2,2-dimethyl-1,3-propanediol and phosphorus tribromide by the procedure of Whitmore, *et al.*,[5] except for the following innovation. Phosphorus tribromide was added to the diol at 70°, the rate of addition being such as to maintain the temperature. The reaction is immediate under these conditions and is easily kept under complete control.[16] It was not necessary to stir the reaction mixture, although this is now believed to be advisable for large runs.

The steam distillate, after drying, was fractionated under reduced pressure at 5 to 10-plate efficiency. Based on diol, a 46% yield of good dibromide was obtained. It had the following physical properties: b. p. 68° (9 mm.), n^{20}_D 1.5050, d^{20}_4 1.6934.

Preparation of 1,1-Dimethylcyclopropane.—The method of cyclization was a modification of that of Gustavson.[2,3] In a 2-liter three-necked flask equipped with a dropping funnel, mercury-sealed stirrer and reflux condenser (connected to a trap surrounded by a Dry Ice–acetone-bath), were placed 900 ml. of 95% ethanol, 90 ml. of distilled water and 628 g. (9.6 moles) of zinc dust; it was necessary to maintain vigorous stirring at all times to prevent caking of the zinc. The mixture was brought to gentle reflux, and 562 g. (2.4 moles) of 1,3-dibromo-2,2-dimethylpropane was added dropwise at this temperature. Heating and stirring were continued for twenty-four hours after the last of the dibromide had been added; the bulk of the hydrocarbon collected in the trap during this period. The remaining 1,1-dimethylcyclopropane (along with some alcohol) was then distilled from the reaction flask and was collected in the trap. The crude product (162 g.) was washed with ice water and dried. The properties and purification of this material have already been described.

Preparation of 2,2-Diethyl-1,3-propanediol.—This compound was prepared from 2-ethylbutyraldehyde (Carbide and Carbon) by the same procedure as was used for the synthesis of 2,2-dimethyl-1,3-propanediol from isobutyraldehyde. Because of the lesser solubility of the resulting diol in water in this case, continuous ether extraction was unnecessary, and the crude product was merely extracted from the reaction mixture with ether. The ether was removed from the extract by distillation, and the residue was distilled from a Claisen flask to give a 91% yield of good product (b. p. 128–132° (12 mm.)). This material was fractionated at about 10-plate efficiency, and the following physical properties were determined on a center fraction: b.p. 131° (13 mm.), m. p. 61.0–61.6°. This compound has not been described previously. *Anal.* Calcd. for $C_7H_{16}O_2$: C, 63.6; H, 12.2. Found: C, 64.0; H, 12.2.

Preparation of 1,3-Dibromo-2,2-diethylpropane.—This dibromide was prepared from the corresponding diol in exactly the same way as 1,3-dibromo-2,2-dimethylpropane was prepared from 2,2-dimethyl-1,3-propanediol. The yield of steam distilled material was 40% (from diol) and was shown to be 90% pure by distillation under reduced pressure at 5 to 10-plate efficiency. The following physical properties were determined on a purified sample: b. p. 97° (10 mm.), m. p. 39.2–40.6°; this compound has not been described previously. *Anal.* Calcd. for $C_7H_{14}Br_2$: Br, 61.9. Found: Br, 62.1.

Preparation of 1,1-Diethylcyclopropane.—The ring closure reaction was carried out in the same way as in the preparation of 1,1-dimethylcyclopropane. Since the dibromide (1,3-dibromo-2,2-diethylpropane) was a solid, it was necessary to heat the dropping funnel in order to use the same technique. The 1,1-diethylcyclopropane was allowed to accumulate in the reaction flask; then the hydrocarbon was distilled from the reaction mixture through a 1.5 × 50 cm. Vigreux column until dilution of the fresh distillate with water did not cause a phase separation. The distillate was washed free of alcohol and was fractionated at about 10-plate efficiency; all of the material distilled at a constant temperature and had a constant refractive index; the total yield was 92% of theory (from dibromide). The physical properties of the distilled hydrocarbon are listed in Table I. This compound has not been described previously. *Anal.* Calcd. for C_7H_{14}: C, 85.6; H, 14.4. Found: C, 85.9; H, 14.2.

Preparation of 2-Ethyl-2-butyl-1,3-propanediol.—This diol was prepared from 2-ethylhexaldehyde (Carbide and Carbon) in the same way 2,2-diethyl-1,3-propanediol was prepared from 2-ethylbutyraldehyde. The crude product distilled at 151–152° (11 mm.) and was obtained in 70% yield. The material was redistilled at about 10-plate efficiency, and the following physical properties were determined on a center cut: b. p. 152° (10 mm.), m. p. 41.4–41.9°. This compound has not been described previously. *Anal.* Calcd. for $C_9H_{20}O_2$: C, 67.4; H, 12.6. Found: C, 67.6; H, 12.5.

Preparation of 1,3-Dibromo-2-ethyl-2-butylpropane.—This dibromide was prepared from the corresponding diol in exactly the same way as 1,3-dibromo-2,2-dimethylpropane was prepared from 2,2-dimethyl-1,3-propanediol. The yield of steam distilled material was 59% (from diol) and was shown to be 80% pure by distillation at about 10-plate efficiency. The following physical properties were determined on a purified sample: b. p. 133° (16 mm.), d^{20}_4 1.4400, n^{20}_D 1.5018. This compound has not been described previously. *Anal.* Calcd. for $C_9H_{18}Br_2$: Br, 55.9. Found: Br, 56.2.

Preparation of 1-Ethyl-1-butylcyclopropane.—1,3-Dibromo-2-ethyl-2-butylpropane was cyclized in the same way as was 1,3-dibromo-2,2-diethylpropane in the preparation of 1,1-diethylcyclopropane. The crude 1-ethyl-1-butylcyclopropane was fractionated at about 10-plate efficiency, and all of the material distilled at a constant temperature and had a constant refractive index. The yield from the dibromide was 94%. The physical constants of the distilled hydrocarbon are listed in Table I. This compound has not been described previously. *Anal.* Calcd. for C_9H_{18}: C, 85.6; H, 14.4. Found: C, 85.6; H, 14.4.

Preparation of 3-Cyclohexene-1-carboxaldehyde.—The procedure used was patterned after that described by Chayanov.[17] Butadiene (5 moles) was placed in a one-

---

[16] At lower temperatures an excess of phosphorus tribromide may accumulate, and a sudden uncontrollable reaction may occur.

[17] N. A. Chayanov, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 460 (1938).

liter steel bomb (American Instrument Company type) which contained acrolein (5 moles) and 5 g. of hydroquinone, the bomb and contents having been cooled previously in a Dry Ice chest. The bomb was sealed, placed in a mechanical shaker, and heated as rapidly as possible to 130°. At this temperature reaction appeared to begin, and the temperature quickly rose to 185° without further external heating. After cooling, the crude adduct (543 g.) was distilled at reduced pressure (75 mm.) through a 122 cm. Vigreux column. A center cut with a refractive index range of 0.0004 and a boiling point range of 1.0° represented 74% of the theoretical yield. Physical properties were determined on a heart fraction (values in parentheses are those of Chayanov[17]): b. p. 164° (760 mm.) (163.5–164.5°), f. p. −96.1°, d^{20}_{4} 0.9709 (d^{19}_{4} 0.965), n^{20}_{D} 1.4725 (n^{19}_{D} 1.4725).

When the reaction was run on a larger scale, lower yields were obtained. This may be explained by the fact that rapid heating to reaction temperature is necessary to minimize the formation of by-products; further, the temperature rise from the heat of reaction is greater in larger batches and may cause undesirable side reactions.[18]

Preparation of 4,4-bis-(Hydroxymethyl)-1-cyclohexene.—This diol was prepared from 3-cyclohexene-1-carboxaldehyde by the same procedure as 2,2-dimethyl-1,3-propanediol was prepared from isobutyraldehyde. On evaporation of the ether from the extract a large crop of crystals separated; the uncrystallized residue was distilled to obtain the remainder of the diol (b. p. 128° (3 mm.)). The total yield of diol was 84% of theory (from aldehyde), and, after two crystallizations, it melted sharply at 92.0°. (literature value,[19] 92.5°).

Preparation of 1,1-bis-(Hydroxymethyl)-cyclohexane.—1,1-bis-(Hydroxymethyl)-3-cyclohexene was dissolved in methanol (40 g. per 100 ml.) and placed in a steel bomb with 9% by weight of Raney nickel catalyst. Absorption of hydrogen began at 45° and 1000 p. s. i. The catalyst was removed by filtration, and the solvent was removed by distillation; white crystals melting at 98.5° remained. No further purification was attempted.

Preparation of 1,1-bis-(Bromomethyl)-cyclohexane.—This dibromide was prepared from the corresponding diol in the same way as 1,3-dibromo-2,2-dimethylpropane was prepared from 2,2-dimethyl-1,3-propanediol. After a twelve-hour heating period at 140–150°, the reaction mixture was hydrolyzed and subjected to superheated (150°) steam distillation. The steam distillate was dried and fractionated at 5 to 10-plate efficiency under reduced pressure to obtain a 27% yield (from diol) of purified dibromide. Physical constants determined on a center cut were: b. p. 117° (6 mm.), d^{20}_{4} 1.6302, n^{20}_{D} 1.5390.

Preparation of Spiro(2.5)octane.—1,1-bis-(Bromomethyl)-cyclohexane was cyclized in the same way as was 1,3-dibromo-2,2-dimethylpropane in the preparation of 1,1-dimethylcyclopropane. The hydrocarbon was allowed to accumulate in the reaction mixture and was isolated by distillation from the reaction flask. The crude product (n^{20}_{D} 1.4660) was washed free of alcohol and was obtained in 91% yield from dibromide.

Preparation of 6-Methyl-3-cyclohexene-1-carboxaldehyde.—This compound was prepared from butadiene and crotonaldehyde. The crotonaldehyde was placed in a steel bomb and heated to 150°. The butadiene was placed in a small cylinder connected to the bomb by small bore steel tubing. Nitrogen (pressure 300 p. s. i.) was used to push the butadiene into the reaction bomb in liquid form, the rate of addition being regulated by a valve so that about 7 g. per minute were added. A 46% yield of the desired aldehyde was obtained after distillation at 5 to 10-plate efficiency under reduced pressure. Its physical properties were: b. p. 99° (64 mm.) or 117.8° (760 mm.), d^{20}_{4} 0.9500, n^{20}_{D} 1.4680.

Preparation of 4,4-bis-(Hydroxymethyl)-5-methylcyclohexene.—This compound was prepared from 6-methyl-3-cyclohexene-1-carboxaldehyde by the same procedure as 2,2-dimethyl-1,3-propanediol was prepared from isobutyraldehyde. Purification was attempted by reduced pressure distillation. The distillate (b. p. 134° (6 mm.)) contained substantial amounts of the cyclic aldehyde (from dissociation during distillation); a yield was not calculated. Some pure crystalline diol was separated and melted at 45°. (This value agrees well with that given by French and Gallagher.[19])

Preparation of 1,1-bis-(Hydroxymethyl)-2-methylcyclohexane.—The crude cyclohexenedicarbinol was hydrogenated at 45° in ethanol solution over 10% by weight of Raney nickel. Distillation of the hydrogenated material at low efficiency gave a 51% yield (from original aldehyde) of saturated diol (m. p. 77°.).

Preparation of 1,1-bis-(Bromoethyl)-2-methylcyclohexane.—This compound was prepared from the corresponding diol by the same procedure as 1,1-bis-(bromomethyl)-cyclohexane was prepared from 1,1-bis-(hydroxymethyl)-cyclohexane; the yield of purified dibromide was 28% (from diol), and it had the following physical properties: b. p. 115° (4 mm.), n^{20}_{D} 1.5380.

Preparation of 4-Methylspiro(2.5)octane.—1,1-bis-(Bromomethyl)-2-methylcyclohexane was cyclized in the same way as was 1,1-bis-(bromomethyl)-cyclohexane in the preparation of spiro(2.5)octane. An 89% yield of crude spirane was obtained.

Acknowledgment.—Sincere appreciation is expressed for the use of the equipment and materials of the American Petroleum Institute Research Project 45.

Summary

1. The synthesis of three *gem*-dialkylcyclopropanes is described; two of these are new compounds; improved physical properties were determined for the third.

2. Spiro(2.5)octane and 4-methylspiro(2.5)octane, both new compounds, have been synthesized in good yield by an extension of the Gustavson reaction. This method appears to be a general one for preparing spiranes containing a cyclopropane ring.

3. Hydrogenation of three of these compounds has been investigated to determine the point of rupture of the cyclopropane ring and the conditions necessary to effect it. Cleavage seems to occur exclusively at the bond opposite to the gem-disubstituted carbon atom. The stability of the cyclopropane ring toward catalytic hydrogenation is discussed.

COLUMBUS, OHIO RECEIVED JULY 7, 1947

---

(18) It has been observed both here and in other laboratories that in Diels–Alder reactions of this kind (especially when butadiene is involved) an extremely exothermic reaction may occur quite suddenly, thus raising the temperature and pressure to extreme values. This is supposedly due to self-polymerization of the diene and is catalyzed by peroxides; it can be checked by use of peroxide free dienes and/or addition of a strongly reducing substance such as hydroquinone. Other essential precautions are that the reactants should be thoroughly mixed, the reaction vessel (bomb) should not be filled to more than two-thirds of its capacity at room temperature, and the vessel should be connected directly to a blow-out assembly with a discharge line leading to the out-of-doors. Neglect of these precautions caused one bad accident in this Laboratory. The head was blown from a 3-liter bomb containing butadiene and crotonaldehyde; the ensuing gas explosion did much damage and burned one man seriously.

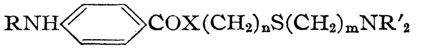
(19) French and Gallagher, THIS JOURNAL, **64**, 1497 (1942).

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Sulfur-containing Amines. V. Local Anesthetics. I

BY R. O. CLINTON, U. J. SALVADOR, S. C. LASKOWSKI AND C. M. SUTER

In continuation of the investigation proceeding in these laboratories on the effect of sulfur-interrupted basic side chains on pharmacological activity[1] there have been prepared a number of local anesthetic type compounds derived from sulfur-containing amines. The majority of these compounds contain the *p*-aminobenzoyl nucleus, as in (I) or (II). As variants of this type, the *p*-amino group has been altered to a *p*-*n*-butylamino group (III), and the amide linkage has been changed from secondary to tertiary (IV). No compounds of these types have previously been described in the literature.



I, X = O, R = H III, X = NH, R = *n*-C_4H_9
II, X = NH, R = H IV, X = NC_2H_5, R = H

Although considerable work has been carried out on investigations of *p*-aminobenzoates, very few *p*-aminobenzamides are described in the literature. Wenker[2] described a short series of N-alkyl and N,N-dialkyl *p*-aminobenzamides, the higher homologs of which were strong surface anesthetics. Einhorn[3] has patented a series of N-(2-dialkylaminoethyl)-*p*-alkylaminobenzamides and ascribes to this series a high local anesthetic activity. Blicke, Parke and Jenner[4] prepared a number of N-(2-dialkylaminoethyl)- and N-(3-dialkylaminopropyl)-4-amino-1-naphthoamides, whose activity was less than that of the corresponding esters. The well known compound 2-butoxy-N-(2-diethylaminoethyl)-cinchoninamide hydrochloride (nupercaine) possesses a very high activity, but also a high toxicity. In general, it appears from statements in the literature that conversion of the ester linkage to the amide linkage in these local anesthetic types produces a moderate to large increase in activity, but the therapeutic index is not affected advantageously.

The favorable toxicity ratios obtained with therapeutically active compounds by inclusion of the thio linkage[5] in the basic side chain indicated that this desirable property might also be obtained in other series. In order to determine both the effect of sulfur on toxicity and the effect as a "weighting" atom in the basic side chain (*i. e.*, considered as equivalent to two methylene groups), the series was extended to include *p*-aminobenzamides containing basic side chains interrupted by oxygen, and in both types the number of methylene groups in the side chain was widely varied.

The basic side chains used in the present work were mostly prepared by methods previously reported.[1,6] However, the sulfur-interrupted basic side chains containing the —$SCH_2CH_2NH_2$ termination were most conveniently prepared by a modification of the method of Brighton and Reid,[7] involving reaction between a thiol and 2-bromoethylamine in the presence of a base. When solutions of equimolecular amounts of thiol and 2-bromoethylamine hydrobromide in methanol were treated with two equivalents of sodium methoxide at −10° to 0° there were obtained 70–90% yields of the desired amines.

Attempts to prepare the 2-(dialkylaminoalkylmercapto)-ethylamines through reaction of a dialkylaminoalkyl halide with 2-aminoethylisothiouronium bromide hydrobromide and a base, or through reaction of a dialkylaminoalkylisothiouronium chloride hydrochloride with 2-bromoethylamine hydrobromide and a base, resulted in considerably lower yields than were obtainable by the above described procedure.

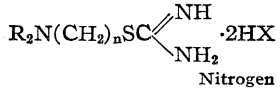
This series of compounds has been tested for local anesthetic activity following subcutaneous administration around the external canthus of rabbits' eyes. The compounds showed varying degrees of activity; at present, however, the data are insufficient to classify them according to activity. A complete report will be published by Dr. T. J. Becker and Dr. F. P. Luduena of these Laboratories at a later date.

Experimental[8]

Isothiouronium Salts.—All of the isothiouronium salts used in the present work were prepared by refluxing equimolecular amounts of a dialkylaminoalkyl chloride

TABLE I

ISOTHIOURONIUM SALTS



$$R_2N(CH_2)_nSC\begin{matrix}\diagup NH \\ \diagdown NH_2\end{matrix}\cdot 2HX$$

R_2	*n*	Yield, %	M. p., °C.	Formula	Nitrogen analyses, % Calcd.	Found
H_2[a]	2	87	194–195	$C_3H_9N_3S\cdot 2HBr$	14.95	14.89
(*n*-C_4H_9)$_2$	2	78	131.5–133	$C_{11}H_{25}N_3S\cdot 2HCl$	13.81	13.66
(*n*-C_4H_9)$_2$[b]	3	80	142–144	$C_{12}H_{27}N_3S\cdot 2HCl$	13.20	12.92
C_5H_{10}[c,d]	2	96	225–225.5	$C_8H_{17}N_3S\cdot 2HCl$	16.16	16.02
C_4H_8O[e]	2	80	233–235	$C_7H_{15}N_3OS\cdot 2HCl$	15.98	15.70

[a] Calcd.: S, 11.41. Found: S, 11.58. [b] Calcd.: S, 10.07. Found: S, 10.20. [c] N-Piperidyl. [d] Calcd.: Cl, 27.25. Found: Cl, 27.14. [e] N-Morpholinyl.

---

(1) For the preceding paper in this series see Laskowski and Clinton, THIS JOURNAL, **69**, 519 (1947).

(2) Wenker, *ibid.*, **60**, 1081 (1938).

(3) Einhorn, U. S. Patent 2,073,100 (1937).

(4) Blicke, Parke and Jenner, THIS JOURNAL, **62**, 3316 (1940).

(5) Huber, Bair, Boehme, Laskowski, Jackman and Clinton, *ibid.*, **67**, 1849 (1945); Huber, Bair, Laskowski, Jackman and Clinton, *ibid.*, **68**, 322 (1946).

(6) Clinton, Suter, Laskowski, Jackman and Huber, *ibid.*, **67**, 594 (1945).

(7) Brighton and Reid, *ibid.*, **65**, 458 (1943).

(8) All melting points and boiling points are corrected. The authors are indebted to Mr. Morris E. Auerbach and staff for the analyses.

hydrochloride (or bromide hydrobromide) and thiourea in three to four volumes of ethanol for six to twenty-four hours.[9] The shorter time could be used with ethyl chlorides or bromides; the longer period is preferable with propyl chlorides and with higher dialkylaminoethyl chlorides. Usually the isothouronium salt partially crystallized during the reflux period. The reaction mixture was cooled, filtered and the filtrate concentrated to a small volume. The combined crops of crystalline material were then recrystallized to a constant melting point, usually from absolute ethanol–ethyl acetate. New isothiouronium salts are listed in Table I.

Thiols.—Two modifications were used in the preparation of the thiols. Examples of each method follow:

2-Dimethylaminoethanethiol.[10] **Method A.**—One mole of 2-dimethylaminoethylisothiouronium chloride hydrochloride (m. p. 182–183°; ref. 10 gives m. p. 181–182°) was dissolved in 350 ml. of warm water and treated with an aqueous solution of two moles of sodium hydroxide in 100 ml. of water. Upon working up by a method analogous to that previously described[9] there was obtained a 22% yield of colorless product, b. p. 142–146° at 750 mm. In this and similar cases of low molecular weight thiols the loss of product by ether co-distillation is very high.

Method B.—For the preparation of large amounts of 2-diethylaminoethanethiol[9] it was found more convenient to proceed as follows:

A mixture of 855 g. (5.00 moles) of 2-chlorotriethylamine hydrochloride, 380 g. (5.00 moles) of thiourea and 3000 ml. of water was refluxed for five hours. The cooled solution was treated with a solution of 408 g. (10.00 moles) of 97% sodium hydroxide in 1000 ml. of water, the mixture saturated with salt, and extracted with ether. The ethereal solution was dried over anhydrous potassium carbonate, filtered, and the ether distilled through an efficient column at atmospheric pressure. The residue was distilled *in vacuo*. There were thus obtained yields of 45–60% of theory of colorless product, b. p. 46–48° at 4 mm.

An additional method, namely, the conversion of the isothiouronium salts to thiols by means of alkoxides in alcohols, is at present being investigated. Preliminary results indicate that this reaction is complicated by the formation of by-products other than the desired thiols (*e. g.*, the corresponding dialkylaminoalkylmercaptoalkanes). These results will be made the subject of a later communication.

The new thiols prepared in the present work are listed and characterized in Table II.

2-(Dialkylaminoalkylmercapto)-ethylamines

2-(2-Diethylaminoethylmercapto)-ethylamine.—Method A.—In a one-liter three-neck flask, equipped with a mechanical Hershberg-type stirrer, internal thermometer and dropping funnel, was placed 102.5 g. of 2-bromoethylamine hydrobromide,[11] 66.5 g. of 2-diethylaminoethanethiol and 400 ml. of methanol. The mixture was cooled to −10° by means of an external ice–salt–Dry Ice bath and there was added during forty-five minutes, with stirring, a solution of 23.0 g. of sodium in 400 ml. of methanol. During the addition of the first half of the sodium methylate solution, no exothermic effect was noted; addition of the second half produced an exothermic reaction. The internal temperature was maintained at −10° throughout this addition. The cold bath was removed and stirring was continued for an additional two hours. The flask was equipped with a 24″ Claisen-Vigreux column and the methanol was distilled with stirring at atmospheric pressure. The semi-solid residue was triturated with several portions of ether, the combined ether triturates were concentrated by distillation, and the residual oil fractionated *in vacuo*. There was obtained 81 g. (92% yield) of colorless product, b. p. 92–94° at 1.1 mm., n^{20}_{D} 1.4912. The dithiocarbamate-alcoholate had m. p. 142–143° (d.).[6]

Method B.—Treatment of a mixture of 124 g. of 2-diethylaminoethylisothiouronium chloride hydrochloride[9] and 102.5 g. of 2-bromoethylamine hydrobromide in 400 ml. of absolute ethanol with a solution of 46.0 g. of sodium in 1000 ml. of absolute ethanol at −10°, under the general conditions outlined in Method A above, gave 47.0 g. (53%) of 2-(2-diethylaminoethylmercapto)-ethylamine. Variation of the temperature during the reaction (*e. g.*, between −15° and 5°) did not improve the yield; however, preparation of the thiol *in situ* by the addition of the equivalent amount of sodium ethylate to the isothiouronium salt at 25°, followed by the addition of 2-bromoethylamine hydrobromide and sodium ethylate at −10°, increased the yield to 84%.

Method C.—Treatment of an equimolecular mixture of 2-aminoethylisothiouronium bromide hydrobromide and 2-chlorotriethylamine hydrochloride in absolute ethanol with four equivalents of sodium ethylate at −10° gave an 18% yield of 2-(2-diethylaminoethylmercapto)-ethylamine. Temperature variation (*e. g.*, between −15° and 10°), or difference in mode of addition of the reaction components did not markedly improve the yield. In all cases substantial amounts of N^1,N^4-diethylpiperazinium diethochloride[12] were formed.

The new 2-(dialkylaminoalkylmercapto)-ethylamines prepared in the present work are given in Table II. All of these compounds were prepared by Method A at −10° in methanol. The yields given represent material boiling within a two degree range; the boiling points reported are those of the analytically pure samples. The thiols used in the preparation of these amines are described in References 1 and 6, in the text above, and in Table II. Characterizing derivatives are listed in Table II.

2-(2-Diethylaminoethylmercapto)-diethylamine.—2-Hydroxydiethylamine[13] was converted by 48% hydrobromic acid to **2-bromodiethylamine hydrobromide**, essentially by the general procedure of Cortese.[11] The compound was obtained in 79% yield, white prisms from absolute ethanol–ether, m. p. 200–203°.

Anal. Calcd. for $C_4H_{10}BrN \cdot HBr$: N, 6.01. Found: N, 5.87.

The bromoamine was condensed with 2-diethylaminoethanethiol in methanol at −10° as described in Method A above, to yield 83% of the desired product, b. p. 88.5° at 0.20 mm., n^{25}_{D} 1.4765.

Anal. Calcd. for $C_{10}H_{24}N_2S$: N, 13.58; S, 15.53. Found: N, 13.50; S, 15.80.

The **dipicrate** formed canary-yellow prisms from dilute ethanol, m. p. 127.0–128.5°.

Anal. Calcd. for $C_{22}H_{30}N_8O_{14}S$: S, 4.82. Found: S, 4.80.

2-(2-Diethylaminoethoxy)-ethylamine.—A mixture of 253.5 g. of 2-chloro-2′-phthalimidoethyl ether,[14] 219 g. of diethylamine and 1500 ml. of ethanol was refluxed for thirty hours, and then concentrated to dryness *in vacuo*. The residual paste was taken up in water and extracted with three 200 ml. portions of ether. Washing and evaporation of the ether gave 218 g. of crude **2-(2-phthalimidoethoxy)-triethylamine** as a mobile light brown oil. The **hydrochloride** formed white prisms from absolute ethanol–ethyl acetate, m. p. 141–142°.

Anal. Calcd. for $C_{16}H_{23}ClN_2O_3$: N, 8.57; Cl, 10.85. Found: N, 8.57; Cl, 10.93.

Cleavage of the phthalimido base with hydrazine hydrate in the usual manner[15] gave a 61% yield (based on 2-phthalimido-2′-chloroethyl ether) of colorless product, b. p. 78.0° at 4.00 mm., n^{25}_{D} 1.4430.

---

[9] *Cf.* Albertson and Clinton, THIS JOURNAL, **67**, 1222 (1945).

[10] J. H. Williams, Doctoral Dissertation, New York University, 1933; Renshaw, Dreisbach, Ziff and Green, THIS JOURNAL, **60**, 1765 (1938).

[11] Cortese, *ibid.*, **58**, 191 (1936).

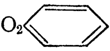
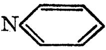
[12] Gough and King, *J. Chem. Soc.*, 2437 (1928); Eisleb, *Ber.*, **74**, 1433 (1941).

[13] Obtained through the courtesy of Sharples Chemicals, Inc.

[14] Cretcher, Koch and Pittenger, THIS JOURNAL, **47**, 1173 (1925).

[15] Ing and Manske, *J. Chem. Soc.*, 2348 (1926).

TABLE II

R_2	X	n	m	Yield,[a] %	Bases M. p. or B. p., °C./mm.	$n^{25}D$	Formula	Analyses, % Calcd.	Found
Thiols, $R_2N(CH_2)_nSH$									
$(n\text{-}C_4H_9)_2$	..	2	..	83[b]	138/26[c]	....	$C_{10}H_{23}NS$	N, 7.39	7.51
$(n\text{-}C_4H_9)_2$	..	3	..	65[d,e]	112/2	1.4994	$C_{11}H_{25}NS$	N, 6.88	6.23
C_5H_{10}[f]	..	2	..	72[d]	85/11	1.4995	$C_7H_{15}NS$	S, 22.07[g]	21.90
C_4H_8O[h]	..	2	..	54[d]	101/15	1.5030	$C_6H_{13}NOS$	S, 21.77	21.62
2-(Dialkylaminoalkylmercapto)-ethylamines, $R_2N(CH_2)_nSCH_2CH_2NH_2$									
$(CH_3)_2$	..	2	..	72	53/0.04	1.4660	$C_6H_{16}N_2S$	N, 18.90	18.80
$(C_2H_5)_2$	..	3	..	78	64/ .04	1.4882	$C_9H_{22}N_2S$	N, 14.72	14.92
$(n\text{-}C_4H_9)_2$	..	2	..	61	90/ .01	1.4813	$C_{12}H_{28}N_2S$	S, 13.79	13.79
$(n\text{-}C_4H_9)_2$	..	3	..	44	115/ .01	1.4800	$C_{13}H_{30}N_2S$	N, 11.37	11.18
C_5H_{10}[f]	..	2	..	81	81/ .15	1.5145	$C_9H_{20}N_2S$	[k]	[k]
C_5H_{10}[f]	..	3	..	74	101/ .10	1.5118	$C_{10}H_{22}N_2S$	N, 13.85	13.56
C_4H_8O[h]	..	2	..	75	109/ .25	1.5198	$C_8H_{18}N_2OS$	S, 16.85	16.96
p-Nitrobenzamides, NO_2$CONH(CH_2)_nX(CH_2)_mNR_2$									
$(CH_3)_2$	S	2	2	73	64.5[n]	....	$C_{13}H_{19}N_3O_3S$	N, 14.15	14.35
$(C_2H_5)_2$	S	2	2	92	oil	....	....	......	...
$(C_2H_5)_2$	S	3	2	96	oil	....	....	......	...
$(C_2H_5)_2$	S	2	3	96	oil	....	....	......	...
$(C_2H_5)_2$	S	3	3	99	oil	....	....	......	...
$(C_2H_5)_2$	S[p]	2	2	98	oil	....	....	......	...
$(n\text{-}C_4H_9)_2$	S	2	2	95	oil	....	....	......	...
C_5H_{10}[f]	S	2	2	92	69.5–70.5[n]	....	$C_{16}H_{23}N_3O_3S$	N, 12.45[q]	12.29
C_5H_{10}[f]	S	2	3	93	61.5–62.5[n]	....	$C_{17}H_{25}N_3O_3S$	N, 11.96[s]	11.82
C_4H_8O[h]	S	2	2	95	101.5–102.0[n]	....	$C_{15}H_{21}N_3O_4S$	N, 4.13[t,u]	4.14
$(C_2H_5)_2$	O	2	2	99	51.5–52.0[n]	....	$C_{15}H_{23}N_3O_4$	N, 13.59	13.50
$(C_2H_5)_2$	O	3	2	99	oil	....	....	......	...
$(C_2H_5)_2$	O	3	3	99	oil	....	....	......	...
p-Aminobenzamides, H_2N$CONH(CH_2)_nX(CH_2)_mNR_2$									
$(CH_3)_2$	S	2	2	58	oil	....	....	......	...
$(C_2H_5)_2$	S	2	2	75	70–71[n]	....	$C_{15}H_{25}N_3OS$	N[v], 14.22	14.04
$(C_2H_5)_2$	S	3	2	92	oil	....	....	......	...
$(C_2H_5)_2$	S	2	3	93	104–105.5[n]	....	$C_{16}H_{27}N_3OS$	N[y], 13.58	13.56
$(C_2H_5)_2$	S	3	3	86	oil	....	$C_{17}H_{29}N_3OS$	N[z], 4.33	[aa], 4.17
$(C_2H_5)_2$	S[bb]	2	2	90	oil	....	$C_{17}H_{29}N_3OS$	N[z], 4.33	[cc], 4.08
$(n\text{-}C_4H_9)_2$	S	2	2	99	oil	....	....	......	...
C_5H_{10}[f]	S	2	2	98	oil	....	....	......	...
C_5H_{10}[f]	S	2	3	98	92.8–94.8[n]	....	$C_{17}H_{27}N_3OS$	N[z], 4.36	[ee], 4.28
C_4H_8O[h]	S	2	2	90	oil	....	....	......	...
$(C_2H_5)_2$	O	2	2	98	67.5–68.5[n]	....	$C_{15}H_{25}N_3O_2$	N, 15.04	14.98
$(C_2H_5)_2$	O	3	2	79	oil	....	....	......	...
$(C_2H_5)_2$	O	3	3	96	oil	....	$C_{17}H_{29}N_3O_2$	N[t], 4.56	[kk], 4.21

Anal. Calcd. for $C_8H_{20}N_2O$: N, 17.48. Found: N, 17.16.

The **dipicrate** formed small, canary-yellow prisms from ethanol, m. p. 130.5–131.5°.

Anal. Calcd. for $C_{20}H_{26}N_8O_{15}$: N, 18.12. Found: N, 18.21.

3-(2-Diethylaminoethoxy)-propylamine and 3-(3-diethylaminopropoxy)-propylamine were prepared by the method of Whitmore, *et al.*,[16] in comparable yields. The amines were characterized through the **dithiocarbamates**, m. p. 134.5–136.0° and 119–121.5°, respectively.

Anal. Calcd. for $C_{10}H_{22}N_2OS_2$: S, 25.55. Found: S, 25.74. Calcd. for $C_{11}H_{24}N_2OS_2$: S, 24.25. Found: S, 23.74

2-(2-Diethylaminoethylmercapto)-ethyl *p*-Nitrobenzoate.—To a cooled solution of 79.5 g. of *p*-nitrobenzoyl chloride in 300 ml. of dry benzene was added a cold solution of 75 g. of 2-(2-diethylaminoethylmercapto)-ethanol[6] in 200 ml. of dry benzene over a period of fifteen minutes with vigorous stirring and maintenance of the internal temperature below 5°. The mixture was then allowed to warm to room temperature, and treated with a slight excess of 35% sodium hydroxide solution with cooling. The benzene layer was separated and concentrated *in vacuo*, yielding 91.6 g. (66%) of crude product as a yellow mobile oil. The *picrate* crystallized in yellow needles from a large volume of ethanol, m.p. 154–155°.

Anal. Calcd. for $C_{21}H_{25}N_5O_{11}S$: S, 5.77. Found: S, 5.77.

3-(2-Diethylaminoethylmercapto)-propyl *p*-Nitrobenzoate.—The condensation of 3-(2-diethylaminoethyl-

---

[16] Whitmore, *et al.*, THIS JOURNAL, **66**, 725 (1944).

TABLE II (*Continued*)

Characterizing derivatives

Derivative	M. p., °C.	Formula	Analyses, % Calcd.	Analyses, % Found
Picrate	147.5–148.5	$C_{16}H_{26}N_4O_7S$	S, 7.66	7.56
Picrate	90–92	$C_{17}H_{28}N_4O_7S$	S, 7.41	7.14
Hydrochloride	204–205	$C_7H_{16}ClNS$	N, 7.71	7.68
Picrate	113–115	$C_{12}H_{16}N_4O_8S$	S, 8.51	8.28
Dithiocarbamate	143–144[i]	$C_7H_{16}N_2S_3$	N, 12.49	12.44
Dithiocarbamate	123.5–124.5[i]	$C_{10}H_{22}N_2S_3$	N, 10.51	10.51
Dithiocarbamate[j]	94.5–96.5[i]	$C_{13}H_{30}N_2OS_3$	N, 8.58	8.39
Dithiocarbamate[j]	120–122[i]	$C_{14}H_{32}N_2OS_3$	N, 8.23	8.10
Dithiocarbamate[l]	143.5–144.5[i]	$C_{12}H_{25}N_2OS_3$	[m]	[m]
Dithiocarbamate	155–156[i]	$C_{11}H_{22}N_2S_3$	N, 10.06	9.91
Dipicrate	99–101	$C_{20}H_{24}N_8O_{15}S$	S, 4.94	4.95
Picrate	156–157	$C_{19}H_{22}N_6O_{10}S$	S, 6.09	6.46
Picrate[o]	120–122	$C_{21}H_{26}N_6O_{10}S$	S, 5.78	5.77
Picrate	120.5–123.5	$C_{22}H_{28}N_6O_{10}S$	S, 5.63	5.60
Picrate	111.5–112.5	$C_{22}H_{28}N_6O_{10}S$	S, 5.63	5.67
Picrate	102.5–105.0	$C_{23}H_{30}N_6O_{10}S$	S, 5.50	5.49
Chloroplatinate	154–155[i]	$C_{17}H_{29}Cl_6N_3O_3PtS$	Pt, 25.57	25.80
Picrate	79.5–80.5	$C_{25}H_{34}N_6O_{10}S$	S, 5.25	5.12
Picrate[r]	142–143	$C_{22}H_{26}N_6O_{10}S$	S, 5.66	5.71
Picrate	115.0–115.5	$C_{23}H_{28}N_6O_{10}S$	S, 5.53	5.45
Picrate	145.5–146.5	$C_{21}H_{24}N_6O_{10}S$	S, 5.63	5.59
Flavianate	190.5–192.0	$C_{25}H_{29}N_5O_{12}S$	S, 5.14	5.16
Picrate	113.5–114.8	$C_{22}H_{28}N_6O_{11}$	N, 15.21	15.00
Picrate	94.5–95.5	$C_{23}H_{30}N_6O_{11}$	N, 14.84	14.73
Diphosphate	133–135	$C_{13}H_{27}N_3O_9P_2S$	N, 9.07	8.84
Dipicrate[w]	132.5–135	$C_{27}H_{31}N_9O_{15}S$	S, 4.25	4.36
Citrate	108–117[i]	$C_{22}H_{35}N_3O_8S$	N[x], 8.37	8.21
Dipicrolonate	117–118	$C_{36}H_{35}N_7O_6S$	S, 3.82	3.82
......	....	....	......	...
Dipicrate	133–133.5	$C_{29}H_{35}N_9O_{15}S$	S, 4.07	4.16
Dipicrate	94.5–95.5	$C_{31}H_{39}N_9O_{15}S$	S, 3.95	4.03
Dihydriodide	210–212[i]	$C_{16}H_{27}I_2N_3OS$	N[dd], 7.46	7.17
Diflavianate[ff,gg]	245–247[i]	$C_{37}H_{39}N_7O_{17}S_3$	S, 10.10	10.11
Dihydrochloride	236–238.5	$C_{15}H_{25}Cl_2N_3O_2S$	S[hh], 8.38	8.27
Dihydrochloride	177–179	$C_{15}H_{27}Cl_2N_3O_2$	N[ii], 11.93	11.87
Citrate	111–113.5	$C_{22}H_{35}N_3O_9$	N[jj], 8.65	8.45
......	....	....	......	...

[a] Yields are based on the pure product except in the case of the *p*-nitrobenzamides. [b] Preparation method A in text. [c] German Patent 631,016, *via Chem. Abs.*, **30**, 6008 (1936), reported b. p. 73–74° at 2 mm. [d] Preparation method B in text. [e] Yield 79% by preparation method A. [f] 1-Piperidyl. [g] Calcd.: C, 57.88; H, 10.41. Found: C, 57.63; H, 10.30. [h] 4-Morpholinyl. [i] With decomposition. [j] Hydrate. [k] Calcd.: C, 57.39; H, 10.70. Found: C, 57.75; H, 10.69. [l] Alcoholate. [m] Calcd.: C. 46.41; H, 8.44. Found: C, 46.66; H, 8.26. [n] M. p., °C. [o] Citrate, m. p. 103–105°. *Anal.* Calcd. for $C_{21}H_{31}N_3O_{10}S$: C, 48.73; H, 6.04. Found: C, 48.91; H, 6.05. [p] N-ethyl-N-(2-(2-diethylaminoethylmercapto)-ethyl)-*p*-nitrobenzamide. [q] Calcd.: S, 9.50. Found: S, 9.63. [r] Phosphate, m. p. 177.5–178.5°. *Anal.* Calcd. for $C_{16}H_{26}N_3O_7PS$: N, 9.66. Found: N, 9.82. [s] Calcd.: S, 9.12. Found: S, 8.99. [t] Tertiary amino nitrogen by titration with perchloric acid in glacial acetic acid solution. [u] Calcd.: S, 9.44. Found: S, 9.31. [v] Calcd.: S, 10.85. Found: S, 10.85. [w] Dihydrochloride; m. p. 172.5–174. Calcd. for $C_{15}H_{25}N_3OS \cdot 2HCl$: N, 11.41; Cl, 19.25. Found: N, 11.26; Cl, 19.18. [x] Calcd.: S, 6.39; Found: S, 6.46. [y] Calcd.: S, 10.36. Found: S, 10.36. [z] Aromatic amino nitrogen by diazotization. [aa] Calcd.: S, 9.89. Found: S, 9.51. [bb] N-Ethyl-N-(2-(2-diethylaminoethylmercapto)-ethyl)-*p*-aminobenzamide. [cc] Calcd.: S, 9.89. Found: S, 9.25. [dd] Calcd.: S, 5.69. Found: S, 5.88. [ee] Calcd.: S, 9.97. Found: S, 10.11. [ff] Shown to be a diflavianate rather than a monoflavianate by determination of aromatic nitrogen. Calcd.: N, 1.47. Found: N, 1.47. [gg] Dihydriodide, m. p. 200° (d.). Calcd. for $C_{17}H_{29}I_2N_3OS$: N, 7.27; S, 5.55. Found: N, 7.12; S, 5.72. [hh] Calcd.: Cl, 18.55. Found: Cl, 18.55. [ii] Calcd.: Cl, 20.13. Found: Cl, 20.11. [jj] Calcd.: C, 54.42; H, 7.26. Found: C, 54.20; H, 7.33. [kk] Tertiary aliphatic nitrogen by titration. Calcd.: N, 4.56. Found: N, 4.56.

mercapto)-propanol[6] with *p*-nitrobenzoyl chloride by the above method gave a 70% yield of the base; pale yellow mobile oil, b. p. 178–180° at 0.1 mm.

Anal. Calcd. for $C_{16}H_{24}N_2O_4S$: N, 8.23. Found: N, 8.16.

The **picrate** formed tiny, canary-yellow needles from ethanol, m.p. 91.5–92.5°.

Anal. Calcd. for $C_{22}H_{27}N_5O_{11}S$: S, 5.63. Found: S, 5.66.

1-(2-Dimethylaminoethylmercapto)-isopropyl *p*-Nitrobenzoate Hydrochloride.—This compound was obtained directly from the alcohol[1] and *p*-nitrobenzoyl chloride by the above method, small white prisms from absolute ethanol–ether, m. p. 133.7–135°.

Anal. Calcd. for $C_{14}H_{21}ClN_2O_4S$: S, 9.19. Found: S, 9.40.

***p*-Nitrobenzamides.**—The condensation of *p*-nitrobenzoyl chloride with the dialkylaminoalkylmercaptoalkylamines could be carried out in cold, dry benzene, as outlined above for the alcohols. The crude yields averaged 70–80%, but under these conditions decomposition and side-reactions were extensive, and the products were very difficult to purify. The following general method was found preferable:

To a solution of 37.8 g. of sodium bicarbonate in 240 ml. of water was added 52.8 g. of 2-(2-diethylaminoethylmercapto)-ethylamine. To the resulting mechanically stirred mixture was added dropwise during one hour a solution of 66.9 g. of *p*-nitrobenzoyl chloride in 600 ml. of dry chloroform at room temperature. The addition proceeded smoothly, without large exothermic effects or vigorous carbon dioxide evolution. After stirring for an additional hour the chloroform layer was separated and the water layer extracted with an additional 50 ml. of chloroform. After washing the combined chloroform layers successively with dilute sodium bicarbonate solution and with water, they were dried over Drierite and concentrated *in vacuo*. The pale yellow, mobile residue of **N-(2-(2-diethylaminoethylmercapto)-ethyl)-*p*-nitrobenzamide** weighed 91.2 g. (92% crude yield). The compound could not be obtained in crystalline form.

Attempts to distil the *p*-nitrobenzamide bases at pressures as low as 10^{-5} mm. failed, due to extensive decomposition at the boiling point. However, in certain cases the bases could be obtained crystalline after purification through a suitable derivative.

The *p*-nitrobenzamide bases prepared in the present work are described and characterized by derivatives in Table II.

2-(2-Diethylaminoethylmercapto)-ethyl *p*-Aminobenzoate.—The reduction of the nitro compound was carried out with reduced iron powder and hydrochloric acid in aqueous alcoholic solution, by a method analogous to that of West.[17] There was obtained a 92% yield of crude product as a pale yellow, mobile oil. The **phosphate hydrate** crystallized from ethanol in tiny white needles, m. p. 141–145°.

Anal. Calcd. for $C_{15}H_{27}N_2O_6PS \cdot H_2O$: N, 6.79. Found: 6.63.

By a similar reduction there was prepared **3-(2-diethylaminoethylmercapto)-propyl *p*-aminobenzoate** in 95% yield. The pale yellow mobile oil could not be induced to crystallize. The **picrate** formed golden yellow needles from ethanol, m. p. 125–126°.

Anal. Calcd. for $C_{22}H_{29}N_5O_9S$: S, 5.94. Found: S, 5.90.

The **citrate** crystallized in rosets of small white needles from absolute ethanol–ethyl acetate, m. p. 103–104.5°.

Anal. Calcd. for $C_{22}H_{34}N_2O_9S$: N, 5.57; S, 6.37. Found: N, 5.35; S, 6.44.

1-(2-Dimethylaminoethylmercapto)-isopropyl *p*-aminobenzoate diphosphate formed white prisms from ethanol– m. p. 128–130°.

Anal. Calcd. for $C_{14}H_{28}N_2O_{10}P_2S$: N, 5.86; S, 6.70. Found: N, 5.88; S, 6.75.

***p*-Aminobenzamides.**—Reduction of the *p*-nitrobenzamide bases by means of reduced iron–hydrochloric acid gave crude yields of 40–50% of impure *p*-aminobenzamides. The yields and purity were substantially improved through the use of ferrous sulfate and ammonia for the reduction:

A three-liter beaker was mounted on a small electric hotplate and equipped with a Hershberg-type mechanical stirrer, an internal thermometer, and two 250-ml. dropping funnels. In one funnel was placed a solution of 42.5 g. of N-(2-(2-diethylaminoethylmercapto)-ethyl)-*p*-nitrobenzamide in 320 ml. of ethanol and in the second was placed a mixture of 135 ml. of concentrated ammonium hydroxide (28%) and 150 ml. of water. A solution of 255 g. of pure ferrous sulfate heptahydrate in 900 ml. of water was prepared in the beaker and heated to 80–85°. While the ferrous sulfate solution was stirred vigorously the contents of the dropping funnels were added dropwise during forty-five minutes, maintaining the ratio so that the mixture in the beaker always remained alkaline. The internal temperature was maintained at 80–85° during this addition, and for an additional one hour of stirring. The volume was maintained nearly constant by the occasional addition of alcohol. Filter-cel was then added to the hot mixture and the slurry was filtered, the filterpad being washed thoroughly with warm ethanol. The ethanol was distilled from the filtrate *in vacuo*, the aqueous residue was made strongly alkaline with concentrated aqueous ammonia, and extracted with ethyl acetate. After drying the combined extracts over Drierite the ethyl acetate was removed *in vacuo*, finally at 60° and 0.05 mm. There was thus obtained 29.5 g. (76%) of **N-(2-(2-diethylaminoethylmercapto)-ethyl)-*p*-aminobenzamide**. Crystallization from ethyl acetate–Skellysolve B gave pure material with but little loss.

The *p*-aminobenzamide bases could not be distilled without decomposition at pressures as low as 10^{-5} mm. The above procedure gave analytically pure material in most cases, however. A number of attempts were made to catalytically reduce the sulfur-containing nitro-bases, using a variety of catalysts and conditions. In all cases catalyst poisoning was rapid and reduction failed. Catalytic reduction of the non-sulfur-containing nitro-bases proceeded readily with Raney nickel or platinum.

The *p*-aminobenzamides prepared in the present work are described, and characterized by derivatives, in Table II.

N-(2-(2-Diethylaminoethylmercapto)-ethyl) *p*-*n*-Butylaminobenzamide.[18]—A mixture of 59.0 g. of N-(2-(2-diethylaminoethylmercapto)-ethyl)-*p*-aminobenzamide, 52.2 g. of pure zinc dust (4 mole proportion), 49.2 ml. of glacial acetic acid (4.10 mole proportion) and 200 ml. of dry benzene was stirred and heated under reflux. To this mixture was added dropwise during thirty minutes a solution of 17.4 g. (1.21 mole proportion) of *n*-butyraldehyde in 20 ml. of dry benzene. After stirring under reflux for an additional one hour the mixture was filtered hot and the filter cake was washed thoroughly with hot benzene. The filtrate (two layers) was made strongly basic to litmus with 35% sodium hydroxide solution, the benzene layer was separated, and the aqueous layer was extracted with two further portions of benzene. The combined benzene extracts were dried over Drierite, decolorized with Darco G-60, and concentrated *in vacuo*, finally at 60° and 0.05 mm. for three hours. The product was a viscous, pale yellow oil.

Anal. Calcd. for $C_{19}H_{33}N_3OS$: S, 9.13; N, 11.98. Found, S, 9.16; N, 11.70.

The **dipicrate** crystallized from glacial acetic acid in small, yellow-orange prisms, m. p. 148–149°.

Anal. Calcd. for $C_{31}H_{39}N_9O_{15}S$: S, 3.96. Found: S, 3.99.

West, *J. Chem., Soc.*, **127**, 494 (1925).

(18) This procedure is an adaptation of the general method of German Patent 491,856 (*Frdl.*, **16**, 356 (1927)).

Summary

There has been described the preparation of a series of dialkylaminoalkylmercaptoalkyl *p*-aminobenzoates and N-(dialkylaminoalkylmercaptoalkyl)-*p*-aminobenzamides, and several of their oxygen analogs. Preliminary pharmacological data indicate a high local anesthetic activity coupled with low toxicity for certain of these compounds.

RENSSELAER, NEW YORK RECEIVED JULY 29, 1947

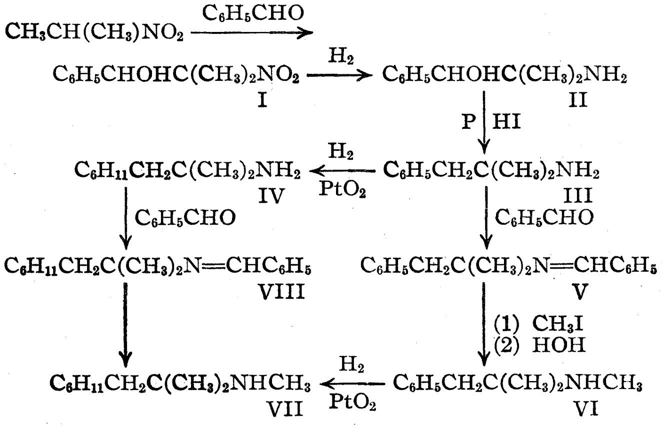
[CONTRIBUTION FROM THE SCIENTIFIC LABORATORIES, FREDERICK STEARNS & COMPANY, DIVISION OF STERLING DRUG, INC.]

Preparation of α,α-Dimethyl- and N,α,α-Trimethyl-β-cyclohexylethylamine

BY BERNARD L. ZENITZ,[1a] ELIZABETH B. MACKS[1b] AND MAURICE L. MOORE[1c]

Since it was found that the series of β-cyclohexylalkylamines previously reported[2a] possesses pressor activity and produces little nervous stimulation, two additional members of this series, α,α-dimethyl-β-cyclohexylethylamine (IV) and its N-methyl derivative (VII), were prepared and their pharmacological activity was investigated.

The following synthetic scheme was employed[2b].



The condensation of benzaldehyde with 2-nitropropane, using an adaptation of Kamlet's procedure,[3] gave only poor yields (8–12%) of the nitro alcohol (I) whereas substantially higher yields were obtained when the condensation was carried out with sodium ethoxide in alcohol.

Gakenheimer and Hartung[4] observed that the catalytic hydrogenation of certain aliphatic nitro alcohols in neutral medium resulted in a fission of the nitro alkanol chain, but that the reduction proceeded satisfactorily in an acid medium. Similar results were experienced in this investigation. Catalytic hydrogenation of the nitro alcohol (I) in neutral alcoholic solution with a palladium-charcoal catalyst at 80° and sixty pounds pressure appeared to produce a fission of the molecule since a strong amine odor was detectable in the reaction mixture and none of the desired amino alcohol could be isolated. However, in the presence of acetic acid, hydrogenation produced a satisfactory yield of the amino alcohol (II).

In addition, the reduction was also accomplished with sodium amalgam and with zinc and acetic acid, the best yield being obtained by this last method.

α,α-Dimethyl-β-phenylethylamine (III) has been obtained by Shelton and Van Campen, Jr.,[5] by the catalytic hydrogenation of α,α-dimethyl-β-chloro-β-phenylethylamine. Mentzer and co-workers[6] have also reported its preparation by the action of slaked lime on *sym*-bis-(α,α-dimethyl-β-phenylethyl)-urea at 230° and by the hydrolysis of α,α-dimethyl-β-phenylethylisocyanate with concentrated hydrochloric acid, but their melting point of 147–148° for the hydrochloride is not in agreement with the 199–200° obtained by us or with the 195–196° reported by Shelton and Van Campen, Jr.

In the present investigation, an attempt to dehydroxylate the amino alcohol (II) by the catalytic reduction method of Rosenmund and Karg[7] was unsuccessful but the dehydroxylation was accomplished with red phosphorus and hydriodic acid, the method previously employed by Suter and Docken.[2b] The phenylalkylamine (III) obtained was N-methylated by the Becker and Decker method, and these two amines were then converted to their corresponding cyclohexyl analogs (IV and VII) by the general catalytic hydrogenation procedure previously described.[2a]

In order to obtain the secondary amine (VII)

[1a] Present address: Sterling–Winthrop Research Institute, Rensselaer, N. Y.

[1b] Present address: Parke, Davis & Co., Detroit, Mich.

[1c] Present address: Smith, Kline & French Laboratories, Philadelphia, Pa.

[2a] Zenitz, Macks and Moore, THIS JOURNAL, **69**, 1117 (1947).

[2b] Although only compound III has been described in the literature (refs. 5 and 6), C. M. Suter in a personal communication indicated that compounds I, III, and VI were previously prepared at Northwestern University by Suter and Docken and that II has been obtained in the laboratories of Commercial Solvents Corp. Compound IV has been mentioned in a patent (ref. 5), but no physical constants were given.

[3] Kamlet, U. S. Patent 2,151,517, March, 1939.

[4] Gakenheimer and Hartung, *J. Org. Chem.*, **9**, 85 (1944).

[5] Shelton and Van Campen, Jr., U. S. Patent 2,408,345, Sept., 1946.

[6] (a) Mentzer, *Compt. rend.*, **213**, 581 (1941); (b) Mentzer, Buu-Hoi and Cagniant, *Bull. soc. chim.*, **9**, 813 (1942).

[7] Rosenmund and Karg, *Ber.*, **75**, 1854 (1942).

directly, an attempt was made to N-methylate the cyclohexyl base (IV) by the Becker and Decker method. Although the intermediate Schiff base (VIII) formed readily, its treatment with methyl iodide in a sealed tube at 100–120° for twenty-eight hours, followed by hydrolysis, failed to produce the desired amine (VII).

A preliminary pharmacological evaluation of the pressor activity in anesthetized dogs of both the phenyl- (III and VI) and the cyclohexylalkylamines (IV and VII) was carried out.[8] The secondary phenylalkylamine (VI) showed practically no activity. The other three amines displayed pressor activity of only low order, the cyclohexyl compounds being somewhat more active than the phenyl and the primary amines more active than the secondary. In general, the activity of the cyclohexyl compounds (IV and VII) is comparable to that of the β,β-dimethyl-β-cyclohexylethylamines, the weaker members of the previously reported series.[2a]

Experimental[9]

1-Phenyl-2-methyl-2-nitropropanol (I).—To a solution prepared from 9.2 g. (0.4 mole) of sodium and 700 ml. of anhydrous methanol was added 187 g. (2.1 moles) of 2-nitropropane and 212 g. (2.0 moles) of freshly distilled benzaldehyde. After twenty-four hours at room temperature, the yellow solution was acidified with acetic acid and the methanol was distilled. The residue was dissolved in a mixture of water and ether. The ether layer was washed with water, extracted with four 200-ml. portions of 15% aqueous sodium bisulfite solution to remove the unreacted benzaldehyde, again washed with water and was dried over anhydrous sodium sulfate.

The ether was distilled. The residual oil was heated on a steam-bath *in vacuo* to remove any remaining benzaldehyde and 2-nitropropane. It was then stirred in an ice-bath with petroleum ether until it solidified. After filtration, the solid was recrystallized from 700 ml. of heptane to give the nitro alcohol as yellow crystals, m. p. 64–66°; reported[2b] m. p. 53–62°; yield of 37%.

1-Phenyl-2-methyl-2-aminopropanol (II). A.—Sodium amalgam, prepared from 27.6 g. (1.2 moles) of sodium and 900 g. of mercury, was added, in portions, over a one-hour period to a stirred solution of 19.5 g. (0.1 mole) of the nitro alcohol (I) in a mixture of 100 ml. of alcohol, 100 ml. of glacial acetic acid and 50 ml. of water. Then, after one-half hour, the mercury was separated. The solution was filtered, diluted with water to 500 ml. and concentrated under reduced pressure to about 250 ml. to remove the alcohol. Acetic acid (6 ml.) and sufficient water to redissolve the sodium acetate which began to precipitate were added.

The solution was washed with ether and made basic with 40% aqueous sodium hydroxide. The amino alcohol which separated was extracted with ether, the ether solution was washed with a little water and dried over anhydrous sodium carbonate. Distillation of the ether and recrystallization of the residue from 200 ml. of heptane gave the amino alcohol as colorless crystals, m. p. 100–101°, in a yield of 41%; reported[2b] m. p. 100–101°.

Anal. Calcd. for $C_{10}H_{15}NO$: N, 8.48. Found: N, 8.68.

B.—A solution of 39 g. (0.2 mole) of the nitro alcohol in a mixture of 150 ml. of alcohol, 165 ml. of glacial acetic acid and 200 ml. of water was stirred with 78.5 g. (1.2 moles) of zinc dust for six hours at 60–70°. Small portions of water were added from time to time to redissolve the precipitate which formed. The mixture was diluted with 350 ml. of water and the unreacted zinc was filtered. The filtrate was washed with ether and made basic with 600 ml. of 40% aqueous sodium hydroxide. The amine which separated was extracted with ether and the ether solution was washed with 40% sodium hydroxide followed by water. After drying over anhydrous sodium carbonate, the ether was distilled and the solid residue was recrystallized from heptane to give the amino alcohol as colorless crystals in a yield of 80–88%, m. p. 101–102°.

The hydrochloride, prepared by adding one equivalent of 2-propanolic hydrogen chloride to a cold solution of the base in 2-propanol and diluting the solution with diisopropyl ether, melted at 201–202° after recrystallization from ethanol–anhydrous ether.

Anal. Calcd. for $C_{10}H_{16}NOCl$: N, 6.95; Cl, 17.58. Found: N, 6.99; Cl, 17.45.

C.—The nitro alcohol (9.8 g., 0.05 mole) was hydrogenated in a mixture of 125 ml. of ethanol and 24 ml. of glacial acetic acid with 2 g. of palladium–charcoal catalyst[10] at 80° and 60 pounds pressure. The theoretical amount of hydrogen was absorbed in about five hours.

The solvent was distilled, the residue was dissolved in 30 ml. of 28% ammonium hydroxide and the solution was saturated with sodium sulfate and cooled. The amino alcohol which separated was extracted with ether, the ether solution was washed with a little cold water and dried over anhydrous sodium carbonate. The crystalline residue remaining after distillation of the ether was recrystallized from a mixture of 10 ml. of benzene and 75 ml. of hexane to give 6.3 g. (76%) of colorless crystals, m. p. 99–101°.

α,α-Dimethyl-β-phenylethylamine (III).—A mixture of 66 g. (0.4 mole) of the amino alcohol (II), 20 g. of red phosphorus and 170 ml. of 57% hydriodic acid was refluxed for twenty-five hours. After standing twelve hours, a large amount of crystalline material had separated from the solution.

The reaction mixture was diluted with 700 ml. of water and was filtered through an asbestos mat to remove the phosphorus. The yellow filtrate was treated with a few crystals of sodium thiosulfate to remove any free iodine and was then made basic with 40% sodium hydroxide. The amine which separated was extracted with ether and the ether solution was washed with water and dried over anhydrous sodium carbonate. After removal of the ether, the residual oil was distilled to give the amine as a colorless oil in a yield of 80–88%, b. p. 89–90° at 10 mm., $n^{20}D$ 1.5130; reported b. p. 88–89° at *ca.* 16 mm.,[2b] 203–205° at 760 mm.,[6a] 100° at 21 mm.[5]

Anal. Calcd. for $C_{10}H_{15}N$: N, 9.39. Found: N, 9.44.

The hydrochloride, prepared by passing hydrogen chloride into a solution of the amine in 2-propanol–diisopropyl ether, melted at 199–200° after recrystallization from a mixture of 2-propanol and diisopropyl ether. Reported m. p. 200–201°,[2b] 195–196°,[5] 147–148°.[6b]

Anal. Calcd. for $C_{10}H_{16}NCl$: N, 7.54; Cl, 19.09. Found: N, 7.49; Cl, 19.01.

N,α,α-Trimethyl-β-phenylethylamine. (VI).—The primary amine (III) was methylated by the Decker and Becker method as described by Woodruff, Lambooy and Burt.[11]

A mixture of 29.8 g. (0.20 mole) of III and 23.3 g. (0.22 mole) of freshly distilled benzaldehyde was heated on a steam-bath for one-half hour and was then distilled. The intermediate Schiff base (V) was obtained as a viscous colorless oil in a yield of 95%, b. p. 146–147° at 2.6 mm., $n^{20}D$ 1.5730.

Anal. Calcd. for $C_{17}H_{19}N$: N, 5.90. Found: N, 5.87.

---

e are indebted to the pharmacology staff of Frederick
& Co., Division of Sterling Drug, Inc., for this pharmacologi-
nary.

l melting and boiling points are uncorrected.

(10) "Organic Syntheses," John Wiley & Sons, New York, N. Y., Vol. 26, 1946, p. 78, catalyst D.

(11) Woodruff, Lambooy and Burt, THIS JOURNAL, **62**, 922 (1940).

The Schiff base (45 g., 0.19 mole) and 28.4 g. (0.20 mole) of methyl iodide were heated in a sealed tube at 100–110° for twenty-eight hours. The contents of the tube were then refluxed for one-half hour with 160 ml. of ethanol and 20 ml. of water. The solution was acidified with acetic acid, diluted with 500 ml. of water and concentrated under reduced pressure to about one-half of the original volume to remove the alcohol and benzaldehyde.

The solution was washed several times with ether, made basic with 40% aqueous sodium hydroxide, and the amine which separated as an oil was extracted with ether. The extract was washed with water, dried over anhydrous sodium carbonate, and the solvent removed. The amine boiled at 94–97° (9 mm.); n^{20}D 1.5112; yield 76%.

Anal. Calcd. for $C_{11}H_{17}N$: N, 8.58. Found: N, 8.59.

The hydrochloride, prepared by passing hydrogen chloride into a solution of the base in isopropyl ether, melted at 174–175° after several recrystallizations from 2-propanol-diisopropyl ether; reported[2b] m. p. 174–175°.

Anal. Calcd. for $C_{11}H_{18}NCl$: N, 7.01; Cl, 17.75. Found: N, 7.14, Cl, 17.65.

α,α-Dimethyl-β-cyclohexylethylamine (IV) and N,α,α-Trimethyl-β-cyclohexylethylamine (VII).—By the catalytic hydrogenation procedure previously described,[2a] the primary amine (IV) was obtained as a colorless oil in a yield of 89%, b. p. 75–76° at 7 mm., n^{20}D 1.4586, and the secondary amine (VII) as a colorless oil in a yield of 80%, b. p. 84–86° at 6 mm., n^{20}D 1.4640.

Anal. of IV. Calcd. for $C_{10}H_{21}N$: N, 9.02. Found: N, 8.80.

Anal. of VII. Calcd. for $C_{11}H_{23}N$: N, 8.27. Found: N, 8.44.

The hydrochlorides were prepared by passing hydrogen chloride into isopropyl ether solutions of the bases. The hydrochloride of IV melted at 158–159° after several recrystallizations from isopropyl ether containing 5% of 2-propanol.

Anal. Calcd. for $C_{10}H_{22}NCl$: N, 7.31; Cl, 18.49. Found: N, 7.31; Cl, 18.35.

The hydrochloride of VII melted at 153–154° after recrystallization from 2-propanol–diisopropyl ether.

Anal. Calcd. for $C_{11}H_{24}NCl$: N, 6.80; Cl, 17.24. Found: N, 6.70; Cl, 17.11.

Summary

Two β-cyclohexylalkylamines, α,α-dimethyl-β-cyclohexylethylamine and its N-methylated derivative, have been prepared by catalytic hydrogenation of the corresponding phenyl analogs.

The synthesis of the phenyl intermediates is described and a pharmacological summary of the pressor activity of the phenyl and cyclohexylalkylamines is presented.

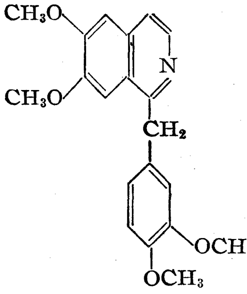
DETROIT, MICHIGAN RECEIVED OCTOBER 1, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

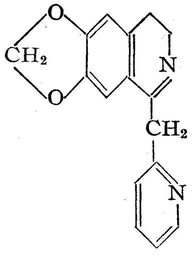
Some Dihydroisoquinolines and their Absorption Spectra

BY JOHN L. BILLS[1] AND C. R. NOLLER

The pharmacological properties of the pyridyl analogs of papaverine (I) would be of interest. Clemo, McIlwain and Morgan[2] have synthesized what was believed to be 1-(α-picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (II). They attempted to dehydrogenate both the dihydroisoquinoline and the tetrahydroisoquinoline derived from it to the isoquinoline, but were unsuccessful. The present work attempted to obtain the isoquinoline by the Pictet and Gams synthesis[3] in which the amide of a β-hydroxy-β-phenylethylamine is dehydrated, and to extend the efforts of Clemo, McIlwain and Morgan to dehydrogenate the hydroisoquinolines, but none of these attempts was successful.



I



II

During the course of the work the greater depth of color of the picolyldihydroisoquinoline and its hydrochloride compared with the 1-methyl or 1-benzyl derivatives prompted an investigation of their absorption spectra in order to obtain further information concerning their structure. Figure 1 gives the absorption in 95% ethyl alcohol of what were considered to be the 1-methyl-, 1-benzyl- and 1-(α-picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinolines. It is seen at once that whereas the curves for the 1-methyl and 1-benzyl derivatives are very similar, they differ markedly from that for the 1-(α-picolyl) derivative. This difference might be due to the presence of the nitrogen in the pyridine ring, or to the position of the double bond which might be either endocyclic or exocyclic to the isoquinoline ring. If one compares the curves for stilbene and α-stilbazole[4] (2 and 3, Fig. 2), it is evident that the introduction of a nitrogen into one of the rings has little effect on the absorption, and it appears, therefore, that the difference in absorption depends on the position of the double bond. Which compound or compounds contain the double bond in the exocyclic position can be determined by recalling that the 1-methyl and 1-benzyl derivatives have practically identical absorption spectra. If the double bor were exocyclic, one would expect the spectrur the 1-benzyl derivative to be shifted marke

---

(1) Du Pont Fellow in Chemistry, 1946–1947.

(2) Clemo, McIlwain and Morgan, *J. Chem. Soc.*, 610 (1936).

(3) Pictet and Gams, *Ber.*, **42**, 2943 (1909).

(4) Blout and Eager, THIS JOURNAL, **67**, 1315 (1945).

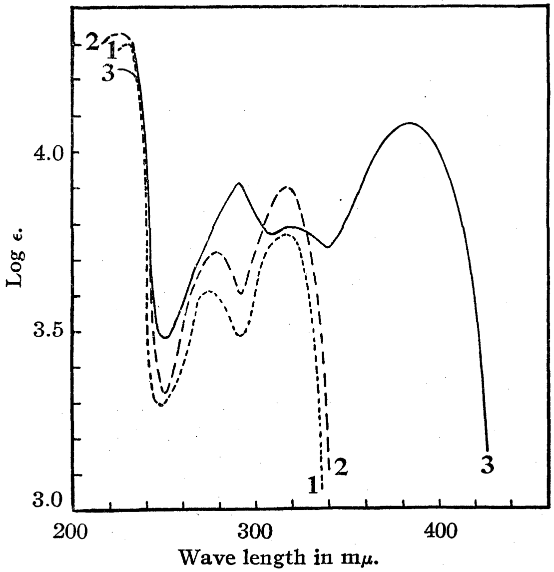
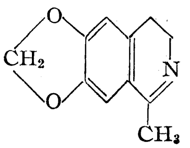
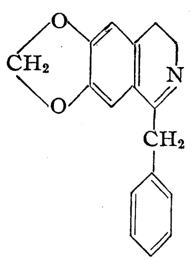


Fig. 1.—Ultraviolet absorption spectra: curve 1, - - - -, structure III; 2, — — — —, structure IV; ——, structure V; all in ethyl alcohol.

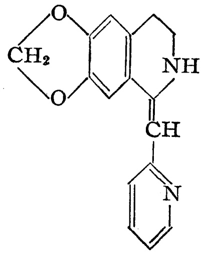
the visible because of the conjugation between the two aromatic rings. For example the maximum for styrene[5] (Curve 1, Fig. 2) is shifted 45 mμ toward the visible, and the intensity of the absorption is greatly increased by conjugation with the second benzene ring in stilbene (Curve 2, Fig. 2). On this basis, the three compounds as free bases can be considered to be 1-methyl-3,4-dihydro-6,7-methylenedioxyisoquinoline (III), 1-benzyl-3,4-dihydro-6,7-methylenedioxyisoquinoline (IV), and 1-(α-picolal)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (V).



III



IV



V

If one compares the absorption of the three compounds in 1.5 *N* alcoholic hydrogen chloride, an entirely different result is obtained (Fig. 3). The spectra for the 1-methyl- and 1-benzylisoquinolines have been spread out considerably toward the visible. In the case of the 1-(α-picolyl)-isoquinoline the position of the maximum nearest the visible has not changed appreciably, but the other maxima have shifted to shorter wave lengths, and all intensities have been changed considerably so that the spectrum now closely resembles that of the other two compounds. Hence there is little

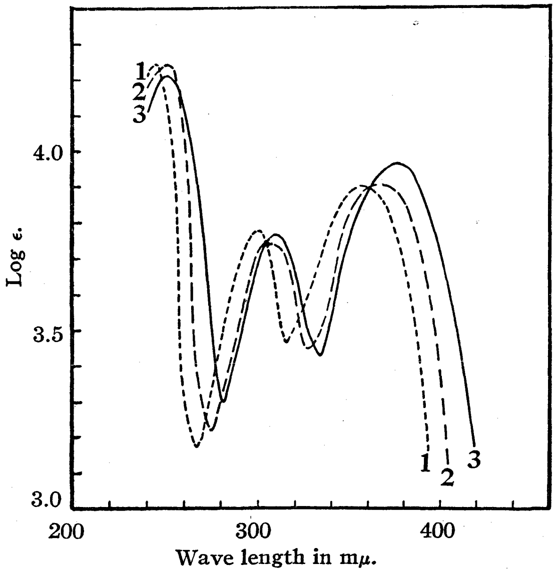
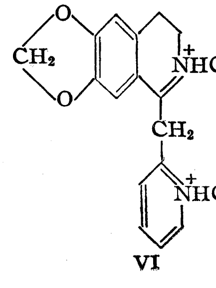
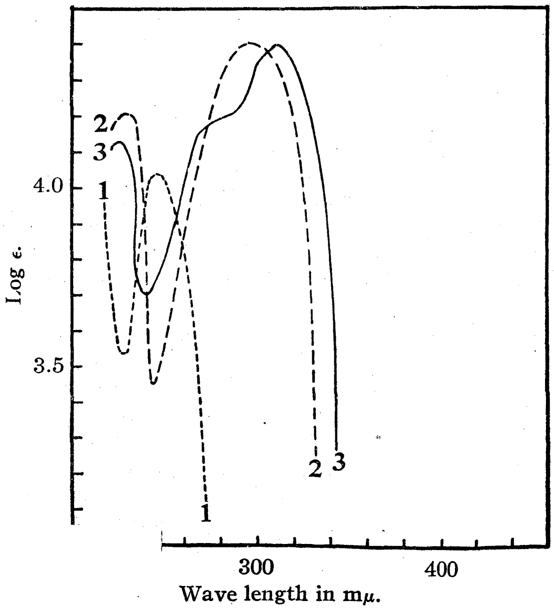


Fig. 3.—Ultraviolet absorption spectra: curve 1, - - - -, hydrochloride of III; 2, — — — —, hydrochloride of IV; 3, ——, dihydrochloride of VI; all in ethyl alcohol.



VI



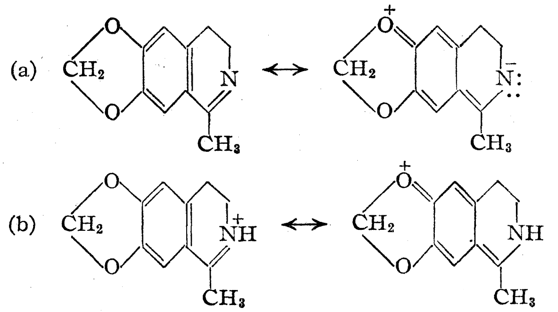
violet absorption spectra: curve 1, - - -, —, stilbene; 3, ——, α-stilbazole; all in

---

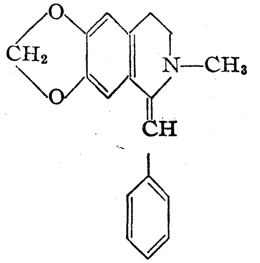
s and Amagat, *Bull. soc. chim.*, [4] 51, 965 (1932).

doubt that the hydrochloride of the 1-(α-picolyl)-isoquinoline has structure VI. It is of interest that the spectra of the hydrochlorides of the 1-methyl and 1-benzyl derivatives in approximately 2×10^{-5} molar solutions in 95% alcohol (not shown in the figures) indicate that they are dissociated to the free base to the extent of 35 and 40%, respectively, whereas the dihydrochloride of the 1-(α-picolyl) derivative shows little dissociation.

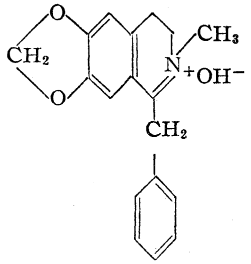
The shift in the absorption toward the visible in going from the free base to the hydrochloride may be explained by assuming that bond resonance for the free base would require a separation of charge within the molecule (a), whereas for the hydrochloride bond resonance can occur without a separation of charge (b). Hence the latter process would take place more readily and could be brought about by light of longer wave length.



As further evidence concerning the structure of the picolyl derivative, it was considered desirable to determine the absorption spectrum of 1-benzal-1,2,3,4-tetrahydro-2-methyl-6,7-methylenedioxyisoquinoline (VII), in the belief that it should resemble the 1-(α-picolal) derivative. Instead, the curve for the free base in 95% ethyl alcohol (1, Fig. 4) was almost identical with that for the chloride in 1.5 *N* alcoholic hydrogen chloride (2, Fig. 4) and for the hydrochloride of the 1-(α-picolyl) derivative (3, Fig. 3). Undoubtedly the free base (VII) is converted in 95% ethyl alcohol into the quaternary ammonium hydroxide (VIII) by the addition of water. To check this point the absorption of the free base in 0.7 *N* alcoholic sodium hydroxide solution was determined. The absorption changed markedly (3, Fig. 4) and now resembled that of the free base of the 1-(α-picolal)-isoquinoline (3, Fig. 1). The presence of sodium hydroxide had no appreciable effect on any of the other bases.



VII



VIII

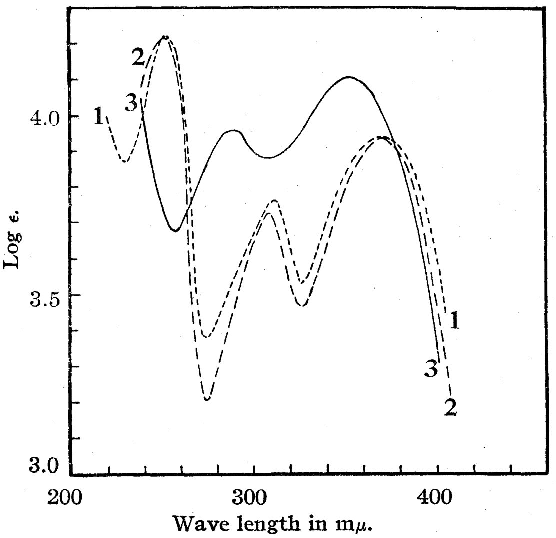
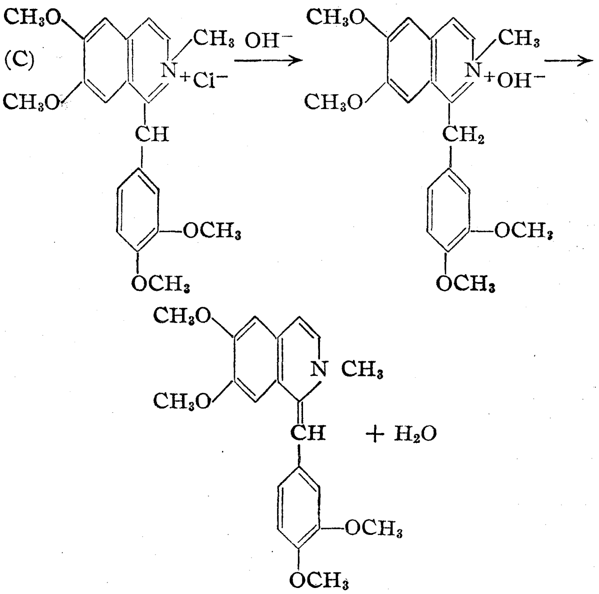


Fig. 4.—Ultraviolet absorption spectra: curve 1, - - - -, structure VIII in ethyl alcohol; 2, — — —, structure VIII in 1.5 *N* alcoholic hydrogen chloride; 3, ——, structure VII in 0.77 *N* alcoholic sodium ethoxide.

It is known that the quaternary salts of papaverine yield N-alkyl isopapaverines on reaction with concentrated alkali (c). It is evident from the above absorption spectra that the proof of structure of the N-alkylisopapaverines based on the production of veratric acid and N-alkyldimethoxyisoquinolones by oxidation with potassium permanganate[6] depends on the oxidation being carried out in alkaline solution, since in neu-



---

[6] For references see Small and Lutz, "Chemistry of the Opium Alkaloids," U. S. Government Printing Office, Washington, 1932, p. 10 ff.

tral solution the N-alkylisopapaverines undoubtedly have a structure analogous to VIII rather than to VII.

The authors are indebted to Professor Melvin Calvin of the University of California for his helpful assistance in interpreting the absorption spectra.

Experimental

β-(3,4-Methylenedioxyphenyl)-ethylamine (Homopiperonylamine).—Piperonal was reduced to piperonyl alcohol in 93% yield in methyl alcohol solution using hydrogen at 800 lb. and 120° and Raney nickel catalyst,[7] or in 90% yields by a crossed Cannizzaro reaction.[8] The piperonyl alcohol was converted to the chloride in 96% yield using concentrated hydrochloric acid and calcium chloride.[7] The chloride was converted to the cyanide in 81% yield by treating 1 mole with 3.5 moles of sodium cyanide and 0.05 mole of mercuric cyanide in 250 cc. of water at 75–80° for six hours.[7] The cyanide was reduced to the amine in 85% yield.[9]

The amine could be prepared in 79% yield by the catalytic reduction of 3,4-methylenedioxy-ω-nitrostyrene.[10] The optimum conditions were the dropwise addition of a solution of 0.01 mole of the nitrostyrene in 50 cc. of dioxane and 0.6 cc. of concentrated sulfuric acid, to a stirred suspension of 0.7 g. of reduced platinum oxide in 50 cc. of dioxane in the presence of hydrogen at atmospheric pressure. Because of the easy preparation of the nitrostyrene this procedure is advantageous for the preparation of small quantities.

Methyl α-Pyridylacetate.—A solution of α-picolyllithium was prepared from 46.5 g. (0.5 mole) of α-picoline according to the procedure given in "Organic Syntheses."[11] While the stream of purified nitrogen continued to flow through the open stopcock of the separatory funnel, the condenser was replaced by a stopper, the stirrer removed, and the central neck fitted with a piece of 8-mm. glass tubing bent in the form of a U and of such dimensions that one leg reached to the bottom of the flask and the other over a 2-liter beaker containing 1 kg. of crushed solid carbon dioxide. When the stopcock of the separatory funnel was closed, the solution was forced onto the solid carbon dioxide which was stirred continuously. After the excess carbon dioxide had evaporated, 500 cc. of water was added, and most of the cream-colored solid dissolved. The mixture was filtered to remove about 10 g. of insoluble material, the filtrate separated with a separatory funnel, and the aqueous layer extracted three times with 100-cc. portions of ether.

The aqueous solution was transferred to a 3-liter beaker, diluted with 1500 cc. of water, and acetic acid added until Hydrion test paper indicated a *p*H of 4. A solution of 37.5 g. (0.15 mole) of copper sulfate pentahydrate in 300 cc. of water then was added gradually with good stirring. After the addition of the first 50 cc. of copper sulfate solution, the mixture was stirred for five minutes to ensure precipitation of the copper salt in a crystalline form before further addition. The precipitate was filtered and washed on the filter with water until the filtrate had only a faint bluish tinge. The air-dried precipitate weighed 40–42 g. (48–50%).

Dry hydrogen chloride was passed into a suspension of 40 g. (0.12 mole) of the dry copper pyridylacetate in 125 cc. of methyl alcohol until solution was complete. Then hydrogen sulfide was passed into the solution, the copper sulfide removed by filtration, and the filtrate saturated with hydrogen chloride. After allowing to stand for three days at room temperature, the solution was concentrated at reduced pressure to 300 cc., and solid sodium bicarbonate was added to neutralize the remaining hydrogen chloride. Dilution with 1500 cc. of water, extraction with two 200-cc. portions of benzene, concentration of the extract at reduced pressure, and distillation of the residue gave 20–22 g. (55–61%), b. p. 126–127° (15 mm.). The boiling point reported for the ester prepared through the anilide, which had been obtained by Beckmann rearrangement of the oxime of 2-phenacylpyridine, is 123° (12 mm.)[12] Ziegler and Zeiser[13] have reported that the carbonation of α-picolyllithium with gaseous carbon dioxide yields only α-picoline.

N-Acetylhomopiperonylamine.—Ten grams (0.06 mole) of homopiperonylamine was added to 10 g. (0.1 mole) of acetic anhydride. After the reaction was complete the acetic acid and excess acetic anhydride were removed by distillation at reduced pressure. The residue solidified on cooling and was recrystallized from ether giving 11.5 g. (93%) of white N-acetylhomopiperonylamine melting at 108–109°. Kaufmann and Radosevic[14] reported 101° for the product obtained by the Beckmann rearrangement of piperonylacetoxime.

N-Phenylacetylhomopiperonylamine.—Ten grams (0.06 mole) of homopiperonylamine and 12 g. (0.08 mole) of phenylacetyl chloride were shaken together in 200 cc. of a 10% potassium hydroxide solution. A thick, viscous, pale yellow oil was formed which soon solidified and was filtered from the aqueous solution. After crystallizing from ethyl alcohol–water, 16 g. (92%) of N-phenylacetylhomopiperonylamine was obtained as fine white needles melting at 96–97°. The compound prepared by Decker[15] from phenylacetic acid and homopiperonylamine melted at 96°.

N-(α-Pyridylacetyl)-β-phenylethylamine.—A mixture of 9.2 g. (0.076 mole) of β-phenylethylamine and 11.4 g. (0.076 mole) of methyl α-pyridylacetate in a 50-cc. round-bottomed flask equipped with an air-cooled reflux condenser was heated in an oil-bath at 200°. At the end of four hours the condenser was removed and the mixture heated an additional two hours. The reaction mixture was poured into a beaker and solidified on cooling. After crystallizing from benzene, 10 g. (55%) of N-(α-pyridylacetyl)-β-phenylethylamine was obtained melting at 74–75°. Three additional recrystallizations from ether raised the melting point to 75–76°.

Anal.[16] Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71. Found: C, 74.81; H, 6.67.

N-(α-Pyridylacetyl)-homopiperonylamine.—A mixture of 3 g. (0.018 mole) of homopiperonylamine and 3 g. (0.020 mole) of methyl α-pyridylacetate was heated at 200° for forty-five minutes in 10 cc. of tetralin[17] contained in a 50-cc. round-bottomed flask. A short air condenser was used to return to the reaction mixture the small amount of tetralin and methyl α-pyridylacetate which distilled. During the heating considerable frothing occurred. At the end of forty-five minutes the contents of the flask was poured into a 50-cc. beaker and allowed to cool. Crystallization was induced either by scratching the side of the beaker or by seeding the supersaturated solution with a trace of the amide. The precipitate was filtered and washed with several portions of petroleum ether to give 4.7 g. (92%) of a white product melting at 90–91°. The compound prepared through the ethyl ester in the absence of a solvent melted at 89°.[2]

1-Methyl-3,4-dihydro-6,7-methylenedioxyisoquinoline Hydrochloride.—A solution of 5 g. (0.024 mole) of N-

---

[7] G. A. Alles, private communication.

[8] "Org. Syn.," Coll. Vol. II, 590 (1943).

[9] "Org. Syn.," **23**, 72 (Note 5) (1943).

[10] Schales, *Ber.*, **68**, 1579 (1935).

[11] "Org. Syn.," **23**, 83 (1943). The lithium was cut into thin shavings by means of a spoke-shave mounted in an inverted position on two blocks to a board in such a way that an evaporating dish containing mineral oil could be placed under the blade of the spoke shave. During the cutting the blade was kept lubricated with mineral oil. The shavings dropped directly into the mineral oil and were washed with dry ether just before use.

[12] Oparina, *Khim. Farm. Prom.*, No. 4, p. 12 (1934); *Chem. Zentr.*, **106**, 2536 (1935).

[13] Ziegler and Zeiser, *Ann.*, **485**, 182 (1931).

[14] Kaufmann and Radosevic, *Ber.*, **49**, 680 (1916).

[15] Decker, *Ann.*, **395**, 294 (1913).

[16] Microanalyses for carbon and hydrogen by Huffman Microanalytical Laboratories, Denver, Colo.

[17] Kindler and Peschke, *Arch. Pharm.*, **272**, 236 (1934).

acetylhomopiperonylamine and 10 cc. of phosphorus oxychloride in 25 cc. of anhydrous toluene was heated under reflux for one and one-half hours. The mixture was cooled and added to a large volume of petroleum ether (b. p. 55–85°). The phosphate of the base separated as a dark yellow oil and solidified on standing. This material was crystallized from alcohol–ether to give pale yellow crystals melting with decomposition at 239–240°. The phosphate was dissolved in a little 10% hydrochloric acid and neutralized with potassium hydroxide. The pale yellow oil which separated was extracted with ether and an ethereal solution of dry hydrogen chloride added. The hydrochloride separated as a powdery yellow precipitate, which was filtered and crystallized from absolute ethyl alcohol to give 4.3 g. (79%) of 1-methyl-3,4-dihydro-6,7-methylenedioxyisoquinoline hydrochloride melting at 245–247° (dec.). The melting point has been reported as 242°.[14]

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: Cl, 15.71. Found: Cl, 15.80, 15.82, 15.87.

1-Benzyl-3,4-dihydro-6,7-methylenedioxyisoquinoline Hydrochloride.—A mixture of 5 g. (0.018 mole) of N-phenylacetylhomopiperonylamine and 10 cc. of phosphorus oxychloride in 25 cc. of dry toluene was heated under reflux for two hours. The light red solution was cooled and poured into a large excess of petroleum ether (b. p. 55–85°), and a red oil separated which solidified on standing. It was crystallized from alcohol, dissolved in dilute hydrochloric acid, and the aqueous solution neutralized with sodium hydroxide. The pale yellow oil which separated was extracted with ether and an ethereal solution of dry hydrogen chloride added. The 1-benzyl-3,4-dihydro-6,7-methylenedioxyisoquinoline hydrochloride precipitated as minute pale yellow crystals. After crystallizing from anhydrous alcohol–ether, 3.3 g. (70%) of the hydrochloride was obtained melting at 215–216° (dec.).

Anal. Calcd. for $C_{17}H_{16}ClNO_2$: Cl, 11.75. Found: Cl, 11.90, 11.73.

The picrate after crystallization from alcohol melted at 202–206°.[18]

1-(α-Picolal)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline.—This compound was prepared in 62% yield by the method of Clemo, McIlwain and Morgan,[2] and melted at 102–103°. The dihydrochloride decomposed at 208–209°.

1-Benzyl-2-methyl-3,4-dihydro-6,7-methylenedioxyisoquinolinium Chloride.—A modification of the procedure described by Hamilton and Robinson[19] for the preparation of 1-benzal-2-methyl-1,2,3,4-tetrahydroisoquinoline was used. A mixture of 7 g. (0.026 mole) of 1-benzyl-3,4-dihydro-6,7-methylenedioxyisoquinoline and 4 g. (0.032 mole) of dimethyl sulfate in 75 cc. of benzene was heated, allowing the benzene to distil slowly. The addition compound gradually separated on the bottom of the flask. The sirupy residue which remained after all of the benzene was distilled was dissolved in water, and the aqueous solution was made strongly basic with solid potassium hydroxide. This basic solution was extracted with four 50-cc. portions of ether, the ether extracts dried over sodium sulfate, and an anhydrous ethereal solution of hydrogen chloride added. A pale yellow precipitate formed which was recrystallized from anhydrous alcohol–ether. Six grams (77%) of 1-benzyl-2-methyl-3,4-dihydro-6,7-methylenedioxyisoquinolinium chloride was obtained.

Anal. Calcd. for $C_{18}H_{18}ClNO_2$: Cl, 11.23. Found: Cl, 11.13, 11.41.

Attempt to Dehydrogenate 1-(α-Picolal)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline.—Dehydrogenation was attempted with nitrobenzene in the presence of Raney nickel, with nitric acid in acetic acid,[20] and with permanganate in acetic acid.[21] In no case could an isoquinoline be isolated.

The picolal derivative was hydrogenated to the picolyl derivative, and a benzene suspension of the latter dropped onto a bed of molybdena-alumina catalyst at 250°. Although the catalyst was capable of dehydrogenating tetralin to naphthalene, and tetrahydroquinoline to quinoline quantitatively, the only product that could be isolated from the picolyl derivative was α-picoline.

Aminomethylphenylcarbinol Hydrochloride.—A saturated solution of 23 g. (0.13 mole) of ω-aminoacetophenone hydrochloride, prepared by the procedure of Rupe,[22] in 95% ethyl alcohol was hydrogenated in the presence 0.52 g. of platinum black at 40 lb. gage pressure. A total of 0.15 mole of hydrogen was absorbed. After no more hydrogen was taken up the catalyst was filtered and the filtrate evaporated to dryness at reduced pressure. Twenty-two grams (97%) of aminomethylphenylcarbinol hydrochloride was obtained melting at 176–177° (dec.). The material could be crystallized from alcohol–ether to give small white crystals of the hydrochloride, but the melting point was not changed. The picrate melted at 153–154° after crystallization from alcohol, and the benzoyl derivative melted at 148.5–149.5° after crystallization from dilute alcohol. Kolshorn[23] prepared the free base by reducing isonitrosoacetophenone with sodium amalgam but could not obtain the hydrochloride in crystalline form. His picrate melted at 146–147° and his benzoyl derivative at 144–145.5°.

Aminomethyl-3,4-dimethoxyphenylcarbinol Hydrochloride.—This compound was prepared by catalytic hydrogenation of ω-aminoacetoveratrone hydrochloride by the same procedure used for the preparation of aminomethylphenylcarbinol hydrochloride. The reduction was nearly quantitative. The material melted at 168–170° after crystallization from ethyl alcohol. Rosenmund[24] reported 163° for the melting point of the hydrochloride prepared by the reduction of α-(3,4-dimethoxyphenyl)-β-nitroethyl alcohol.

N-(α-Pyridylacetyl)-aminomethylphenylcarbinol.—Thirteen grams (0.075 mole) of aminomethylphenylcarbinol hydrochloride was added to 30 cc. of dilute sodium hydroxide. The two layers were separated, and the aqueous layer was extracted with two 15-cc. portions of benzene. The benzene extracts were added to the free amine, the benzene solution was washed once with water, and the benzene removed by distillation at reduced pressure. Ten grams (0.073 mole) of free amine was obtained, which was added to 15 g. (0.10 mole) of methyl α-pyridylacetate, and the mixture was heated for two hours in an oil-bath at 200°. It then was cooled and the green mass poured into 100 cc. of benzene. After several days the material separated as fine white crystals which were filtered and recrystallized from benzene. Nine grams (48%) of N-(α-pyridylacetyl)-aminomethylphenylcarbinol melting at 114–115° was obtained. A sample was prepared for analysis by recrystallizing four times from benzene and drying at 100° at reduced pressure. The melting point of the purified product was unchanged at 114–115°.

Anal.[16] Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.67; H, 6.29. Found: C, 70.91; H, 6.24.

A picrate was prepared by adding an alcoholic picric acid solution to the base dissolved in alcohol. An orange sirup precipitated and solidified on long standing. After recrystallizing once from benzene–alcohol and twice from ethyl acetate the picrate melted at 131–132°.

Attempts to cyclize the free base to 1-(α-picolyl)-isoquinoline using phosphorus pentoxide in toluene[25] or in tetralin[26] were unsuccessful. Red oils were obtained from which only α-picoline could be isolated as the picrate.

N-(α-Pyridylacetyl)-aminomethyl-(3,4-dimethoxyphenyl)-carbinol.—An alcoholic solution of aminomethyl-(3,4-dimethoxyphenyl)-carbinol was prepared by neutralizing 3.5 g. (0.011 mole) of the hydrochloride in 15 cc. of alcohol

---

[18] Decker, Kropp, Hoyer and Becker, *Ann.*, **395**, 305 (1913).

[19] Hamilton and Robinson, *J. Chem. Soc.*, **109**, 1029 (1916).

[20] Rodionov and Yavorskaya, *J. Gen. Chem.* (*U. S. S. R.*), **11**, 446 (1941); *C. A.*, **35**, 6592 (1941).

[21] Pictet and Kay, *Ber.*, **42**, 1973 (1909).

[22] Rupe, *ibid.*, **28**, 254 (1895).

[23] Kolshorn, *ibid.*, **37**, 2474 (1904).

[24] Rosenmund, *ibid.*, **46**, 1049 (1913).

[25] Späth and Lang, *Monatsh.*, **42**, 273 (1921).

[26] Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930).

with sodium ethylate using phenolphthalein as an indicator. The precipitated sodium chloride was removed by filtration and 2.5 g. (0.016 mole) of methyl α-pyridylacetate added. The mixture was heated gradually in a 50-cc. round-bottomed flask to 200° by allowing the alcohol to escape through a short air-cooled reflux condenser. The mixture was heated at 200° for twenty minutes. On cooling, a thick red-brown resin was obtained which was soluble in benzene, alcohol, or chloroform, but insoluble in ether or petroleum ether. A number of attempts to crystallize the amide were unsuccessful. Some of this sirupy material was dissolved in ethyl alcohol, and an alcoholic solution of picric acid was added. A resinous precipitate formed which could not be made to solidify. An anhydrous alcoholic solution of hydrogen chloride was added to an anhydrous alcoholic solution of the amide. Upon the addition of dry ether a sirupy hydrochloride precipitated which did not crystallize even at −80°. The solvent was decanted and the hydrochloride placed in a vacuum desiccator. The material gradually crystallized but on exposure to the atmosphere immediately became a sticky mass. The dried hydrochloride melted with decomposition at 105–110°. No analysis was made.

Attempts to cyclize the crude free base by the procedures of Clemo, McIlwain and Morgan,[2] of Pictet and Gams,[3] or of Bruckner and Fodor,[27] gave tars from which only α-picoline could be isolated as the picrate.

Absorption Spectra.—Absorption spectra not previously reported were obtained with a Beckman Quartz Spectrophotometer, Model DU, using 1-cm. quartz cells, a hydrogen discharge lamp for the ultraviolet light source, and a tungsten filament lamp for wave lengths above 325 mμ. The concentrations were from 1 to 2 × 10^{-5} molar in 95% ethyl alcohol or alcohol containing dry hydrogen chloride or sodium hydroxide. In each case freshly recrystallized material was used, and the absorption determined immediately without allowing the solutions to stand. If these precautions were not taken, inconsistent results sometimes were obtained. The spectra for styrene,[5] stilbene[4] and α-stilbazole[4] were taken from the literature.

Summary

It is concluded from their absorption spectra that the cyclization products of N-acetyl- and N-phenylacetylhomopiperonylamine are 1-methyl- and 1-benzyl-3,4-dihydro-6,7-methylenedioxyisoquinoline, respectively, whereas the cyclization product of N-(α-pyridylacetyl)-homopiperonylamine is 1-(α-picolal)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline. Reaction of the last compound with hydrochloric acid converts it into 1-(α-picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline hydrochloride. It is further concluded that 1-benzal-1,2,3,4-tetrahydro-2-methyl-6,7-methylenedioxyisoquinoline has the structure corresponding to this name when in solution, only in the presence of strong bases, and that when dissolved in alcohol alone it is largely in the form of the quaternary hydroxide. Further attempts to synthesize 1-(α-picolyl)-isoquinolines have been unsuccessful.

STANFORD UNIVERSITY, CALIFORNIA

RECEIVED JULY 12, 1947

---

[27] Bruckner and Fodor, *Ber.*, **71**, 547 (1938).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Reaction of 2,5-Dimethylfuran with *p*-Nitrobenzenediazonium Chloride

BY RICHARD H. EASTMAN AND FRANCIS L. DETERT[1]

The ease with which the furan nucleus undergoes typical aromatic substitution reactions is well known[2] and suggested to us that alkylated furans, as analogs of mesitylene,[3] should undergo a coupling reaction with reactive dizonium halides. Both Gilman and Ochaiai[4] have reported that furan reacts with diazonium halides. Johnson[5] has reported formation of 2-(and some 3-)arylfurans by interaction of furan with a diazotate. Recently, a report[6] of the coupling of sodium *anti-p*-nitrobenzenediazotate with ethyl 2-furylcarbamate has appeared.

We chose for our study of this reaction an available furan with unsubstituted β-positions, 2,5-dimethylfuran and the reactive *p*-nitrobenzenediazonium chloride. These components were combined in an ice-cold aqueous alcoholic solution that contained an excess of potassium acetate as a buffer.[7] The initial coupling product separated as a semi-solid red mass which could not be crystallized to a state of assured purity. When the initial coupling product was heated *in vacuo* or hydrolyzed with dilute acid it was converted in good yield to a substance $C_{12}H_{11}O_3N_3$ which is formulated as 1-*p*-nitrophenyl-3-acetyl-5-methylpyrazole (II) on the basis of its giving a positive iodoform reaction and its smooth oxidation to an acid, $C_{11}H_9O_4N_3$ shown to be identical with 1-*p*-nitrophenyl-5-methyl-3-pyrazolecarboxylic acid (III), m. p.[8] 216–217°, prepared by an unequivocal synthesis.

Consideration of the properties and easy transformation to II of the initial, red coupling product (*cf.* Experimental Part) suggests the tentative structual assignment I for this material.

---

[1] Part of the work described in this article is taken from a thesis presented to Stanford University by Francis L. Detert in partial fulfillment of the requirements for the degree of Master of Science.

[2] Gilman and Towne, *Rec. trav. chim.*, **51**, 1054 (1932); Gilman, Calloway and Burtner, THIS JOURNAL, **57**, 906 (1935).

[3] Meyer and Tochtermann, *Ber.*, **54**, 2283 (1921).

[4] Gilman, Wooley and Vanderwal, *Proc. Iowa Acad. Sci.*, **29**, 176 (1932); Ochaiai, *J. Pharm. Soc., Japan*, **58**, 1025 (1938).

[5] A. W. Johnson, *J. Chem. Soc.*, 895 (1946).

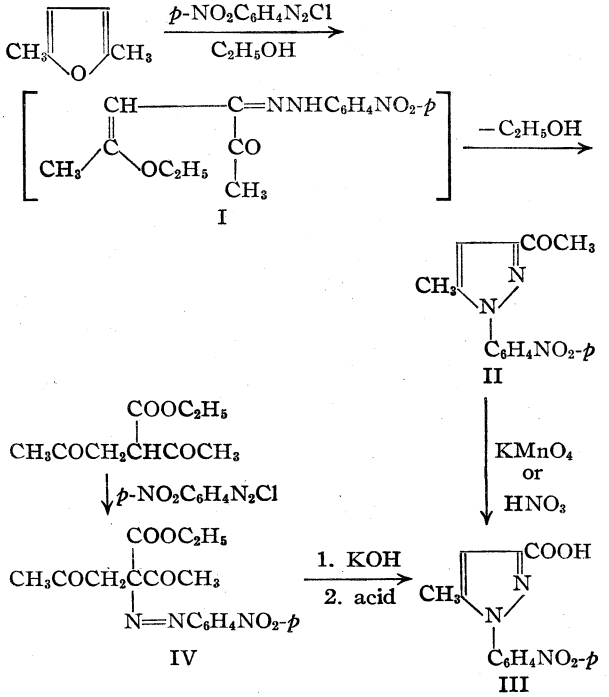
[6] Hurd and Priestley, THIS JOURNAL, **69**, 859 (1947).

[7] Similar reaction conditions were employed by Fischer and Hepp (*Ber.*, **19**, 2251 (1886)) in the successful coupling of pyrrole with diazonium halides, and by Johnson (Ref. 5).

[8] An isomer of this compound, but reported in Beilstein, 4th ed., **25**, 120, as this compound, was prepared by Knorr and Macdonald, *Ann.*, **279**, 224 (1894). It melted at 122° and was prepared by reaction of 1-phenyl-5-methyl-3-pyrazolecarboxylic acid with fuming nitric acid. On repeating this work we obtained an acid of m. p. 153–154° without establishing its identity.

Synthesis of III was accomplished by reaction of ethyl 2-acetyl-2-*p*-nitrophenylazolevulinate (IV) with alcoholic alkali followed by acidification. IV, prepared by the coupling of ethyl acetonylacetoacetate with *p*-nitrobenzenediazonium chloride changed spontaneously into the ethyl ester of III on standing.

The pyrazolecarboxylic acid III was also obtained as one product of the condensation of *p*-nitrophenylhydrazine with the sodium derivative of oxalacetone followed by alkaline hydrolysis and acidification.



Experimental

Reaction of 2,5-Dimethylfuran with *p*-Nitrobenzenediazonium Chloride.—To an ice-cold solution of 4.8 g. of 2,5-dimethylfuran, 250 ml. of ethanol and 15 g. of potassium acetate was added all at once the diazonium salt solution prepared from 7.0 g. of *p*-nitroaniline in 150 ml. of water, 30 ml. of 10% hydrochloric acid, and 3.5 g. of sodium nitrite. The reaction mixture was kept in ice for three hours and then poured into twice its volume of water, giving a gummy, orange solid that was crystallized from benzene to yield 3.9 g. of golden yellow plates which melted at 129–131° with gas evolution. Attempts to prepare sharply melting samples of assured purity failed. When a sample was heated *in vacuo* at 100°, quantitative conversion to **1-*p*-nitrophenyl-3-acetyl-5-methylpyrazole** (II) of m. p. 134–135° occurred. This initial coupling product is tentatively formulated as I.

When the coupling reaction was carried out under the same conditions but using methanol as solvent the initial product was obtained in the form of a gummy, red solid which could not be purified but which, on acid hydrolysis underwent conversion to II in good yield (see below).

Hydrolysis of Initial Coupling Product.—The above described red product (4.0 g.) from the coupling reaction carried out in methanol was boiled for a few minutes in 25 ml. of alcohol which contained 3 ml. of 6 *N* hydrochloric acid. When the hydrolysis mixture was poured into an excess of water a red solid separated that on crystallization from aqueous alcohol and treatment with decolorizing carbon yielded pale-yellow needles (2.2 g.) of m. p. 134–135°. The substance was 1-*p*-nitrophenyl-3-acetyl-5-methylpyrazole and readily gave iodoform, m. p. 115–118°, with sodium hypoiodite.

Anal. Calcd. for $C_{12}H_{11}O_3N_3$: C, 57.8; H, 4.52. Found: C, 57.9; H, 4.68.

Under the same conditions of hydrolysis the initial deep-yellow coupling product of m. p. 129–131° (1.5 g.) from the coupling reaction carried out in ethanol yielded 0.90 g. of pale-yellow needles of m. p. 134–135° that showed no depression when mixed with the materials of the same melting point obtained as described above.

Anal. Found: C, 58.0; H, 5.00.

Oxidation of 1-*p*-Nitrophenyl-3-acetyl-5-methylpyrazole (II).—To 2.5 g. of II suspended in 200 ml. of water containing 5 ml. of 5% sodium hydroxide solution was added a solution of 3.2 g. of potassium permanganate in water. The mixture was heated at 60° until the permanganate color had disappeared, and after the precipitated manganese dioxide had been destroyed by the addition of sodium bisulfite, the tan solid which remained was separated, extracted with ether, and dissolved in dilute sodium hydroxide. The alkaline solution was filtered, and from the filtrate there was obtained on acidification a gelatinous greenish precipitate which was separated and crystallized from aqueous alcohol to yield 0.4 g. of white micro-crystals of m. p. 216–217°.

Anal. Calcd. for $C_{11}H_9O_4N_3$: C, 53.4; H, 3.67. Found: C, 53.5, 53.9; H, 3.75, 3.61.

The identity of this material and **1-*p*-nitrophenyl-5-methyl-3-pyrazolecarboxylic acid** (III), the synthesis of which is described below, was established in a mixed melting point determination (m. p. 216–217°).

When 1.5 g. of II was boiled with 15 ml. of concentrated nitric acid until brown fumes were no longer evolved there resulted after crystallization of the crude acid product from aqueous alcohol 0.8 g. of white micro-crystals of m. p. 216–217°, taken alone or mixed with the material of the same melting point described above.

Ethyl 2-Acetyl-2-*p*-nitrophenylazolevulinate (IV).—To an ice-cold solution of 17.0 g. of ethyl acetonylacetoacetate[9] and 65 g. potassium acetate in 250 ml. of alcohol was added all at once the filtered diazonium salt solution prepared from 13.8 g. of *p*-nitroaniline in 100 ml. of 6 *N* hydrochloric acid and 7.0 g. of sodium nitrite. The mixture became deep orange immediately and after fifteen minutes at ice temperature the addition of 500 ml. of water threw down a heavy, red-orange precipitate that was separated and crystallized from alcohol to yield 17.0 g. of ethyl 2-acetyl-2-*p*-nitrophenylazolevulinate (IV) of m. p. 80–81°.

Anal. Calcd. for $C_{15}H_{17}O_6N_3$: C, 53.8; H, 5.11. Found: C, 53.7, 53.8; H, 5.70, 5.31.

Both the analytical sample and the less highly purified samples of the red-orange IV after two weeks had decomposed with loss of acetic acid to yield a pale-yellow crystalline solid, 3.0 g. of which on two crystallizations from alcohol yielded 1.5 g. of straw-colored needles of m. p. 96–97° which proved to be **ethyl 1-*p*-nitrophenyl-5-methyl-3-pyrazolecarboxylate** (V).

Anal. Calcd. for $C_{13}H_{13}O_4N_3$: C, 56.7; H, 4.74. Found: C, 56.8; H, 4.93.

1-*p*-Nitrophenyl-5-methyl-3-pyrazolecarboxylic Acid (III): (a) **From Condensation of *p*-Nitrophenylhydrazine with Sodium Oxalacetone.** To 3.06 g. of *p*-nitrophenylhydrazine in 35 ml. of glacial acetic acid was added 3.60 g. of sodium oxalacetone dissolved in 10 ml. of water. The reaction mixture was heated for fifteen minutes on the steam-bath and poured into an excess of water. The tan crystalline precipitate which appeared was separated and one-half of it was hydrolyzed by boiling for fifteen minutes with a solution of 6.0 g. of potassium hydroxide in 10 ml. of water and 30 ml. of methanol. The hot hydrol-

---

[9] Ossipow and Korschun, *Chem. Zentr.*, **74**, II, 1281 (1903). Our material had b. p. 97–104° at 2 mm. and d. 1.061 at 21°.

ysis mixture was diluted with an equal volume of water, decolorized with carbon and acidified. The precipitate which appeared was removed from the hot solution by filtration and the filtrate on being cooled deposited 0.14 g. of tan solid which after three crystallizations from glacial acetic acid yielded yellowish-white crystals of m. p. 215–217° taken alone or mixed with the oxidation product (III) of 1-*p*-nitrophenyl-3-acetyl-5-methylpyrazole (II).

(b) **By Hydrolysis of Ethyl 1-*p*-Nitrophenyl-5-methyl-3-pyrazolecarboxylate** (V).—Five-tenths of a gram of the ester (V) was heated on the steam-bath with a mixture of 1 ml. of concentrated hydrochloric acid and 3 ml. of glacial acetic acid for four hours. The hydrolysis mixture was cooled, the solid which crystallized therefrom was separated and crystallized three times from aqueous alcohol to yield 0.15 g. of pure-white, crystalline 1-*p*-nitrophenyl-5-methyl-3-pyrazolecarboxylic acid of m. p. 216.5–217.5° taken alone or mixed with III.

Anal. Found: C, 53.5; H, 4.14.

(c) **By Hydrolysis of Ethyl 2-Acetyl-2-*p*-nitrophenylazolevulinate** (IV).—To one gram of the dye IV in 20 ml. alcohol and 5 ml. water at the boiling point was added 0.4 g. of potassium hydroxide in 5 ml. of water. After three hours of heating, the dark reaction mixture was acidified, and on being cooled the acidic solution deposited a gelatinous yellowish precipitate that was separated and treated with warm dilute solution bicarbonate solution. The cloudy bicarbonate solution was filtered and acidified to yield a yellowish-white precipitate that gave after separation and three crystallizations from glacial acetic acid 0.10 g. of 1-*p*-nitro-phenyl-5-methyl-3-pyrazole carboxylic acid in the form of white needles of m. p. 215.5–216.5° taken alone or mixed with III.

Summary

The furan nucleus of 2, 5-dimethylfuran on reaction with *p*-nitrobenzenediazonium chloride followed by acid hydrolysis of an initial, unstable coupling product is cleaved with the formation of 1-*p*-nitrophenyl-3-acetyl-5-methylpyrazole.

RECEIVED AUGUST 25, 1947

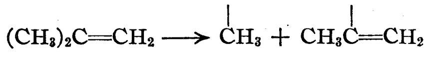
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE CATHOLIC UNIVERSITY OF AMERICA]

The Thermal Decomposition of Mono-olefins: Isobutylene

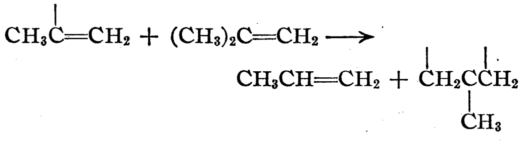
BY FRANCIS OWEN RICE AND W. STUART HAYNES[1]

The mechanism of the thermal decomposition of paraffin hydrocarbons from the free radical standpoint[2] has already been studied in considerable detail and appears to give a satisfactory interpretation of the complicated chemical changes that occur in the pyrolysis of saturated, open chain hydrocarbons. Even when this picture is applied to the decomposition of paraffins as high as the octanes, the amounts of products calculated are in reasonable agreement[3] both qualitatively and quantitatively with the amounts found experimentally.

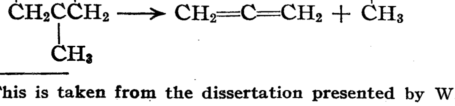
In contrast with the decomposition of paraffin hydrocarbons, the mechanism of olefin decompositions is not well understood in spite of a considerable amount of study. This is surprising because the predictions made on the basis of the free radical theory proposed by Rice[2] are rather straightforward and are shown for example in the case of isobutylene by the equations



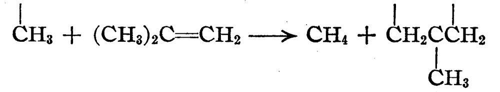
$$(CH_3)_2C{=}CH_2 \longrightarrow \overset{|}{C}H_3 + CH_3\overset{|}{C}{=}CH_2 \tag{1}$$



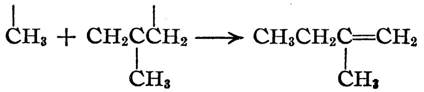
$$CH_3\overset{|}{C}{=}CH_2 + (CH_3)_2C{=}CH_2 \longrightarrow CH_3CH{=}CH_2 + \overset{|}{C}H_2\underset{\underset{CH_3}{|}}{\overset{|}{C}}H_2 \tag{2}$$



$$\overset{|}{C}H_2\underset{\underset{CH_3}{|}}{\overset{|}{C}}H_2 \longrightarrow CH_2{=}C{=}CH_2 + \overset{|}{C}H_3 \tag{3}$$



$$\overset{|}{C}H_3 + (CH_3)_2C{=}CH_2 \longrightarrow CH_4 + \overset{|}{C}H_2\underset{\underset{CH_3}{|}}{\overset{|}{C}}H_2 \tag{4}$$



$$\overset{|}{C}H_3 + CH_2\underset{\underset{CH_3}{|}}{\overset{|}{C}}H_2 \longrightarrow CH_3CH_2\underset{\underset{CH_3}{|}}{C}{=}CH_2 \tag{5}$$

The initial step produces radicals and the final step removes them. Reactions (3) and (4) constitute the chain which yields equal molecular quantities of methane and allene. If the chain is fairly long (50 or more chain cycles), we would expect methane and allene to be the predominant products and to be accompanied by only negligible amounts of other compounds. If, however, the chain is short and consists of only a few cycles, the amount of propylene, methane and other molecules resulting from the non-chain radical reactions would be increased. There are several other non-chain radical reactions that can be written but we have omitted them since they should produce only a small proportion of the decomposition products.

The pyrolysis of isobutylene has been the subject of a number of investigations.[4] Methane, hydrogen, ethylene and propylene were found to constitute the bulk of the gaseous products. Although the conditions were varied widely, allene was found to be completely absent or, at most, present in traces. In all cases the decomposition was accompanied by considerable quantities of oily and tarry material, containing benzene and

---

[1] This is taken from the dissertation presented by W. Stuart Haynes for the degree of Doctor of Philosophy in The Catholic University of America.

[2] F. O. Rice and K. K. Rice, "The Aliphatic Free Radicals," The John Hopkins Press, Baltimore, Md., 1935.

[3] A. Kossiakoff and F. O. Rice, THIS JOURNAL, **65**, 590 (1943).

[4] (a) Hurd and Spence, *ibid*, **51**, 3561 (1929); (b) Hurd and Eilers, *Ind. Eng. Chem.*, **26**, 776 (1934); (c) Tropsch, Parrish and Egloff, *ibid.*, **28**, 581 (1936); (d) Hurd and Blunck, THIS JOURNAL, **59**, 1869 (1937).

its homologs and various polynuclear aromatic ring systems.

In view of this last observation we decided to undertake a new investigation of the isobutylene decomposition with the hope of finding conditions for avoiding the formation of tar and oil. These can only have resulted from successive reactions involving the first products of the decomposition and if we are to understand the mechanism we must be able to identify the primary products of the decomposition before they react further, either with themselves or with the substrate to produce finally tars and oils.

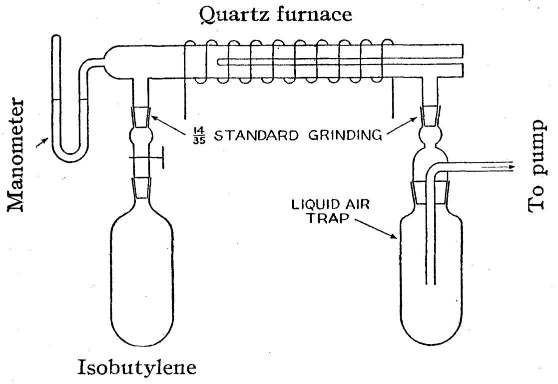


Fig. 1.—Thermal decomposition of isobutylene.

A flow system was used in which the isobutylene was passed through a quartz furnace 8″ × 1″, as shown in Fig. 1. The gases leaving the furnace were passed through two liquid air traps and the non-condensable portion was pumped out through a glycerol pump and collected over a solution of zinc sulfate.

The gases condensed in the traps, consisting of C_1 to C_4 hydrocarbons, were distilled at low temperature in a Podbielniak column and separated into different fractions. Three of our fractions boiled within ±0.3° of the boiling points of methylacetylene, allene and propylene which are reported respectively as −23.3°, −34.3° and −47.7° at 760 mm. pressure. We obtained in this way a fairly good analysis of the condensable products, but in each case the fraction was analyzed in a Shepherd type gas analysis apparatus.[5] The gases not condensed by liquid air were also measured and analyzed.

The identification of the C_3 hydrocarbons was accomplished by hydrogenating a portion of each fraction in the gas analysis apparatus over a nickel catalyst. The lowest boiling fraction (propylene) had one double bond whereas both the other fractions proved to be hydrocarbons having either one triple bond or two double bonds. Additional evidence was obtained by showing that the methylacetylene fraction gave an immediate and copious precipitate with an aqueous solution of ammoniacal silver nitrate. On the other hand, the allene fraction gave a white precipitate with an aqueous solution of mercuric chloride but no precipitate with the ammoniacal silver nitrate solution.

In the series of experiments reported in this paper, the conditions were such that there was practically complete absence of tar or carbon throughout the course of a run. This was accomplished by adjusting the temperature, pressure and contact time to values at which there was no formation of carbonaceous material on the glass walls at the outlet of the furnace. In experimental runs 2, 3, 9 and 10, evidence of some tar formation was noticed, the greatest amounts relative to the quantity of isobutylene used appearing in runs 2 and 10. One observes that in these runs occur the highest temperatures, the greatest contact times, or the highest pressures. Thus by fixing two of these variables and increasing the third, one would get a critical value for each at which incipient tar formation occurs, followed by abundant tar formation for higher values of this variable. The three variables would obviously be interdependent with respect to the conditions under which tar formation will occur.

Table I contains a summary of all the results on the isobutylene decomposition. Figure 2 shows the relation between the pressure and the yield of the various hydrocarbon products. From these results it appears likely that isobutylene decomposes through a free radical mechanism but the chain is rather short since there are appreciable quantities of propylene formed, presumably by some non-chain reaction such as reaction (2). We would not be able to detect the presence of

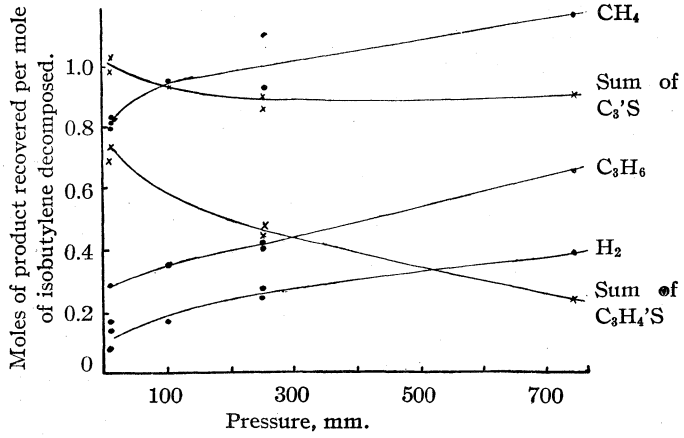


Fig. 2.—Curves showing the relation between the pressure in the furnace and the moles of different products recovered per mole of isobutylene decomposed. Experiments 2 and 3 have been omitted because of the large fraction of isobutylene decomposed and experiment 6 has been omitted because of loss of material.

---

[5] Shepherd, *J. Research Nat. Bur. Standards*, **6**, 121 (1931).

TABLE I

DECOMPOSITION OF ISOBUTYLENE

The last ten rows of figures contain the number of moles of the respective substance recovered per mole of isobutylene decomposed. In Experiment 6 the furnace broke near the end of the run and some material was lost.

Expt.	1	2	3	4	5	6	7	8	9	10
Moles C_4H_8 through furnace	1.21	0.354	0.69	2.89	3.38	2.88	2.98	2.76	1.76	1.30
Per cent. decomposed	2.6	49.5	43.9	7.8	5.6	7.1	5.7	3.6	9.8	5.5
Temp. furnace, °C.	885	945	897	790	790	717	773	714	753	630
Press. in furnace, mm.	8	10	12	8	9	20	100	250	250	743
Contact time, sec.	0.07	0.56	0.29	0.026	0.301	0.053	0.46	0.43	0.42	2.1
H_2	0.17	0.61	0.23	0.08	0.14	0.11	0.17	0.25	0.28	0.39
CH_4	0.81	1.58	0.94	0.73	0.83	0.61	0.95	1.10	0.93	1.16
C_2H_6	0.02	0.00	0.01	0.05	0.03	0.01	0.02		0.03	0.06
C_2H_4	0.07	0.29	0.11	0.05	0.03	0.02	0.04	0.025[a]	0.125	0.27
C_2H_2	0.01	0.19	0.05	0.03	0.02	0.02	0.01		0.01	0.02
C_3H_6	0.20	0.25	0.20	0.29	0.29	0.11	0.35	0.42	0.41	0.66
$CH_2{=}C{=}CH_2$	..	0.07	0.05	0.37	0.49	0.25	0.21	0.23	0.21	0.14
$CH_3C{\equiv}CH$	..	0.36	0.20	0.325	0.25	0.23	0.38	0.26	0.24	0.10
ΣC_3H_4	0.80	0.43	0.25	0.695	0.74		0.59	0.49	0.45	0.24
ΣC_3's	1.00	0.68	0.45	0.985	1.03		0.94	0.91	0.86	0.90

[a] This is the sum of C_2H_6, C_2H_4 and C_2H_2.

pentenes because they would be present in only small quantity and since they boil at a higher temperature than isobutylene, they would be reported as this substance.

We are inclined to think that the methylacetylene is formed from allene by means of a radical chain. A free methyl radical, for example, reacting either with methylacetylene or allene would, in each case, give the same radical $\overset{|}{C}H_2{-}\overset{|}{C}{=}\overset{|}{C}H$. When this radical removes a hydrogen atom from an organic molecule, methylacetylene is formed, if a hydrogen atom attaches itself to the left-hand side of the molecule and allene is formed if a hydrogen atom is attached to the right-hand side of the molecule. We plan to investigate this point in a later paper.

Summary

1. The thermal decomposition of isobutylene probably proceeds through a short chain, producing methane and allene.

2. Under proper conditions of temperature, pressure and contact time, the decomposition of isobutylene occurs without appreciable production of carbonaceous and tarry material.

3. Both allene and methylacetylene are major products of the reaction. It has not yet been determined whether the methylacetylene is produced by isomerization of allene or by molecular dehydrogenation of the isobutylene.

4. Under best conditions there were about 60 moles per cent. yields of allene–methylacetylene based on the decomposed isobutylene.

WASHINGTON, D. C. RECEIVED JULY 25, 1947

[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Apparent Molal Expansibilities of Potassium, Barium and Lanthanum Chlorides as a Function of Concentration and Temperature[1]

BY GRINNELL JONES,[2] E. FOLGER TAYLOR[3] AND RICHARD C. VOGEL[4]

The apparent molal thermal expansibility of a solute may be defined by the equations

$$\phi \bar{E}_2 = V_s\alpha_s - V_w\alpha_w = \left(\frac{\partial \phi V_2}{\partial T}\right)_P \qquad (1)$$

where V_s is the volume of solution containing one mole of solute, V_w is the volume of water used, α_s and α_w are the thermal coefficients of expansion of the solution and water, respectively, and ϕV_2 is the apparent molal volume of the solute.

Gucker[5] has obtained the limiting law for the partial molal expansibility, $\bar{E}_2$ of the solute as a function of the concentration from the Debye–Hückel theory, when $\bar{E}_2$ is defined by the equation

$$\bar{E}_2 = (\partial \bar{V}_2/\partial T)_P \qquad (2)$$

---

(1) This paper represents part of the thesis material submitted by E. Folger Taylor and by R. C. Vogel in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Harvard University, Cambridge, Massachusetts.

(2) Deceased, June 23, 1947.

(3) Present address: Du Pont Company, Waynesboro, Virginia. E. Folger Taylor is responsible for the development of the mercury dilatometer described in this paper and for the studies carried out on water and on solutions of potassium chloride from 20 to 80°.

(4) Present address· Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois. R. C. Vogel was the grateful holder of an Allied Chemical and Dye Corporation Fellowship. He conducted experiments on water and solutions of barium chloride and lanthanum chloride from 20° to 60°.

(5) F. T. Gucker, Jr., THIS JOURNAL, **56**, 1017 (1934).

where $\bar{V}_2$ is the partial molal volume of the solute. If each molecule furnishes ν_i ions of charge z_i' then

$$\bar{E}_2 - \bar{E}_2^0 = \frac{A}{2}\,\frac{(\Sigma \nu_i z_i^2)^{3/2}}{D^{3/2}T^{1/2}} f(D,P,V,T)c^{1/2} \tag{3}$$

and

$$f(D,P,V,T) = -1/2\left[\frac{3}{D}\frac{\partial D}{\partial T} + \frac{1}{T} + \alpha\right]\left(\frac{3}{D}\frac{\partial D}{\partial P} - \beta\right) + \frac{\partial}{\partial T}\left[\frac{3}{D}\frac{\partial D}{\partial P} - \beta\right]$$

$$A = \left[\frac{\pi N^3\,\epsilon^6}{1000k}\right]^{1/2} = 2.457 \times 10^{14} \text{ in c. g. s. units}$$

The coefficient of compressibility of the solvent is β, and the dielectric constant is D; T is the absolute temperature, N is Avogadro's number, ϵ the charge on the electron, k is Boltzmann's constant, and c is the volume concentration. On the basis of this equation and by an estimation of the value of $\partial^2 D/\partial T \partial P$, Gucker arrives at the limiting law

$$\phi E_2 = \phi E_2^0 + 8 \times 10^{-3} c^{1/2} \tag{4}$$

for the apparent molal expansibility of uni-univalent electrolytes at 20°.

Without considering the numerical value of the coefficient, Gucker's equations predict three things: (a) at low concentration ϕE_2 should be a linear function of $c^{1/2}$; (b) the limiting slopes, $\partial \phi E_2/\partial c^{1/2}$, should be the same for all electrolytes of the same valence type; and (c) the limiting slopes should be greater for electrolytes of higher valence types. If the numerical value of the slope is considered, a fourth prediction will be that the slope should be positive.

Gucker[5] calculated the apparent molal expansibilities from the data on the density of aqueous solutions found in the literature for sodium chloride, potassium chloride, lithium chloride, hydrochloric acid, lithium hydroxide and sodium sulfate by an approximate method. Gibson and Kincaid[6] have obtained the apparent molal expansibilities of barium chloride, potassium nitrate, potassium bromide, lithium bromide and sodium iodide at 25° and at 35°. The lowest concentration which these investigators studied was 0.25 mole per liter for the barium chloride solutions and about 0.5 mole per liter for the rest of the solutions. The apparent molal expansibility of barium chloride showed an unusually large departure from linearity when plotted against $c^{1/2}$. Gibson and Loeffler[7] recently determined the apparent molal expansibilities of sodium chloride and of sodium bromide from 25° to 85°. The lowest concentration studied was around 0.5 mole per liter.

All of these investigators found that an increase of temperature decreased the apparent molal expansibility for a given concentration and increased the slope of ϕE_2 plotted against $c^{1/2}$. From the data of these investigators it is apparent that of the four predictions made by Gucker's limiting law, only one is correct in the concentration ranges studied, *i. e.*, ϕE_2 is usually a linear function of $c^{1/2}$ for uni-univalent electrolytes. But contrary to the predictions from Gucker's equations, the data show that at 25° the slopes are widely different for various uni-univalent electrolytes, and in the case of the uni-bivalent electrolyte, sodium sulfate, the slope is considerably less than that of any uni-univalent electroyte yet studied.

Perhaps part of the lack of agreement between theoretical predictions and experimental results is because the solutions studied have been no more dilute than about 0.25 mole per liter. In the calculation of apparent molal expansibilities from experimental data, the experimental error in measuring the coefficient of expansion is multiplied by about $1000/c$. Therefore, if a study of dilute solutions is to be undertaken, apparatus capable of giving results more accurate than those yet obtained must be used.

A new type of dilatometer has been developed which is capable of measuring changes in volume of electrolyte solutions over a wide range of temperature to ±0.0003 cc., the total volume being about 275 cc. This apparatus has been used to study solutions of potassium chloride from 20 to 80° and solutions of barium chloride and of lanthanum chloride from 20 to 60° The lowest concentrations which gave reproducible results were 0.06 molar.

Experimental Technique

Dilatometers.—The mercury dilatometer, which measures a change in volume in terms of the weight of mercury expelled or drawn in when the temperature is varied, is a well-known instrument used by a number of investigators. The first dilatometer to employ the unique principle of being a thermal regulator for its thermostat as well as a dilatometer was used by Jones and Jelen[8] for determining the cubical coefficients of expansion of solids. Thus, this type of dilatometer controls the temperature of the bath so that the dilatometer's contents exactly occupy the entire volume. The Jones and Jelen dilatometer was redesigned for use with solutions.

Two dilatometers, as nearly alike as the glassblower could make them, were used in this research. They each (Fig. 1) have an over-all height of 30 cm. and are made of Pyrex glass. The main part of the dilatometer, A, is closed at the top by stopcock F. A smaller tube, B, is attached at the bottom of the main part of the dilatometer. In the upper part of B there is a capillary restriction, D, about 2 cm. long and 1 mm. in inside diameter. A tantalum wire, J, is sealed in tube, B, above the capillary, D, in such a manner that its sharp point extends into the upper end of the capillary. Below the capillary, D, is sealed a platinum wire, K. Both the tantalum wire, J, and the platinum wire, K, extend into wells which may be filled with mercury. By placing wires from a thyratron circuit in the mercury-filled wells, H and C, the dilatometer can be made to control part of the heat input to the thermostat by making or breaking the circuit through the tantalum wire and the mercury in the capillary, D. This principle is exactly the same as that of a conventional mercury thermo-regulator. The capacity of each dilatometer (275 cc.) is such that when they are filled with mercury and water in a typical experiment a temperature change of 0.001° at 25° will produce a change in height of the mercury in capillary D of 0.1 mm. and at 75° of 0.2 mm.

---

(6) R. E. Gibson and J. F. Kincaid, THIS JOURNAL, **59**, 25 (1937).

(7) R. E. Gibson and O. H. Loeffler, *ibid.*, **63**, 443 (1941).

(8) Grinnell Jones and F. T. Jelen, *ibid.*, **57**, 2532 (1935).

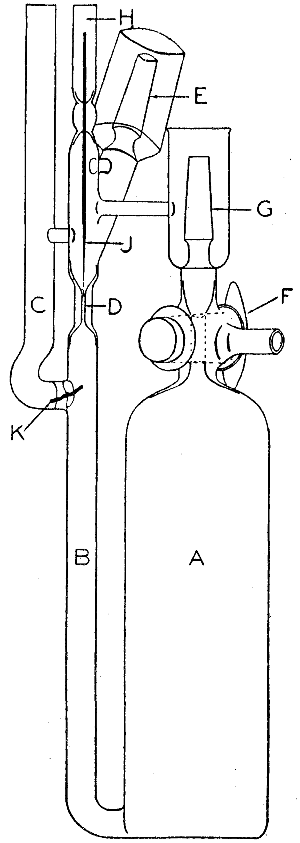


Fig. 1.—Mercury dilatometer.

The tube, E, is provided for the withdrawal or addition of mercury. After one equilibrium temperature has been determined, some mercury is removed from the dilatometer, and the instrument will then equilibrate at a higher temperature. The mercury removed is weighed. It is also possible to go from a higher to a lower equilibrium temperature by adding a weighed quantity of mercury through the tube, E.

The dilatometers are first calibrated, using mercury as a standard. During these runs the instruments are completely filled with mercury. At an equilibrium temperature the mercury is in the capillary, D, just at the tip of the tantalum wire, and thereby controlling the intermittent heaters in the usual manner, through a thyratron tube. When a water (or solution) experiment is being carried out, the mercury fills the tube, B, and forms a layer about 1 cm. deep on the bottom of the dilatometer, A, with water (or solution) on top of this layer of mercury filling the rest of the volume of the dilatometer.

A tantalum wire is much better for the upper contact than platinum because tantalum is not wet by mercury. There is no tendency for a small drop of mercury to cling to the sharp point of the tantalum wire causing erratic regulation of the thermostat. For this reason tantalum is to be highly recommended for use in thermoregulators. The resistance of tantalum to hot nitric and sulfuric acids, which are used in cleaning the dilatometers, was tested, and the metal was found to be quite inert.

Filling the Dilatometers.—There are two different filling techniques. One is used in calibration experiments when the dilatometer is to be entirely filled with mercury. The other is used when the dilatometer is to be partly filled with water or solution. Since the standard on which all the changes in volume of the solutions are based is mercury, the first experiments dealt with this substance.

The stopcock, F, is greased with Dow–Corning silicone stopcock grease. During the first part of this research Fisher's Cellogrease was used, but the new silicone grease was found to be superior at higher temperatures. The empty dilatometer is weighed. Mercury is filtered through a sintered glass disk, and it then is allowed to run down through a long capillary tube which has been inserted through the bore of the stopcock, F. This capillary tube reaches very nearly to the bottom of the dilatometer. When the dilatometer is completely full, the capillary is withdrawn and a rubber tube is attached to the joint, E (Fig. 1). The position of the mercury in the tube, B, of the dilatometer is adjusted to a point slightly above the capillary, D, by increasing or decreasing the pressure through the rubber tube. After this adjustment the stopcock, F, is turned through an angle of 90°, thus closing off A completely, but connecting the bore of the stopcock and the tube above to the side outlet tube on stopcock, F. The excess mercury in the bore of the stopcock and in the tube above it is then removed. There should now be enough mercury in the dilatometer to establish the first thermal equilibrium at about 20°. The dilatometer is weighed on a large balance to the nearest milligram.

If a water run is to be conducted, the stopcock, F, is greased, mercury is placed in the wells, C and H, and the dilatometer is weighed. After weighing, 50 cc. of mercury is placed in the bottom of the dilatometer in the same manner as if the dilatometer were to be completely filled with mercury. The instrument is reweighed.

A special 500-cc. round-bottom flask is used to fill the dilatometer with water. To the bottom of this flask (Fig. 2) is sealed a stopcock, *n*, and below the stopcock is sealed a ground joint, h. The movable plug of the stopcock has a three-way bore. Thus, by facing the bore in a "T" position with respect to the ground joint, h, it is possible to evacuate the bore. On the neck of the flask is a large ground-glass joint, m. The inside diameter of this joint is about 2 cm. The neck of the flask is 20 cm. long, and the 500 cc. graduation mark is about 4 cm. above the body of the flask. The large diameter and length of the neck allows the water (or solution) in the flask to be boiled without liquid being splashed or carried by entrainment from the flask. A special stopper for the flask consists of a large ground glass joint fitting the one on top of the flask; a stopcock, e, is sealed on top of this joint, and above the stopcock is another ground glass joint, d.

This special flask is used in removing the dissolved gases from the water. The flask is connected at the joint, d, to a trap which is cooled externally by a "Dry Ice"–alcohol mixture which is in turn connected to a vacuum pump. Thus, when the stopcocks a, b, and e are opened, and c and e are closed, and tube p is plugged (Fig. 2) the water boils under reduced pressure, and that vaporized is caught in the trap. When the dissolved gases are expelled, the stopcock, e, is closed.

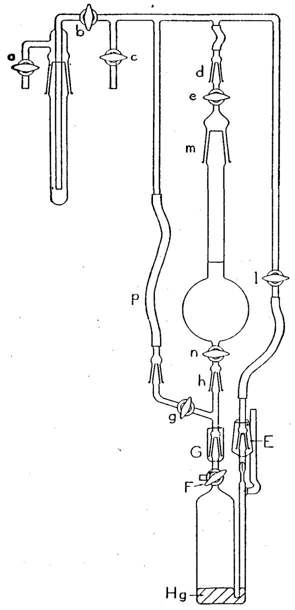


Fig. 2.—Mercury dilatometer and auxiliary apparatus assembled for filling with water or solution.

An extension tube is placed on the dilatometer at the joint, G (Fig. 1), and to the extension tube is attached the filling flask. The joint, E, of the dilatometer and the arm on the extension tube are attached to the vacuum line. The joints, G and E, of the dilatometer are not greased but are mercury sealed. The other joints are greased. The stopcocks, a and b, are closed, and g, l and F are opened. The vacuum supplied by a Langmuir mercury vapor diffusion pump backed by an oil pump is applied to the system by opening stopcock c. When the system is evacuated according to a McLeod gage, the stopcocks c, g and l are closed and n is slowly opened; the water flows into the dilatometer on top of the mercury.

As the water collects on the mercury, the mercury rises up into the tube, B (Fig. 1), of the dilatometer. The position of the mercury in B is adjusted to about 6 mm. above the top of the capillary by opening stopcock e slightly, thus applying pressure to the water in the filling flask. When the dilatometer is full and the position of the mercury above the capillary, D, is adjusted correctly, stopcock F is closed in such a manner that the bore is connected to the outlet tube. Full atmospheric pressure is then applied to the system by opening stopcocks c and l.

The mercury in the mercury seal cups of joints E and G and the water in the bore of the stopcock, F, are removed through the tube on the side of the stopcock barrel, and the apparatus is disassembled. The dilatometer is weighed.

If, instead of water, the dilatometer is to be filled with a solution, the filling procedure is the same except that the proper weighed amount of salt is dissolved in water in the flask. The solution is boiled under reduced pressure until the flask contains exactly 500 cc., and the solution is free of air. However, in the case of lanthanum chloride, because of the indefinite amount of water of crystallization in the salt, it is not possible to make solutions of known concentration by directly weighing the salt. The concentration can be determined by using the equation developed by Jones and Ray[9] giving the density in grams per milliliter at 25° as a function of concentration

$$d = 0.997074 + 0.229398c - 0.011911c^{3/2} \qquad (5)$$

Since the density data are known from the experimental data of the authors, the above equation may be solved for c.

Operation of the Dilatometer.—After the dilatometer has been filled with mercury (or mercury and water or solution) it is clamped in a special brass frame. The dilatometer is then mounted in the thermostat and wires from the thyratron circuit are placed in the mercury wells, C and H (Fig. 1), so that the dilatometer acts as the thermoregulator.

In order that the substance whose coefficient of expansion is to be determined is at a standard pressure of one atmosphere, pressure adjustments are applied. The ground glass joint, E (Fig. 1), is attached to a manometer by means of a rubber tube. If the dilatometer contains only mercury, the air pressure on the mercury in the capillary D is adjusted to 760 mm. The pressure adjustment when mercury alone is in the dilatometer is really only a formality unless the barometric pressure is very high or very low. A pressure change of 34 mm. will change the temperature of the bath by only 0.001°. When there is solution or water in the dilatometer, a pressure change in barometric pressure of 2 mm. will cause the temperature of the bath to change by 0.001° and, therefore, the pressure adjustment must be applied much more carefully. There is a pressure on the water or solution in addition to atmospheric pressure due to the head of mercury in the tube B (Fig. 1). There is also an additional pressure caused by the capillary depression of the mercury. Thus the pressure on the dilatometer's contents must be decreased by the sum of the two amounts in addition to the proper compensation for the difference between the prevailing atmospheric pressure and 760 mm.

After the dilatometer has been placed in the thermostat, the thyratron circuit connected and the pressure adjusted, various thermostat controls (steady heater, intermittent heaters, cooling coils) are adjusted until the dilatometer comes to equilibrium at about 20°. Equilibrium is attained when the intermittent heaters in the thermostat go off and on quite rapidly and the temperature is constant within 0.001°. The temperature is then determined.

The equilibrium temperatures of the thermostat were determined with a 25 ohm four-lead platinum resistance thermometer, made by Leeds and Northrup, provided with a Bureau of Standards certificate giving the constants. The resistance of the thermometer was measured by means of a Mueller bridge (Leeds and Northrup). The bridge was calibrated by using a 10-ohm standard resistance calibrated by the Bureau of Standards. In addition to calibrating the Mueller bridge, the resistance of the thermometer at the ice-point must be determined. The ice-bath used was prepared in the manner recommended by Roper.[10] A table was compiled from these data giving the resistance of the thermometer at various temperatures. A change of 0.001° brings about a change in resistance of about 0.0001 ohm. This change can be reliability determined by the Mueller bridge.

After the first equilibrium temperature is determined, the dilatometer is placed in an auxiliary water-bath whose temperature is 31°. This will cause the mercury to expand up above the capillary, D. Weighed pipets of special design (Fig. 3) are used to withdraw mercury. The tip of a pipet reaches down through the joint E (Fig. 1) of the dilatometer to the mercury which has been expelled from the main volume of the dilatometer through the capillary, D. When a pipet has been inserted into the dilatometer, a ground glass joint attached to a rubber tube is fixed to the pipet at B (Fig. 3), and most of the mercury above the capillary of the dilatometer is sucked out of the dilatometer, through the tube A into the pipet. The slight bend in the main part of the pipet, D, is to slow down the descent of the mercury as it falls to the bottom of the pipet thereby minimizing the scattering of mercury droplets. The constriction C in the tube A of the pipet is to prevent the escape of any mercury drops remaining in A from the pipet.

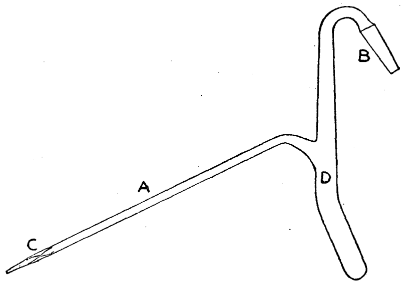


Fig. 3.—Pipet used for withdrawal and addition of mercury.

After the mercury has been withdrawn from the dilatometer, which is in the auxiliary bath, the dilatometer is returned to the thermostat and the thermostat comes to a new equilibrium temperature at about 30°. In the manner just outlined, readings are obtained at approximately 10° intervals from 20° to 60°. In the case of the earlier work on potassium chloride solutions, the observations were carried to 80°. After the dilatometer has been adjusted to regulate the bath at 60° (if this is the highest temperature), the pipets containing mercury are all weighed at once against a tare. In this manner the weights of mercury withdrawn from the dilatometer to produce each new temperature equilibrium are determined.

The procedure followed in going from higher temperatures to lower temperatures is but slightly different from the one used in adjusting the dilatometers on the "up run." After the highest equilibrium temperature has been determined, the dilatometer is placed in the auxiliary bath which is 5° warmer than the equilibrium temperature. The tip of the pipet containing the mercury withdrawn from the dilatometer in the last adjustment is placed below the surface of the mercury which has expanded above the top of the capillary, D, of the dilatometer. The pipet during this step is held in such a manner that the mercury in the bottom of the compartment D (Fig. 3) is undisturbed. The pipet is now rotated about the tube A as an axis until the main part, D, of the pipet is practically horizontal. The mercury in the pipet will run down the tube A into the dilatometer. The tip of the tube A is kept below the surface of the mercury to prevent splashing of drops of mercury. The dilatometer has now been adjusted to equilibrate at 50° (70° if the highest equilibrium temperature was 80° instead of 60°). In this way the "down run" is carried out in ten degree intervals down to 20°. As the pipets are emptied, they are again weighed. There are always a few milligrams of mercury remaining in each pipet. Therefore the tem-

---

[9] Grinnell Jones and Wendell A. Ray, THIS JOURNAL, **63**, 288 (1941).

[10] E. F. Roper, *ibid.*, **60**, 866 (1938).

peratures on the down run are not the same as on the up run.

Careful experiments were carried out to determine if there was any possibility that hysteresis of the glass might have introduced an error. The dilatometer was kept at a specific equilibrium temperature in the thermostat for an extended time, then immersed in either colder or hotter water, and kept in this auxiliary bath for several hours. Then the dilatometer was returned to the thermostat, and the same equilibrium temperature was very quickly obtained, thus demonstrating that hysteresis of the glass does not introduce an error.

Purification of Materials.—Mercury is purified by placing a small amount in a large beaker. Concentrated sulfuric acid is poured into it, and the mixture is stirred. The sulfuric acid is allowed to remain on top of the mercury for about half an hour, and it is then poured off. This treatment ensures that all of the Dow–Corning silicone stopcock grease will be removed from the mercury. The mercury is then thoroughly washed with water. The mercury is next allowed to fall in fine drops down a tower filled with 8% nitric acid solution.[11] After treatment in the tower, the mercury is distilled in a stream of air under reduced pressure according to the method of Hulett.[12] The distillate is then pinholed and redistilled. The redistilled mercury is pinholed into a clean storage bottle. Before using in the dilatometer, it is passed through a sintered glass disk to remove any particles of dust or traces of grease it may have picked up while standing in the laboratory.

The water used was conductivity water prepared in a Barnstead still. This water is free from dissolved materials except for air. The dissolved gases were removed by boiling under reduced pressure.

The potassium chloride was purified by recrystallization and fusion according to the method of Jones and Bradshaw.[13]

The barium chloride was purified by recrystallizing twice from an ethyl alcohol–water solution. The alcohol was purified by double distillation. The barium chloride was then further purified by a recrystallization from pure water. The barium chloride dihydrate obtained was dried at room temperature under a bell jar arranged in such a manner that circulation of dust-free air was permitted. After the barium chloride had dried in this manner for about a month, it was removed and ground up in a clean mortar and further dried for another month in the same manner. An analysis showed that the salt contained 14.799% water. The theoretical value is 14.752%. The experimentally obtained value was used in calculating the solution concentrations.

The lanthanum chloride was originally prepared by Professor Charles James[14] of the University of New Hampshire. It was purified by recrystallization from alcoholic hydrochloric acid using gaseous hydrogen chloride. It was then kept over solid sodium hydroxide to remove the excess solvent and hydrochloric acid.

Experimental Data

Mercury.—The dilatometers are first calibrated using mercury as a standard because (a) it is necessary to know the grams of mercury which must be withdrawn per gram of mercury in the dilatometer to raise the equilibrium temperature of the dilatometer one degree centigrade, and (b) it is necessary to know the coefficient of expansion of the Pyrex glass of which the dilatometers are made. Since the density of mercury has been determined at various temperatures in containers whose coefficient of expansion is very well known[15] the coefficient of expansion of the Pyrex can be calculated.

A sample data sheet obtained for one "up run" of dilatometer No. 1 is given in Table I. Column 1 gives the temperatures at which the equilibria were established. Column 2 gives the temperature difference, Δt, between each two successive equilibria. Column 3 gives the average temperature, t_{av}, of two successive equilibria. Column 4 gives the number of grams of mercury, ΔW, which are withdrawn to establish a new equilibrium. Column 5 is the total weight of mercury, W, in the dilatometer at the corresponding equilibrium temperature given in Column 1. Column 6 is the mercury factor, f_{Hg}, and is $\Delta W/W\Delta t$. The weight of mercury in Column 5 used to calculate f_{Hg} is that at the higher temperature. The use of the weight of mercury at the higher temperature may appear arbitrary but can be justified by an algebraic treatment of the method of calculating the ultimate results of the water and solution runs.

TABLE I

SAMPLE DATA SHEET FROM A MERCURY RUN

(1)	(2) Δt	(3) $t_{av.}$	(4) ΔW	(5) W	(6) f_{Hg}
20.048				3766.502_9	
	12.113	26.105	7.8098		0.0001715_3
32.161				3758.693_1	
	7.552	35.937	4.8567		$.0001713_2$
39.713				3753.836_4	
	8.878	44.152	5.6952		$.0001711_5$
48.591				3748.141_2	
	10.574	53.878	6.7619		$.0001709_2$
59.165				3741.379_3	

The mercury factor, f_{Hg}, expresses the grams of mercury withdrawn per degree centigrade per gram of mercury in the dilatometer at the higher temperature.

A linear equation relating f_{Hg} to t_{av} has been obtained for each of the two dilatometers using the method of least squares to evaluate the parameters. For dilatometer no. 1, the early equation (Taylor) used in connection with the potassium chloride solutions is

$$f_{Hg} = 0.0001719_4 - 0.000000017_4 t_{av} \qquad (6)$$

For dilatometers 1 and 2, respectively, the equations (Vogel) used in calculating the barium chloride and lanthanium chloride data are

$$f_{Hg} = 0.0001721_3 - 0.0000000218_5 t_{av} \qquad (7)$$

and

$$f_{Hg} = 0.0001719_4 - 0.0000000161_5 t_{av} \qquad (8)$$

From an analysis of the data based on the differences between the observed values of f_{Hg} and those calculated by means of Equation (6), it is found that the probable error of a single observation is ±0.000000145. The probable error of a single observation for dilatometer no. 1 using Equation (7) is ±0.000000039, and for dilatometer no. 2 using Equation (8) it is ±0.000000114.

---

(11) J. H. Hildebrand, THIS JOURNAL, **31**, 933 (1909); C. J. Moore, *ibid.*, **32**, 971 (1910).

(12) G. A. Hulett, *Phys. Rev.*, **33**, 307 (1911).

(13) Grinnell Jones and B. C. Bradshaw, THIS JOURNAL, **55**, 1780 (1933).

(14) This material had been used by Grinnell Jones and C. F. Bickford, *ibid.*, **56**, 692 (1934).

(15) J. A. Beattie, B. E. Blaisdell, J. Kaye, H. T. Gerry and C. H. Johnson, *Proc. Am. Acad. Arts Sci.*, **74**, 371 (1941).

TABLE II

SAMPLE DATA SHEET FOR A WATER RUN[a]

(1) t°C.	(2) Δt	(3) t_{av}	(4) f_{Hg} at t_{av}	(5) W	(6) G. Hg expelled due to expansion of Hg	(7) ΔW	(8) G. Hg expelled due to expansion of H_2O	(9) f_w
19.513				676.5239				
	10.429	24.728	0.0001715_9		1.1944	9.0759	7.8815	0.003318_6
29.942				667.4480				
	10.288	35.086	$.0001713_7$		1.1558	11.8675	10.7117	$.004572_2$
40.230				655.5804				
	10.300	45.380	$.0001711_4$		1.1303	14.4021	13.2718	$.005658_3$
50.530				641.1783				
	9.908	55.484	$.0001709_2$		1.0588	15.9870	14.9282	$.006616_3$
60.438				625.1913				

[a] Wt. of water in dilatometer = 227.723_6 g.

The slight superiority of dilatometer no. 1 is believed to be due to the unavoidable difference in the shape of the capillary D at the point where the tip of the tantalum wire enters the capillary. Equations (7) and (8) cover a range of temperature from 25° to 55°, while Equation (6) covers a range from 25° to 75°. Since dilatometer no. 2 does not appear to function quite as well as dilatometer no. 1, the former was used for the more concentrated solutions where the experimental error is not as important. The values of f_{Hg} given in Table I were some of those used in arriving at Equation (7).

It is necessary to obtain the cubical coefficient of expansion, a, of the Pyrex glass of the dilatometer. An implicit definition of a is given by

$$V_t = V_{20}[1 + a(t - 20)] \qquad (9)$$

where V_t is the volume of the dilatometer at the temperature t°C., and V_{20} is the volume of the dilatometer at 20°. Since

$$V_t = W_t/d_t \qquad (10)$$

where W_t is the weight of mercury in the dilatometer and d_t is the density in grams per cc. of mercury at t°C., we get

$$\frac{W_t d_{20}}{d_t W_{20}} - 1 \Big/ (t - 20) = a \qquad (11)$$

If a calculation of a is to be made, d_{20}/d_t needs to be known for various temperatures. Accurate densities of mercury have been determined recently by Beattie, Blaisdell, Kaye, Gerry and Johnson.[15] After determining the apparent density of mercury in vitreous silica bulbs these investigators cut cross-sections from the bulbs and determined the coefficient of expansion of the silica by an interferometer method. They then corrected their data for the expansion of the silica.

In addition to d_{20}/d_t, W_{20} needs to be known. This was calculated by determining f_{Hg} for 20° from the equations relating f_{Hg} to t_{av}. Using this value of f_{Hg}, all the weights of mercury observed close to 20° were corrected to exactly 20°. The ratios, W_t/W_{20}, for each up and down run for both dilatometers were determined and hence a number of values of the coefficient of expansion of Pyrex glass, a, were obtained. These were averaged. Using the mercury calibration data obtained by R. C. Vogel in 1945 for dilatometers 1 and 2, a was found to be 0.00000966 for both instruments. Using the mercury calibration data of E. F. Taylor obtained in 1940 for dilatometer no. 1, a was found to be 0.00000968.

Saunders and Tool[16] found that the annealing temperature is the dominant factor in determining the coefficient of thermal expansion of Pyrex. Dilatometer no. 1 was annealed at 594° which should mean that a is 0.00000985 per degree centigrade, according to Saunders and Tool. Dilatometer no. 2 was annealed at 646° and thus should have a coefficient of expansion of 0.00001023 per degree centigrade. Our measurements do not support the idea that the coefficient of expansion of the Pyrex is controlled by the annealing temperature, at least within the range (594–646°) which we used. Moreover, trial calculations have shown that the same coefficient of expansion of Pyrex must be used for both dilatometers in order to get identical results for water.

Water.—Since the coefficient of expansion of water is needed to calculate the apparent molal expansibility of an electrolyte, it is necessary to make water runs with both dilatometers. It is also desirable to be able to compare the specific volumes of water at various temperatures calculated from our data with the best values obtained by other investigators.

A sample data sheet obtained for an up run for one of the dilatometers is given[17] in Table II. Columns 1, 2 and 3 have the same significance for the water data as for the mercury data. Column 4 gives the mercury factor, f_{Hg}, calculated at t_{av} using Equation (7). Column 5 gives the total weight of mercury in the dilatometer at t°C., the equilibrium temperature. Column 7 gives the weight of mercury withdrawn from the dilatometer to establish each new equilibrium temperature. Column 6 gives the grams of mercury expelled from the dilatometer in going from one equilibrium temperature to another due to the expansion of the mercury only. Column 8 shows

(16) J. B. Saunders and A. Q. Tool, *Bur. Standards J. Res.*, **11**, 799 (1933).

(17) The complete data may be obtained from the Harvard University thesis, "Dilatometry of Mercury, Water, and Solutions of Electrolytes," by E. F. Taylor, pp. 101–108, and "Dilatometry of Mercury, Water, and Solutions of Electrolytes," by Richard C. Vogel, pp. 125–128, 130. Photostats can be obtained for a nominal fee by writing to Librarian, Department of Chemistry, Harvard University, Cambridge, Mass.

TABLE III

SPECIFIC VOLUMES OF WATER MEASURED BY VARIOUS INVESTIGATORS IN CUBIC CENTIMETERS PER GRAM

t°C.	Taylor dilatometer no. 1	Vogel dilatometer no. 1	Vogel dilatometer no. 2	Tilton and Taylor	"I. C. T."
20	(1.001796_6)	(1.001796_6)	(1.001796_6)	1.001796_6	1.001797_9
30	1.004368	1.004368	1.004369	1.004367_6	1.004369_3
40	1.007837	1.007840	1.007842	1.007840_5	1.007842_4
50	1.012098	1.012101	1.012103		1.01210
60	1.017074	1.017078	1.017079		1.0170_8
70	1.022718				1.0227_3
80	1.029000				1.0290_2

the grams of mercury expelled from the dilatometer due to the expansion of water alone and is obtained by subtracting Column 6 from Column 7. Column 9, the water factor f_W, is calculated by dividing Column 8 by Column 2 and by the weight of water in the dilatometer. It represents the grams of mercury expelled from the dilatometer per degree centigrade per gram of water.

By using Newton's method of non-linear interpolation, the water factors, f_W, have been determined at average temperatures, t_{av}, of 25, 35, 45, 55 and for part of the data, 65 and 75°.[2,3] When f_W is multiplied by the specific volume of mercury at the lower temperature of the interval over which f_W is calculated, the apparent change of the specific volume of water in Pyrex glass results. If to this apparent change in specific volume is added the change in specific volume due to the expansion of the Pyrex glass of the dilatometer, the true change in the specific volume over each ten-degree interval is obtained. Thus, to the specific volume at 20° of water, which is taken as a starting point, is added the true change in specific volume due to raising the temperature to 30°. This gives the specific volume at 30°. The specific volumes at other temperatures are calculated in the same manner. The specific volume of water at 20° is assumed to be 1.001796_6 cc. per gram. This is the value given by Tilton and Taylor[18] based on the excellent data of Chappuis.[19] The specific volumes of mercury in cc. per gram given by Beattie, Blaisdell, Kaye, Gerry and Johnson[15] are used. The results are given in Table III.

The integral coefficient of expansion of water at the average temperature of the temperature change in question can be obtained by dividing the change in specific volume by the specific volume of water at the average temperature and by the temperature change. Thus, if $\tilde{V}$ is the specific volume, the coefficient of expansion would be $\tilde{V}_{30} - \tilde{V}_{20} \div 10\ \tilde{V}_{25}$. Since the change in specific volume at best is known to about 0.01%, it is only necessary to know the specific volume at the average temperature, *i. e.*, $\tilde{V}_{25}$, to one part in ten thousand. A linear interpolation of specific volumes between round temperatures ten degrees apart may introduce an error of about one part in ten thousand. Thus, specific volumes calculated in this manner are sufficiently accurate for computing the coefficients of expansion of water and also of salt solutions. These are given in Table IV.

TABLE IV

INTEGRAL COEFFICIENTS OF EXPANSION OF WATER AND SOLUTIONS OF POTASSIUM, BARIUM AND LANTHANUM CHLORIDES IN RECIPROCAL DEGREES CENTIGRADE × 10^4

Molality	25°	35°	45°	55°	65°	75°
Water						
0.0000[a]	2.5628	3.4515				
.0000[b]	2.5633	3.4491	4.2194	4.9047	5.5333	6.1235
.0000[c]	2.5632	3.4507	4.2198	4.9049		
.0000[d]	2.5647	3.4514	4.2189	4.9055		
Potassium Chloride						
0.06022	2.6018	3.4705	4.2258	4.9018		
.06022	2.6038	3.4704	4.2268	4.8988		
.10053	2.6277	3.4842	4.2296	4.8985	5.5122	6.0850
.10053	2.6273	3.4851	4.2285	4.8984	5.5108	6.0837
.10064	2.6265	3.4881	4.2297	4.8974	5.5115	6.0843
1.0294	3.0798	3.7496	4.3281	4.8583	5.3513	5.8220
1.0308	3.1049	3.7513	4.3292	4.8592	5.3499	5.8240
1.0308	3.1063	3.7499	4.3309	4.8600	5.3516	5.8210
3.2731	3.6642	4.0365	4.3885	4.7238	5.0436	5.3579
Barium Chloride						
0.01005	2.5718	3.4579	4.2196	4.9029		
.01005	2.5744	3.4562	4.2207	4.9020		
.06028	2.6409	3.4898	4.2299	4.8917		
.06028	2.6421	3.4887	4.2302	4.8926		
.10054	2.6921	3.5187	4.2389	4.8859		
.10054	2.6922	3.5194	4.2400	4.8856		
.25239	2.8776	3.6229	4.2782	4.8729		
.25239	2.8804	3.6192	4.2794	4.8719		
.50852	3.1581	3.7779	4.3434	4.8609		
.50852	3.1575	3.7788	4.3446	4.8587		
1.03382	3.6008	4.0410	4.4533	4.8436		
1.03382	3.5995	4.0425	4.4553	4.8409		
Lanthanum Chloride						
0.06464	2.6108	3.4498	4.1826	4.8355		
.06464	2.6119	3.4521	4.1804	4.8360		
.09045	2.6337	3.4520	4.1688	4.8116		
.09045	2.6332	3.4525	4.1695	4.8116		
.16154	2.6850	3.4610	4.1384	4.7494		
.16154	2.6865	3.4597	4.1385	4.7502		
.36453	2.8242	3.4836	4.0638	4.6011		
.36453	2.8240	3.4835	4.0648	4.5991		
.70812	3.0060	3.5023	3.9601	4.3892		
.70812	3.0071	3.5045	3.9618	4.3854		
1.04320	3.1215	3.5023	3.8681	4.2172		
1.04320	3.1226	3.5040	3.8679	4.2161		

[a] Calculated from the data of Tilton and Taylor.[18] [b] Calculated from the results of E. Folger Taylor using dilatometer 1. [c] Calculated from the results of R. C. Vogel using dilatometer 1. [d] Calculated from the results of R. C. Vogel using dilatometer 2.

---

(18) L. W. Tilton and J. K. Taylor, *J. Research Nat. Bur. Standards*, **18**, 205 (1937).

(19) P. Chappuis, Travaux et Mémoires du Bureau International des Poids et Mésures, **13**, d3 (1907).

Solutions of Potassium, Barium and Lanthanum Chlorides.—The data for solutions are treated in general in the same manner as those of water. In calculating the specific volume of the solution, the amounts of mercury and of solution in the dilatometer at exactly 40° (50° for potassium chloride solutions) are calculated by adding to the weight of mercury a correction term which compensates for the fact that weights of the contents of the instrument are known at temperatures slightly different from 40°. This correction term consists of the weight of mercury associated with the expansion of solution over the temperature interval between equilibrium temperature and exactly 40°, and a similar term for the expansion of mercury. The solution term is calculated by multiplying the weight of solution by the average value of the factors, f_S, at 35° and 45° (f_S is the same for solutions as f_W is for water) and by the difference between the equilibrium temperature and exactly 40°. The mercury term is calculated by multiplying the weight of mercury by the mercury factor, f_{Hg}, for 40° and by the same difference in temperature. Since the volume of the dilatometer and the specific volume of mercury are known at 40°, the volume of the solution is calculated easily.

After the specific volumes at 40° are calculated for each solution, the specific volumes at other temperatures are then computed by adding or subtracting the sum of the apparent change in volume of solution in Pyrex glass and the change in volume of the Pyrex glass from the value at 40°.

The coefficients of expansion of solutions are calculated in exactly the same manner as they were for water. These are given in Table IV and plotted in Figs. 4, 5 and 6 against temperature.

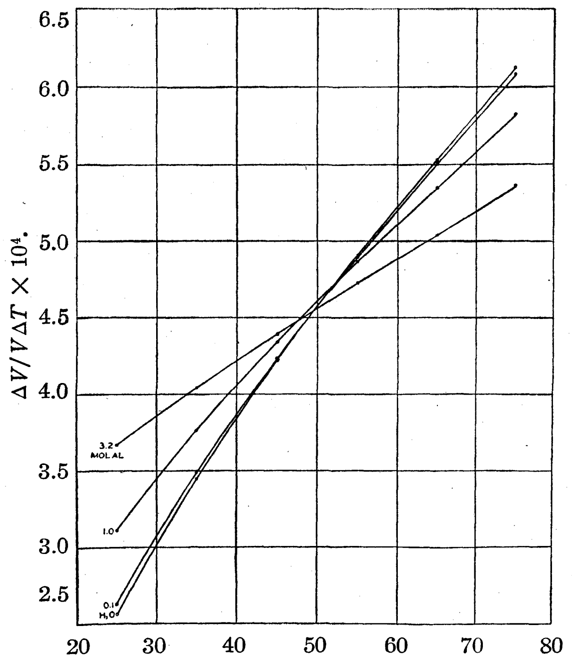


Fig. 4.—Coefficients of expansion of potassium chloride solutions plotted against temperature.

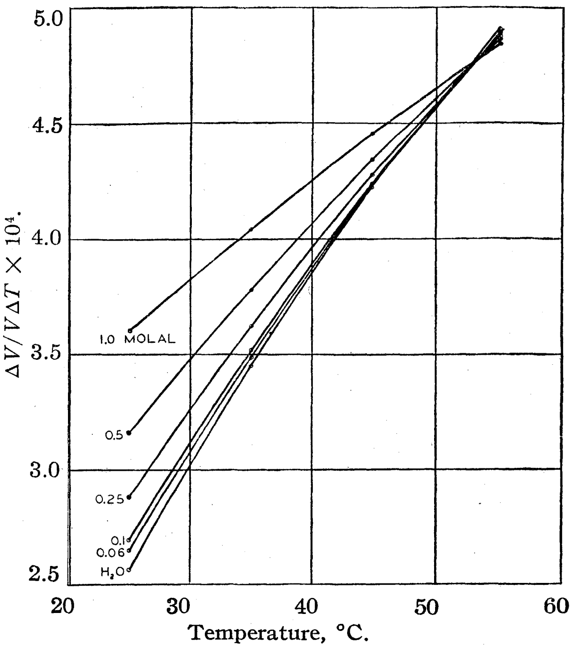


Fig. 5.—Coefficients of expansion of barium chloride solutions plotted against temperature.

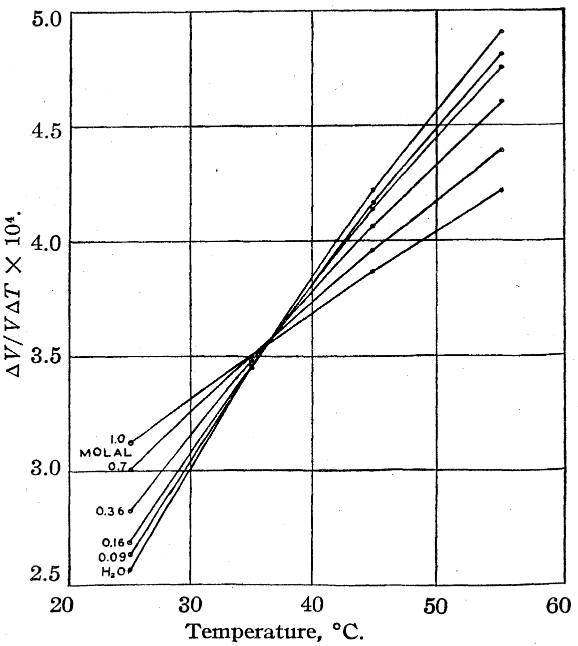


Fig. 6.—Coefficients of expansion of lanthanum chloride solutions plotted against temperature.

As previously mentioned, the concentrations of the lanthanum chloride solutions were determined from the solution densities obtained from the dilatometer data. It was decided that a linear interpolation of the specific volumes at 20° and

TABLE V

THE APPARENT MOLAL EXPANSIBILITIES OF POTASSIUM, BARIUM AND LANTHANUM CHLORIDES AT VARIOUS TEMPERATURES IN CC. PER MOLE PER °C.

25°		35°		45°		55°		65°		75°	
c	ϕE_2	c	ϕE_2	c	ϕE_2	c	ϕE_2	c	ϕE_2	c	ϕE_2
						KCl					
0.05994	0.0720	0.05976	0.0433	0.05953	0.0226	0.05926	0.0091				
.05994	.0753	.05976	.0431	.05953	.0243	.05926	.0041				
.09996	.0715	.09965	.0449	.09927	.0222	.09882	.0076	0.09831	−0.0003	0.09774	−0.0228
.09996	.0711	.09965	.0458	.09927	.0211	.09882	.0075	.09831	− .0077	.09774	− .0241
.10007	.0701	.09976	.0486	.09938	.0221	.09893	.0064	.09841	− .0072	.09784	− .0236
.99675	.0592	.99335	.0404	.98934	.0235	.98481	.0100	.97979	− .0021	.97434	− .0127
.99817	.0617	.99476	.0405	.99074	.0236	.98620	.0100	.98118	− .0022	.97571	− .0125
.99817	.0618	.99476	.0404	.99074	.0238	.98620	.0101	.98118	− .0020	.97571	− .0128
2.9562	.0454	2.9449	.0311	2.9325	.0195	2.9191	.0098	2.0049	+0.0012	2.8899	−0.0065
						$BaCl_2$					
0.01002	0.094	0.00999	0.082	0.00995	0.008	0.00990	−0.005				
.01002	.120	.00999	.065	.00995	.019	.00990	− .014				
.06001	.1364	.05982	.0749	.05959	.0287	.05932	− .0086				
.06001	.1383	.05982	.0731	.05959	.0292	.05932	− .0071				
.09998	.1356	.09967	.0776	.09928	.0310	.09883	− .0056				
.09998	.1357	.09967	.0783	.09928	.0321	.09883	− .0059				
.24993	.1328	.24912	.0788	.24814	.0356	.24700	+ .0012				
.24993	.1339	.24912	.0774	.24814	.0361	.24700	+ .0008				
.49987	.1259	.49814	.0756	.49612	.0376	.49338	+ .0059				
.49987	.1258	.49814	.0758	.49612	.0379	.49384	+ .0054				
.99989	.1113	.99608	.0698	.99185	.0369	.98725	+ .0093				
.99989	.1112	.99608	.0700	.99185	.0371	.98725	+ .0091				
						$LaCl_3$					
0.06437	0.0788	0.06418	0.0052	0.06393	−0.0503	0.06364	−0.0998				
.06437	.0805	.06418	.0088	.06393	− .0538	.06364	− .0995				
.0900	.0833	.0898	.0081	.0894	− .0486	.0890	− .0954				
.0900	.0828	.0898	.0087	.0894	− .0478	.0890	− .0954				
.1605	.0812	.1600	.0137	.1594	− .0422	.1587	− .0880				
.1605	.0821	.1600	.0129	.1594	− .0422	.1587	− .0875				
.3604	.0779	.3593	.0171	.3579	− .0334	.3564	− .0739				
.3604	.0779	.3593	.0171	.3579	− .0332	.3564	− .0745				
.6934	.0703	.6911	.0164	.6885	− .0265	.6857	− .0625				
.6934	.0705	.6911	.0168	.6885	− .0263	.6857	− .0631				
1.0107	.0623	1.0074	.0148	1.0037	− .0230	.9996	− .0551				
1.0107	.0624	1.0074	.0150	1.0037	− .0230	.9996	− .0552				

30° would not be accurate enough to obtain the specific volume at 25° in this case. The factor f_S is obtained for 27.5° for each solution. This is multiplied by 5°, the temperature interval, and by the specific volume of mercury at 25°. The coefficient of expansion of Pyrex was also multiplied by 5 and by the less accurate specific volume of the solution at 25° obtained by linear interpolation. The sum of these two corrections was subtracted from the specific volumes at 30° to give the specific volume at 25°. The concentration can then be obtained as previously described. This method was checked by calculating the specific volumes of barium chloride solutions from an equation giving the densities as a function of concentration derived by Jones and Ray.[20] These specific volumes checked with those obtained from the dilatometer data within a few parts per one hundred thousand, which shows that the method is sufficiently accurate.

Apparent molal expansibility of the salts may be calculated by means of Equation (1), and these are presented in Table V and plotted against $c^{1/2}$ at various temperatures in Figs. 7, 8 and 9. The value of the integral coefficient of expansion of water used at a given temperature to calculate ϕE_2 was determined by the dilatometer in which the particular solution was studied and the observer (Vogel or Taylor). The values of ϕE_2 for barium chloride are quite erratic when the concentration is as low as 0.01 molar. The reason for this is that at low concentrations the apparent molal expansibility represents the difference between two quantities which are almost identical. In order to obtain significant results for 0.01 molar solutions, the coefficients of expansion will have to be known ten times better than they are now known. The value of the apparent molal expansibility of the 0.06 molal lanthanum chloride solution at 25° appears to be in error. It is difficult to offer an explanation for this.

As has been previously mentioned, the coefficients of expansion obtained by our method of calculation are integral coefficients and not differential coefficients. Strictly speaking, the latter should be used in calculating the apparent molal expansibility. The molal expansibility as we have calculated it is

$$\phi E_2' = \frac{V_s}{\tilde{V}_s}\frac{\Delta \tilde{V}_s}{\Delta t} - \frac{\tilde{V}_w}{\tilde{V}_w}\frac{\Delta \tilde{V}_w}{\Delta t}$$

where $\tilde{V}_s$ and $\tilde{V}_w$ are the specific volumes of solu-

---

[20] Grinnell Jones and Wendell A. Ray, THIS JOURNAL, 63, 288 (1941).

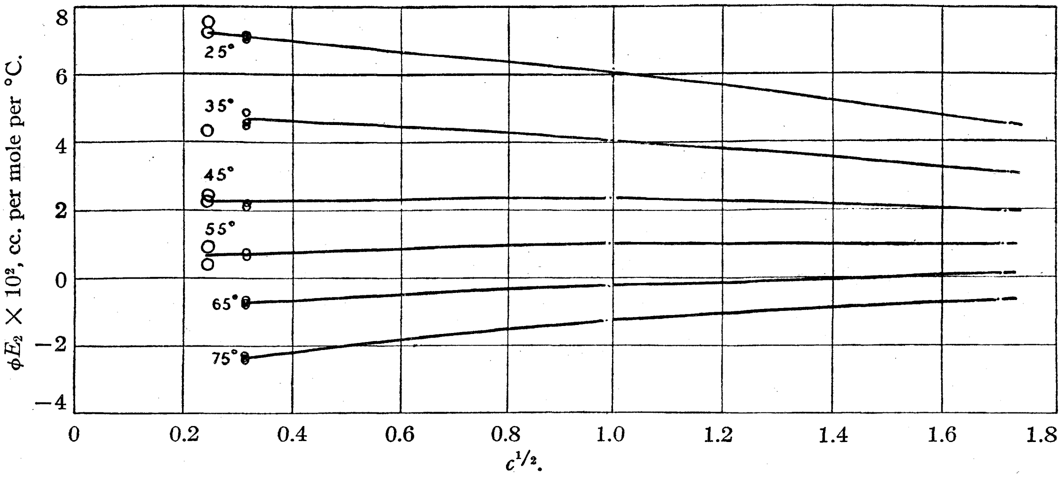


Fig. 7.—Apparent molal expansibility of potassium chloride plotted against $c^{1/2}$.

tion and water, V_s is the volume of solution containing a mole of solute and V_w is the volume of water used to make the solution. Let

$$\frac{\partial \tilde{V}_s}{\partial t} = \frac{\Delta \tilde{V}_s}{\Delta t} + x$$

$$\frac{\partial \tilde{V}_w}{\partial t} = \frac{\Delta \tilde{V}_w}{\Delta t} + y$$

Then if ϕE_2 is the true apparent molal expansibility, as defined by Equation (1)

$$\phi E_2 - \phi E_2' = W_w\,(x - y) + M_2 x$$

where W_w is the weight of water used to make the solution containing one mole of solute and M_2 is the molecular weight of the solute.

When $\tilde{V}_{w,t} - \tilde{V}_{w,25°}$ is plotted against temperature (Fig. 10) on the same graph with plots of $\tilde{V}_{s,t} - \tilde{V}_{s,25°}$ a rather remarkable fact becomes clear for many of the dilute solutions. These points fall approximately on the same curve. This means that

$$\frac{\partial \tilde{V}_s}{\partial t} = \frac{\partial \tilde{V}_w}{\partial t} \text{ and } \frac{\Delta \tilde{V}_s}{\Delta t} = \frac{\Delta \tilde{V}_w}{\Delta t}$$

which leads to the fact that for dilute solutions x equals y.

From the equation derived by Tilton and Taylor[18] giving the density of water as a function of temperature, the differential coefficients of expansion can be obtained.

$$\frac{1}{\tilde{V}_w}\left(\frac{\partial \tilde{V}_w}{\partial t}\right)_{25°} = 0.0002570_4 \text{ and } \frac{1}{\tilde{V}_w}\left(\frac{\partial \tilde{V}_w}{\partial t}\right)_{35°} = 0.0003456_5$$

Since the dilatometer data give $\frac{1}{\tilde{V}_w}\,\frac{\Delta \tilde{V}_w}{\Delta t}$, y can be determined. At 25° and 35° y is 5×10^{-7}.

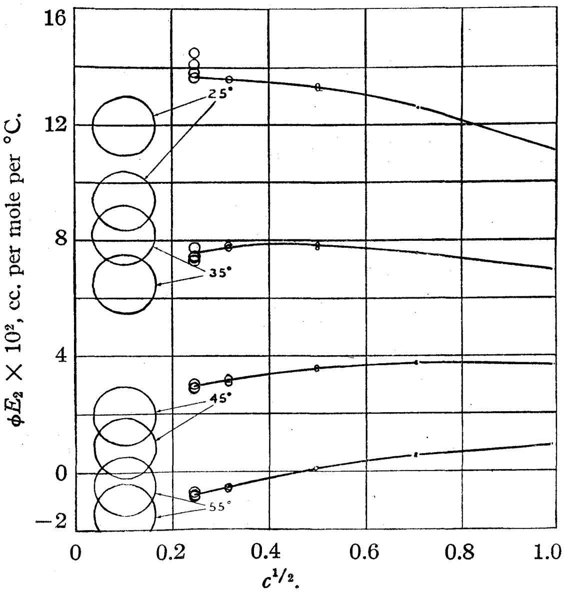


Fig. 8.—Apparent molal expansibility of barium chloride plotted against $c^{1/2}$.

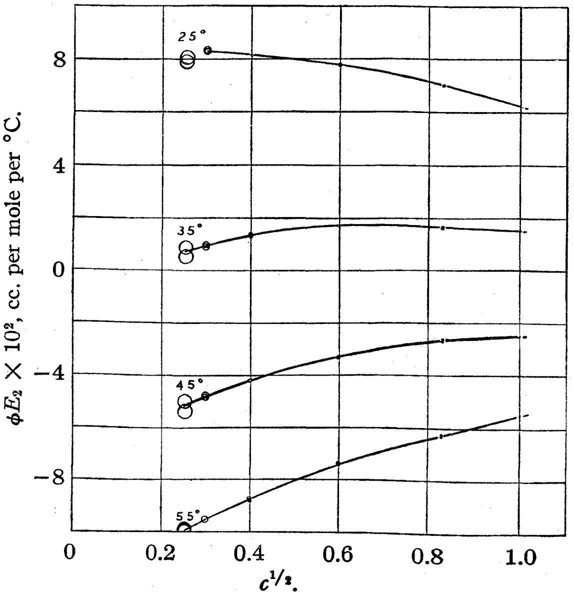


Fig. 9.—Apparent molal expansibility of lanthanum chloride plotted against $c^{1/2}$.

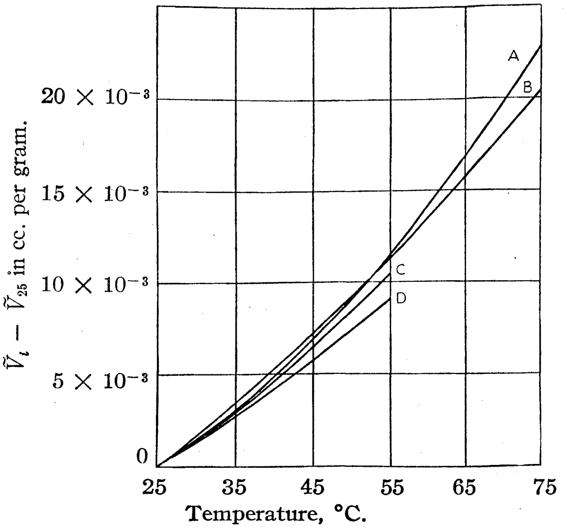


Fig. 10.—$\bar{V}_t - \bar{V}_{25°\text{C.}}$ plotted against temperature for water and solutions: curve A, water, 0.06 *M* KCl, 0.1 *M* KCl, 1 *M* KCl, 0.06 *M* $BaCl_2$, 0.1 *M* $BaCl_2$, 0.5 *M* $BaCl_2$, 1 *M* $BaCl_2$, 0.06 *M* $LaCl_3$ and 0.9 *M* $LaCl_3$; curve B, 3 *M* KCl; curve C, 0.36 *M* $LaCl_3$, curve D, 1 *M* $LaCl_3$.

This is also the value of x. Since as temperature increases the curvature of the plot of $\bar{V}_t - \bar{V}_{25°}$ decreases, the value 5×10^{-7} represents a maximum value of both x and y. Now $\phi E_2 - \phi E_2'$ can be calculated, and it is found that for lanthanum chloride, the salt of largest M_2, the error involved in using the integral coefficient instead of the differential coefficient of expansion would be only 0.0001 cc. per mole per degree. This treatment applies to 0.06, 0.1 and 1 *M* KCl solutions, to 0.06, 0.1 *M* $BaCl_2$ and very nearly to the 0.5 and 1 *M* $BaCl_2$ solutions. It also applies to 0.06 and 0.09 *M* $LaCl_3$ solutions.

A further analysis is needed in the case of the rest of the solutions. An extreme case is the 1 molar lanthanum chloride solution (Curve D, Fig. 10). This curve falls considerably below the curve for water, approaching a straight line. Thus x will tend to become zero. If we assume that x is zero, the error will be approximately $W_w y$ or 0.0005 cc. per mole per degree. The assumption that x is zero is an extreme one since it is quite obvious that the curve for 1 molar lanthanum chloride is still slightly curved. Although 0.0005 cc. per mole per degree is an appreciable error since it is applicable for concentrated solutions and could not possibly influence the shape of the curves of ϕE_2 plotted against $c^{1/2}$ it is clear that a more complicated treatment is not justified.

Discussion of Results.—A study of Figs. 4, 5, and 6, in which the coefficient of expansion of solutions of potassium chloride, barium chloride and lanthanum chloride are plotted against the temperature, show that in all cases, within the range of temperature studied, 20° to 60° (or 80°) and throughout the range of concentrations studied it is true that

$$\frac{\partial V}{V\partial t} > 0, \quad \frac{\partial}{\partial t}\left(\frac{\partial V}{V\partial t}\right) > 0, \quad \frac{\partial^2}{\partial t^2}\left(\frac{\partial V}{V\partial t}\right) < 0$$

At 25° all three salts studied have the effect of increasing the coefficient of expansion of water; $(\partial/\partial c)(\partial V/V\partial t) > 0$. For each salt there is a particular temperature at which the coefficient of expansion becomes independent of the concentration; $(\partial/\partial c)(\partial V/V\partial t) = 0$. In the case of potassium chloride solutions and of barium chloride solutions this temperature is about 52°, whereas for lanthanum chloride solutions it is about 37°. At higher temperatures $(\partial/\partial c)(\partial V/V\partial t) < 0$ in all cases. A qualitative explanation may be that at lower temperatures the introduction of the ions causes a change in the structure of the water (a depolymerization) so as to permit a closer packing, similar to the effect caused by raising the temperature. Then when the temperature of the solutions is raised there is less opportunity for this shift in structure and therefore less compensation for the normal thermal expansion.

Gucker's limiting equations (7 and 14) predict that, at low concentrations, the apparent molal expansibility ϕE_2, should (1) be a linear function of $c^{1/2}$; (2) the slopes $\partial\phi E_2/\partial c^{1/2}$ should be positive; (3) the slopes should increase greatly for salts of higher valence types. An examination of Fig. 7, 8 and 9 and Table V shows that (1) the curves are not linear for any of the salts, although approximately so for potassium chloride. (2) At 25° the slopes are negative throughout the range of concentrations studied, although a study of the curves indicates the possibility that if sufficient precision could be obtained at lower concentrations the slopes might become positive. Raising the temperature tends to increase the slopes and at 55° or above the slopes are all positive. (3) The great influence of the valence type, which is predicted by the theory does not seem to be supported by the curves.

It is therefore concluded that it is not possible to confirm these predictions from Gucker's equation at the concentrations which can be successfully studied experimentally. A substantial further increase in precision would be necessary to obtain significant data in solutions so dilute that they could be used with confidence to test the validity of a limiting law.

Summary

1. A new type of precision dilatometer which also serves as the thermoregulator of its own thermostat is described.

2. The new instrument has been used to determine the thermal expansion of water over the interval from 20° to 80°. Values for the specific volume of water at ten-degree intervals have been computed from these data.

3. Coefficients of expansion of aqueous solutions of potassium chloride ranging in concentration from 0.06 to 2.9 molal have been mea-

sured at ten-degree intervals from 25° to 75°.

4. Coefficients of expansion of aqueous solutions of barium chloride and of lanthanum chloride ranging in concentration from 0.06 to 1 molal have been determined at ten-degree intervals from 25° to 55°.

5. The apparent molal expansibilities of potassium chloride, barium chloride and lanthanum chloride in aqueous solutions have been calculated and their significance in relation to Gucker's theoretical equations is discussed.

CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 28, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

Conductivities of Quaternary Ammonium Chlorides Containing Two Long-chain Alkyl Groups

BY A. W. RALSTON, D. N. EGGENBERGER AND P. L. DU BROW

The concentration of colloidal electrolyte at the critical point for micelle formation has repeatedly been shown to decrease with increase in the chain length of the colloidal electrolyte. That this is true for the cationic colloidal electrolytes has been shown by a comparison of the equivalent conductivities of the alkylammonium chlorides of varying chain length[1] and of several of the alkyltrimethylammonium bromides.[2] It has recently been observed[3] that the position of the critical point is not materially influenced by the substitution of short-chain hydroxyalkyl groups for methyl groups in the higher alkyltrimethylammonium chlorides. The opinion has previously been expressed by Hartley[4] that the critical concentration is more dependent upon the chain length than upon the nature of the ionized groups. On the other hand, compounds which form two long-chain ions, such as octyltrimethylammonium octanesulfonate[5] and 1,1-dimethyl-3-hydroxybutylammonium caprylate,[6] form micelles at much lower concentrations than compounds which yield only one of the single long-chain, component ions. When we consider the long-chain alkyltrimethylammonium chlorides it appears that, although the replacement of methyl groups by other short-chain groups may not decidedly influence the electrical behavior, if a methyl group is replaced by a radical the chain length of which is comparable with that of the original long chain, such a substitution should be attended by a decided change in the conductivity values. We have, therefore, determined the equivalent conductivities of aqueous solutions of dioctyl-, didecyl-, didodecyl-, ditetradecyl-, dihexadecyl- and octyldodecyl-dimethylammonium chlorides and have compared the results with those obtained for several of the higher alkyltrimethylammonium chlorides. The comparisons have shown that significant differences exist between the conductivity behaviors of the higher dialkyldimethylammonium chlorides and those of the alkyltrimethylammonium chlorides. This comparison suggests that with the former the total number of carbon atoms in the long chains is determinative as regards their conductivity characteristics.

Experimental

Preparation of Dioctyl-, Didecyl-, Didodecyl-, Ditetradecyl- and Dihexadecyldimethylammonium Chlorides.—All the quaternary ammonium chlorides were similarly prepared. The preparation of didodecyldimethylammonium chloride will be described in detail as an example of the procedure employed.

Predistilled dodecylamine was carefully fractionated through a Stedman-packed column. In a two-necked flask fitted with a mercury-sealed stirrer and an air condenser, 212 g. of this distillate (f. p. 28.26°) and 8.5 g. of 50% Raney nickel suspended in dodecylamine were heated with stirring at 200° for two and one-half hours. The resulting product was taken up in ethyl acetate, the Raney nickel removed by filtration, and the didodecylamine crystallized from the solvent.

To 77 g. of the recrystallized didodecylamine dissolved in 200 cc. of ethanol, 49 cc. of 85% formic acid was slowly added, the temperature being maintained at about 40°. After this addition, 46 cc. of a 36% aqueous formaldehyde solution was added and the temperature raised to 60°. After the evolution of carbon dioxide had subsided, the temperature was maintained at the reflux point for one-half hour. The solution was then neutralized with aqueous sodium hydroxide, and the top layer was drawn off, dried over anhydrous potassium carbonate, filtered, and distilled (b. p. 183° at 0.35 mm.). The didodecylmethylamine so obtained (f. p. 10.4°) was dissolved in ethyl acetate, methyl chloride was added, and the mixture was heated in a bomb at 80° for one hour. The didodecyldimethylammonium chloride was recrystallized twice from ethyl acetate to give a white, crystalline, hygroscopic product. Dioctyldimethyl- and didecyldimethylammonium chlorides are extremely hygroscopic. This property was not observed with ditetradecyldimethyl- and dihexadecyldimethylammonium chlorides. The freezing points of the intermediate methyldialkylamines are as follows: methyldioctyl-, −30.1°; methyldidecyl-, −7.4°; methylditetradecyl-, 26.0°; and methyldihexadecylamine, 36.5–37.5°.

Preparation of Octyldodecyldimethylammonium Chloride.—To 102 g. of dodecyl chloride dissolved in 50 cc. of ethanol was added 38.7 g. of methylamine and the solution was heated in a bomb at 125° for eight hours. The contents of the bomb were neutralized with aqueous sodium hydroxide, the top layer dissolved in Skellysolve F, dried over anhydrous potassium carbonate, filtered, and the methyldodecylamine distilled. To 64 g. of distillate was added 56.3 g. of freshly distilled octyl bromide and the mixture was heated at 90° for five hours. One-half of the

---

(1) Ralston and Hoerr, THIS JOURNAL, **64**, 772 (1942).

(2) Scott and Tartar, *ibid.*, **65**, 692 (1942).

(3) Ralston and Eggenberger, *ibid.*, **69**, 2095 (1947).

(4) Hartley, *Kolloid-Z.*, **88**, 22 (1939).

(5) Scott, Tartar and Lingafelter, THIS JOURNAL, **65**, 698 (1943).

(6) Gonick, *ibid.*, **68**, 177 (1946).

theoretical amount of aqueous sodium hydroxide required for complete neutralization was added at the end of two and one-half hours and the remainder added slowly during the last two and one-half hours. The top layer was extracted with Skellysolve F, dried over anhydrous potassium carbonate, filtered, and the octyldodecylmethylamine distilled (b. p. 170° at 0.25 mm.). This distillate was converted to the quaternary ammonium chloride by heating with methyl chloride in a bomb at 80° for one hour. The product was recrystallized twice from cold ethyl acetate. Octyldodecyldimethylammonium chloride is very hygroscopic.

Conductivity Determinations.—Conductivities were determined in the manner and with the equipment previously described.[7] In order to eliminate errors due to adsorption the cell was brought into equilibrium with the various solutions before the conductance measurements were made.

Results and Discussion

The equivalent conductivities of aqueous solutions of dioctyldimethyl-, didecyldimethyl- and didodecyldimethylammonium chlorides at 30° are shown in Fig. 1. The most significant feature of these is the maxima which occur at concentrations between the critical points and infinite dilution. These inflections increase with increasing length of the alkyl chain, and with didodecyldimethylammonium chloride the equivalent conductivity at 0.0001 N is materially higher than that at infinite dilution. Similar maxima have been found to occur upon the addition of methanol to aqueous solutions of octadecylpyridinium chloride[8] and of ethanol to aqueous solutions of dodecylammonium chloride.[9] The occurrence of a maximum conductivity in dilute solutions of colloidal electrolytes was first observed by Hartley and associates,[10] who reported that at dilutions approximating 0.0004 N the conductivity of methylene blue is approximately 30% higher than at infinite dilution. A recent communication[11] has called attention to the presence of maxima in the conductivity curves of aqueous solutions of hexadecyl- and octadecylpyridinium iodates.

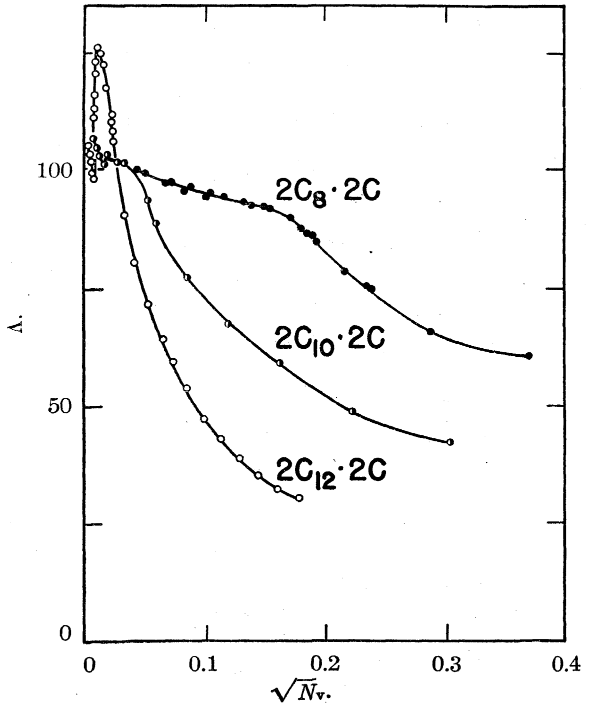


Fig. 1.—Equivalent conductivities of dialkyldimethylammonium chlorides at 30°.

The maxima in the curves shown in Fig. 1 occur at progressively lower concentrations with increase in the number of carbon atoms in the molecule. That the positions of these maxima are a function of the total number of carbon atoms in the two long alkyl chains is shown by a comparison of the equivalent conductivity curves of didecyl- and octyldodecyldimethylammonium chlorides, Fig. 2, both of which contain twenty carbon atoms in the two long alkyl chains. The close similarity of these curves is evident and in contrast to that of didodecyldimethylammonium chloride. Both ditetradecyldimethyl- and dihexadecyldimethylammonium chlorides, Fig. 3, show much larger equivalent conductivities in very dilute solutions than would be anticipated on the basis of their high molecular weights. Since these curves fall very abruptly and since even moderately concentrated solutions of these salts show low values for their equivalent conductivities, we are of the opinion that the high values of the very dilute solutions are evidence of the presence of maxima.

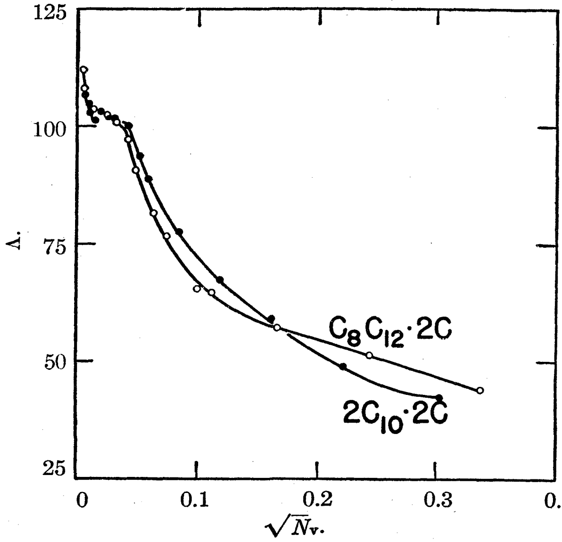


Fig. 2.—Equivalent conductivities of dialkyldimethylammonium chlorides at 30°.

The conductivity behaviors of the abovementioned compounds are strikingly different from those of the alkyltrimethylammonium chlorides which we have examined. These include do-

---

[7] Ralston, Hoerr and Hoffman, *ibid.*, **64**, 97 (1942).

[8] Evers, Grieger and Kraus, *ibid.*, **68**, 1137 (1946).

[9] Ralston and Hoerr, *ibid.*, **68**, 2460 (1946).

[10] Moilliet, Collie, Robinson and Hartley, *Trans. Faraday Soc.*, **31**, 120 (1935).

[11] Brown, Grieger, Evers and Kraus, This Journal, **69**, 1835 (1947).

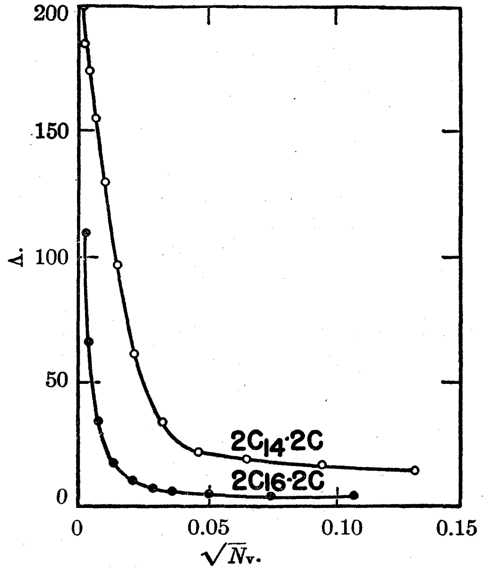


Fig. 3.—Equivalent conductivities of dialkyldimethylammonium chlorides at 30°.

decyl-, tetradecyl-, hexadecyl- and octadecyltrimethylammonium chlorides. Figure 4 shows a comparison of the equivalent conductivity of dodecyltrimethylammonium chloride with that of didodecyldimethylammonium chloride and also of hexadecyltrimethylammonium chloride with dioctyldimethylammonium chloride. The latter comparison shows that the critical point occurs at a much lower concentration when the carbon atoms are in a single chain, although the curve for the dioctyldimethylammonium chloride shows evidence of a maximum which is not apparent with hexadecyltrimethylammonium chloride. None of the alkyltrimethylammonium chlorides which we have investigated has exhibited a maximum in its equivalent conductivity.

It has formerly been customary to consider the equivalent conductivity curves of colloidal electrolytes to be characterized by three ranges. In the first range the conductivity falls linearly with concentration, in the second range an abrupt drop is encountered, and in the third range the values either remain essentially constant or exhibit a slight rise. All workers are in agreement that this characteristic behavior of colloidal electrolytes is occasioned by the formation of associated particles; however, diverse opinions have been expressed as to the nature of these particles and the concentration at which they first appear. McBain[12] has held that associated ions are present in very dilute solutions, well within the first range, although Hartley[4] has stated that below the critical point for micelle formation the colloidal electrolyte functions as an ordinary strong electrolyte. The occurrence of maxima in the conductivity curves of the higher dialkyl quaternary ammonium chlorides indicates that association into ionic aggregates occurs at low concentrations followed by the formation of less-conducting micelles. This phenomenon can be attributed to the incorporation of undissociated molecules into the ionic aggregates. Since the present study has been confined to a limited number of compounds of a specific type we are not justified in drawing extensive conclusions. High hydrocarbon loading of the molecule apparently favors the formation of maxima, and a number of unpublished observations on long-chain cationic electrolytes lead us to believe that this phenomenon is frequently encountered.

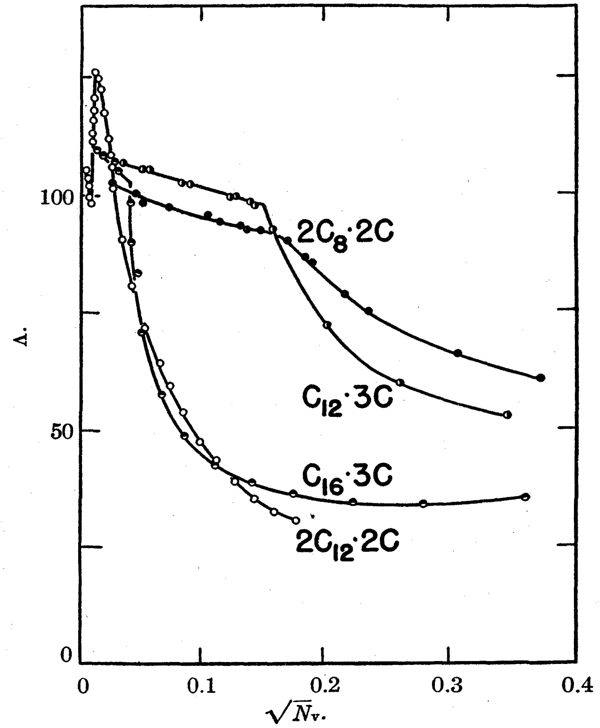


Fig. 4.—Comparison of equivalent conductivities of alkyltrimethylammonium chlorides at 30°.

Summary

The equivalent conductivities of dioctyl-, didecyl-, didodecyl-, ditetradecyl-, dihexadecyl- and octyldodecyldimethylammonium chlorides have been determined. Didodecyldimethylammonium chloride shows a maximum value at concentrations below the critical point and evidences of maxima are also present with both its lower and its higher homologs.

The conductivity behavior of the dialkyldimethylammonium chlorides has been compared with that of several alkyltrimethylammonium chlorides.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 2, 1947

---

[12] McBain, *Nature*, **145**, 702 (1940).

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

The Effects of Electrolytes upon the Conductivity of Aqueous Solutions of Dodecylammonium Chloride[1]

BY A. W. RALSTON AND D. N. EGGENBERGER

The presence of electrolytes is known to have a significant effect upon the behavior of aqueous solutions of colloidal electrolytes. In general, the effect of added salts is to magnify the colloidal properties of the colloidal electrolyte. This manifests itself in a lowered conductivity on the part of the colloidal electrolyte, a lowered concentration of colloidal electrolyte at the critical point, and an increased solvent power for a number of organic non-electrolytes. Several observations of these effects have been recorded in the literature. For example, it has been shown[2] that an increase in the sodium ion concentration materially reduces the concentration of sodium dodecyl sulfate at the critical point for micelle formation. Tartar and Cadle[3] have shown that the presence of sodium chloride reduces the aqueous solubilities of sodium dodecyl sulfate and sodium tetradecyl sulfate and increases their tendencies toward micelle formation. Hartley[4] has observed that the solubility of azobenzene in aqueous solutions of hexadecylpyridinium chloride is greatly increased by the presence of sodium chloride. The addition of salts to both dilute and concentrated soap solutions has been shown by McBain and co-workers[5] to materially increase the solubilizing power of such solutions for water-insoluble dyes. The osmotic studies of McBain and Brady[6] showed that the presence of either potassium chloride or potassium sulfate promotes micelle formation in aqueous solutions of potassium laurate. Quite recently, Corrin and Harkins[7] have described a method by which the critical point can be determined by titration with an aqueous dye solution, the critical concentration being indicated by a visual color change in the dye. This method was employed in an investigation[8] of the effect of the addition of electrolytes upon the critical concentrations of a number of anionic and cationic electrolytes. It was stated that the critical concentration is affected only by the concentration of the ion opposite in charge to that on the colloidal aggregate and that the concentration and nature of the other ion is without effect. More recently, however, Harkins and associates[9] have observed that the increase in solubilizing power of soap solutions upon the addition of an electrolyte is dependent upon both the nature of the cation and the anion of the added salt. This present study reports the effects of several electrolytes upon the equivalent conductivity of aqueous solutions of dodecylammonium chloride. The effects observed are undoubtedly associated with the colloidal behavior of this amine salt.

Experimental

The preparation and properties of the dodecyl- and hexadecylammonium chlorides used in this investigation have been described elsewhere.[10] The conductivities were determined in the manner and with the equipment previously described.[11] The conductivity by difference was calculated by substracting the specific conductance of the added electrolyte from the specific conductance of the solution containing the electrolyte and the amine salt. For example, if a 0.005 *N* sodium chloride solution is employed as the solvent the specific conductance of this solution is subtracted from the observed values.

Results and Discussion

The conductivities of aqueous solutions of dodecylammonium chloride at 30° and the conductivities by difference of this colloidal electrolyte in 0.005 *N* and 0.015 *N* sodium chloride are shown in Fig. 1. The material reduction in equivalent conductivity of the amine salt occasioned by the presence of sodium chloride is clearly evident. This effect can be attributed to the increased chlorine ion concentration which reduces the ionization of the amine salt, the marked reduction of the critical concentration evidencing the presence of undissociated molecules at lower concentration of colloidal electrolyte. The magnitude of this common ion effect may overshadow other changes produced in the system by the presence of the sodium chloride such as dehydration of the micelles resulting from the lowered partial pressure of the water or any possible effects of the sodium ions. If the predominant influence of the sodium chloride is to retard the ionization of the amine salt a similar effect should be noted when the amine salt is a non-colloidal electrolyte. Figure 2 shows that the addition of sodium chloride to a solution of hexylammonium chloride materially lowers the conductivity attributable to the amine salt.

---

[1] Presented before the Physical Section, Fifteenth Midwest Regional Meeting of the American Chemical Society, Kansas City, Missouri, June, 1947.

[2] Wright, Abbott, Sivertz and Tartar, THIS JOURNAL, **61**, 553 (1939).

[3] Tartar and Cadle, *J. Phys. Chem.*, **43**, 1173 (1939).

[4] Hartley, *J. Chem. Soc.*, 1968 (1938).

[5] Merrill and McBain, *J. Phys. Chem.*, **46**, 10 (1942); McBain and Merrill, *Ind. Eng. Chem.*, **34**, 915 (1943); McBain and Johnson, THIS JOURNAL, **66**, 9 (1944); McBain and Green, *ibid.*, **68**, 1731 (1946).

[6] McBain and Brady, *ibid.*, **65**, 2072 (1943).

[7] Corrin and Harkins, *ibid.*, **69**, 679 (1947).

[8] Corrin and Harkins, *ibid.*, **69**, 683 (1947).

[9] Stearns, Oppenheimer, Simon and Harkins, *J. Chem. Phys.*, **15**, 496 (1947).

[10] Ralston and Hoerr, THIS JOURNAL, **68**, 851 (1946).

[11] Ralston, Hoerr and Hoffman, *ibid.*, **64**, 97 (1942).

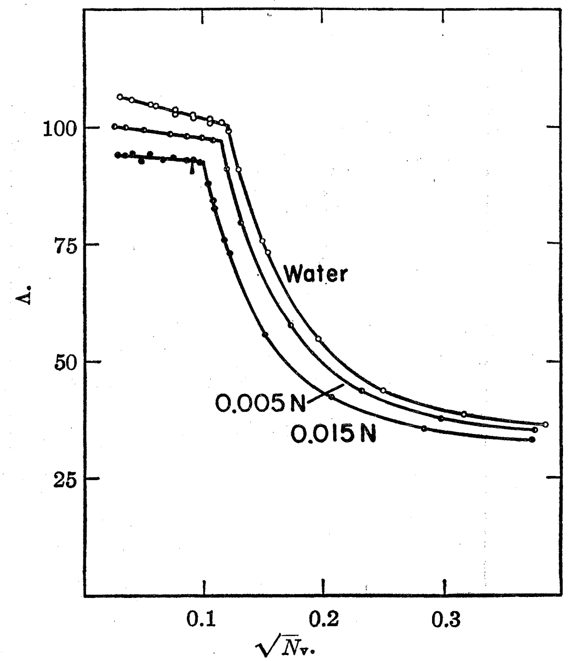


Fig. 1.—Conductance by difference of dodecylammonium chloride in sodium chloride at 30°. The numbers on the curves refer to the molality of sodium chloride.

A somewhat more involved problem is presented when we study the effect of electrolytes which do not possess an ion in common with the amine salt.[12] Much of the previous work upon the effect of salts on the physical behavior of solutions of colloidal electrolytes has been confined to salts having an ion in common with the colloidal electrolyte and the common ion effect has been used as the basis for interpretation of many of the observed phenomena. On the other hand, Corrin and Harkins[8] have shown that salts not possessing an ion in common with the colloidal electrolyte are as effective in lowering the critical concentration as those which have a common ion. Figure 3 shows the conductivity by difference at 30° of dodecylammonium chloride in 0.0261 *N* sodium acetate, 0.0169 *N* potassium acetate, and 0.0107 *M* calcium acetate. These salt concentrations were selected because they possess specific conductances comparable with the previously employed 0.015 *N* sodium chloride solution. The effects of these three salts upon the equivalent conductance of the colloidal electrolyte are approximately equal and are comparable with that of the 0.015 *N* sodium chloride solution. This indicates that the effect of a salt not possessing an ion in common with the colloidal electrolyte is similar to that of one which contains a common ion. It also shows that, for the salts investigated, the effect of the salt upon the electrical behavior of the cationic electrolyte is independent of the nature and concentration of the cation of the added salt.

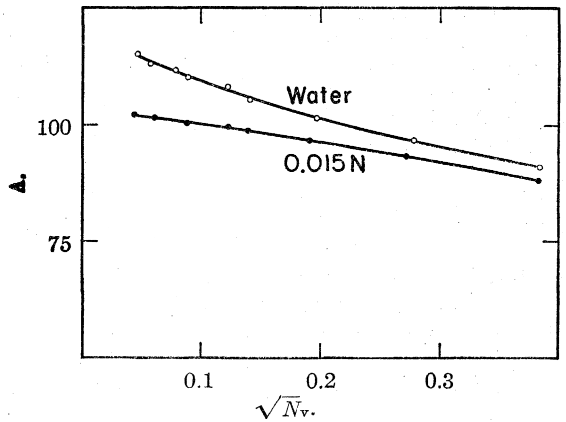


Fig. 2.—Conductance by difference of hexylammonium chloride at 30° in sodium chloride.

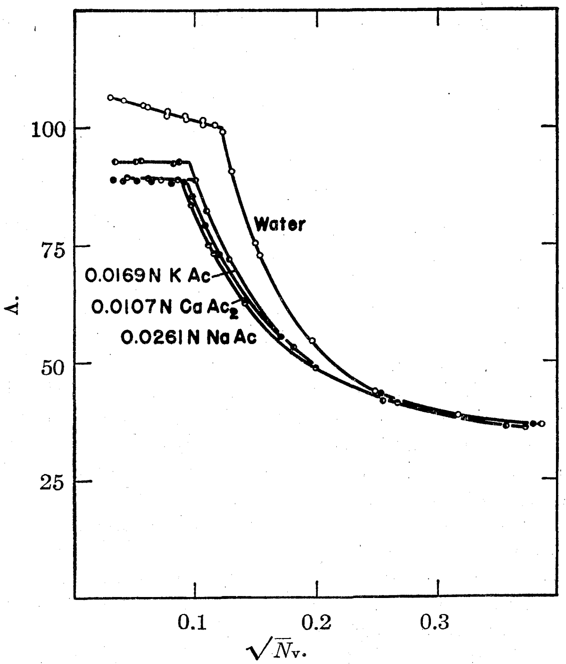


Fig. 3.—Conductance by difference of dodecylammonium chloride at 30° in presence of acetates.

The first of these conclusions is explainable on the basis of a general consideration of the behavior of solutions of colloidal electrolytes. Such solutions differ from solutions of ordinary electrolytes in that at a certain critical concentration the ions and undissociated molecules associate into colloidal particles. For colloidal electrolytes of similar structure the concentration at which this phenomenon occurs is a function of the chain length. The X-ray studies made by Harkins, Mattoon and Corrin[13] on aqueous solutions of mixtures of potassium laurate and potassium myri-

---

(12) See for example, Sherrill, THIS JOURNAL, **32**, 741 (1910); Mackay, *ibid.*, **33**, 308 (1911); Bray and Hunt, *ibid.*, **33**, 781 (1911); Smith and Gortner, *J. Phys. Chem.*, **37**, 79 (1933); Davies, *J. Chem. Soc.*, 448 (1938).

(13) Harkins, Mattoon and Corrin, *ibid.*, **68**, 220 (1946).

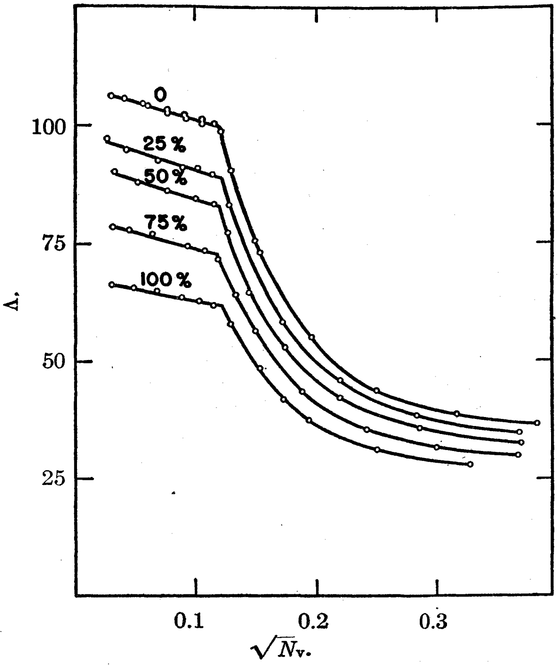


Fig. 4.—Conductances of mixtures of dodecylammonium acetate and dodecylammonium chloride at 30°. The numbers on the curves refer to the weight per cent. of dodecylammonium acetate.

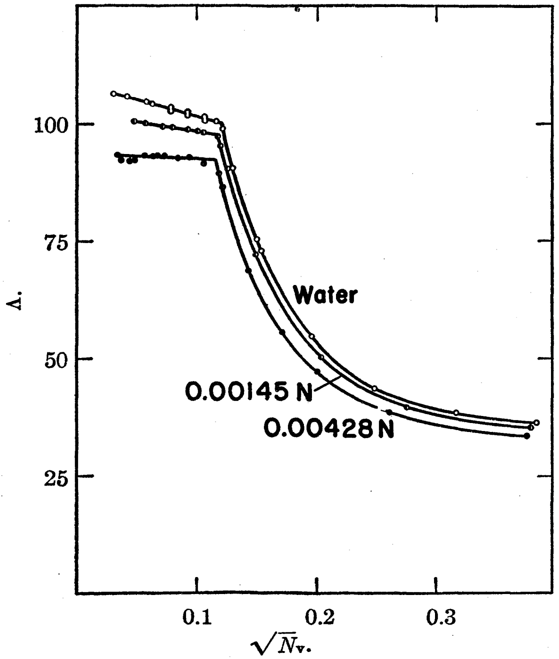


Fig. 5.—Conductance by difference of dodecylammonium chloride in hydrochloric acid at 30°.

state show only one maximum which is intermediate between the maxima exhibited by the pure soaps. Figure 4 shows the equivalent conductivities at 30° of solutions of pure dodecylammonium chloride and dodecylammonium acetate and of mixtures of these amine salts. These results show that the micelles formed from a solution of dodecylammonium chloride and its acetate incorporate both components and that the position of the critical point is not influenced by the nature of the anion. This is in conformity with previous observations[14] that the concentration of colloidal electrolyte at the critical point is a function of the chain length. When sodium acetate is added to an aqueous solution of dodecylammonium chloride an equilibrium will be set up which involves both the chloride and acetate of the colloidal electrolyte and, as a consequence, both the chloride and acetate ions are common to the components of the micelles. A similar situation will result when any salt is added to a solution of a colloidal electrolyte.

In view of the above-described effect of salts, it is surprising to find that the addition of acids to solutions of dodecylammonium chloride has only a negligible effect upon the position of the critical point. Figure 5 shows that, although the conductivities by difference at 30° of dodecylammonium chloride in 0.00145 and 0.00428 *N* hydrochloric acid are materially lower than that of the salt in pure water, the position of the critical point is not materially shifted. The lowered conductivity can be ascribed to depression of the ionization of the colloidal electrolyte, since it was observed that the conductivity by difference of the non-colloidal electrolyte, hexylammonium chloride, in 0.0043 *N* hydrochloric acid is appreciably lower than its conductivity in pure water. We have no present explanation as to why this effect is not attended by a more significant shift in the critical concentration of the colloidal electrolyte.

The conductivities by difference of dodecylammonium chloride at 30° in 0.15 and 1.43 *N* acetic acid compared to that of the pure salt are shown in Fig. 6. It will again be noted that the addition of acetic acid does not influence the position of the critical point. At concentrations of dodecylammonium chloride beyond the critical point, the presence of acetic acid brings about an appreciable increase in the conductivity attributable to the colloidal electrolyte. It must, however, be borne in mind that the conductivity by difference incorporates all changes brought about in the system as a whole. Incorporation of undissociated dodecylammonium acetate into the micelles will remove it from solution and will result in an appreciable conversion of dodecylammonium chloride to its acetate. The increased conductivity may possibly be attributed to the simultaneous formation of hydrochloric acid attending this conversion.

The effect of tartaric acid upon the conductivity of dodecylammonium chloride is shown in Fig. 7 which compares the conductivity of the amine salt at 30° in pure water with its conductivity by difference in 0.0091 *N* tartaric acid. At concentrations higher than the critical point the effect

---

(14) Ralston and Hoerr, *ibid.*, **69**, 883 (1947).

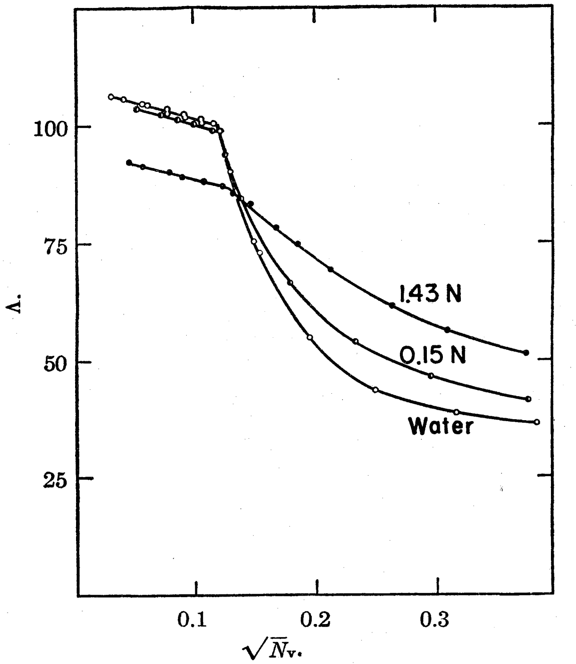


Fig. 6.—Conductance by difference of dodecylammonium chloride in acetic acid at 30°.

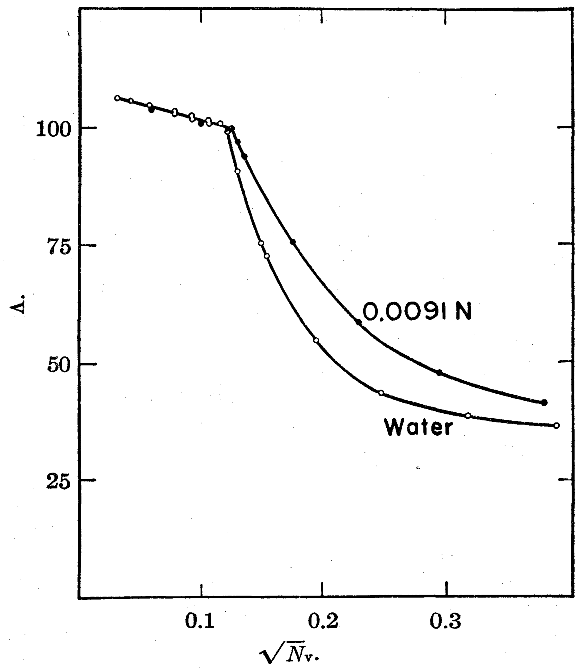


Fig. 7.—Conductance by difference of dodecylammonium chloride in tartaric acid.

of tartaric acid is qualitatively similar to that of acetic acid; however, at lower concentrations the presence of tartaric acid does not influence the conductivity of the colloidal electrolyte. In conformity with this latter observation we have found that the presence of tartaric acid does not lower the conductivity of aqueous solutions of the non-colloidal electrolyte, hexylammonium chloride.

The above observations show that the effect of the addition of acids upon the conductivity of dodecylammonium chloride differs in several respects from the effects resulting from the additions of salts. We have no present explanation for this difference and feel that much more work is required before any explanation should be attempted.

Summary

The effect of the presence of sodium chloride, sodium acetate, potassium acetate, calcium acetate, hydrochloric acid, acetic acid and tartaric acid upon the equivalent conductivity of aqueous solutions of dodecylammonium chloride has been determined.

The results have been discussed in relation to the micelle theory.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 27, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

The Effect of Organic Non-electrolytes upon the Conductivities of Aqueous Solutions of Cationic Colloidal Electrolytes

BY A. W. RALSTON AND D. N. EGGENBERGER

The ability to solubilize water-insoluble organic non-electrolytes is one of the characteristic properties of aqueous solutions of colloidal electrolytes.[1] McBain and co-workers have made extensive investigations of the solubilization of water-insoluble dyes,[2,3,4] water-insoluble organic liquids,[5] and of hydrocarbon vapors[6] by aqueous solutions of colloidal electrolytes. In 1939, Kiessig and Philipoff[7] observed an increase in the size of the micelles of sodium oleate upon the addition of benzene to aqueous solutions of this soap and this has been subsequently interpreted[3] as indicating that the solubilized material is incorporated in layers within the micelles. A recent X-ray investigation[8] has shown that the thickness of micelles of potassium laurate or potassium myristate

---

(1) Hartley, *J. Chem. Soc.*, 1968 (1938).

(2) McBain, Merrill and Vinograd, THIS JOURNAL, **63**, 670 (1941).

(3) McBain and Johnson, *ibid.*, **66**, 9 (1944).

(4) McBain and Green, *ibid.*, **68**, 1731 (1946).

(5) McBain and Richards, *Ind. Eng. Chem.*, **38**, 642 (1946).

(6) McBain and O'Connor, THIS JOURNAL, **63**, 875 (1941).

(7) Kiessig and Philipoff, *Naturwissenschaften*, **27**, 593 (1939).

(8) Mattoon, Stearns and Harkins, *J. Chem. Phys.*, **15**, 209 (1947).

is materially increased by the presence of hydrocarbons such as hexane, benzene or ethylbenzene. The recent work of Harkins and associates[9] has given support to the opinion previously expressed by Hartley[1] that solubilization does not occur below the critical point for micelle formation. Factors such as molecular volume, molecular weight, polarity, and structure exert a marked influence upon solubilization.

Many conductivity measurements upon aqueous solutions of colloidal electrolytes have been published. It is universally accepted that the colloidal electrolytes exhibit conductivity behaviors which distinguish them from ordinary electrolytes. Since solubilization is occasioned by the incorporation of water-insoluble substances into the micelles, it follows that this process should materially influence the conductivities of solutions of colloidal electrolytes. We have, therefore, made a study of the effect of the presence of a number of organic non-electrolytes upon the conductivities of several cationic colloidal electrolytes. The data permit certain generalizations regarding the phenomenon of solubilization and also allow certain speculations regarding the mechanism of micelle formation in aqueous solutions of colloidal electrolytes.

Experimental

The preparation of the hexadecyltrimethylammonium chloride used in this study has been previously described.[10] The dodecyltrimethylammonium chloride was prepared by a similar procedure. The dodecylammonium chloride was from the same lot as that previously employed in recent conductivity determinations.[11] Conductivities were determined in the manner and with the equipment previously described.[12] In all cases the solution of the colloidal electrolyte was saturated with the organic non-electrolyte. This was accomplished by progressively adding the non-electrolyte to the solution, vigorously shaking, and allowing the system to come to equilibrium at the temperature of the determination. In several instances this process required from twelve to forty-eight hours. Excess of non-electrolyte is indicated by the formation of a separate layer which was removed. Conductivity water was used for dilution; however, in all cases care was exercised to make certain that the solution was saturated with the non-electrolyte. All the curves were checked by determining the conductivity of individually prepared samples, and the cell was permitted to come to equilibrium with the solution before any conductivity values were recorded.

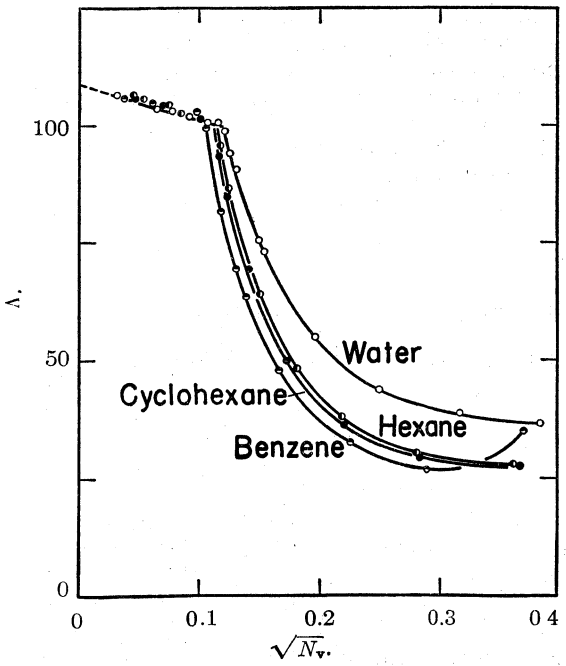


Fig. 1.—Equivalent conductivities at 30° of dodecylammonium chloride in the presence of six-carbon-membered hydrocarbons.

Results and Discussion

The three six-carbon-membered hydrocarbons, *n*-hexane, benzene, and cyclohexane are solubilized in an aqueous solution of dodecylammonium chloride and Fig. 1 shows that their presence brings about an appreciable lowering of the conductivity of the colloidal electrolyte. It is interesting to note that all three of these hydrocarbons lower the concentration at the critical point which indicates that they assist in micelle formation. This is in agreement with the previous observations of McBain and others[2,13] that the presence of water-insoluble, organic, non-electrolytes lowers the critical concentration for micelle formation. The effect of hexane is less than that of benzene, whereas that of cyclohexane is intermediate. This shows that either the benzene is solubilized to a somewhat greater extent than cyclohexane or its effect when incorporated into the micelles is greater. In any event, the curves indicate that the structure of the compound solubilized is a factor in its effect upon the conductivity. The fact that the presence of these hydrocarbons lowers the critical point is explainable on the basis of their affinity for the hydrocarbon portion of the associated ions. Solubility determinations of benzene and cyclohexane in dodecane[14] show that both are extremely soluble in this hydrocarbon; however, the former is somewhat less soluble than the latter.

The influences of the higher straight chain hydrocarbons, octane, dodecane, heptadecane and octadecane upon the equivalent conductivity of

---

[9] Stearns, Oppenheimer, Simon and Harkins, *ibid.*, **15**, 496 (1947).

[10] Ralston, Eggenberger, Harwood and Du Brow, THIS JOURNAL, **69**, 2095 (1947).

[11] Ralston and Eggenberger, *ibid.*, **70**, 436 (1948).

[12] Ralston, Hoerr and Hoffman, *ibid.*, **64**, 97 (1942).

[13] McBain, "Advances in Colloid Science," Interscience Publishers, Inc., New York, N. Y., 1942, Vol. I, p. 133.

[14] Ralston, Hoerr and Crews, *J. Org. Chem.*, **9**, 319 (1944).

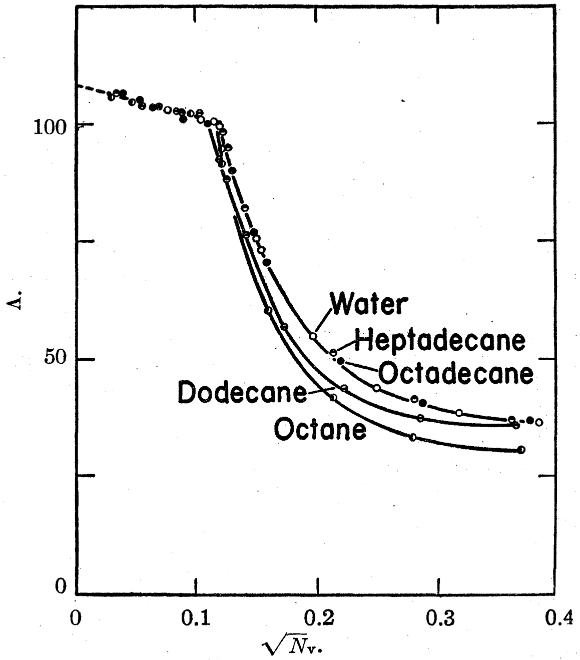


Fig. 2.—Equivalent conductivities at 30° of dodecylammonium chloride in the presence of straight-chain, saturated hydrocarbons.

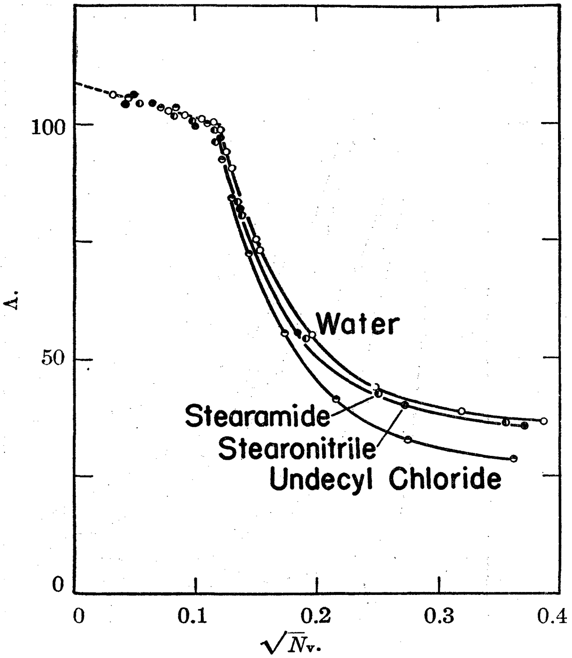


Fig. 3.—Equivalent conductivities at 30° of dodecylammonium chloride in the presence of polar aliphatic compounds.

dodecylammonium chloride are shown in Fig. 2. It is evident that their effects are appreciably less than those of the six-carbon-membered hydrocarbons, and that they decrease progressively with increase in chain length. Both heptadecane and octadecane are without apparent effect on the equivalent conductivity of this colloidal electrolyte. This shows that increase in chain length of the hydrocarbon is attended by a drastic reduction in its ease of solubilization and is in conformity with the previous findings of McBain and Richards[5] that hydrocarbons of high molecular weight are scarcely solubilized. An important observation with regard to the effect of hydrocarbons is that their presence does not significantly influence the conductivity values at concentrations lower than the critical concentration for micelle formation.

If the long-chain compound possesses a polar group, its presence lowers the equivalent conductivity of dodecylammonium chloride. Figure 3 shows that both stearonitrile and stearamide lower the conductivity of this amine salt, in contrast to octadecane, Fig. 2, which was observed to be without effect. The lowering of the conductivity by the presence of undecyl chloride, Fig. 3, is quite similar to that produced by octane and substantially greater than that resulting from the presence of dodecane, Fig. 2. This shows that even though the corresponding hydrocarbon is solubilized, the presence of a polar group increases either the amount of solubilization or the specific conductivity effect. None of the compounds shown in Fig. 3 appear to exert a significant influence on the conductivity of the amine salt at concentrations lower than the critical concentration for micelle formation. This is contrary to our previously published results[15] which reported that dodecane, lauronitrile and N-methyllauramide lower the conductivity of aqueous solutions of dodecylammonium chloride at concentrations below the critical point.

The higher alcohols, hexanol, octanol, dodecanol and octadecanol have a profound influence upon the conductivity of dodecylammonium chloride. Figure 4 shows that these alcohols decidedly lower the conductivity over the entire range of concentration, the lowering being at a maximum with dodecanol and at a minimum with octadecanol. As the concentration of the amine salt is increased all these solutions go from milky liquids to sirupy liquids and finally to gels. We interpret these results as indicating that long-chain compounds which contain a hydrophilic group are not only solubilized but that they can also enter into the structure of the ionic micelles and thus assist in the solubilization process. McBain and McHan[16] have ascribed the solubilization of dodecyl alcohol in solutions of potassium laurate to the polar portion of the detergent.

The effect of the presence of organic nonelectrolytes upon two long-chain alkyltrimethylammonium chlorides has been investigated. The results obtained with aqueous solutions of hexadecyltrimethylammonium chloride in the presence

---

(15) Ralston and Hoerr, THIS JOURNAL, **69**, 883 (1947).

(16) Paper presented before the Division of Colloid Chemistry, 112th Meeting, A. C. S., New York, Sept., 1947.

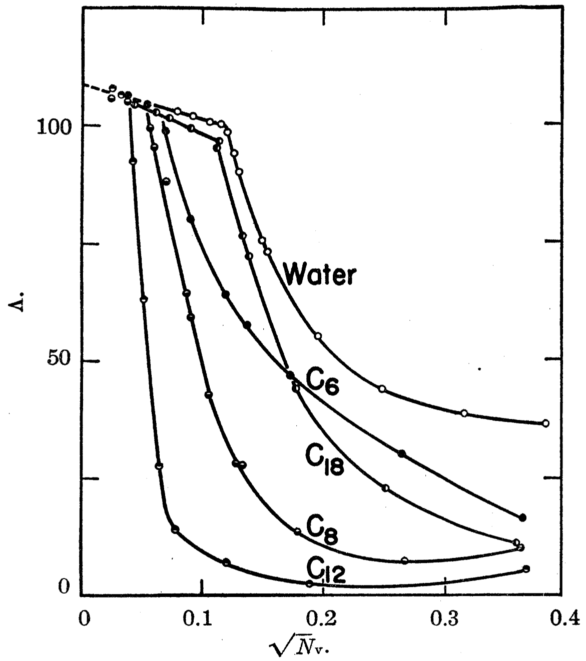


Fig. 4.—Equivalent conductivities at 30° of dodecylammonium chloride in the presence of aliphatic alcohols.

of dodecane, octadecane and lauronitrile agree quite closely with those which would be expected from the above-described observations upon dodecylammonium chloride. Figure 5 shows that the presence of dodecane and lauronitrile lowers the equivalent conductivity of aqueous solutions of dodecyltrimethylammonium chloride. The polar compound exerts the greater effect, and although both compounds lower the critical concentration, they do not significantly influence the conductivity within the first range. These results are qualitatively similar to those observed with dodecylammonium chloride and indicate that the presence of the methyl groups in the colloidal electrolyte is without material influence.

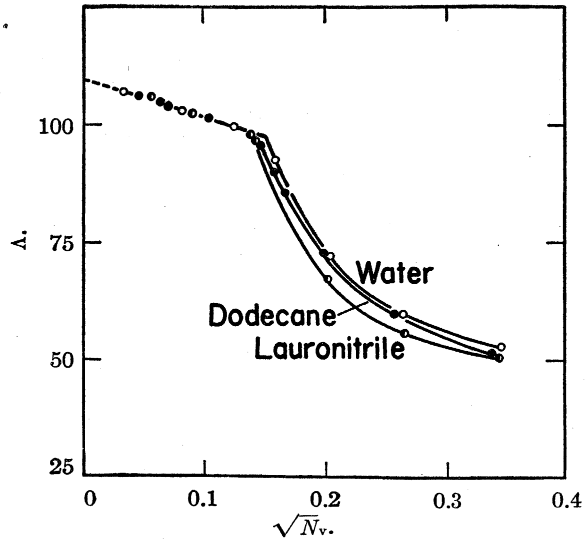


Fig. 5.—Equivalent conductivities of dodecyltrimethylammonium chloride in the presence of dodecane and lauronitrile.

In the above discussion we have assumed that the observed results are dependent upon the incorporation, by solubilization or otherwise, of the organic non-electrolytes into the colloidal aggregates. Although this assumption appears reasonable it certainly requires experimental verification. As a consequence, we have determined the effect of the presence of several organic non-electrolytes upon the conductivity of aqueous solutions of hexylammonium chloride. This salt has been previously shown[17] to function as an ordinary electrolyte even in concentrated solutions. Since it does not form micelles the conductivity of its aqueous solutions should not be influenced by the presence of water-insoluble substances. Figure 6 shows the conductivities of aqueous solutions of hexylammonium chloride and of solutions of this salt in the presence of dodecane, dodecanol, lauronitrile and N-methyllauramide. None of these compounds influence the equivalent conductivity of this amine salt and we are, therefore, safe in assuming that the effects noted above with its higher homologs are dependent upon the colloidal nature of the latter.

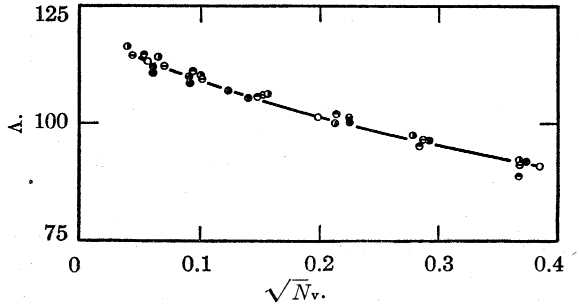


Fig. 6.—Equivalent conductivities of hexylammonium chloride in the presence of non-electrolytes: ○, hexylammonium chloride; ⊖, methyllauramide; ◑, lauronitrile; ●, dodecanol; ◓, dodecane.

The phenomenon of solubilization appears to be of more fundamental significance than has hitherto been considered. The fact that the critical concentration for micelle formation in solutions of colloidal electrolytes is materially lowered by the presence of water-insoluble organic non-electrolytes indicates that the effect is more complex than a simple incorporation of the water-insoluble substance into a previously formed micelle. It is, therefore, possible that solubilization and micelle formation are allied phenomena. As the concentration of an aqueous solution of a colloidal electrolyte is increased, the number of undissociated molecules also increases and these undissociated molecules function as non-electrolytes. Their inclusion into the ionic micelles would be attended

[17] Ralston and Hoerr, *ibid.*, **68**, 2460 (1946).

by a marked and abrupt drop in the equivalent conductivity and by an abnormal increase in the cationic transference number in the case of the cationic colloidal electrolytes. It is well known that both of these effects are observed in aqueous solutions of colloidal electrolytes. The essential difference between ionic and lamellar micelles is that the latter has solubilized the undissociated colloidal electrolyte.

Transference data on the effect of non-electrolytes upon solutions of colloidal electrolytes would be extremely helpful in explaining the mechanism of micelle formation and studies are now underway to determine the effect of various non-electrolytes upon the transference numbers of solutions of dodecylammonium chloride.

Summary

The effect of the presence of benzene, cyclohexane, hexane, octane, dodecane, heptadecane, octadecane, hexanol, octanol, dodecanol, octadecanol, undecyl chloride, stearonitrile and stearamide upon the equivalent conductivity of aqueous solutions of dodecylammonium chloride has been determined. The influence of the presence of dodecane and lauronitrile upon the equivalent conductivity of aqueous solutions of dodecyltrimethylammonium chloride has also been investigated.

With the exception of heptadecane and octadecane all the compounds investigated lowered the equivalent conductivity and the critical concentration for micelle formation in the amine salt solutions.

The results have been discussed in relation to the micelle theory and it has been proposed that solubilization and micelle formation are allied phenomena.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 27, 1947

[CONTRIBUTION FROM THE NATIONAL BUREAU OF STANDARDS]

The Dissociation of Diborane by Electron Impact

BY VERNON H. DIBELER AND FRED L. MOHLER

Introduction

The theory of the structures of some electron-deficient molecules, the hydroborons in particular, have recently received considerable attention. In 1942 the most fully developed valence theory of the hydroborons, as reviewed by Bauer,[1] assumed hydrocarbon-like structures. Because of inconsistencies between the hydrocarbon analogy and chemical and physical properties, Pitzer[2] and others further developed the four-membered-bridge bond originally proposed by Dilthey[3] to a "protonated double bond" theory in which two protons are placed symmetrically between the boron atoms, one above and one below an ethylene-like double bond. More recently, Burg,[4] in order to account for the lack of proton–deuteron exchange between ammonia and ammoniated diborane, proposed a "pseudoethane" structure in the form of a trigonal antiprism in which two sp^2 planar BH_3 groups are held together by resonating cross linkages between the B–B and B–H atoms. Another structure which he considers possible is a four-proton-bridge model in which the two boron atoms and four of the hydrogen atoms form the corners of a cube. The remaining two hydrogens extend outward along the diagonal of the cube connecting the two boron atoms.

Rundle[5] accepts Pitzer's developed theory in the case of the hydroborons with an interpretation of the protonated double bond as two hydrogen bridges consisting of "half-bonds." Each hydrogen bonds two boron atoms using its ls-orbital and one electron pair. Thus, the bridge contains two pairs of electrons and should have the properties of the ethylene-like double bond.

Hipple[6] has published a note on the mass spectrum of diborane. An analysis of this mass spectrum made by the authors differs significantly from the results reported by Hipple. As the results have a direct bearing on the structure of the diborane molecule we report in detail the analysis of this spectrum as compared with the mass spectra of ethane and ethylene.

Experimental

The Consolidated mass spectrometer used to obtain the mass spectra has been described elsewhere in detail.[7] The gas to be studied is admitted to the ionization chamber at about 10^{-4} mm. pressure and ionized by a beam of electrons at 50 or 70 electron volts energy. The positive ions formed in the electron beam are accelerated by an electric field and sorted into 180° arcs by a constant magnetic field used as a velocity analyser. By varying the electric field the ions are separately collected and recorded. The ionizing current is automatically maintained constant and the ionization chamber is thermostated to maintain a temperature of about 245°. Two samples of diborane were obtained. Sample 1 was prepared at the U. S. Naval Research Laboratory and supplied by Roman R. Miller. About 25 ml. of gas (S.T.P.) were removed from the liquid phase and transferred from the stainless steel cylinder into a glass bulb. The glass bulb was stored at −78° to minimize decomposition to hydrogen and heavy hydroborons. A mass spectrometric analysis of the original sample showed a purity of about 99.4% with small amounts of tetraborane, ethane and diethyl ether. Sam-

---

(1) S. H. Bauer, *Chem. Rev.*, **31**, 43 (1942).

(2) K. S. Pitzer, THIS JOURNAL, **67**, 1126 (1945).

(3) W. Dilthey, *Z. angew. Chem.*, **34**, 596 (1921).

(4) A. B. Burg, THIS JOURNAL, **66**, 747 (1947).

(5) R. E. Rundle, *ibid.*, **69**, 1327 (1947).

(6) J. A. Hipple, Jr., *Phys. Rev.*, **57**, 350 (1940), abstract.

(7) H. W. Washburn, H. F. Wiley, S. M. Rock and C. E. Berry, *Ind. Eng. Chem., Anal. Ed.*, **15**, 54 (1943).

ple 2 was prepared at the University of Southern California by Anton B. Burg. The sample of about 70 ml. at slightly above atmospheric pressure was shipped by air-express in a glass tube with an inner break-off seal. Upon arrival it was stored under the same conditions as Sample 1. Except for a small amount of hydrogen, Sample 2 showed no impurities volatile at −78°. An additional precaution was taken by cooling both samples to −183° and pumping off accumulated hydrogen before each run.

The ethylene and ethane were Phillips Petroleum Company "Research Grade" hydrocarbons.

Results

The mass spectrum of diborane permits a determination both of the isotope abundance ratio of boron and the monoisotopic spectrum of diborane. By trial approximations on Sample 1 it was found that an abundance ratio $B^{10}/B^{11} = 0.251$ gives the best fit with the observed spectrum. In the same manner, Sample 2 showed a ratio $B^{10}/B^{11} = 0.256$. The former value is in good agreement with a value of 0.250 obtained in this Laboratory from the boron trifluoride spectrum. It is not in agreement, however, with a value of 0.232 found by Inghram.[8] It seems probable that there are real differences in the isotope ratio depending on the previous history of the sample used in the experiments. For Sample 1, using the ratio $B^{10}/B^{11} = 0.251$, one derives the abundance ratios $B^{10}B^{11}/B_2^{11} = 2 \times 0.251 = 0.502$, and $B_2^{10}/B_2^{11} = 0.063$. To separate the mixture spectrum into monoisotopic spectra (Table I), one can start at the heavy mass end and use these ratios to compute the contribution of each B_2 and B_1 ion to each value of m/e. The peak at $m/e = 28$ is due entirely to the $B_2^{11}H_6^+$ ion; hence, the $B^{10}B^{11}H_6^+$ ion ($m/e = 27$) is $0.65 \times 0.502 = 0.33$ and the $B_2^{10}H_6^+$ ion ($m/e = 26$) is $0.65 \times 0.063 = 0.04$. The $B_2^{11}H_5^+$ ion ($m/e = 27$) is then $97.28 - 0.33 = 96.95$. From this in turn, the $B^{10}B^{11}H_5^+$ ion ($m/e = 26$) and the $B_2^{10}H_5^+$ ion ($m/e = 25$) are similarly computed. Again, the $B_2^{11}H_4^+$ ion is calculated by difference and the cycle is repeated until all contributions to each peak are computed. There are three checks on the computations. The mass 21 peak is calculated to be 1.94 compared with 2.02 observed. The mass 20 peak agrees exactly with the calculations while the mass 10 peak is computed as 6.47 compared with 6.48 observed. A small change in the B^{10}/B^{11} ratio, *e. g.*, 0.251 to 0.253, materially increases the residuals. A similar calculation for sample 2 using $B^{10}/B^{11} = 0.256$ shows equally good agreement between computed and observed peaks.

TABLE I

SUMMARY OF THE MONOISOTOPIC SPECTRUM CALCULATIONS OF THE SAMPLE 1 MASS SPECTRUM FOR 50-VOLT ELECTRONS

		Monoisotopic spectrum[a]				
m/e	Mixture spectrum	$B^{10}H_x$	$B^{11}H_x$	$B_2^{10}H_x$	$B^{10}B^{11}H_x$	$B_2^{11}H_x$
10	6.48	6.47	0	..	...	...
11	28.86	3.12	25.74	..	...	...
12	18.50	6.07	12.43	..	...	...
13	24.34	0.17	24.17	..	...	...
14	0.68	0	0.68	..	...	...
20	0.18	..	...	0.18	0	0
21	2.02	..	...	0.48	1.46	0
22	11.52	..	...	4.79	3.81	2.92
23	47.32	..	...	1.65	38.05	7.62
24	92.41	..	...	3.24	13.10	76.07
25	58.04	..	...	6.11	25.75	26.18
26	100	..	...	0.04	48.49	51.47
27	97.28	..	...	0	0.33	96.95
28	0.65	..	...	0	0	0.65

[a] "*x*" assumes integral values from zero to six.

The polyisotopic diborane dissociation pattern is now obtained by summing the contributions of all ions with the same number of hydrogen atoms regardless of isotopic species. The most abundant ion ($m/e = 27$) is given the value of 100. Other ion abundance values are relative to $m/e = 27$. Table II gives these patterns for 50 and 70-volt energies of the ionizing electrons.

TABLE II

DISSOCIATION PATTERNS OF DIBORANE, ETHYLENE AND ETHANE AT IONIZING VOLTAGES OF 50 AND 70 VOLTS

	Diborane			Ethylene		Ethane	
Ion	50 v.	70 v.	Ion	50 v.	70 v.	50 v.	70 v.
H^+	3.91	3.98	H^+	3.85	4.11	2.14	2.58
H_2^+	2.72	2.71	H_2^+	0.52	0.51	0.22	0.30
B^+	21.2	21.0	C^+	1.73	2.14	0.42	0.56
BH^+	10.2	10.6	CH^+	3.19	3.48	0.96	1.19
BH_2^+	19.9	19.5	CH_2^+	6.16	6.24	3.00	3.41
BH_3^+	0.55	0.62	CH_3^+	0.56	0.54	4.48	4.62
B_2^+	3.05	3.43	C_2^+	3.01	3.71	0.49	0.75
B_2H^+	7.74	7.00	C_2H^+	11.5	11.7	3.47	4.13
$B_2H_2^+$	78.4	76.8	$C_2H_2^+$	61.1	61.9	23.1	23.7
$B_2H_3^+$	27.0	26.2	$C_2H_3^+$	62.1	64.7	33.1	33.5
$B_2H_4^+$	52.9	52.6	$C_2H_4^+$	100	100	100	100
$B_2H_5^+$	100	100	$C_2H_5^+$			21.6	21.7
$B_2H_6^+$	0.67	0.64	$C_2H_6^+$			24.9	24.7

The dissociation patterns obtained for both samples were very similar. Except for the $B_2H_6^+$ ion, the maximum deviation was about 3% (B_2H^+ ion). The disagreement of the $B_2H_6^+$ ion (0.49 compared to 0.67) may be due to a small amount of impurity in the latter sample.

The results differ from the published data of Hipple in several respects. The peaks at masses 11, 12, and 13 are unambiguously interpreted in terms of BH^+ and BH_2^+ polyisotopic ions of abundance 10.6% and 19.5% at 70 volts while Hipple reported BH^+ as zero and BH_2^+ as uncertain. We find a small $B_2H_6^+$ peak of about 0.5% while he reported it as 0 or less than 0.1%. The B_2H^+ ion abundance is 7% here as compared with 2.9%. We have measured the mass pattern at 100 volts and find only minor changes as compared with 50 and 70 volts. Hipple's measurements were at 90 volts. A more important difference in the experiments is that Hipple used an ionization chamber at about room temperature while ours operated at 245°. Relative intensities of mass spectra always depend on the temperature and in diborane there may be some thermal dissociation in the ioniza-

---

(8) M. Inghram, *Phys. Rev.*, **70**, 653 (1946).

tion chamber. It is known that above 100° at pressures of the order of an atmosphere boron and solid boron hydrides of higher molecular weight begin to form (Gmelin's "Handbook"). The mass spectra show that there is no production of heavier boron hydrides within the ionization chamber.

For comparison with ethane and ethylene, the dissociation patterns of these molecules taken under similar conditions are also given in Table II.

Omitted from Table II for the sake of brevity, is a small peak in diborane at $m/e = 11.5$ amounting to 0.39% of the maximum peak at 50 volts and 0.43% at 70 volts. This is a doubly charged ion of mass 23 and can be either $B_2^{11}H^{++}$ or $B^{10}B^{11}H_2^{++}$ or both. These ions give other peaks coincident with the large peaks at $m/e = 11$ and $m/e = 12$. The $B_2^{10}H^{++}$ ion, expected at $m/e = 10.5$ is too small to observe so there is no basis for a unique interpretation of the peak at $m/e = 11.5$. The contribution of these doubly charged ions to peaks 11 and 12 is too small to introduce any serious uncertainty in the computation of monoisotopic spectra. Ethylene shows a small peak at $m/e = 13.5$ due to the $C_2H_3^{++}$ ion which is 0.41% of the maximum peak at 70 volts. Ethane shows two peaks at $m/e = 13.5$ and $m/e = 14.5$ due to the $C_2H_3^{++}$ ion and the $C_2H_5^{++}$ ion. The abundances are 0.07 and 0.72%, respectively, of the maximum. Also omitted from the table are two metastable-ion transition[9] peaks near 21.1 and 22.1. These can be ascribed to the transition $B_2H_4^+ \rightarrow B_2H_2^+ + 2H$, which occurs after the B_2H_4 ion has traversed the electric field. The apparent mass, m_a, is given by the relation $m_a = m_f^2/m_i$ where m_f and m_i are the final and initial masses. For $B_2^{11}H_4$, $m_a = 22.2$; for $B^{10}B^{11}H_4$ $m_a = 21.2$. The observed peak at 22.2 is the larger peak in agreement with the isotope abundance although the peaks are too small for a quantitative check. A corresponding metastable transition $C_2H_4^+ \rightarrow C_2H_2^+ + 2H$ ($m_a = 24.1$) is found in both ethane and ethylene.

Discussion

No certain theoretical basis has yet been proposed for interpreting mass spectra in terms of molecular structure. The general rule is that ionization of a polyatomic molecule by electrons of 50 volts or more energy produces the molecular ion and ions of every possible dissociation process. Were it not for a large number of exceptions to this rule, mass spectra would give very specific information as to the structure of the polyatomic molecules. The mass spectra of ethane and ethylene (Table II) illustrate this fact. The spectrum of ethane clearly suggests that C_2H_6 consists of two distinct methyl groups. In the spectrum of ethylene the structure of two methylene groups is also indicated. However, there is a small CH_3^+ ion, not expected from the ethylene structure. There are plausible explanations for this small peak but its presence is a warning that we cannot uncritically infer structure solely on the basis of mass spectra.

In the diborane mass spectrum the relatively intense BH_2^+ ion and the very small BH_3^+ ion are quite like the ethylene pattern and not at all like ethane. This strongly suggests that the diborane consists of an ethylene-like structure which as a whole binds two additional hydrogen atoms. The very small $B_2H_6^+$ ion is unexpected and unusual. One can only conclude that the $B_2H_6^+$ ion is quite unstable. This, of course, weakens the argument for the ethylene structure for it could likewise be argued that the BH_3^+ ion is unstable and its absence gives no positive evidence that BH_3 radicals do not exist. There is little theoretical basis for predicting which ion configurations are stable and which are not. However, as a matter of experiment, there seem to be relatively few configurations which cannot exist as single-charged ions. Thus, it is probable but not certain that BH_3 is not the unit structure.

The existence of a metastable transition $B_2H_4^+ \rightarrow B_2H_2^+ + 2H$ gives no further evidence as to the structure. The corresponding transition $C_2H_4^+ \rightarrow C_2H_2^+ + 2H$ is observed in both ethylene and ethane.

The fact that the H_2^+/H^+ ratio is much larger in diborane than the hydrocarbons may not be significant since there is some doubt as to whether all of the H_2^+ is from the ionization of diborane. It has been noted in the experimental section that diborane slowly decomposes at room temperature to give hydrogen, and in spite of the precaution of pumping off hydrogen immediately before measuring the spectrum, some hydrogen may accumulate in the inlet system during the run

Summary

The mass spectrum of diborane at ionizing voltages of 50 and 70 volts resembles ethylene more than ethane. This suggests that BH_2 is a unit structure in diborane rather than BH_3 and that two of the hydrogen atoms are not bound directly to the boron. The $B_2H_6^+$ ion is apparently quite unstable as evidenced by the low abundance of this ion in the mass spectrum.

WASHINGTON, D. C. RECEIVED SEPTEMBER 18, 1947

---

(9) J. A. Hipple, R. E. Fox and E. U. Condon, *Phys. Rev.*, **69**, 347 (1946).

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1142]

The Configurations of Active 2,3-Epoxybutane and *erythro*-3-Chloro-2-butanol

BY HOWARD J. LUCAS AND HAROLD K. GARNER

At the time when the lower boiling 2,3-epoxybutane was shown to be the *trans* isomer,[1] it was not possible to determine the configuration of the active form, since the configuration of the active 2,3-butanediols had not yet been established. Also the stereochemical relationships of the various compounds involved in passing from the glycol to the oxide, although correctly surmised, were not definitely determined until later.[2] Moreover, the sample of active oxide obtained in the earlier work was not optically pure, for it possessed only a relatively low rotation.

Now that levorotatory 2,3-butanediol has been obtained in a high state of optical purity,[3,4,5] and the configurations of the active forms have been established,[6,7] it has been possible to prepare an optically pure 2,3-epoxybutane by methods which establish its configuration. In the changes, which are shown by I to V in Fig. 1, the stereo relationships of the compounds involved are based upon previous results, as discussed below. In addition, the configuration of the C-3 carbon atom in dextrorotatory *erythro*-3-chloro-2-butanol has been independently established as L, by converting the chlorohydrin, through the bromoform reaction, to levorotatory α-chloropropionic acid, VI, which is known to have the L configuration.[8]

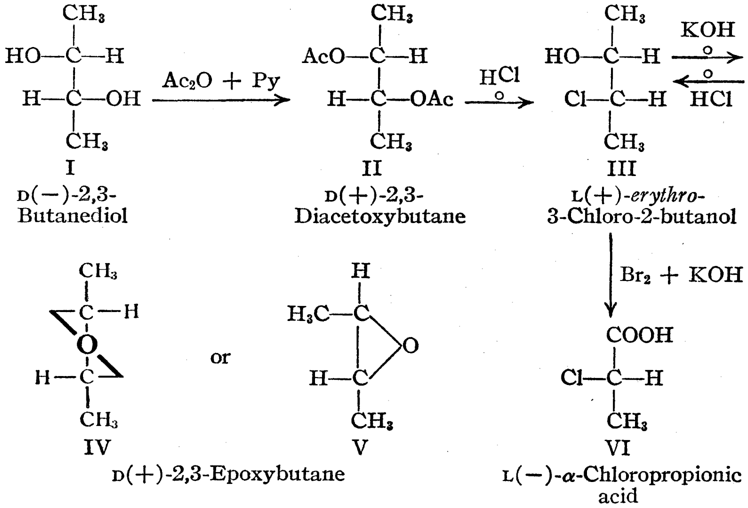


Fig. 1.—Configurational relationships of D(+)-2,3-epoxybutane and L(+)-*erythro*-3-chloro-2-butanol to D(−)-2,3-butanediol.

In D(−)-2,3-butanediol, I, each carbon atom has the D configuration.[6,7] When the glycol is converted to D(+)-2,3-diacetoxybutane, II, by acetic anhydride with either sulfuric acid or pyridine as a catalyst, the configuration of each carbon atom is still D. When II is converted to L(+)-*erythro*-3-chloro-2-butanol, III, by hydrochloric acid, the configuration of carbon atom C-3 is inverted, for a single Walden inversion has been shown to accompany the displacement of one of the acetoxy groups by chlorine in the change of DL-2,3-diacetoxybutane to DL-*erythro*-3-chloro-2-butanol.[9,10] In the last step, III to D(+)-*trans*-2,3-epoxybutane, IV, the configuration of carbon atom C-3 is again inverted, for a single Walden inversion accompanies the closing of the oxide ring. This has been shown to be the case when DL-*trans*-2,3-epoxybutane is formed from DL-*erythro*-3-chloro-2-butanol.[9,11] There could not have been an odd number of inversions, otherwise the final product would have been the optically inactive *cis* oxide, rather than the active *trans* oxide. Thus it seems reasonable to conclude, on the basis of the changes I to IV, that the configuration of each carbon in IV is D, since there has been no inversion at C-2, and two inversions at C-3.

The conversion of the chlorohydrin, III, to chloropropionic acid, VI, by establishing the configuration of carbon atom C-3 as L, presents additional proof that one inversion is associated with each of these changes, *viz.*, II to III, and III to IV. In addition, it confirms the earlier evidence that the higher boiling chlorohydrin has the *erythro* configuration.[9]

The configuration of α-chloropropionic acid cannot be unequivocally established by relating it directly to hydroxy compounds such as lactic

---

[1] C. E. Wilson and H. J. Lucas, THIS JOURNAL, **58**, 2396 (1936).

[2] (a) S. Winstein and H. J. Lucas, *ibid.*, **61**, 1576 (1939); (b) **61**, 1583 (1939).

[3] G. E. Ward, O. G. Pettijohn, L. B. Lockwood and R. D. Coghill, *ibid.*, **66**, 541 (1944).

[4] A. C. Neish, *Can. J. Research*, **23B**, 10 (1945).

[5] J. W. Knowlton, N. C. Schieltz and D. Macmillan, THIS JOURNAL, **68**, 208 (1946).

[6] E. Grivsky, *Bull. soc. chim. Belg.*, **51**, 63 (1942).

[7] S. A. Morell and A. H. Auernheimer, THIS JOURNAL, **66**, 792 (1944).

[8] (a) K. Freudenberg and A. Lux, *Ber.*, **61**, 1083 (1928); (b) K. Freudenberg, W. Kuhn and I. Bumann, *ibid.*, **63**, 2380 (1930); (c) W. A. Cowdrey, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 1208 (1937); (d) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman and A. D. Scott, *ibid.*, 1265 (1937).

[9] H. J. Lucas and C. W. Gould, THIS JOURNAL, **63**, 2541 (1941).

[10] In the analogous change of DL-2,3-diacetoxybutane to DL-*erythro*-3-bromo-2-butanol by hydrobromic acid, the single Walden inversion has been located at the step where DL-*threo*-3-acetoxy-2-butanol is changed to DL-*erythro*-2-acetoxy-3-bromobutane.[2b]

[11] A single Walden inversion is known to be associated with closing of the epoxy ring when *cis*-2,3-epoxybutane is formed from DL-*threo*-3-bromo-2-butanol.[2a]

TABLE I

PHYSICAL CONSTANTS OF THE D AND L COMPOUNDS

	B. p., °C. (cor.)	Mm.	M. p., °C. (cor.)	d^{25}_4	n^{25}_D	M_D Calcd.	M_D Obs.	α^{25}_D obs. pure liquid	$[\alpha]^{25}_D$ pure liquid
D(−)-2,3-Butanediol	77.5–77.6	10	19.4–19.7[a]	0.9869[b]	1.4308[b]	23.72	23.63	−13.00°	−13.17°[c]
D(+)-2,3-Diacetoxybutane	82.2	10	25.7–25.9	1.0244	1.4134	42.45	42.34	+14.10°	+13.76°[d]
L(+)-*erythro*-3-Chloro-2-butanol	56.0	30		1.061	1.4397	27.06	26.95	+ 9.47°	+ 8.92°
D(+)-2,3-Epoxybutane	53.5–53.7[e]	745		0.7998[f]	1.3705[g]	20.11	20.41[h]	+47.23°	+59.05°

[a] Previous values[3,5]: 19°, 19°. [b] Ref. 5, also 3, 4; n^{25}_D 1.4307, 1.4318. [c] Previous values[3,4,5,7]: −13.0°, −13.19°, −13.34°, −12.85°. [d] $[\alpha]^{25}_D$ +18.7° in $CHCl_3$; 0.9895 g. in 10 ml. $CHCl_3$; previous values[13]: $[\alpha]^{28}_D$ 13.65°. [e] Previous value[2a]: *cis*-oxide, 59.7°, 742 mm.; DL-*trans* oxide, 53.5°, 742 mm. [f] Previous value[2a]: *cis*-oxide, 0.8226; DL-*trans* oxide, 0.8010. [g] Previous value[2a]: *cis*-oxide, 1.3802; DL-*trans* oxide, 1.3705. [h] No correction for three-membered ring.

acid by reactions not involving the asymmetric center. Neither can the Walden inversions in the steps II to III, III to IV, and IV to III be proven unequivocally, although there is no reason to doubt that they occur. Nevertheless, the evidence presented here is consistent with the accepted configuration of α-chloropropionic acid, and with the assumption that one inversion accompanies each of the changes mentioned above. We believe that there can, therefore, no longer be any doubt in regard to the configuration of the active α-chloropropionic acids, for the satisfactory way in which active 3-chloro-2-butanol forms a configurational link with active 2,3-butanediol confirms the conclusions reached by Freudenberg, Ingold, *et al.*[8]

When the carbon chain is written vertically, the configuration of the dextrorotatory oxide is correctly represented by IV. However, since this is an awkward looking formula, it seems preferable to write the oxide ring on one side, as shown by V. This, therefore, is the preferred way of writing the configuration of D(+)-*trans*-2,3-epoxybutane, or more simply, D(+)-2,3-epoxybutane, since there are only two active isomers of 2,3-epoxybutane. Structures IV and V are equivalent.

The configurations of the dextrorotatory oxide and the dextrorotatory chlorohydrin are reasonably certain, since carbon atom C-2 is unaffected during the changes, and the configuration of carbon atom C-3 in the chlorohydrin is established by its conversion to levorotatory α-chloropropionic acid. The designation of these compounds as D or L is somewhat arbitrary, however, since there are no rules of nomenclature which specifically apply in this case. Either of the two asymmetric centers in the molecule might be taken as the point of reference. It seems preferable to take carbon atom C-3 as the point of reference, so as to correlate the nomenclature with that of the carbohydrates.[12] This is in agreement with the designation of the 2,3-butanediols given by Morell and Auernheimer.[7] On this basis, the configuration of the highest numbered asymmetric carbon atom determines the family to which the compound belongs. Thus I, II and IV belong to the D family, since in these the functional group at carbon atom C-3 lies on the right, and III belongs to the L family, since the functional group lies on the left, as a result of inversion during its formation from II.

The oxide is believed to be of high optical purity for the following reasons: (1) the active glycol used as starting material had one of the highest optical rotatory powers recorded for this compound in the literature; (2) the reactions involved have been shown to yield configurationally pure compounds; (3) absence of *cis* oxide was indicated by agreement in physical properties with previously prepared DL-oxide[2a]; (4) rotations of two preparations agreed well, *viz.*, 58.65 and 59.05°.

The importance of (3) as an argument for optical purity is based on the assumption that if any reaction proceeded otherwise than with 100% retention or inversion of the configuration of carbon atom C-3, the resulting diastereomeric compound would lead to the presence of some *cis*-oxide in the final product. This would be the main contaminant, not the L(−)-oxide. In order for the latter to be formed there would have to be inversion at carbon atom C-2, as well as at C-3.

Rotations and some other physical constants of the compounds involved are shown in Table I. The rotation of the cyclic oxide is one more example of the well-known effect of ring structure in enhancing rotations.

The specific rotation of the chlorohydrin prepared by the action of hydrochloric acid on the active oxide was +8.87°, only 0.05° less than that of the chlorohydrin prepared from the diacetate, +8.92°. This indicates that in going from III to IV and back to III, the reactions proceed with essentially 100% inversion of configuration.

The sample of optically active 2,3-butanediol was furnished by the Northern Regional Research Laboratory, Peoria, Illinois. The authors express their appreciation to the Laboratory and especially to Dr. A. F. Langlykke for this courtesy.

Experimental

D(−)-2,3-Butanediol.—Dr. A. F. Langlykke of the Northern Regional Research Laboratory stated that the glycol was produced in a fermentation of starch induced by *Bacillus polymyxa*. The glycol contained a small amount

---

[12] This has been done in conformity with the third progress report of the Committee on Carbohydrate Nomenclature, Charles D.

of water and had an observed rotation, −12.4°. This became −13.00° ($[\alpha]^{25}\mathrm{D}$ −13.17°) after one distillation at reduced pressure.

D(+)-2,3-Diacetoxybutane; **Acid Catalyzed Reaction.**—The diacetate could be prepared, as previously described for the inactive diacetate,[1] from the glycol and acetic anhydride using as catalyst one drop of sulfuric acid per 0.5 mole of glycol. Vacuum fractionation of the reaction mixture gave a 90% yield of material with an observed rotation of +13.8°. On standing at room temperature (approximately 22°) overnight, about two-thirds of the material crystallized in large, clear prisms. The liquid was decanted from these, and the solid recrystallized from 30–60° petroleum ether and redistilled. The diacetate thus obtained melted at 25.7–25.9° and had an observed rotation of +14.10°. These values could not be raised by further purification. Additional amounts of pure diacetate could be obtained by crystallization and distillation of the liquid fraction. The total yield of purified diacetate was 70%.

The amount of sulfuric acid used to catalyze the acetylation should not exceed two drops per mole and the temperature should not rise above 80°; otherwise some optical inversion may occur.

Pyridine Catalyzed Reaction.—In a 1-liter Erlenmeyer flask were placed 90.0 g. (1 mole) of redistilled active 2,3-butanediol and 400 g. (5 moles) of redistilled anhydrous pyridine. The contents were thoroughly mixed, and then 224 g. (2.2 mole) of acetic anhydride were added slowly from a dropping funnel with stirring. As the mixture warmed, cooling was supplied to keep the temperature below 40°. After the reaction had subsided, the mixture was allowed to stand overnight, and was then fractionally distilled at reduced pressure, the final cut being taken at 82.1–82.2° (cor.), at 10 mm. The product weighed 170 g. (98%) and had an observed rotation of +13.94°. This material could be further purified so that finally $\alpha^{25}\mathrm{D}$ obs. +14.06° and $[\alpha]^{25}\mathrm{D}$ +13.72°; but this was found to be unnecessary since the chlorohydrin and oxide prepared from it had the same rotation as those from the more highly purified material.[13]

L(+)-*erythro*-3-Chloro-2-butanol.—This was prepared as previously described for the inactive chlorohydrin,[9] from the active diacetate and concentrated aqueous hydrochloric acid saturated with dry hydrogen chloride at −20°. The crude material isolated in 70% yield from the reaction mixture contained some 3-chloro-2-acetoxybutane. Three fractionations of a portion of the crude product gave a pure sample of the chlorohydrin for the measurement of physical properties, but it is not necessary to separate the chlorohydrin from the chloroacetate in the preparation of 2,3-epoxybutane, since both are converted into the oxide.

D(+)-2,3-Epoxybutane.—This was prepared, as previously described for the inactive oxides,[1] from active chlorohydrin and concentrated potassium hydroxide. The material was dried over potassium hydroxide and purified by fractional distillation; no trace of the higher boiling *cis*-oxide was detected. The over-all yield of purified active oxide from the glycol was 49%. The rotations of two preparations were $[\alpha]^{25}\mathrm{D}$, 59.05° and 58.65°.

DL-α-Chloropropionic Acid.—Inactive 3-chloro-2-butanol was prepared, in the manner previously described,[8] from a supply of inactive oxide (mixture of *cis* and *trans*) and concentrated hydrochloric acid. The yield was 79%.

A three-necked 1-liter flask was fitted with a mechanical stirrer and two dropping funnels. In the flask was placed 27 g. (0.25 mole) of the inactive chlorohydrin, and in the two separatory funnels 160 g. (1.00 mole) of liquid bromine and 195 g. of potassium hydroxide (Baker C.P., 86%; 3 moles) dissolved in 500 ml. of water, respectively. The stirrer was started, and the bromine added rapidly, about fifteen minutes being required for the addition. When about one quarter of the bromine had been added, the addition of the base was begun and continued at such a rate that the bromine was always present in the reaction mixture in good excess. The mixture became hot, and cooling was supplied with an ice-bath to keep the temperature around 50°. After all the bromine was in, addition of the base was continued until the reaction mixture became colorless, and then a slight excess was run in. A yellow color developed in the presence of the excess base.

Stirring was continued for about fifteen minutes, after which the mixture was transferred to a separatory funnel, and the heavy layer of bromoform drawn off. The aqueous layer was washed once with 50 ml. of chloroform, and then acidified with 50% sulfuric acid, a 20-ml. excess of the acid being used. The bromine which formed was destroyed with formic acid, and the solution extracted five times with 100-ml. portions of ethyl ether. Following removal of the ether by ordinary distillation, the α-chloropropionic acid was distilled at 30 mm., b. p. 100–105°, yield, 3.5 g. (13%). The product was redistilled at atmospheric pressure, the fraction boiling at 184–186° being collected. The product gave a strong positive test for chlorine and had a neutralization equivalent of 115 (theoretical, 108.5). Its anilide melted at 89.5–90.5° (cor.),[14] and its salt with phenylhydrazine at 95–96° (cor.).[15]

Other modifications of the above procedure were tried, but no improvement of the yield could be realized. It is important that there be no excess of base until all of the bromine has been added; otherwise considerable amounts of the chlorohydrin are lost by conversion to oxide.

L(−)-α-Chloropropionic Acid.—The active chlorohydrin used in the oxidation was prepared from the active oxide and concentrated hydrochloric acid as previously described for the inactive compound,[8] and had the following constants: b. p. 55.9–56.0° (cor.) at 30 mm.; $\alpha^{25}\mathrm{D}$ +9.42; $[\alpha]^{25}\mathrm{D}$ +8.87°; $n^{25}\mathrm{D}$ 1.4394. The yield was 75%.

The oxidation of the active chlorohydrin was carried out similarly to that of the inactive material. From 12.0 g. of chlorohydrin was obtained 1.9 g. (16%) of α-chloropropionic acid, b. p. 100–102° (cor.) at 30 mm.; 184–187° (cor.), at 745 mm.; neutralization equivalent, 108 (theoretical, 108.5). The rotations were as follows: pure liquid, $\alpha^{25}\mathrm{D}$ −14.2°, $[\alpha]^{25}\mathrm{D}$ −11.3°; aqueous soln. (0.0433 g. in 2.00 ml. water soln.), $[\alpha]^{25}\mathrm{D}$ −9.1°; sodium salt (0.0736 g. made up to 2.00 ml. with 3.94 *f* NaOH) $[\alpha]^{25}\mathrm{D}$ +3.8°.[16,17]

Summary

Optically active 2,3-epoxybutane has been prepared through the following series of reactions: D(−)-2,3-butanediol → D(+)-2,3-diacetoxybutane → L(+)-*erythro*-3-chloro-2-butanol → D(+)-2,3-epoxybutane. In addition, the configuration of carbon atom C-3 in the chlorohydrin has been established by conversion to L(−)-α-chloropropionic acid.

It has been possible to assign absolute configurations to the compounds prepared, since levorotatory 2,3-butanediol is known to belong to the D series, and the mechanisms of all the reactions used are known. Thus dextrorotatory 2,3-diacetoxybutane and dextrorotatory 2,3-epoxybutane belong to the D series, while dextrorotatory *erythro*-3-chloro-2-butanol belongs to the L series.

PASADENA, CALIFORNIA RECEIVED JULY 21, 1947

---

(13) K. A. Clendenning, *Can. J. Research*, **24B**, 269 (1946), gives these values for active diacetate: $n^{25}\mathrm{D}$ 1.4132; d^{20}_{4} 1.029; $[\alpha]^{28}\mathrm{D}$ 13.65°.

(14) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," second ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 181, give the m. p. of the anilide as 92°.

(15) G. Stempel and G. Schaffel, THIS JOURNAL, **64**, 470 (1942), give the m. p. of the phenylhydrazine salt as 95°.

(16) P. Levene and H. Haller, *J. Biol. Chem.*, **81**, 703 (1929), observed that the sign of rotation changed in going from acid to basic solution.

(17) K. Freudenberg, W. Kuhn and I. Bumann[8b] report the rotation of L-α-chloropropionic acid as $\alpha_{578} = -19.30°$; $[\alpha]_{578} = -15.4°$, pure liquid.

[Contribution from the Noyes Chemical Laboratory, University of Illinois]

Polyalkylene Sulfides from Diolefins and Dimercaptans

By C. S. Marvel and R. R. Chambers[1a]

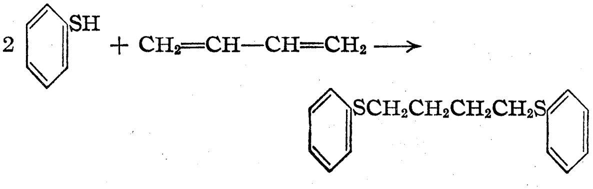
The addition of a thiol to an olefin in the presence of a peroxide catalyst[1b] or under the influence of ultraviolet light[2] has been demonstrated to be a general reaction which proceeds smoothly to give high yields of a product of definite composition. Thus, the reaction meets the requirements for a suitable polymer-forming reaction.

$$nHS(CH_2)_xSH + nCH_2{=}CH{-}(CH_2)_x{-}CH{=}CH_2 \longrightarrow H[S(CH_2)_x{-}SCH_2CH_2(CH_2)_x]_n{-}CH{=}CH_2$$

$$nCH_2{=}CH{-}(CH_2)_xSH \longrightarrow CH_2{=}CH(CH_2)_x{-}S[CH_2CH_2(CH_2)_x{-}S]_{n-1}H$$

Cahours and Hoffman,[3] who first made allyl mercaptan, did not mention any loss due to polymer formation, but Braun and Hahn[4] did report a loss of product in non-distillable residue each time they distilled their product. Braun and Plate[5] also found that several other unsaturated mercaptans gave liquid polymers. Vaughan and Rust[2a] obtained low molecular weight (less than 300) polyalkylene sulfides from hydrogen sulfide and diallyl or diallyl ether. Coffman,[6] using dithiols and diolefins without a solvent, obtained a wide variety of liquid polymeric alkylene sulfides with molecular weights up to about 1300.

In the present work we have tried to extend the reaction described by Coffman[6] and to obtain larger polymers which might have more interesting properties. Some experiments using 1,3-butadiene showed that an aromatic thiol would add readily to give the expected sulfide. However, with an aliphatic mercaptan the addition reaction was accompanied by some diene polymerization and the nature of the product was not immediately evident. Hence, in further studies non-conjugated diolefins were selected for study so that this side reaction might be avoided.



The preliminary search for conditions which favor formation of large molecules was made using hexamethylenedithiol and 1,5-hexadiene (diallyl). When these two reagents were mixed in Pyrex test-tubes and exposed to a source of ultraviolet light only a little solid polymer was formed. When the reaction was carried out in an open beaker with an excess of 1,5-hexadiene, polymerization took place quickly and a white waxy product was formed in about five minutes. However, the product was of low molecular weight (about 1100) due to loss of much butadiene by evaporation. By use of cyclohexane as a solvent a polymer with a molecular weight of about 1700 was obtained by the open-beaker method. These experiments indicated that if large molecules were to be obtained it would be necessary to balance closely the quantities of the two reacting species so that one would not be in excess and thus stop the growth of the polymer chain.

A series of reactions was run with one-hundredth molar quantities of hexamethylenedithiol and 1,5-hexadiene in cyclohexane solution in closed quartz test-tubes. The monomers were weighed out with an accuracy of somewhat better than one-half of one per cent. Cyclohexane proved to be a fairly satisfactory solvent since it does not absorb ultraviolet light nor react with the free radical intermediates produced during polymerization. Chloroform is a better solvent for the polymers but gave lower-molecular-weight products and yellow-colored by-products which makes it seem probable that it reacts with free radical intermediates formed in the polymerization reaction.[7] The polymers were separated as solids from cyclohexane and were isolated by filtration. The reaction time was varied from two to three hours to forty-eight hours. Usually the shorter period of time was sufficient, and the time factor did not seem to affect the type of polymer obtained. These polymers were white solids soluble in benzene or cold chloroform. The low-molecular-weight materials (mol. wt. about 1400) were waxy and the higher-molecular-weight materials (about 8000 to 14000) were solids. They were insoluble in ethanol, acetone and low-boiling petroleum ether.

In order to determine whether these polymers had the expected structure resulting from a non-Markownikoff type of addition the infrared absorption of an addition polymer ($[\eta] = 0.206$) was compared with those of two synthetic polymers made from alkali, hexamethylenedithiol and 1,6-dibromohexane and 2,5-dibromohexane, respectively.[8] The two polymers made from the bro-

---

(1a) Allied Chemical and Dye Corporation Fellow, 1944 to 1945; Monsanto Fellow, 1946 to 1947. Present address: Sinclair Refining Co., East Chicago, Ind.

(1b) See Mayo and Walling, *Chem. Rev.*, **27**, 387 (1940).

(2) (a) Vaughan and Rust, *J. Org. Chem.*, **7**, 473 (1942); (b) Rust and Vaughan, U. S. Patents 2,392,294, 2,392,295 (*C. A.*, **40**, 2453 (1946)); (c) Vaughan and Rust, U. S. Patents 2,398,429, 2,398,480 (*C. A.*, **40**, 3765 (1946)).

(3) Cahours and Hoffmann, *Ann.*, **102**, 291 (1857).

(4) Braun and Hahn, *Ber.*, **59**, 1202 (1926).

(5) Braun and Plate, *Ber.*, **67B**, 281 (1934).

(6) Coffman, U. S. Patent 2,347,182; *C. A.*, **39**, 226 (1945).

(7) Kharasch, Read and Mayo, *Chem. and Ind.*, **57**, 752 (1938).

(8) In U. S. Patent 2,201,884 Carothers mentions that polyhexamethylene sulfide can be made by this reaction but no details are given.

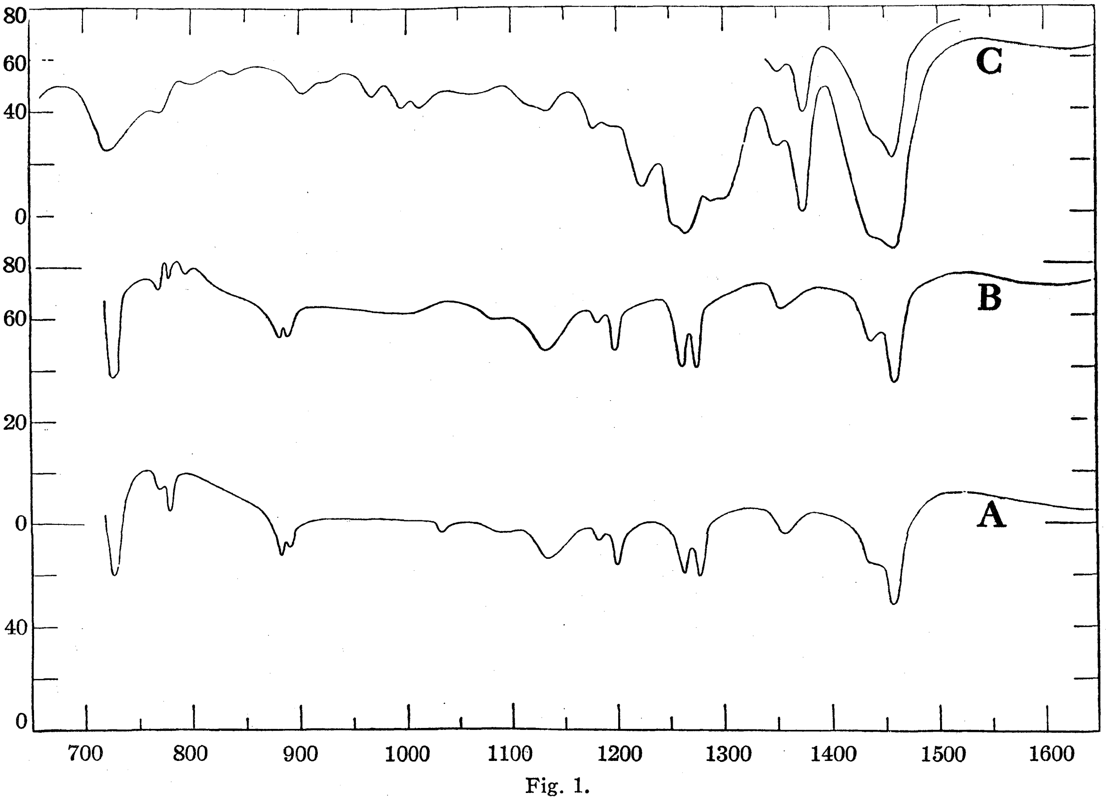


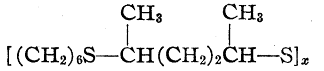
Fig. 1.

mides were of low molecular weight and analysis indicated that they had bromine end-groups.

$$HS(CH_2)_6SH + CH_2{=}CH(CH_2)_2CH{=}CH_2 \longrightarrow \text{Polymer A}$$

$$HS(CH_2)_6SH + Br(CH_2)_6Br \xrightarrow{NaOR} [(CH_2)_6S{-}(CH_2)_6{-}S]x \quad \text{Polymer B}$$

$$HS(CH_2)_6SH + CH_3CHBr(CH_2)_2CHBrCH_3 \xrightarrow{NaOR}$$



$$[(CH_2)_6S{-}\overset{CH_3}{\overset{|}{C}}H(CH_2)_2\overset{CH_3}{\overset{|}{C}}H{-}S]_x$$

Polymer C

Figure 1 contains the infrared absorption patterns[9] of polymer Samples A, B and C. It is evident that A and B are very similar and C is markedly different. Polymer C shows the typical methyl group deformational frequency at 1375 cm.$^{-1}$ and bands at 1225 and 1300 cm.$^{-1}$ which are not present in the spectrum of B and A. This seems fairly conclusive evidence that the expected linear non-Markownikoff polymers result from the addition reaction. The differences in the spectra of A and B samples can probably be attributed to the different end-groups present.

Other polymers were obtained from a variety of dithiols and diolefins. Where the monomers were unbranched, solid products resulted. Where there were side groups in the monomers which would be responsible for optical isomerism in the polymer, only liquid products were obtained. In Table I the various polymers which have been obtained in this work are listed. All were prepared by the procedure described for hexamethylenedithiol and 1,5-hexadiene. All had essentially the same solubility in benzene and chloroform as reported for that polymer.

Since the solid polymers had sharp melting points, some X-ray diffraction patterns were taken

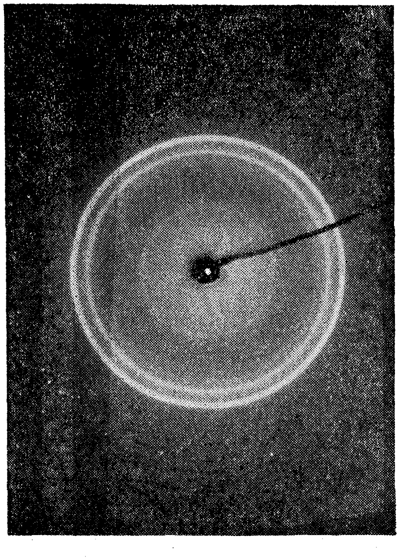


Fig. 2.—Hexamethylenedithiol–1,5-hexadiene polymer.

---

[9] We are indebted to Dr. F. A. Miller and Mrs. J. L. Johnson for the infrared measurements and their interpretation.

TABLE I

Monomers Dithiol	Diolefin	M. p., °C.	(η)	Calculated, % C	H	S	Found, % C	H	S
Ethanedithiol	1,5-Hexadiene	82–86		54.49	9.15	36.36	54.65	9.06	36.56
Tetramethylenedithiol	1,5-Hexadiene	65–67		58.76	9.86	31.37	58.91	10.05	31.28
Pentamethylenedithiol	1,5-Hexadiene	64–65	0.256	60.49	10.15	29.36	60.32	10.10	29.30
Hexamethylenedithiol	1,5-Hexadiene	71–76	.206	62.00	10.41	27.59	62.29	9.98	27.88
Decamethylenedithiol	1,5-Hexadiene	76–78	.238	66.60	11.18	22.22	66.76	11.41	21.99
Hexamethylenedithiol	1,10-Undecadiene	72–78	.217	67.48	11.33	21.19	65.91	11.03	22.89
Decamethylenedithiol	1,10-Undecadiene	74–78	.143	70.32	11.80	17.88	69.58	11.69	18.31
bis-(*p*-β-Mercaptoethylphenyl)-methane	1,5-Hexadiene	84–88		74.54	8.16	17.30	74.05	7.96	17.85
Hexamethylene dithiol	bis-(*p*-Vinylphenyl)-methane	gel[a]		74.54	8.16	17.30	74.19	8.10	16.27 16.05
bis-(*p*-β-Mercaptoethylphenyl)-methane	bis-(*p*-Vinylphenyl)-methane	105–108		80.26	7.13	12.60	80.40	7.22	12.66
Hexamethylenedithiol	3,4-Dimethyl-1,5-hexadiene	Liquid	.097	64.55	10.83	24.62	63.62	10.68	25.46
Hexamethylenedithiol	Vinyl-3-cyclohexene	Liquid	.072	65.05	10.14	24.81	63.86	9.75	...
2-Methyl-1,4-butanedithiol	1,5-Hexadiene	Liquid		60.49	10.15	29.36	59.99	10.16	29.75

[a] This gel did not melt or otherwise change at 220°.

to see if they would furnish evidence of crystallinity.[10] Figures 2, 3 and 4 are the patterns for the hexamethylenedithiol–1,5-hexadiene polymer, ethanedithiol–1,5-hexadiene polymer and decamethylenedithiol–1,10-undecadiene polymer, respectively. These diagrams indicate that the polymers are crystalline and that the spacings that can be calculated from their measurement show the roughly paraffinic packing of the chains that might be expected.

The various liquid polymers described in Table I did not tend to crystallize even when cooled, whereas the solids were crystalline as shown for the above samples by X-ray methods. It was thought that some interesting products might be attained by making polymers from the three components hexamethylenedithiol, 1,5-hexadiene and 3,4-dimethyl-1,5-hexadiene. Table II gives the results of three such experiments.

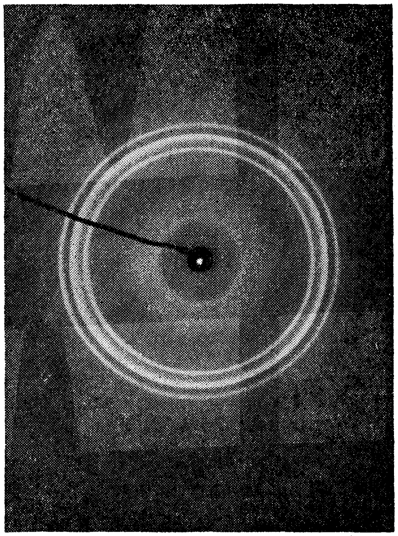


Fig. 3.—Ethanedithiol–1,5-hexadiene polymer.

TABLE II

Expt.	Hexamethylenedithiol mole	1,5-Hexadiene, mole	3,4-Dimethyl-1,5-hexadiene, mole	Softening point of product, °C.
1	0.005	0.004	0.001	62.5–65
2	.005	.003	.002	56–60
3	.005	.002	.003	Greasy

No analysis of these polymers is reported since the results do not indicate whether the two olefins are both present in the chain.

Attempts have been made to oxidize the polymer from hexamethylenedithiol and 1,5-hexadi-

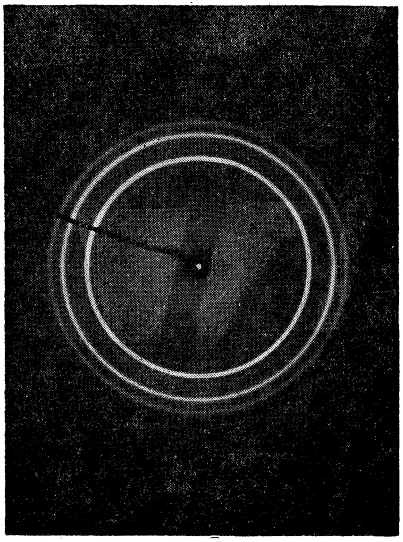


Fig. 4.—Decamethylenedithiol–1,10-undecadiene polymer.

---

[10] We are indebted to Professor G. L. Clark and Mr. D. L. Leussing for these X-ray diffraction measurements and their interpretation.

ene with bromine, potassium permanganate solution, perbenzoic acid and hydrogen peroxide. The polymer took up a large amount of bromine and liberated hydrogen bromide, giving a heavy liquid product which solidified on standing but was intractable. The other three oxidizing agents gave a white solid polymer insoluble in benzene and chloroform as well as other common solvents. It could be dissolved in hot *m*-cresol.

Some attempts were made to determine the end-groups in the polyhexamethylene sulfide but they were not very satisfactory. As indicated above, bromine appears to react with the sulfide sulfur atoms. Using traces of perbenzoic acid or iodine as oxidizing agents did produce polymers with increased intrinsic viscosities which would indicate mercaptan end-groups. These experiments, however, are somewhat inconclusive.

The authors are glad to acknowledge their indebtedness to Professor H. A. Laitinen and Mrs. H. E. Fritz for amperometric titration of the mercaptans used.

Experimental

1,4-bis-(Phenylmercapto)-butane.[11]—In a Pyrex tube were placed 11 g. of thiophenol and 5 g. of liquid butadiene. The tube was cooled and sealed and exposed to a source of ultraviolet light for sixteen hours and then allowed to stand about two weeks. It was then cooled and opened, the unreacted butadiene evaporated and the residue cooled in an ice-bath. From the unreacted thiophenol, a small amount of crystalline material separated and it was collected on a filter and recrystallized. The yield was 0.47 g. of 1,4-bis-(phenylmercapto)-butane, m. p. 84–84.5°. Bennett and Mosses[12] report a melting point of 85° for a sample of this material prepared in a different manner.

1,4-bis-(*p*-Tolylmercapto)-butane.[11]—In a similar manner 4.6 g. of butadiene and 13.8 g. of *p*-thiocresol were exposed to ultraviolet light for eighteen hours and allowed to stand fifteen days. The butadiene was evaporated and the thiocresol removed by distillation under 6 mm. pressure. The residue solidified and on recrystallization from 90% alcohol there was obtained 6.4 g. of bis-1,4-(*p*-tolylmercapto)-butane, m. p. 65–65.5°.

Anal. Calcd. for $C_{18}H_{22}S_2$: C, 71.45; H, 7.33. Found: C, 71.49; H, 7.50.

Butadiene and *n*-Butyl Mercaptan.[11]—Three grams of butadiene and 10 g. of *n*-butyl mercaptan were sealed in a Pyrex tube and exposed to ultraviolet light for eighteen hours and then allowed to stand for about two weeks. The tube was opened and the contents distilled. A 0.97-g. fraction of material boiling at 53–55° at 3 mm. was obtained; n^{20}_D 1.4749; d^{20}_4 0.9002. Analysis indicated the ratio of butadiene to mercaptan was approximately 1 mole to 1 mole, yet the boiling point is too high for such a molecule. It was not further identified.

Anal. Calcd. for $C_4H_8 \cdot C_4H_9SH$: C, 64.6; H, 12.7; S, 21.25. Calcd. for $C_4H_8 \cdot 2C_4H_9SH$: C, 60.9; H, 11.85; S, 27.00. Found: C, 66.93; H, 10.39; S, 22.71.

Addition of Hexamethylenedithiol and 1,5-Hexadiene.—In a typical polymerization a solution of 1.5 g. of hexamethylenedithiol and 0.82 g. of 1,5-hexadiene in 10 cc. of cyclohexane was placed in a tightly stoppered quartz test-tube under an ultraviolet lamp. After twelve hours the white solid was filtered off and dried. The yield was 1.69 g. This polymer softened in a melting point tube at 70° and was liquid at 74°. A solution of 0.4188 g. in 100 cc. of benzene showed an intrinsic viscosity of 0.156.

Anal. Calcd. for $(C_6H_{12}S)_x$: C, 62.00; H, 10.41; S, 27.59. Found: C, 62.19; H, 9.98; S, 27.88.

To the mother liquor from which this product had been isolated was added 1 cc. of absolute alcohol. A second crop of solid material weighing 0.13 g. was obtained. This polymer melted at 63–67° and had an intrinsic viscosity of only 0.082.

In other similar experiments the various polymers of hexamethylenedithiol and 1,5-hexadiene listed in Table III were isolated. One polymer isolated from cyclohexane solution by the open vessel method melted at 63–67° and had a molecular weight of 1700 as determined ebullioscopically in benzene. Another polymer made in an open vessel without solvent melted at 60–65° and had a molecular weight of 1100.

Table III

Expt.	[η]	Melting range, °C.	Cryoscopic mol. wt.	Approximate molecular weights
57	0.139	70–72	..	4500– 5600
55	.271	73–76	..	9000–11000
58	.293	74–76	..	12000–14000
3B1[a]	.05	50–56	1400	....
5B2[a]	.07	62–64	2100	....

[a] These low molecular weight polymers were characterized by Paul H. Aldrich and used as a basis for approximating the molecular weights of those products with a greater intrinsic viscosity.

Hexamethylenedithiol and 1,6-Dibromohexane.—To a solution of 0.26 g. of sodium in 20 cc. of absolute alcohol in a 50-cc. Erlenmeyer flask was added 1.5 g. of hexamethylenedithiol and then dropwise 2.44 g. of hexamethylene dibromide. The reaction proceeded rapidly and the product separated. It was filtered off and the alcohol diluted with water and filtered again. The two precipitates were taken up in benzene and the polymer precipitated with methanol. This process was repeated. There was obtained about 0.26 g. of product.

Anal. Calcd. for $(C_6H_{12}S)_x$: C, 62.00; H, 10.41; S, 27.59. Found: C, 58.57; H, 9.65; S, 29.07; Br, 3.19. This is Polymer B used in the infrared study.

Hexamethylenedithiol and *meso*-2,5-Dibromohexane.—To a solution of sodium ethylate prepared from 15 cc. of absolute alcohol and 0.24 g. of sodium hydride was added 1.5 g. of hexamethylenedithiol and 2.44 g. of *meso*-2,5-dibromohexane[13] (m. p. 37–39°) dissolved in 15 cc. of absolute alcohol. This solution was refluxed for about four hours. To the mixture was added 50 cc. of water and 20 cc. of ether. The ether solution was separated and the solvent evaporated. The remaining liquid was treated with sufficient methanol to dissolve about half of it and the methanol solution was decanted. The undissolved liquid was taken up in low-boiling petroleum ether. The solution was decolorized with Norite and filtered. The solvent was evaporated and the residue heated to 100° for two hours to remove traces of solvent. The product was a yellow, fairly mobile liquid containing some halogen.

Anal. Calcd. for $(C_6H_{12}S)_x$: C, 62.00; H, 10.41; S, 27.59. Found: C, 54.83; H, 9.60; Br, 6.45. It is perhaps significant to note that a polymer of the expected type with a molecular weight of 2500 having bromine end group would have the following analysis: C, 58.01; H, 9.74; Br, 6.43. This liquid product was used as sample C in the infrared work.

Oxidation of Polyhexamethylene Sulfide.—In a 500-cc. Erlenmeyer flask was placed a solution of 1.16 g. of polyhexamethylene sulfide in 150 cc. of chloroform and to it was added 150 cc. of a chloroform solution containing

---

[11] This experiment was performed by Robert J. Buswell and submitted in his M. A. thesis, University of Illinois, 1937.

[12] Bennett and Mosses, *J. Chem. Soc.*, 2364 (1930).

[13] Wislicenus, *Ber.*, **34**, 2580 (1901).

0.0287 mole of perbenzoic acid.[14] The mixture was shaken on a shaking machine for twenty four hours. Titration of an aliquot portion indicated that about 0.01 mole of perbenzoic acid had been used up. To the original reaction mixture was added 150 cc. of methanol and the precipitate was collected on a filter. The precipitate was extracted in a Soxhlet extractor for five hours with hot benzene. The undissolved material melted at 189–194°. Another similar oxidation carried out at −10° for two and a half hours, at 0° eleven hours and at room temperatures for five hours showed that the oxidation was complete in the first hour and a half at −10° since after that no more perbenzoic acid was used up. This gave a 66% yield of solid melting at 190–194°. This polymer was slightly brown after purifying by solution in hot *m*-cresol and precipitation with benzene.

Anal. Calcd. for $C_6H_{12}SO$: C, 54.50; H, 9.15. Calcd. for $C_6H_{12}SO_2$: C, 48.62; H, 8.16. Found: C, 49.16; H, 8.38.

It therefore appears that a polysulfone is the oxidation product. A similar product was obtained using aqueous potassium permanganate as the oxidizing agent.[15] Carothers[15] has oxidized the polyhexamethylene sulfide made from hexamethylene bromide and sodium hexanedithiol to a polysulfone which melted at 196–198°. Our product is apparently similar if not identical with his.

End Group Oxidation.—A one-tenth gram sample of polyhexamethylene sulfide (intrinsic viscosity of 0.293, m. p. 74–76°) in 25 cc. of benzene was treated with 3 drops of dilute perbenzoic acid solution in chloroform (0.186 millimoles of perbenzoic per cc. solution) and shaken ten minutes. Then an additional 3 drops of oxidizing solution was added and the mixture shaken again for two minutes. The polymer was precipitated with methanol. In benzene solution the oxidation product had an intrinsic viscosity of 0.326. It melted at 75–77°.

A similar experiment using 0.1 g. of polymer in 20 cc. of benzene, 0.01 g. of iodine and 10 cc. of very dilute sodium hydroxide solution changed the intrinsic viscosity of the polymer from 0.293 to 0.443 and the melting point increased from 74–76° to 75–77°.

Pentamethylenediisothiouronium Bromide.—In a 500-cc. Erlenmeyer flask was placed 82 g. ($^1/_3$ mole) of pentamethylene dibromide, 54 g. ($^2/_3$ mole) of thiourea and 200 cc. of 95% ethanol. The mixture was refluxed on a steam cone for six hours, and then cooled in an ice-bath. When scratching the side of the beaker did not induce crystallization, the solvent was removed from a small sample of solution on a metal spatula and the mixture seeded with the residue. The crystals were filtered and dried in a vacuum desiccator over calcium chloride. There was obtained 124.5 g. (91% of the theoretical amount). After recrystallization from a concentrated water solution, the compound melted at 160–160.5°. This intermediate does not appear to have been isolated before.

Anal. Calcd. for $C_7H_{18}S_2N_4Br_2$: C, 22.00; H, 4.75. Found: C, 22.16; H, 4.75.

bis-(*p*-β-Mercaptoethylphenyl)-methane Diacetate.—A mixture of 10 g. of crude bis-(*p*-vinylphenyl)-methane[16] containing about 1 g. of water, and 16 g. of thiolacetic acid were placed in a quartz flask and irradiated with ultraviolet light. In a half hour the mixture became quite hot, but in another half hour it had cooled and solidified. The compound was recrystallized twice from methanol and once from low petroleum ether. There was obtained 6.5 g., melting point 75–77°. Upon further recrystallization from low petroleum ether small shiny flakes were obtained which melted at 75.5–77.5°.

Anal. Calcd. for $C_{21}H_{24}S_2O_2$: C, 67.70; H, 6.50; S, 17.21. Found: C, 67.74; H, 6.70; S, 17.06.

bis-(*p*-β-Mercaptoethylphenyl)-methane.—To a hot solution of 5 g. of bis-(*p*-β-mercaptoethylphenyl)-methane diacetate in 50 cc. of ethanol was added 10 cc. of 10% sodium hydroxide solution, and the mixture heated on the steam cone for twenty minutes. Then the solution was poured into 100 cc. of water containing 25 cc. of concentrated hydrochloric acid. The milky solution was extracted with ether, and the ether solution dried over magnesium sulfate. Removal of the ether left an oil which crystallized from low petroleum ether. A further small amount of the product was recovered from the aqueous solution by allowing it to remain in the refrigerator for several days. Further recrystallization of a sample of this compound from low petroleum ether gave white flakes melting at 34.5°. There was obtained 1.5 g. which is 39% of the theoretical yield.

Anal. Calcd. for $C_{17}H_{20}S_2$: C, 70.78; H, 6.99; S, 22.23. Found: C, 70.80; H, 6.97; S, 22.23.

2-Methylbutenethiol Acetate.—The method of adding thiolacetic acid used here was that of Frank and Hein.[17] A mixture of 22.6 g. of isoprene and 55 g. of thiolacetic acid was placed in a quartz flask cooled by an ice-bath and irradiated by ultraviolet light for fifteen minutes. On distillation fractions came over at 34–75° (12.2 g.); 85–90° (37.2 g.); and 40° (2 mm.) (12.8 g.). Apparently the first fraction is unchanged isoprene and the second unchanged thiolacetic acid. On redistillation, the third fraction, a colorless liquid, distilled at 49–51° (2 mm.), $n^{20}D$ 1.4916. This appeared to be an addition product of one mole of thiolacetic acid to one mole of isoprene.

Anal. Calcd. for $C_7H_{12}SO$: C, 58.29; H, 8.39; S, 22.23. Found: C, 58.52, 58.66; H, 8.74, 8.55; S, 22.64.

2-Methyl-1,4-butanedithiol Diacetate.—The thirty-seven grams of thiolacetic acid recovered from the previous experiment, and 16.5 g. of isoprene were placed in a quartz flask under the ultraviolet light for thirty minutes while in an ice-bath. Then the flask was removed from the ice-bath, and irradiated for an hour, during which time it heated up considerably. On distillation 3.9 g. of material was obtained which distilled at 38–75°, while the remainder distilled at 75–100° (1 mm.). On redistillation of the latter through a six-inch helices packed column, there was obtained 36.3 g. (a quantitative yield) of material distilling at 97–99° (1 mm.); $n^{20}D$ 1.5137. A sample from the middle of this fraction was analyzed.

Anal. Calcd. for $C_9H_{16}S_2O_2$: C, 49.06; H, 7.32; S, 29.10. Found: C, 49.65; H, 7.26; S, 29.46.

2-Methyl-1,4-butanedithiol.—A mixture of 36 g. of 2-methyl-1,4-butanedithiol diacetate, 40 g. of potassium hydroxide, 180 cc. of water and 200 cc. of 95% ethanol was refluxed for a half hour. The solution was then neutralized with acetic acid, and extracted with ether. The ether solution was dried over sodium sulfate, and then the ether removed. The residue, which existed in two layers, was distilled. The first fraction which distilled at 30° (80 mm.) was colorless, but the second fraction which distilled at 47–49° (3 mm.) was yellow and had an unpleasant odor. The second fraction which contained 8.3 g. of material was redistilled through a six-inch helices packed column at 46–48° (1 mm.), $n^{20}D$ 1.5202. There was obtained 6.4 g. (35% of the theoretical amount).

Anal. Calcd. for $C_5H_{12}S_2$: C, 44.07; H, 8.88; S, 47.05. Found: C, 44.61; H, 8.87; S, 47.22.

Summary

Hexamethylenedithiol and 1,5-hexadiene react in cyclohexane solution under the influence of ultraviolet light to produce polymers having molecular weights varying upward from 1000. The addition gives a linear polyhexamethylene sulfide.

The reaction is general for other dimercaptans and unconjugated diolefins. The polyalkylene

---

[14] This preparation of the perbenzoic acid solution was carried out by the procedure of Braun, "Organic Syntheses," Col. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 431, as modified by Kolthoff, Lee and Mairs, *J. Polymer Sci.*, **2**, 199 (1947).

[15] The procedure of Carothers, U. S. Patent 2,201,884, was followed.

[16] We are indebted to Dr. D. W. Hein for this sample.

[17] R. L. Frank and D. W. Hein, private communication.

sulfides from unbranched dienes and dimercaptans are solids showing definite crystallinity in their X-ray patterns. Attempts at end group determination by oxidation gave increased molecular weights as measured by intrinsic viscosity but conclusive evidence of thiol end groups was not obtained.

Urbana, Illinois Received October 14, 1947

[Contribution from the B. F. Goodrich Research Center]

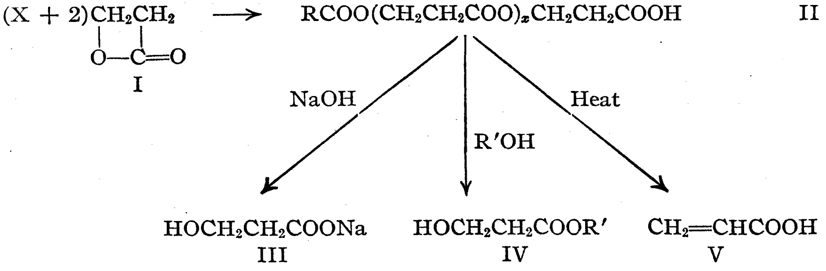
β-Propiolactone. I. Polymerization Reactions

By T. L. Gresham, J. E. Jansen and F. W. Shaver

β-Propiolactone (I) was first prepared[1] from the silver salt of β-iodopropionic acid. Only a few reactions such as its hydrolysis with acids and bases were described. Apparently no further investigations of this interesting β-lactone have been made.

The availability of I, by the practical synthesis from ketene and formaldehyde discovered by Küng,[2] has made possible an extensive study of its many reactions. This has revealed that β-propiolactone is a highly reactive and synthetically useful chemical.

Pure I polymerizes slowly when heated, and several hours at 150° are required for complete reaction. This polymerization is markedly catalyzed by acids, bases or salts. The most effective catalysts, such as ferric chloride, stannic chloride, sulfuric acid and sodium hydroxide, are moderately soluble in the lactone. Such catalyzed reactions are extremely vigorous and explosive in nature and are highly exothermic. Less effective catalysts are sodium chloride, calcium hydroxide, anhydrous hydrogen chloride and acetic acid. Solutions of polymerization catalysts in I at 0° are relatively stable. The polymerization reaction may be controlled by adding I slowly to a solution of the catalyst in an inert solvent. It is of interest to note that polymerization does not occur with sulfuric acid in ether solution even at the reflux temperature.



R represents $CH_2{=}CH$—(IIa) or $HOCH_2CH_2$—(IIb)

The polymers of I, prepared with or without added catalysts, are similar and are poly-ester acids (II). They vary from colorless viscous oils to white solids depending on the degree of polymerization and their alkali metal salts are soluble in water. Precipitation of the higher molecular weight fractions by dilution of hot acetone solutions with water yields solid polymers melting about 86°, with an average molecular weight in the range of 800–1000 as determined ebullioscopically in chloroform. Titration with base indicates a similar molecular weight range and thus shows that the polymers contain one carboxyl group per molecule. The other end group is either vinyl or a β-hydroxyethyl. The analysis for carbon and hydrogen and iodine number indicate that there are more vinyl than β-hydroxyethyl groups present in the mixture. These analyses are characteristic of a certain polymer since less unsaturation but similar molecular weights are sometimes obtained without known variants in the preparation. This could be due to variations in traces of moisture.

In boiling aqueous caustic, the polymers are saponified to salts of hydracrylic acid (III) and saponification equivalents are in close agreement with those expected for the basic unit of 72. Prolonged treatment of the polymers with alcohols when catalyzed by acids results in almost complete conversion to hydracrylate esters (IV). Basic catalysts are unsatisfactory for this alcoholysis due to the sensitivity of the hydracrylate esters to alkali. Pyrolysis[3] of the poly-ester acids to acrylic acid (V) is rapid and complete at 150°.

Other reactions of β-propiolactone to be reported in later papers include reactions with salts of inorganic acids, salts of dithiocarbamic acids, salts of carboxylic acids, alcohols, phenols and thiophenols, amines, organic and inorganic acid chlorides, metal organic compounds, inorganic acids and compounds with labile hydrogen or active methylene groups. Further work is now being undertaken to determine the mechanisms of these reactions.

Experimental

β-Propiolactone (I).—Physical constants: b. p. 51° at 10 mm., 150° at 750 mm., (with extensive decomposition); m. p. −33.4°; d^{20}_{4} 1.1460; n^{20}_{D} 1.4131; dipole moment 3.8 ± 0.1 *D*.

---

(1) Johannson, Lund University Annual, New Series, Div. 2, Vol. 12, No. 8 (1915).

(2) Küng, U. S. Patent 2,356,459 (1941).

(3) Küng, U. S. Patent 2,361,036 (1944).

Anal. Calcd. for $C_3H_4O_2$: C, 50.0; H, 5.56; neut. equiv., 72; *MR*D, 15.51; mol. wt., 72. Found: C, 49.87; H, 5.57; neut. equiv., 72.3; *MR*D, 15.67; mol. wt. (cryoscopic in benzene), 74.

Pure I is relatively stable at room temperature. There is no evidence of change in two to three months. However, it reacts rapidly and exothermically at room temperature with a wide variety of organic and inorganic compounds. In many cases polymerization of I is a competing reaction and in general this polymerization is minimized by operating at low temperatures.

The lactone is miscible at room temperature with most organic solvents such as ether, acetone, alcohol, benzene and acetic acid. It is 37% soluble (by volume) in water at 25° but the lactone is slowly hydrolyzed to hydracrylic acid and at least five days are required for complete reaction. With an equal molar quantity of water the hydracrylic acid obtained contains about 20% poly-hydracrylic acids as determined by acid and saponification equivalents.

Polymerization to Poly-ester Acids (II).—A. With Heat.—Three hundred grams (4.16 moles) of I was heated at 130–150° for five hours with stirring. The material gradually became more viscous and the cooled product (300 g.) was a viscous oil which partially solidified. No materials volatile at 100° under vacuum were present.

B. With Ferric Chloride.—A trace of ferric chloride (0.1 g.) was added to 25 g. of I in an open beaker at 25°. Within thirty seconds a violent exothermic reaction occurred and the entire contents were expelled.

A controlled polymerization was carried out by adding 300 g. of I dropwise to a stirred solution of ferric chloride (3 g.) in 125 ml. of benzene. Reflux was maintained by the rate of addition which required thirty minutes. The benzene was decanted from the poly-ester acid (300 g.) which partially solidified on cooling.

C. With Sulfuric Acid.—Addition of I (3 moles, 216 g.) slowly (one hour) to 1 g. of concentrated sulfuric acid at 60–80° with external cooling gave a semi-solid reaction product (210 g.). The product was melted, dissolved in 1000 ml. of hot acetone which in turn was poured into 3000 ml. of cold water. The solid which separated was filtered, washed with water, and dried; wt. 176 g. (82%), m. p. 84–86°.

Anal. Calcd. for $C_{36}H_{48}O_{24}$, IIa: C, 50.00; H, 5.56; neut. equiv., 864; mol. wt., 864; sapn. equiv., 72; iodine no., 29.4. Calcd. for $C_{36}H_{50}O_{25}$, IIb: C, 48.98; H, 5.67; neut. equiv., 882; mol. wt. 882; sapn. equiv., 73.5; iodine no., 0. Calcd. for 63% IIa and 37% IIb: C, 49.61; H, 5.60; neut. equiv., 870; iodine no., 18.5. Found: C, 49.48; H, 5.70; neut. equiv., 870; mol. wt. (ebullioscopic in chloroform), 850; sapn. equiv., 74; iodine no. (by perbenzoic acid oxidation), 18.5.

The agreement of the calculated mixture analysis with that found is significant only to establish a possible composition of poly-ester acids with an average molecular weight of about 870.

Alcoholysis of II, Ethyl Hydracrylate (IV).—A mixture of 100 g. of II (prepared by procedure A, B, or C) and 192 g. anhydrous ethanol containing 1 g. of concentrated sulfuric acid was refluxed for thirty-six hours. The acid catalyst was neutralized with calcium carbonate, most of the excess alcohol distilled at atmospheric pressure, and the residual oil filtered to remove calcium salts. Distillation of the residue at 13 mm. yielded 16.4 g. of forefraction, b. p. 60–81°, and 137 g. (84%) of ethyl hydracrylate, b. p. 81–83°, n^{20}_D 1.4222, d^{20}_4 1.0545.

Anal. Calcd. for $C_5H_{10}O_3$: sapn. equiv., 118. Found: sapn. equiv., 118.2.

Pyrolysis of II, Acrylic Acid (V).—Three hundred grams of II and 3 g. of anhydrous copper acetate (to inhibit polymerization of acrylic acid) were heated to 200° at 80 mm. A fraction of crude acrylic acid (275 g.), b. p. 84–131°, was collected. Redistillation gave 200 g. (67%) of acrylic acid, b. p. 79–80° at 80 mm., m. p. 12–13°. A mixture melting point with an authentic sample of acrylic acid was not depressed.

Summary

The polymers of β-lactone are poly-ester acids. The polymerization is markedly catalyzed by certain acids, bases and salts. The poly-ester acids are characterized by pyrolysis to acrylic acid and by alcoholysis to hydracrylates.

Brecksville, Ohio Received July 21, 1947

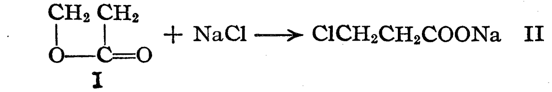
[Contribution from the B. F. Goodrich Research Center]

β-Propiolactone. II. Reactions with Salts of Inorganic Acids

By T. L. Gresham, J. E. Jansen, F. W. Shaver and J. T. Gregory

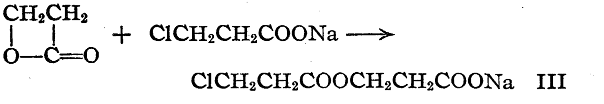
In the previous paper[1] the rapid polymerization of β-propiolactone (I) as catalyzed by certain inorganic salts was described. In water solutions of inorganic salts beta substituted propionic acid salts are formed in good yields.

With aqueous sodium chloride I yields sodium β-chloropropionate (II) and a considerable quantity of sodium β-(β-chloropropionoxy)-propionate (III) and higher analogs.



I

II



III

The secondary reaction of I with the primary product is minimized by increasing the molar ratio of salt to I and by the addition of hydrochloric acid. This latter effect may be due to reduction in the concentration of the chloropropionate ion at the lower *p*H.

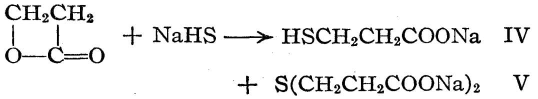
Reactions of I with lithium, ammonium, calcium, barium or ferric chloride in aqueous solution give salts of β-chloropropionic acid in a manner similar to that with sodium chloride. With sodium bromide and iodide there is less tendency for the secondary reactions to occur. The yields of *beta* substituted propionic acids under similar conditions increase in the order: NaCl < NaBr < NaI. In all of the above reactions some hydrolysis of I occurs.

The reaction of I with aqueous sodium hydrogen sulfide results in excellent yields of sodium β-mercaptopropionate (IV). The secondary reaction occurs only at the mercapto group to give

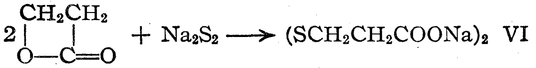
---

[1] Gresham, Jansen and Shaver, This Journal, **70**, 998 (1948).

a small amount of the salt of bis-(2-carboxyethyl) sulfide (V) and is not minimized by the use of an excess of sodium hydrogen sulfide. The addition of I to a solution containing equal molar amounts of sodium chloride and sodium hydrogen sulfide results in almost exclusive reaction with the sodium hydrogen sulfide. With aqueous sodium sulfide the reaction is more complex and hydrolysis occurs to a major extent. In concentrated solutions, however, a mixture of sodium β-mercaptopropionate (IV) and bis-(2-carboxyethyl) sulfide (V) is obtained in poor yield. The ratio of IV to V is about 1:2 even when an excess of sodium sulfide is present, indicating a preference for I to react at the alkyl mercapto group. With aqueous sodium disulfide a high yield of bis-(2-carboxyethyl) disulfide (VI) is obtained.

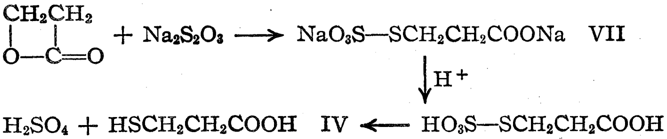


$$\begin{matrix}\text{CH}_2\text{CH}_2\\ |\quad\ |\\ \text{O—C=O}\end{matrix} + \text{NaHS} \longrightarrow \text{HSCH}_2\text{CH}_2\text{COONa}\ \ \text{IV} + \text{S(CH}_2\text{CH}_2\text{COONa)}_2\ \ \text{V}$$



$$2\begin{matrix}\text{CH}_2\text{CH}_2\\ |\quad\ |\\ \text{O—C=O}\end{matrix} + \text{Na}_2\text{S}_2 \longrightarrow (\text{SCH}_2\text{CH}_2\text{COONa})_2\ \ \text{VI}$$

β-Mercaptopropionic acid is the product formed from I and sodium thiosulfate. An intermediate thiosulfate (VII) and the corresponding acid are both stable in the solution at 25° but the acid is hydrolyzed by boiling. A by-product of this reaction is bis-(2-carboxyethyl) disulfide (VI) formed by the oxidation of IV with the small amount of sodium thiosulfate present when the solution is acidified.



$$\begin{aligned}&\begin{matrix}\text{CH}_2\text{CH}_2\\ |\quad\ |\\ \text{O—C=O}\end{matrix} + \text{Na}_2\text{S}_2\text{O}_3 \longrightarrow \text{NaO}_3\text{S—SCH}_2\text{CH}_2\text{COONa}\ \ \text{VII}\\ &\qquad\qquad\qquad\qquad\qquad\qquad\downarrow \text{H}^+\\ &\text{H}_2\text{SO}_4 + \text{HSCH}_2\text{CH}_2\text{COOH}\ \ \text{IV} \longleftarrow \text{HO}_3\text{S—SCH}_2\text{CH}_2\text{COOH}\end{aligned}$$

Experimental

β-Choropropionic Acid (II).—One mole (72 g.) of I was added (five minutes) to a solution of one mole (58.5 g.) of sodium chloride in 400 ml. of water. The reaction was stirred and held at 25° with external cooling for one hour after which there was no detectable temperature rise. After three hours, the clear solution was acidified with concentrated hydrochloric acid. The product, part of which separated as a heavy oil layer, was separated by continuous extraction with ether. The residue from evaporation of the ether extract was distilled at reduced pressure to give 37.2 g. (34%) of β-chloropropionic acid, b. p. 69–75° (1 mm.); m. p. 36–39°; m. p. 41–42° (after one recrystallization from ether–petroleum ether).

Anal. Calcd. for $C_3H_5O_2Cl$: C, 33.19; H, 4.61; Cl, 32.7; neut. equiv., 108.57. Found: C, 33.16; H, 4.57 Cl, 32.6; neut. equiv., 108.7.

The residue (35.7 g.) from the above distillation was a viscous slightly colored oil consisting of a mixture of β-(β-chloropropionoxy)-propionic acid III and higher analogs.

Anal. Calcd. for $C_6H_9O_4Cl$ (III): Cl, 19.66; neut. equiv., 180.5; for $C_9H_{13}O_6Cl$: Cl, 14.06; neut. equiv., 252.2. Found: Cl, 14.8; neut. equiv., 229.

When the above experiment was carried out with one mole of I and three moles of salt in 400 ml. of water the yield of III was 73.7% and the residue weighed 17 g.

With one mole of I, 1.4 moles of salt and 1.1 moles of concentrated hydrochloric acid in 338 ml. of water a yield of 91.2% of β-chloropropionic acid was obtained. The residue weighed 2 g.

β-Bromopropionic Acid.—This experiment was carried out similar to the preparation of II but substituting one mole (103 g.) of sodium bromide. After cooling and acidification the product was extracted in a continuous manner with a mixture of one part of ether and fifteen parts of hexane and finally with ether alone. The combined residues from the extracts were distilled at reduced pressure to give 88.5 g. (58%) of β-bromopropionic acid, b. p. 88° (0.5 mm.); m. p. 58–60°. After recrystallization from hexane the acid melted at 61–62°.

Anal. Calcd. for $C_3H_5O_2Br$: C, 23.55; H, 3.29; Br, 52.23; neut. equiv., 152.9. Found: C, 23.69; H, 3.43; Br, 52.17; neut. equiv., 153.8.

The residue (15 g.) was a slightly colored viscous oil.

Anal. Calcd. for $C_6H_9O_4Br$: Br, 35.55; neut. equiv., 255. Calcd. for $C_9H_{13}O_6Br$: Br, 26.85; neut. equiv., 297. Found: Br, 28.1; neut. equiv., 252.

β-Iodopropionic Acid.—An experiment similar to that for the preparation of II but substituting one mole (150 g.) of sodium iodide was held at 0° after acidification. The crystals of β-iodopropionic acid which separated were filtered, washed with cold water and dried at 25°; m. p. 75–82°; yield, 123 g. (61.5%); m. p. 82–83° (after recrystallization from chloroform–hexane).

Anal. Calcd. for $C_3H_5O_2I$: C, 18.01; H, 2.52; I, 63.5; neut. equiv., 200. Found: C, 18.10; H, 2.59; I, 63.4; neut. equiv., 201.

β-Mercaptopropionic Acid (IV) (From Sodium Hydrogen Sulfide).—Seventy-two grams (1 mole) of I was added while stirring (15 min.) to a solution of 1.06 moles (59 g.) of sodium hydrogen sulfide, freshly prepared from sodium hydroxide and hydrogen sulfide, in 160 ml. of water. A reaction temperature of 5° was maintained. After an additional hour the solution was acidified with concentrated hydrochloric acid and the product isolated by continuous extraction with ether. Distillation of the ether extract residue at reduced pressure gave 85.6 g. (80.7%) of β-mercaptopropionic acid; b. p. 114–115.5° at 13 mm.; d^{20}_4 1.2188; n^{20}_D 1.4921.

Anal. Calcd. for $C_3H_6O_2S$: C, 34.0; H, 5.66; S, 30.19; neut. equiv., 106. Found: C, 34.0; H, 5.84; S, 30.21; neut. equiv. (neutral red), 105.4.

The residue (13.4 g.) from the above distillation was dissolved in acetone, the solution decolorized with Nuchar and evaporated. The solid residue was recrystallized from hot water yielding 8 g. (9.0%) of bis-(2-carboxyethyl) sulfide; m. p. 128–130°.

Anal. Calcd. for $C_6H_{10}O_4S$: C, 40.45; H, 5.65; S, 17.97; neut. equiv., 89. Found: C, 40.50; H, 5.67; S, 18.04; neut. equiv., 88.8.

A similar experiment but using two moles of sodium hydrogen sulfide gave 89 g. (84%) of β-mercaptopropionic acid and 6.6 g. (7.4%) of bis-(2-carboxyethyl) sulfide.

A third experiment wherein the water was replaced with 500 ml. of anhydrous ethanol gave a reaction mixture containing a heavy precipitate of the mono-sodium salt of β-mercaptopropionic acid. The suspension was acidified with 128 ml. of concentrated hydrochloric acid, filtered from sodium chloride, and concentrated by distillation at atmospheric pressure. Fractional distillation of the residue at 20 mm. gave a forerun (25 g., b. p. 23–76°) the water insoluble portion of which was returned to the distillation flask. Completion of the rectification gave two fractions. The first fraction, 47.7 g. (35.6%), b. p. 79–79.5° (20 mm.), was redistilled to give pure ethyl β-mercaptopropionate, b. p. 79–79.5° (20 mm.); n^{20}_D 1.4561; d^{20}_4 1.0550.

Anal. Calcd. for $C_5H_{10}O_2S$: C, 44.78; H, 7.52; S, 23.87; sapn. equiv., 134.1; MR_D, 34.53. Found: C, 44.79; H, 7.58; S, 23.91; sapn. equiv., 136; MR_D 34.63.

The second fraction, b. p. 122–123.5° (20 mm.), wt.

158.8 g. (55.5%) was β-mercaptopropionic acid, $n^{20}D$ 1.4902; d^{20}_4 1.2169.

Anal. Calcd. for $C_3H_6O_2S$: neut. equiv., 106. Found: neut. equiv., 108.5 (neutral red).

β-Mercaptopropionic Acid (IV) (From Sodium Sulfide).—One mole (72 g.) of I was added slowly (thirty minutes) to a stirred solution of 1.2 moles (288.5 g. nonahydrate) of sodium sulfide in 200 ml. of water with control of the temperature at 15°. Part of the sodium sulfide was undissolved at the start. After several hours the clear solution was acidified with concentrated hydrochloric acid and the product isolated by ether extraction. Distillation of the ether extract residue at reduced pressure gave 11 g. (10%) of β-mercaptopropionic acid, b. p. 100° (7 mm.); $n^{20}D$ 1.4921.

Anal. Calcd. for $C_3H_6O_2S$: neut. equiv., 106. Found: neut. equiv., 108 (neutral red).

The solid residue from the above distillation was recrystallized twice from ether–petroleum ether to give 16.2 g. (18.2%) of bis-(2-carboxyethyl) sulfide, m. p. 128–130°. The melting point of a mixture with an authentic sample was not depressed.

An experiment carried out as above but with no control of the temperature resulted in its rise to 99°. The product was a mixture consisting of 9 g. (8%) of β-mercaptopropionic acid and 20.5 g. (22%) of bis-(2-carboxyethyl) sulfide.

Another experiment at 0° and at greater dilution, 1000 ml. of water, resulted in no ether extractable product.

bis-(2-Carboxyethyl) Disulfide (VI) (From Sodium Disulfide).—A solution of 0.5 mole (43.5 g.) sodium disulfide was prepared from 61 g. (1.1 mole) of sodium hydrogen sulfide and 16 g. (0.5 mole) of sulfur in 400 ml. of water by warming the suspension at 50° while stirring. To the orange-red solution was added slowly (thirty minutes) 72 g. (1 mole) of I at 0°. After an additional hour the clear yellow solution was acidified with concentrated hydrochloric acid, diluted with water and the copious white precipitate filtered, washed with water and recrystallized from 1000 ml. of hot water. The yield of impure bis-(2-carboxyethyl) disulfide was 98.5 g. (94%), m. p. 135–149°. The mixture melting point with an authentic sample (m. p. 153–155°) was 148–153°.

β-Mercaptopropionic Acid (IV) (From Sodium Thiosulfate).—I (144 g., 2 moles) was added slowly (two hours) to a stirred solution of 496 g. (2 moles) sodium thiosulfate pentahydrate in 400 ml. water at 30°. After acidification with 330 ml. concentrated hydrochloric acid an ether extraction yielded no product. However, after heating the water layer for three hours at 100° a white precipitate of bis-(2-carboxyethyl) disulfide separated. This was filtered and recrystallized from hot water, m. p. 153–155°; wt. 29 g. (13.8%).

Anal. Calcd. for $C_6H_{10}O_4S_2$: C, 34.25; H, 4.79; S, 30.42. Found: C, 34.28; H, 4.77; S, 30.46.

The above filtrate was continuously extracted with ether and the residue, after evaporation of the ether, was distilled at reduced pressure. β-Mercaptopropionic acid, 148.5 g. (70%) was collected, b. p. 94° (5 mm.); $n^{20}D$ 1.4921; d^{20}_4 1.2188.

Anal. Calcd. for $C_3H_6O_2S$: neut. equiv., 106. Found: neut. equiv., 105.4 (neutral red).

The residue (12 g.) from the distillation yielded 11 g. (5%) of crude bis-(2-carboxyethyl) disulfide after recrystallization from hot water, m. p. 131–144°.

bis-2-(Carboxyethyl) Disulfide (VI) (By Oxidation).—A solution containing 95.4 g. (0.9 mole) β-mercaptopropionic acid, 25 g. (0.1 mole) sodium thiosulfate pentahydrate in 360 ml. of water was acidified with 16.5 ml. of concentrated hydrochloric acid. The solution was held at 100° for one hour during which time the small sulfur deposit disappeared and hydrogen sulfide was evolved. An equal volume of hot water was added and after cooling, the precipitate of bis-(2-carboxyethyl) disulfide was filtered and recrystallized from 600 ml. of hot water; wt. 80 g. (84.5%); m. p. 150–152.5°. A mixture melting point with an authentic sample was not depressed.

Summary

Reactions of β-propiolactone with aqueous solutions of alkali halides, sodium hydrogen sulfide, sodium sulfide, sodium disulfide and sodium thiosulfate are described. The primary products are salts of *beta* substituted propionic acids. In certain cases salts of poly-ester acids are formed as secondary reaction products.

BRECKSVILLE, OHIO RECEIVED JULY 21, 1947

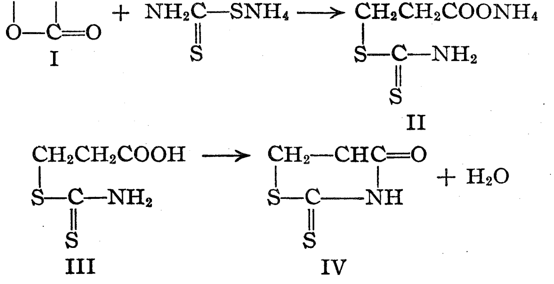
[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER]

β-Propiolactone. III. Reactions with Dithiocarbamic Acids, their Salts and Thiourea

BY T. L. GRESHAM, J. E. JANSEN AND F. W. SHAVER

The previous work[1] showed that salts of *beta*-substituted propionic acid were formed from β-propiolactone (I) and salts of inorganic acids. Similar products are formed from salts of dithiocarbamic acids and there is no tendency for secondary reactions to occur.

With ammonium dithiocarbamate, an excellent yield of ammonium β-dithiocarbamyl propionate (II) is obtained and the corresponding acid is readily cyclized to 2-thiono-4-keto-1,3-thiazane (IV). Similarly salts of N-alkyl and N,N-dialkyl dithiocarbamic acids form salts of *beta*-substituted propionic acids. Ring closure occurs only with the mono alkyl substituted acids.

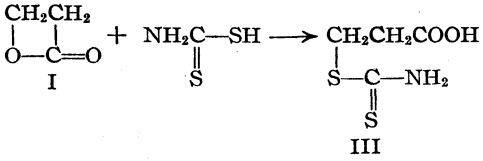


β-Dithiocarbamylpropionic acids III are also formed from I and the free dithiocarbamic acids in water solution. The yields are equally high.

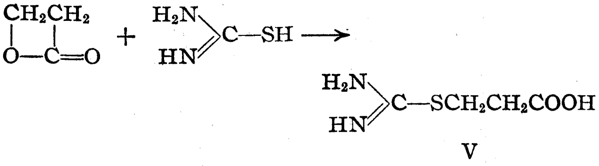
With thiourea, I forms β-isothioureido propionic

---

(1) Gresham, Jansen, Shaver and Gregory, THIS JOURNAL, **70**, 999 (1948).



acid (V). In polar solvents such as water, the reaction is rapid and nearly quantitative but it does not occur at all in non-polar solvents such as ether.



Experimental

β-Dithiocarbamylpropionic Acid (III).—One mole (72 g.) of β-propiolactone was added dropwise (twenty minutes) to a solution of 110 g. (1 mole) of ammonium dithiocarbamate[2] in 300 ml. of water at 20° with stirring. The clear solution was acidified with concentrated hydrochloric acid and after two hours the copious white precipitate was filtered, washed with water and dried; m. p. 124–126°; yield, 152 g. (92%). After recrystallization from ether–petroleum ether the product was collected as small prisms, m. p. 125–126°.

Anal. Calcd. for $C_4H_7O_2NS_2$: C, 29.10; H, 4.24; N, 8.50; S, 38.80; neut. equiv., 165. Found: C, 29.17; H, 4.25; N, 8.59; S, 38.85; neut. equiv., 168.

A solution of dithiocarbamic acid was prepared by carefully acidifying a solution of ammonium dithiocarbamate (110 g., 1 mole in 500 ml. of water) with 100 g. concentrated hydrochloric acid at 0°. One mole (72 g.) of β-propiolactone was added dropwise (thirty minutes) to this solution while stirring. The temperature was maintained at 0° throughout and after three hours the copious white precipitate which had separated was filtered, washed thoroughly with water, and dried; yield, 152 g. (92%); m. p. 124–126°. A mixture melting point with the above sample of β-dithiocarbamylpropionic acid was not depressed.

Reactions with other dithiocarbamates were carried out in a manner similar to the above. Solutions of sodium N-ethyl dithiocarbamate were prepared from ethylamine, carbon disulfide and sodium hydroxide in the usual manner. Solutions of sodium N,N-dimethyl and N,N-diethyl dithiocarbamate were prepared by dissolving the salts in water.

β-(N-Ethyl Dithiocarbamyl)-propionic Acid.—The product separated as fine needles on recrystallization from ether–hexane; m. p. 97–98°; yield, 35 g.[3] (20%).

Anal. Calcd. for $C_6H_{11}O_2NS_2$: C, 37.30; H, 5.74; N, 7.26; S, 33.18; neut. equiv., 193. Found: C, 37.36; H, 5.73; N, 7.25; S, 33.25; neut. equiv., 194.

β-(N,N-Dimethyldithiocarbamyl)-Propionic Acid.—The product separated as prisms from ether–petroleum ether; m. p. 142–143°; yield, 187 g. (97%).

Anal. Calcd. for $C_6H_{11}O_2NS_2$: C, 37.30; H, 5.74; N, 7.26; S, 33.18; neut. equiv., 193. Found: C, 37.24; H, 5.67; N, 7.11; S, 33.25; neut. equiv., 194.

β-(N,N-Diethyldithiocarbamyl)-Propionic Acid.—Yield after recrystallization from ether–petroleum ether, 175 g. (80%); m. p. 97–98°.

Anal. Calcd. for $C_8H_{15}O_2NS_2$: C, 43.44; H, 6.79; N, 6.34; S, 29.00; neut. equiv., 221. Found: C, 43.48; H, 6.78; N, 6.38; S, 29.08; neut. equiv., 222.

2-Thiono-4-keto-1,3-thiazane[4] (IV).—A suspension of 47 g. of III in 100 ml. of acetic anhydride containing 0.1 g. of concentrated sulfuric acid, was stirred and warmed to 50°. The resulting deep yellow solution was poured into ice and water and the solid which separated was filtered, dried, and recrystallized from benzene; m. p. 119–120°; yield, 42 g. (92%).

Anal. Calcd. for $C_4H_5ONS_2$: C, 32.61; H, 3.42; N, 9.52; S, 43.56. Found: C, 32.91; H, 3.52; N, 9.66; S, 43.82.

2-Thiono-3-ethyl-4-keto-1,3-thiazane.—Using a procedure similar to that for IV above this product was obtained as yellow plates, m. p. 65–66°; yield, 78%.

Anal. Calcd. for $C_6H_9ONS_2$: C, 41.15; H, 5.14; N, 8.00; S, 36.60; mol. wt., 175. Found: C, 41.27; H, 5.15; N, 8.04; S, 36.67; mol. wt., 175 (ebullioscopic in benzene).

β-Isothioureidopropionic Acid (V).[5]—One mole (72 g.) of β-propiolactone was added all at once to a solution of 76 g. of thiourea in 300 cc. of water while stirring. The temperature rose about 30° and the product started to separate in a few minutes. After standing for two hours at 10°, the solid hydrate was filtered and recrystallized from hot water. After drying at 100°, anhydrous crystals were obtained; yield, 132 g. (90%); m. p. 178–179°. The mixture melting point with a sample, prepared as directed by Andreasch, was not depressed.

Anal. Calcd. for $C_4H_8O_2N_2S$: N, 18.90. Found: N, 18.72.

Acknowledgment.—The authors express their thanks to Marie Prendergast and R. W. Dundon for their part in the experimental work.

Summary

Reactions of β-propiolactone with dithiocarbamic acids, their salts, and with thiourea are described. In certain cases the products were cyclized to substituted 1,3-thiazanes.

BRECKSVILLE, OHIO RECEIVED JULY 21, 1947

---

[2] Mathes, U. S. Patent 2,117,619 (1938), Example 2.

[3] The yield was low due to the poor yield of dithiocarbamate.

[4] Holmberg, *Ber.*, **47**, 159 (1914).

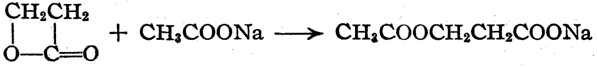
[5] Andreasch, *Monatsh.*, **6**, 832 (1885).

[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER]

β-Propiolactone. IV[1,2] Reactions with Salts of Carboxylic Acids

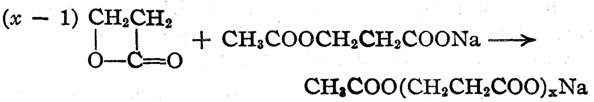
BY T. L. GRESHAM, J. E. JANSEN AND F. W. SHAVER

Salts of β-acetoxypropionic acid II and poly-ester acids (III) are formed in the reaction of β-propiolactone (I) with aqueous sodium acetate. The strong tendency for the reaction of I with the primary products is minimized by increasing the mole excess of sodium acetate.



$$\begin{array}{l}CH_2CH_2\\ |\quad\;\; |\\ O{-}C{=}O\end{array} + CH_3COONa \longrightarrow CH_2COOCH_2CH_2COONa$$

I II



$$(x-1)\begin{array}{l}CH_2CH_2\\ |\quad\;\; |\\ O{-}C{=}O\end{array} + CH_3COOCH_2CH_2COONa \longrightarrow CH_3COO(CH_2CH_2COO)_xNa$$

III

β-Acetoxypropionic acid (IV) is completely pyrolyzed to acetic acid and acrylic acid by distillation at atmospheric pressure.

$$\underset{\text{IV}}{CH_3COOCH_2CH_2COOH} \longrightarrow CH_3COOH + CH_2{=}CHCOOH$$

Attempts to prepare esters of IV by direct esterification result in alcoholysis and esterification to hydracrylates and acetates.

The poly-ester acids V are colorless oils and they differ from polymers obtained from I by heat or with catalysts[3] only in the end acetoxy group. Alcoholysis with methanol, using acid catalysis, results in a mixture of methyl acetate and methyl hydracrylate in amounts as expected from the average molecular weight, assuming one acetoxy group per molecule.

$$\underset{\text{V}}{CH_3COO(CH_2CH_2COO)_xH} + CH_3OH \longrightarrow CH_3COOCH_3 + xHOCH_2CH_2COOCH_3 + H_2O$$

With several moles of I and one mole of sodium acetate the products are exclusively salts of poly-ester acids (III). Low temperatures are required to avoid hydrolysis of I. Since the yield of polymer is higher than that expected from the molecular weight if each polymer molecule contains an acetoxy group, some polyhydracrylic acid is present due to hydrolysis of the polymers or polymerization of I.

Products similar to those with sodium acetate are formed with salts of other carboxylic acids. The poly-ester acids from sodium caprate (VI) and disodium phthalate (VII) were viscous oils.

$$\underset{\text{VI}}{CH_3(CH_2)_8COO(CH_2CH_2COO)_{2.5}H}$$

$$\underset{\text{VII}}{C_6H_4[(COO(CH_2CH_2COO)_{2.5}H]_2}$$

Direct esterification of these products resulted in alcoholysis to esters of the parent acids and esters of hydracrylic acid.

Experimental

β-Acetoxypropionic Acid (IV).—One mole (72 g.) of I was added (fifteen minutes) to a stirred solution of 82 g. (1 mole) of sodium acetate in 300 ml. of water at 20° with cooling. After stirring for one hour the colorless solution was cooled to 0°, acidified with concentrated hydrochloric acid and the product extracted with ether. The ether extract was dried over anhydrous sodium sulfate, evaporated under reduced pressure and the residue fractionally distilled at reduced pressure. After removal of some acetic acid, 42.5 g. (32%) of β-acetoxypropionic acid was collected; b. p. 83–84° (0.4 mm.); n^{25}_D 1.4311; d^{25}_4 1.1963.

Anal. Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.06; neut. equiv., 132; sapn. equiv., 66; *MR*D 28.48. Found: C, 45.32; H, 6.16; neut. equiv., 132; sapn. equiv., 68; *MR*D, 28.56.

The residue (46 g.) from the above distillation was a viscous colorless oil and consisted of a mixture of poly-ester acids. These poly-ester acids are soluble in acetone, chloroform and aqueous sodium hydroxide from which they are reprecipitated on acidification.

Anal. Calcd. for $C_{11}H_{16}O_8$ (V, $x = 3$): neut. equiv., 276; sapn. equiv., 69. Found: neut. equiv., 268; sapn. equiv., 67.

When the above reaction was repeated, except that two moles of sodium acetate were used, 75 g. (57%) of β-acetoxypropionic acid and 22 g. of residue were obtained. Similarly, with four moles of sodium acetate, 97 g. (73%) of β-acetoxypropionic acid and 9.5 g. of residue resulted.

Ethyl β-Acetoxypropionate.—β-Acetoxypropionic acid (23 g.) was treated with thionyl chloride (40 g.) for five hours at 25°. The excess thionyl chloride was removed at reduced pressure and absolute ethanol (16 g.) was added to the crude acid chloride residue. After standing for two hours, the mixture was diluted with ether, washed with aqueous sodium carbonate and water and dried over anhydrous sodium sulfate. Distillation of the residue at reduced pressure, after evaporation of the ether, gave ethyl β-acetoxypropionate; b. p. 33.5–35° (0.3 mm.); n^{20}_D 1.4163.

Anal. Calcd. for $C_7H_{12}O_4$: C, 52.50; H, 7.50; sapn. equiv., 80. Found: C, 52.36; H, 7.54; sapn. equiv., 83.

Pyrolysis of β-Acetoxypropionic Acid (IV).—β-Acetoxypropionic acid (122 g.) was rapidly distilled through a short open column at atmospheric pressure. Distillation started at a flask temperature of 190° and 118 g. of colorless distillate was collected, b. p. 130–150°. One gram of anhydrous copper acetate was added to the distillate, to inhibit polymerization of acrylic acid, and it was fractionally distilled. The first fraction was acetic acid; b. p. 118°; n^{20}_D 1.3790.

Anal. Calcd. for $C_2H_4O_2$: neut. equiv., 60. Found: neut. equiv., 63.

The second fraction was acrylic acid; b. p. 135–140°; m. p. 6°; after redistillation, m. p. 12–13°; mixture melting point with an authentic sample, 12–13°.

Alcoholysis of V.—A solution of the poly-ester acid residues (115 g., neut. equiv., 268) and 1 g. of sulfuric acid in 320 g. of methanol was refluxed for sixteen hours. The catalyst was neutralized with 3 g. of calcium carbonate; the solution filtered from calcium salts and fractionally distilled using a 30-plate Oldershaw column and a reflux ratio of 20:1. The first fraction was methyl alcohol–methyl

---

(1) Gregory, Gresham, Jansen and Shaver, THIS JOURNAL, 70, 999 (1948).

(2) Gresham, Jansen and Shaver, *ibid.*, 70, 1001 (1948).

(3) Gresham, Jansen and Shaver, *ibid.*, 70, 998 (1948).

acetate binary; b. p. 53–53.8°; $n^{20}\mathrm{D}$ 1.3531; wt. 28 g. (81.3%, 22.7 g. methyl acetate). After removal of the excess methanol, the residue was distilled through a 10 × 2 cm. packed column at reduced pressure and gave 81 g. of methyl hydracrylate; b. p., 70–71° (13 mm.); $n^{20}\mathrm{D}$ 1.4213; d^{20}_4 1.1205.

Anal. Calcd. for $C_4H_8O_3$: sapn. equiv., 104. Found: sapn. equiv., 104.5.

The residue, due to incomplete alcoholysis, weighed 38 g.

β-(β-Acetoxypolypropionoxy)-propionic Acids (V).—One mole (72 g.) of I was added (thirty minutes) to a stirred solution of 0.2 mole (16.4 g.) of sodium acetate in 100 ml. of water at 15° while cooling. After four hours, heat was no longer evolved and the clear solution was acidified with 25 g. of concentrated hydrochloric acid. The oil layer was separated, washed with water and dried to constant weight at 40° and 0.5 mm.; wt. 62 g. (76%).

Anal. Calcd. for $C_{11}H_{16}O_8$ (V, $x = 3$): neut. equiv., 276. Found: neut. equiv., 280.

A similar experiment but adding 2 moles (144 g.) of I resulted in a mixture of solid and oil after acidification of the reaction mixture. This was dissolved in chloroform, the solution washed with water and the chloroform distilled, partly at atmospheric pressure and finally at reduced pressure (40° (1 mm.)) until there was no further weight loss (four hours). The resulting oil slowly crystallized to a waxy solid; wt. 140.5 g. (90%); m. p. 30–40°.

Anal. Calcd. for $C_{20}H_{28}O_{14}$ (V, $x = 6$): neut. equiv., 492. Found: neut. equiv., 506.

Acknowledgment.—The authors wish to thank Marie Prendergast for assistance in the experimental work.

Summary

The reaction of β-propiolactone with aqueous sodium acetate gives a mixture of salts of β-acetoxypropionic acid, β-(β-acetoxypropionoxy)-propionic acid and higher analogs. The effect on the mixture of varying mole ratios of reactants is described and the poly-ester acids are characterized by pyrolysis and alcoholysis. Similar reactions occur with other carboxylic acid salts.

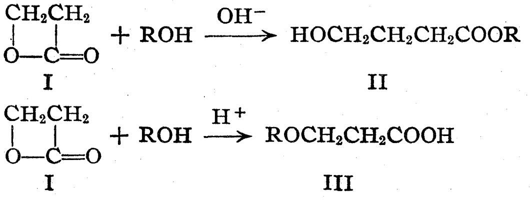
Brecksville, Ohio Received July 21, 1947

[Contribution from The B. F. Goodrich Research Center]

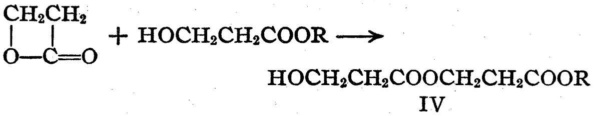
β-Propiolactone. V. Reaction with Alcohols

By T. L. Gresham, J. E. Jansen, F. W. Shaver, J. T. Gregory and W. L. Beears

With alcohols, β-propiolactone (I) forms two products, depending on the catalysis. With base catalysis the ring opens at the oxygen–carbonyl carbon bond forming hydracrylate esters II. Without added catalysts or with acid catalysis *beta*-alkoxy acids III are formed as a result of ring opening at the oxygen–methylene carbon bond. This latter ring opening is similar to that observed in the previously described salt reactions.[1]



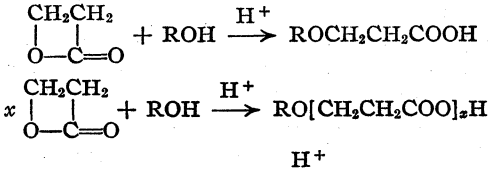
The base catalyzed reaction gives high yields of hydracrylates. It is extremely rapid with primary alcohols and must be run at low temperatures and in the presence of an excess of alcohol to avoid polymerization. Strong bases, such as sodium hydroxide, sodium alkoxide or trimethylbenzylammonium hydroxide are satisfactory catalysts. The polymers differ from the poly-ester acids previously described[1] in that they are esters of polyhydracrylic acid. Their formation may be due to the reaction of I with the hydracrylate or by the alcoholysis of the hydracrylates with themselves. With secondary alcohols it is more difficult to avoid the polymerization of I, probably due to a slower rate of the primary reaction.



$$2HOCH_2CH_2COOR \longrightarrow HOCH_2CH_2COOCH_2CH_2COOR + ROH$$
IV

The non-catalyzed reaction of I with alcohols[2] is extremely slow and β-alkoxypropionic acids and polymers are the only products. Some esterification of the alkoxy acids occurs, especially with the lower alcohols at higher temperatures. With secondary and tertiary alcohols these non-catalysed reactions are indeed slow, more of I polymerizes and no esters of the alkoxy acids are isolated.

The acid catalyzed reaction of I with alcohols is complex. β-Alkoxypropionic acids and their esters, hydracrylic acid esters and poly-ester acids



$$RO[CH_2CH_2COO]_xH + ROH \xrightarrow{H^+} ROCH_2CH_2COOR + (x-1)HOCH_2CH_2COOR + H_2O$$

$$ROCH_2CH_2COOH + ROH \xrightarrow{H^+} ROCH_2CH_2COOR + H_2O$$

---

[1] (a) Gregory, Gresham, Jansen and Shaver, This Journal, **70**, 999 (1948); (b) Gresham, Jansen and Shaver, *ibid.*, **70**, 1001 (1948); (c) Gresham, Jansen and Shaver, *ibid.*, **70**, 1003 (1948).

[2] Küng, U. S. Patent 2,352,641 (1944).

TABLE I

BASE CATALYZED REACTIONS OF β-PROPIOLACTONE WITH ALCOHOLS

Alcohol	Hydracrylate yield, %	B. p. °C.	B. p. Mm.	$n^{20}\text{D}$	d^{20}_4	Mol. refraction Calcd.	Mol. refraction Found	Sapn. equiv. Calcd.	Sapn. equiv. Found	Polymeric residue, yield, %
Methyl	85.1[a]	71	13	1.4225	1.1153	23.85	23.73	104	104.5	10
Ethyl	80.1[b]	75	8	1.4222	1.0545	28.47	28.45	118	117.2	13
n-Propyl	65.5	98	19	1.4251	1.0217	33.09	33.04	132	132	28
n-Butyl	77.2	114	20	1.4284	0.9989	37.71	37.63	146	147.7	9[c]
n-Octyl	64.5	104	4	1.4392	0.9484	56.18	56.05	202	202	7[c]

[a] 76% yield at 25°. [b] 69% yield with 4 g. trimethylbenzylammonium hydroxide. [c] Some pyrolysis of the residues occurred due to the higher flask temperatures at the end of the distillation.

with terminal alkoxy groups are formed. The composition of the mixture obtained is dependent on the reaction conditions employed, the most important factors of which are the acid catalyst concentration, the temperature, time and the molar excess of alcohol. The primary reaction of I gives β-alkoxypropionic acids. A competing reaction is polymerization. Secondary reactions of esterification and alcoholysis account for the other products.

The rate of the acid catalyzed reaction is intermediate between that of the non-catalyzed and base catalyzed. As is shown in Table II, the amount of hydracrylate formed by the secondary reaction increases with time with a corresponding decrease of polymer and none of it is formed in incomplete reactions. Also, more esterification occurs with increased time while the combined yields of alkoxy acid and ester remain constant.

The polymerization, alcoholysis and esterification are favored with increasing catalyst concentration and temperature. However, with high acid concentration only insoluble higher molecular weight polymers result. These, therefore, are alcoholized very slowly.[1a] Decrease in the excess alcohol favors the polymerization.

Both the primary and secondary reactions are slower with the higher primary alcohols. Secondary and tertiary alcohol reactions are still slower and little if any secondary reactions occur.

The polymeric residues from these acid catalyzed reactions contain poly-ester acids with end alkoxy groups. It was possible to isolate methyl β-(β-methoxypropionoxy)-propionate from the methyl alcohol residues in fair amounts. Neutralization equivalents show, however, that most of the residue consists of poly-ester acids.

Experimental

Base Catalyzed Reactions.—One mole of β-propiolactone was added dropwise with stirring to a solution of 2 g. of sodium hydroxide in six moles of the alcohol. The reactions were highly exothermic and a Dry Ice–acetone-bath was employed to maintain the temperature at 0° with a fifteen-minute addition time. The catalyst was neutralized with an equivalent of concentrated hydrochloric acid, the solution filtered from salt, and the alcohol and the product were distilled at reduced pressure. Yields and other data are listed in Table I.

Methyl β-(Hydroxypropionoxy)-propionate (IV).—The oily residues from base catalyzed reactions with methanol were insoluble in aqueous caustic. Distillation of 34 g. gave a fraction of IV (30 g.), b. p. 85–86° (0.3 mm.); $n^{20}\text{D}$ 1.4429; d^{20}_4 1.1902.

Anal. Calcd. for $C_7H_{12}O_5$: sapn. equiv., 88; *MR*D, 39.36. Found: sapn. equiv., 89; *MR*D, 39.21.

Acid Catalyzed and Non-catalyzed Reactions.—One mole of β-propiolactone was added dropwise over a twenty minute period to six moles of the alcohol. A three-neck ground-glass jointed flask fitted with a glass stirrer, thermometer, dropping funnel and a reflux condenser was used and the desired reaction temperature maintained by immersing the flask in a constant temperature bath. Stirring was continued throughout the experiment. With the acid catalyzed experiments the sulfuric acid was added at the start and neutralized at the end by the addition of two grams of calcium carbonate per gram of acid used and the solution filtered from calcium salts before distillation. The excess alcohol was distilled rapidly at reduced pressure keeping the flask temperature below 30° and the residue was fractionally distilled through a 1″ × 24″ packed column. The experimental data are listed in Table II and the physical and analytical data for the products in Table III.

TABLE II

ACID CATALYZED AND NON-CATALYZED REACTIONS OF β-PROPIOLACTONE WITH ALCOHOLS[a]

Alcohol	H_2SO_4,[e] g.	Temp., °C.	Time, hr.	Alkoxy acid yield, %	Alkoxy ester yield, %	Hydracrylate yield, %	Recovered lactone, %	Polymeric residue yield, %
Methyl	0	0	72	0	0	0	70	12
Methyl	0	46	16	42	2	0	12	17
Methyl	0	65	16	73	4	0	0	16
Methyl	1	0	6	8	0	0	..	81[b]
Methyl	1	0	72	8	25	23	0	36
Methyl	1	46	3	15	23	24	0	34[c]
Methyl	1	46	6	11	28	29	0	21
Methyl	1	46	16	0	34	40	0	13
Methyl	0.12	65	2	24	45	11	0	19[c]
Methyl	0.5	65	2	11	37	26	0	11
Methyl	1.0	65	2	0	34	43	0	23
Methyl	2.0	65	2	0	25	50	0	27[c]
Methyl	4.0	65	2	0	0	0	0	100
Ethyl	0	65	16	73	2	0	0	15
Ethyl	1	46	6	7	47	0	0	50[c]
Ethyl	1	80	2	0	54	25	0	23[c]
n-Propyl	0	65	16	73	4	0	4	14
n-Propyl	1	46	6	20	25	0	..	47[b]
n-Propyl	1	80	2	0	53	0	..	46[b]
n-Butyl	0	65	16	65	6	0	5	22
n-Butyl	1	46	6	0	28	0	39[d]	35[c]
n-Butyl	1	80	2	0	25	0	25[d]	56[c]
i-Propyl	0	65	16	45	0	0	36	16
i-Propyl	1	80	2	27	11	0	..	65[c]

[a] All reactions carried out with 5 moles of β-propiolactone. [b] Includes recovered lactone. [c] The combined yields and residues total more than 100% due to an undetermined amount of ester and alkoxy groups combined in the polymers. [d] Unreacted lactone distilled with the butanol and was determined by titration. [e] Grams of acid per mole of the lactone.

TABLE III

ALKOXY ACIDS AND THEIR ESTERS[a]

Compound	B. p. °C.	B. p. Mm.	$n^{25}D$	d^{25}_4	Mol. refraction Calcd.	Mol. refraction Found	Neut. equiv. Calcd.	Neut. equiv. Found
$CH_3OCH_2CH_2COOH$	102	13	1.4160	1.0982	23.85	23.76	104	106
$C_2H_5OCH_2CH_2COOH$	108	10	1.4178	1.0450	28.47	28.44	118	118
n-$C_3H_7OCH_2CH_2COOH$	76	1	1.4204	1.0043	33.09	33.29	132	133
i-$C_3H_7OCH_2CH_2COOH$	70	1	1.4222	1.0032	33.09	33.43	132	131
n-$C_4H_9OCH_2CH_2COOH$	72	0.1	1.4240	0.9876	37.71	37.73	146	146
$CH_3OCH_2CH_2COOCH_3$	63	40	1.3993	1.0052	28.59	28.40	118[b]	119[b]
$C_2H_5OCH_2CH_2COOC_2H_5$	60	13	1.4041	0.9461	37.82	37.77	146[b]	145[b]
n-$C_3H_7OCH_2CH_2COOC_3H_7$-n	87	13	1.4139	0.9369	47.06	46.40	174[b]	170[b]
i-$C_3H_7OCH_2CH_2COOC_3H_7$-i	67	13	1.4059	0.9150	47.06	46.71	174[b]	170[b]
n-$C_4H_9OCH_2CH_2COO.C_4H_9$-$n$	97	6	1.4190	0.9109	56.30	56.00	202[b]	198[b]

[a] Data for hydracrylates in Table I. [b] Saponification equivalents.

Methyl β-(β-Methoxypropionoxy)-propionate.—Combined distillation residues (77 g.) from acid catalyzed experiments with methanol were distilled through a short column. Only one fraction could be collected before pyrolysis set in. This fraction was methyl β-(β-methoxypropionoxy)-propionate; b. p. 86° (1.5 mm.), wt. 29.4 g., $n^{25}D$ 1.4260.

Anal. Calcd. for $C_8H_{14}O_5$: C, 50.51; H, 7.37; mol. wt., 190; sapn. equiv., 95. Found: C, 50.58; H, 7.37; mol. wt. (ebullioscopic in benzene), 187; sapn. equiv., 94.

Summary

The base catalyzed reaction of β-propiolactone with alcohol is rapid and results in hydracrylates. Without added catalysts, alkoxy acids are slowly formed. The acid catalyzed reaction gives alkoxy acids by direct reaction and hydracrylates by alcoholysis of poly-ester acids formed in the competing polymerization of the lactone. The effects of time, temperature and catalyst concentration on the proportions of products in the mixture are demonstrated.

BRECKSVILLE, OHIO

RECEIVED JULY 21, 1947

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

Evidence of an Induction Period in the Alkylation of Isobutane by 2-Butene

BY T. D. STEWART AND WILLIAM H. CALKINS

The reaction between isobutane and 2-butene at 0° in the presence of 96% sulfuric acid is not extremely rapid. This may be shown by passing 2-butene gas at a constant rate into a stirred mixture of sulfuric acid and isobutane. In our experiments the isobutane was initially at atmospheric pressure; the isobutane consumption was measured by observing the input of isobutane required to maintain a constant pressure in the reactor. Figure 1 shows the observations made during a typical experiment.

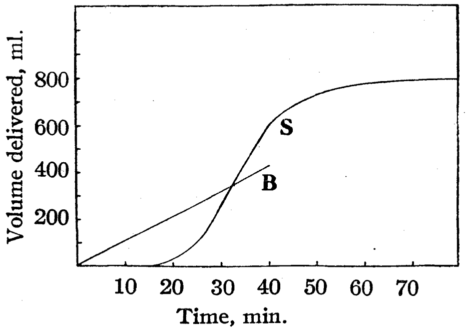


Fig. 1.—Rate of consumption of isobutane (S) gas produced by the addition of 2-butene (B) gas at a constant rate, in sulfuric acid.

At first little or no isobutane is consumed. After about twenty minutes, during which about 200 ml. of 2-butene has been introduced, the consumption of isobutane approaches a constant rate. When the 2-butene supply is shut off the consumption of isobutane continues for over an hour. These periods will be referred to as the induction period, the steady state period and the terminal reaction period, respectively. When the steady state is established the rate of consumption of isobutane is two to three times that of 2-butene. The best yields of alkylate accompanied the higher ratios. An approximate calculation shows that if the alkylation reaction involves a ratio of unity and if the condensed isoöctanes dissolve the expected amount of isobutane, a ratio of about three should be observed. Any ratio less than that involves polymerization or other consumption of 2-butene apart from alkylation.

The reaction studied is a complex one leading to a variety of products.[1a,b,c] Under the conditions

(1) (a) S. H. McAllister, J. Anderson, S. A. Ballard and W. E. Ross, *J. Org. Chem.*, **6**, 647 (1941), list two main fractions of trimethylpentanes and some 2,3-dimethylbutane from the reaction catalyzed by sulfuric acid. (b) L. Schmerling, THIS JOURNAL, **68**, 275 (1946), lists nineteen products from the reaction catalyzed by aluminum chloride. (c) M. H. Gorin, C. S. Kuhn and C. B. Miles, *Ind. Eng. Chem.*, **38**, 795 (1946), list six fractions from the reaction catalyzed by hydrogen fluoride.

described here, a poor yield of liquid alkylate is obtained prior to establishment of the steady state; but if a liter or more of the alkene is used up, and the reaction is allowed to run to saturation with the isobutane, a good yield (5–6 ml. per liter of gaseous alkene) of alkylate can be obtained. About half of the alkylate distils above the isoöctane range. For present purposes the initial predominating net reaction will be considered to be

$$C_4H_8(\text{gas}) + C_4H_{10}(\text{gas}) \xrightarrow{H_2SO_4} C_8H_{18} \text{ (liquid and dissolved } C_4H_{10})$$

and attention centered upon the factors which start the series of events leading to the formation of the actual products.

The Rate of Solution of 2-Butene.—It was necessary to know the instantaneous partial pressure of 2-butene in the reactor during introduction of the gas. This was observed with the reactor filled with nitrogen gas. As the flow of 2-butene was started the pressure in the reactor rose from five to twenty mm., depending upon the rate of flow of the 2-butene. A rise of 1 mm. of pressure corresponded to about 1 ml. of gas. This increase in pressure does not represent merely an accumulation of 2-butene as gas in the reactor, however, since whenever the flow of 2-butene was stopped the decrease in pressure was only 1–3 mm., and was complete in about one minute. Part of the permanent pressure increase, after starting and stopping the 2-butene, was eventually shown to be mechanical, *i. e.*, some 2-butene lodged in the manometer line. The remainder was due to an actual evolution of isobutane, produced through dismutation of the alkene, and will be dealt with separately. A pressure increase would operate to delay an apparent consumption of isobutane during alkylation, since isobutane entered the system only as a result of pressure drop. However, delay from this cause was a minor effect, inasmuch as the isobutane consumption eventually reached 20–30 ml. per minute; the observed induction is therefore extended by not more than one minute by this gas accumulation. Neither is the apparent induction due to slowness in the rate of solution of the 2-butene.

The Steady State Concentrations.—The delay in apparent isobutane consumption could have been due merely to a low specific reaction rate, in which case a finite concentration of 2-butene in the system would have to be built up before a steady-state condition would be reached. Experiments were accordingly made in which a part of the 2-butene was introduced rapidly, followed by a waiting period, with finally the usual slow addition of the alkene at a constant rate. Such a course is plotted in Fig. 2. It is seen that the isobutane consumptions of Figs. 1 and 2 are similar; the rate of reaction is not dependent merely upon the amount of 2-butene present but involves the production of a steady-state concentration of some intermediate compound.[2] The type of experiment shown in Fig. 2, which arrived at a given steady-state condition through a variation in the time of input of a critical amount of reactant, was performed many times and never failed to show a period of induction.

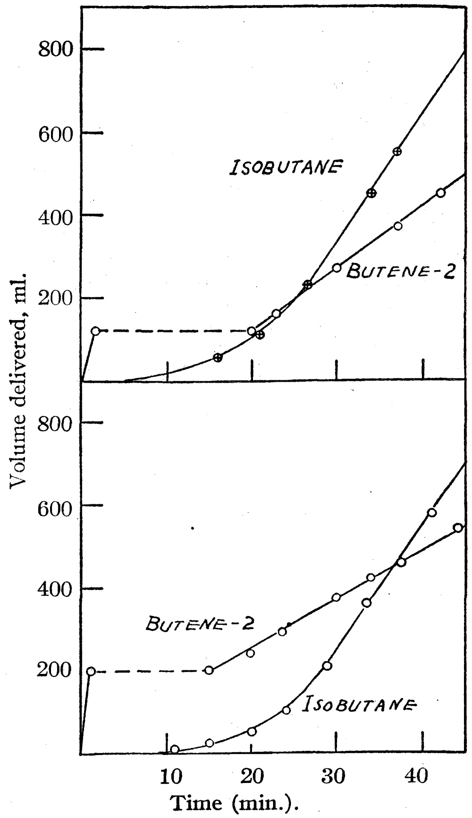


Fig. 2.—Rate of consumption of isobutane gas with interrupted addition of 2-butene.

Factors Affecting the Induction Period.—The length of the induction period may be varied by changing the rate of introduction of 2-butene and the amount of sulfuric acid present in the reactor. Table I presents some typical data.

TABLE I

INDUCTION PERIOD AS A FUNCTION OF RATE OF BUTENE INPUT

Volume acid, ml.	Rate of butene-2 input, ml./min.	Induction period, min.
25	7.5	35
25	7.5	32
25	10	25
25	13	18
25	24	18
25	30	15
100	10	40
100	12	38
100	30	22

---

(2) We see no evidence for the assumption that removal of inhibitors is responsible for the induction period.

It is seen that with increasing rate of input with either 25 ml. or 100 ml. of catalyst present, the induction time is decreased; a three-fold increase in rate of alkene input about halves the induction period. The four-fold increase in acid at a given rate of input less than doubles the induction period. It is evident that isobutane consumption is not related to a concentration of accumulated 2-butene as such; at the lower rates of input the time available for production of the critical intermediates tends to shorten (relatively) the induction period. Both a time and a concentration factor are required for the production of the steady-state condition.

The addition of about 0.005 mole of secondary butyl alcohol shortened the induction period from twenty-five minutes to seventeen minutes, but a similar amount of *t*-butyl alcohol more than halved the induction period (Fig. 3). The reaction of isobutylene with isobutane passes through a similarly shortened induction period.

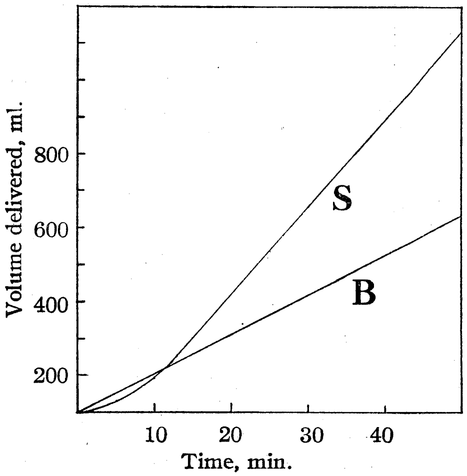


Fig. 3.—The effect upon the induction period of added *t*-butyl alcohol: S, isobutane; B, butene-2.

The presence of liquid alkylate made no difference in the length of the induction period. This was shown in two ways. A sample of the alkylate was recovered by steam distillation from the diluted contents of the reactor; after drying, this sample was added to fresh sulfuric acid in the reactor, with the same result as in the absence of the alkylate. In other cases the 2-butene was shut off, and saturation of the system with isobutane was started. In varying times after cessation of the flow of the alkene, a new run was started. The length of the new induction period depended upon the time of saturation. After two hours the used catalyst behaved as fresh catalyst and the induction period was normal; after one hour of saturation the induction period was about half of normal (see Table II). After twenty minutes the consumption of isobutane was slow but readmission of 2-butene was accompanied by only a short induction period.

Table II

Comparison of the Induction Periods in Fresh and Used Catalyst; the Effect of Saturation Time

Rate of butene input, ml./min.	Time of saturation, min.	Induction period	
		Used acid	Fresh acid
5	19	10	Long
7.5	35	15	32
10	42	15	25
8	50	16	30
16	100	16	18
11	120	18–20	20

Apparently a long-lived intermediate reacts with isobutane and also promotes establishment of the steady state condition.

The induction period was not affected by the partial pressure of the isobutane. In one experiment, using 25 ml. of sulfuric acid, the reactor was filled with equal partial pressures of nitrogen and isobutane, and the 2-butene introduced at 10 ml./min. The induction period was twenty-five minutes. In this case the ratio of isobutane to 2-butene during the steady state was about 1.5, since, at the reduced partial pressure of the isobutane, less of the alkane dissolved in the alkylate.

Discussion of Results.—A mechanism of the type suggested by Schmerling[1b] lends itself to an explanation of an induction period in the reaction studied. The essential feature of this mechanism is based upon the fact that isobutane acts as a reducing agent upon certain carbinol derivatives in the presence of alkylation catalysts.[3] In so doing it is oxidized to the *t*-butyl derivative.

$$(CH_3)_3CH + R'X \xrightarrow{\text{catalyst}} (CH_3)_3CX + R'H$$

The latter reacts with the alkene component of the alkylation, under the influence of the catalyst, to produce RX, which is reduced by isobutane either before or after isomerization to a form R'X.

$$C_nH_{2n} + (CH_3)_3CX \longrightarrow RX \text{ and } R'X \xrightarrow{\text{iso-}C_4H_{10}} RH \text{ and } R'H + (CH_3)_3CX$$

The intermediates RX and R'X may be considered as solvated carbonium ions, R^+ and R'^+ as outlined by Bartlett and co-workers.[3] The multiplicity of products is accounted for by side reactions and by the multiplicity of possible rearrangement products and their specific reaction rates toward isobutane, 2-butene and cracking. The reaction of isobutane, however, rests upon the above transhydrogenation with these intermediates, the concentrations of which are initially zero and reach a steady state value as 2-butene is introduced. The rate-determining step[4] in the

---

(3) See also Ciapetta, *Ind. Eng. Chem.*, **37**, 1210 (1945); Paul D. Bartlett, Francis E. Condon and Abraham Schneider, This Journal, **66**, 1531 (1944); L. Schmerling, *ibid.*, **66**, 1422 (1944).

(4) An editorial referee points out that the main reactions occurring during the induction period are of the type classified by Ipatieff and Pines (*J. Org. Chem.*, **1**, 464 (1936)) as conjunct polymerization. This is polymerization accompanied by *trans*-hydrogenation and results in saturated and unsaturated hydrocarbons; the latter are considered to undergo transhydrogenation with isobutane; the

formation of the final products could be a reaction rearrangement. The time required to approach steady-state conditions is largely independent of the activity of the isobutane, but is influenced by the rate of input of 2-butene, by the stirring and by the amount of catalyst. The steady-state concentration of a *t*-butyl derivative can be approached by adding *t*-butyl alcohol or isobutylene; otherwise it is built up by isomerization of the normal butene or through transhydrogenation reactions involving polymers of 2-butene and isobutane.

Further evidence pointing toward the viewpoint outlined above is observed in a study of the kinetics of the terminal reaction which will be reported separately.

Apparatus and Materials.—The reactor vessel was a 500-ml. three-necked flask fitted with a separatory funnel and a Hershberg-type stirrer made of nichrome wire. The stirrer shaft was housed in a vacuum and pressure tight bearing; the stirrer was of such size that it was not completely covered by 25 ml. of sulfuric acid but was completely covered by 100 ml. of acid. At the bottom of the flask a glass capillary tube, which carried a stopcock, was sealed in. The reactor could be filled, emptied, and washed without disturbing any of the connections; it was surrounded by a metal tub which held cracked ice and water. The degree of agitation could be varied; normally there was violent spattering of the liquid phase.

Into an opening of the reactor was passed one arm of a T-tube; a second arm was connected to a mercury manometer, while the third arm was used to lead in the desired gases. The isobutane and 2-butene were stored over 85% phosphoric acid under a hydrostatic head held constant automatically. The 2-butene line contained a pump designed to deliver gas at small, constant, rates of flow even against minor changes in pressure; the pump was bypassed by a line used for rapid delivery of 2-butene. The flow of isobutane was controlled by an automatic gas valve which was actuated by a mercury manometer connected to the line of the main manometer. The gas pressure in the isobutane gasometer was always constant and essentially the same as the total pressure in the reactor, since rates of flow were low.

A typical procedure involved testing for leaks under both vacuum and pressure; evacuation of the reactor to less than 1 cm. pressure; delivery of the desired amount of 96% sulfuric acid to the cooled reactor; flushing out and filling the reactor with isobutane gas; stirring to assure saturation of the sulfuric acid and adjusting the pressure; starting the 2-butene pump and thereafter recording the delivered volume of the two gases.

The sulfuric acid used was Baker and Adamson C.P. 96% acid. The 2-butene and isobutane were of highest purity, supplied by the Shell Development Co., Emeryville, California. Several different batches, of better than 99% purity, gave the same results.

Acknowledgment.—We wish to acknowledge the assistance of the Shell Development Co. in furnishing the pure isobutane and 2-butene for this investigation. We are also indebted to Miss Eva Herzberg, of this Laboratory, whose preliminary work suggested the existence of an induction period in the reaction studied.

Summary

Gaseous 2-butene was passed at a constant slow rate into a vessel filled with isobutane and containing vigorously stirred 96% sulfuric acid at 0°. The 2-butene dissolved rapidly without reaction of the isobutane; after from ten to twenty-five minutes, consumption of isobutane started and from then on the ratio of the two gases consumed was constant. The length of the induction period was largely independent of the time required to introduce a given amount of 2-butene, and was not affected by the presence or absence of an oil phase initially. It was affected by the rate of continued addition of the alkene, by the amount of acid present, and by the addition of small amounts of *t*-butyl alcohol. It is concluded that steady state concentrations of intermediate compounds develop during an inhibition period, consisting of (1) *t*-butyl derivatives, which react with the incoming 2-butene, and (2) the products of that condensation, which undergo transhydrogenation with isobutane, in accordance with Schmerling's mechanism.

BERKELEY, CALIFORNIA RECEIVED AUGUST 7, 1947

---

former conceivably dealkylate and the resulting alkene portions also engage in transhydrogenation. The initial rate of reaction of isobutane, he considers, "may be dependent on the actual concentration of olefinic polymer present, and the rate of transhydrogenation of isobutene with the polymers of 2-butene and also the rate of the dealkylation reaction." These factors would be influenced by the experimental conditions and "would not require the assumption of long-lived intermediates of the carbonium type." The point at issue seems to be whether a single course is set for the whole reaction at the start, or whether, after some time, a new course develops which finally predominates. If there is a single path followed from the start, then our induction period is an accident of the experimental conditions, and, we feel, would not be so little influenced by changes in those conditions. But if the Schmerling mechanism operates during our steady state, and is self-perpetuating, then the major, if not only, role of conjunct polymerization is that of a side-reaction which aids in producing a critical intermediate.

The reactions of dealkylation are not observable, nor do they seriously affect the observed rate during the steady state. This is because they are slow compared to the major reaction and are likely to generate as much isobutane as they consume. If the steady-state reaction does not depend largely upon either conjunct polymerization or dealkylation, but rather upon transhydrogenation of products formed from 2-butene and a tertiary butyl derivative present in small amount, there remains in question the identity of the rate-determining step during the steady-state reaction.

[CONTRIBUTION FROM THE SCRIPPS METABOLIC CLINIC]

The Inhibition of D-Amino Acid Oxidase by Benzoic Acid and Various Monosubstituted Benzoic Acid Derivatives

BY GRANT R. BARTLETT

Benzoic acid has been reported to give a marked and selective inhibition of the enzyme D-amino acid oxidase.[1] This inhibition is apparently due to a reaction with the activating protein rather than with the flavine-nucleotide prosthetic group, and involves a competitive reversibility with substrate amino acid.[1,2]

In this paper enzyme inhibition is used as a tool to study the influence of ring substitution on the reaction between benzoate and amino acid oxidase protein. There is also presented a more rigorous proof of the substrate competitive nature of the benzoate inhibition and more information on the specificity of the reaction.

Experimental

The D-amino acid oxidase preparation was essentially that described by Krebs.[3]

Pig kidney acetone powder was extracted with five volumes of water in a Waring Blendor, centrifuged and the supernatant lyophilized. The dry powder retains its activity for at least six months at room temperature. Enzyme activity was assayed by oxygen consumption with DL-alanine as substrate in standard Warburg manometric equipment. Unless otherwise specified, conditions were as follows: 1.0 ml. containing 10 mg. of lyophilized pig kidney extract, 0.5 ml. 0.2 *M* *p*H 7.6 pyrophosphate buffer, 0.3 ml. of 0.3 *M* DL-alanine added from side arm at −3 min., 0.3 ml. of inhibitor solution, water to 3.0 ml. total volume in main part of vessel, 0.2 ml. of 20% potassium hydroxide in center cup, air as gas phase, oxygen consumption measured from 0 to thirty minutes, temperature 38°. Substrate, inhibitor and other solutions were neutralized before adding to vessels.

To check the degree of inhibition each benzoate was tested at 10^{-2}, 10^{-3}, 10^{-4}, and 10^{-5} molar concentrations. Inhibitory values between 10 and 90%, when plotted against the log of the inhibitor concentration fell on a straight line. There was some deviation at each end of the curve. The slopes for all benzoates tested were identical; 50% inhibition values were calculated from the log benzoate–per cent. inhibition curves. A typical analysis is given in Table I, demonstrating the relationship of inhibitory capacity to concentration of benzoate and showing the reproducibility of data obtainable with two different enzyme preparations.

TABLE I

SAMPLE ANALYSIS. INHIBITION OF D-AMINO ACID OXIDASE BY *p*-TOLUIC ACID[a]

Exp.	Concn. of *p*-toluic	µl. O_2 consumed per 30 min.	% Inhib.
1	0	170	...
	10^{-5} *M*	169	0
	10^{-4} *M*	122	28
	10^{-3} *M*	32	81
	10^{-2} *M*	0	100
2	0	178	...
	10^{-5} *M*	178	0
	10^{-4} *M*	126	29
	10^{-3} *M*	38	79
	10^{-2} *M*	0	100

Calcd. 50% inhibition: 2.5×10^{-4} *M*

[a] Warburg manometric analyses, see text for details.

All benzoates used were commercial products, which when necessary were recrystallized until melting points and titration equivalents checked with accepted values. *o*-Fluorobenzoic acid was kindly supplied by Dr. M. Kilpatrick. The author is indebted to Mr. and Mrs. Francis E. Fowler, Jr., and members of their family, whose generosity has made these studies possible. The helpful encouragement and advice of Dr. E. M. MacKay is gratefully acknowledged.

Results and Discussion

Benzoic acid inhibited D-amino acid oxidase approximately 50% at 10^{-4} *M*, less than 10% at 10^{-5} *M*, and more than 90% at 10^{-3} *M*; see Table II for 50% inhibition values for benzoic acid and a number of ring monosubstituted derivatives. A wide variety of other enzyme systems were inhibited less than 10% by the relatively high benzoate concentration of 10^{-2} *M*; oxidation of acetate by baker's yeast, hydrolysis of edestin by pepsin, decarboxylation of pyruvate by dried brewer's yeast, hydrolysis of acetylcholine by serum, hydrolysis of urea by urease, glycolysis of hexosediphosphate by muscle acetone powder, hydrolysis of monobutyrin by liver esterase, decomposition of hydrogen peroxide by catalase, and oxidation of succinate, choline, uricate and tyramine by a minced, washed rat liver preparation. These results provide a more extensive verification of Klein and Kamin's[1] observations on the highly selective action of benzoate toward D-amino acid oxidase.

From the viewpoint of structural similarity one would not expect benzoate to compete reversibly with the substrate amino acid. However, such a relationship does occur. Concentrations of D-alanine from 0.0032 to 0.316 *M* were tested with 10^{-3} and 10^{-4} *M* benzoate. In Fig. 1, the per cent. inhibitions are plotted against the log concentration of D-alanine. At all ratios of alanine to benzoate there was strict reversible competition. The inhibition is independent of the absolute amount of benzoate and a function of the ratio of alanine to benzoate. Fifty per cent. inhibition results at a ratio of D-alanine to benzoate of 100 to 1. High concentrations (0.1 *M*) of potassium chloride, glycine or of L-alanine had no reversing effect on the inhibition of the oxidation of D-alanine by benzoate. Glycine and L-amino acids are not acted upon by the enzyme nor do they affect the oxidation of D-amino acids. The competition

---

[1] Klein and Kamin, *J. Biol. Chem.*, **138**, 507 (1941).

[2] Hellerman, Lindsay and Bovarnick, *ibid.*, **163**, 553 (1946).

[3] Krebs, *Biochem. J.*, **29**, 1620 (1935).

experiments prove that substrate displacement adequately accounts for the inhibition: probably both substrate and inhibitor having a high affinity for the same position on the protein.

Various other compounds were tested in order to give some definition of the relationship of structure to enzyme inhibition. Phenyl carboxylate ion proved to be the essential structural unit. At the *p*H of the test system more than 99% of any of the benzoates used would exist as carboxylate ion. Substitutions on carboxyl, replacement of carboxyl by another acidic radical, replacement with alkyl carboxylates, all resulted in negative activity. For example, the following compounds gave less than 10% inhibition at 10^{-2} *M* concentrations: benzamide, ethyl benzoate, phenyl acetate, phenyl propionate, mandelate, sulfanilate, phenyl phosphate, benzenesulfonate.

Although alteration of carboxyl completely destroys the toxicity, ring substitution results in a wide variation in the inhibiting capacity, probably by altering the electron configuration at carboxyl carbon or in the case of *ortho* substituents, giving rise to steric hindrance. The inhibiting power of a series of monosubstituted benzoates is given in Table II. The following points can be emphasized. Except for hydroxy and amino, *meta* gives the greatest inhibition, *para* is intermediate and *ortho* is very low. With hydroxy and amino there is not a marked *ortho* effect, the *para* position giving the lowest inhibitions. In general, halogen, methyl and nitro are stronger inhibitors than hydroxy, amino, methyl and a second carboxyl. The dicarboxylic acids give practically no inhibition. The halogens show a striking series of increasing inhibition in order of increasing electronegativities. *Ortho* substitution apparently blocks access of phenyl carboxylate to the reacting position on protein. It is felt that this can best be looked upon as a geometrical steric hindrance following the notions originally postulated by Victor Meyer for the *ortho* blocking of esterification of benzoates. No analysis will be given here of the relationship of structure to the benzoate protein reaction in terms of current notions on the influence of inductive and resonance effects. However, it is suggested that the quantitative data on the monosubstituted benzoates should provide an interesting series for checking such theories.

TABLE II

THE REACTIVITY OF MONOSUBSTITUTED BENZOIC ACIDS TOWARD D-AMINO ACID OXIDASE

Benzoic acid 1.2×10^{-4} [a]

Substituent group	Ring position *Para*	*Meta*	*Ortho*
I	1.8×10^{-3}	1.6×10^{-4}	1.0×10^{-2}
Br	2.8×10^{-4}	3.1×10^{-5}	3.3×10^{-2}
CL	1.6×10^{-4}	1.6×10^{-5}	5.0×10^{-3}
F	4.0×10^{-5}	....	1.0×10^{-3}
CH_3	2.5×10^{-4}	4.0×10^{-5}	3.3×10^{-2}
NO_2	3.6×10^{-4}	2.5×10^{-4}	1.7×10^{-2}
OH	5.0×10^{-3}	2.2×10^{-4}	6.3×10^{-4}
NH_2	1.0×10^{-2}	1.0×10^{-3}	1.0×10^{-3}
OCH_3	2.2×10^{-3}	1.8×10^{-3}	3.3×10^{-2}
COOH	1.0×10^{-2}	3.3×10^{-2}	5.0×10^{-2}

[a] Figures represent the molar concentration giving 50% inhibition.

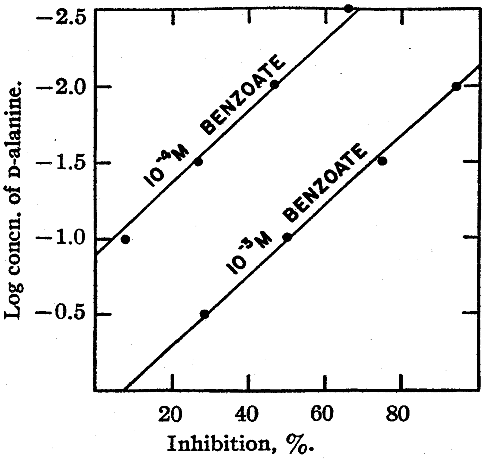


Fig. 1.—Substrate competitive nature of the inhibition of D-amino acid oxidase by benzoate.

Summary

Benzoate was incubated with a variety of enzyme systems and found to be highly specific for inhibiting D-amino acid oxidase.

Benzoate and D-alanine showed a reversible competition for protein over a wide range of concentrations, 50% inhibition of enzyme resulting at a ratio of alanine to benzoate of 100 to 1.

Phenyl carboxylate proved to be the essential structural unit necessary for the D-amino acid oxidase inhibition. Quantitative data is given on the affinities for D-amino acid oxidase of a number of ring monosubstituted derivatives of benzoic acid.

LA JOLLA, CALIFORNIA

RECEIVED AUGUST 9, 1947

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

Quinolines. V. Some Polysubstituted 4-(4′-Diethylamino-1′-methylbutylamino)-quinolines[1]

BY EDGAR A. STECK, LOUIS L. HALLOCK, ARNOLD J. HOLLAND AND LYNN T. FLETCHER

Chloroquine (SN 7618, 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-quinoline)[2,3] has been found to be the most effective of the quinoline antimalarials bearing the basic chain in position 4. In our program, which has involved the preparation of numerous analogous compounds bearing an alkyl group in the pyridine moiety,[4] we have attempted to evaluate the influence of the position and nature of several groups upon antiplasmodial activity. The 4-(4′-diethylamino-1′-methylbutylamino)-quinolines here discussed will include all possible bz-fluoro-3-methyl types, 3,6,5/7-trimethyl, 7-chloro-2-methyl, and also the 5/7-chloro-3-propyl.

As in our previous work,[4] the fundamental plan of synthesis was based upon the Conrad–Limpach synthesis, employing several recent modifications in the technique of cyclization. The bz-fluoro-3-methylquinoline series were obtained from the requisite fluoroanilines by reaction with ethyl α-ethoxalylpropionate. To separate the ethyl 5/7-fluoro-4-hydroxy-3-methylquinoline-2-carboxylates, which were prepared from *m*-fluoroaniline, fractional crystallization was required (*cf.* 4 c,d). Oxidation of the acids derived from the esters (which had been crystallized to constant m. p.) by use of alkaline permanganate solution was unexpectedly difficult. No pure specimens of the oxidation products from either series could be identified with certainty as 4-fluoroanthranilic acid,[5] and the attempt was abandoned. The series giving rise to the higher melting 4-chloro compound, was designated as the 7-fluoro type; the parent ester was not only the higher-melting of the two, but, more characteristically, less soluble in alcohol. The earlier experiences with the other isomeric 5/7-halo-3-methylquinolines[4c,d] have formed the basis for this decision. Separation of the ethyl 3,6,5/7-trimethyl-4-hydroxyquinoline-2-carboxylates by crystallization from alcohol was not attended by noteworthy difficulties. The attempts to prove conclusively the location of the 5/7-methyl group by oxidative means were not successful. Intractable mixtures of high-melting materials (polycarboxylic acids?) resulted. It was necessary to resort to an arbitrary designation of structure upon the above-noted basis.

The investigations of Strukov (1932), which were referred to by Gal'perin,[6] indicated a lack of antimalarial activity among several quinaldine types, but disagreement[7,8] or lack of testing data[9,10] concerning similar compounds led to interest in 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-quinaldine. Although it was expected[4c,d] that application of the Conrad–Limpach procedure to *m*-chloroaniline and ethyl acetoacetate would lead to both 5- and 7-chloro-4-hydroxyquinaldine, such was not the case. Despite careful study, only one discrete compound could be isolated. Oxidation with alkaline permanganate[4c] led to 4-chloroanthranilic acid, hence the product was proven to be the 7-chloro isomer. Price, *et al.*,[11] prepared 7-chloro-4-hydroxyquinaldine by this method, but a proof of structure was lacking. Conversion of the 4-hydroxy compound to the desired base was accomplished in the usual manner.

The application of the Conrad–Limpach procedure to *m*-chloroaniline and ethyl α-ethoxalylvalerate[12] was designed to yield a series of 5- and 7-chloro-3-propylquinolines. This investigation was hampered by poor yields, as in the preparation of the β-keto ester and its cyclization to the quinoline derivatives, and the tedious fractional crystallization required for the isomer separation. The fraction having the lower solubility in alcohol was demonstrated to be ethyl 7-chloro-4-hydroxy-3-propylquinoline-2-carboxylate through oxidation of its derived acid.

Of the bz-fluoro-4-(4′-diethylamino-1′-methylbutylamino)-3-methylquinolines which were tested, none showed activity comparable to the related chloro compound. Neither 4-(4′-diethylamino-1′-methylbutylamino)-3,5,6-trimethylquinoline nor its 3,6,7-trimethyl isomer exhibited marked antiplasmodial action. Although 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-quinaldine did show promise at first, its toxicity was unfavorable. This behavior was of interest because several other quinaldine types had not been of particular value.[6,8] Insufficient amounts of the bases of the 5/7-chloro-3-propylquinoline compounds were available for testing. Most of the antimalarial tests were carried out under the direction

---

(1) A portion of this paper was presented before the 109th meeting of the A. C. S. in Atlantic City, N. J., April 9, 1946.

(2) (a) Andersag, Breitner and Jung, U. S. Patent 2,233,970; (b) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(3) Loeb, *et al.*, *J. Am. Med. Assoc.*, **130**, 1069 (1946).

(4) Steck, Hallock and Holland, THIS JOURNAL, **68**, (a) p. 129 (1946); (b) p. 132; (c) p. 380; (d) p. 1241.

(5) Steck and Fletcher, *ibid.*, **70**, 439 (1948).

(6) Gal'perin, *Med. Parasitol. Parasitic Diseases* (*U. S. S. R.*), **7**, 1896 (1937); *Am. Rev. Soviet Med.*, **1**, 220 (1943–1944).

(7) Krichevskii, Shternberg and Gal'perin, *J. Microbiol., Epidemol. and Immunobiol.* (*U. S. S. R.*), **14**, 642 (1935).

(8) Holcomb and Hamilton, THIS JOURNAL, **64**, 1309 (1942).

(9) Van Arendonk and Shonle, *ibid.*, **66**, 1284 (1944).

(10) Kermack and Smith, *J. Chem. Soc.*, 356 (1930).

(11) Price, Leonard and Reitsema, THIS JOURNAL, **68**, 1259 (1946).

(12) Steck and Holland, *ibid.*, **70**, 440 (1948).

TABLE I

BZ-FLUORO-3-METHYLQUINOLINE DERIVATIVES

					Analyses, %					
					Calcd.			Found		
Compound	Yield, %[a]	Appearance	Solvent[b]	M. p.[c]	C	H	N	C	H	N
		Ethyl Bz-Fluoro-3-methyl-4-hydroxyquinoline-2-carboxylates								
5-F	45[d,e]	Yellowish needles	E	198–199	62.64	4.84	5.62	62.87	4.84	5.44
6-F	89[d]	White platelets	aAc	233.5–234				62.36	4.61	5.68
7-F	53[d,e]	White needles	E	224.5–225				62.60	4.78	5.73
8-F	80[d]	Creamy needles	aE	133–135				62.33	5.19	5.81
		Bz-Fluoro-3-methyl-4-hydroxyquinoline-2-carboxylic Acids								
5-F	92	White needles	E	240D	59.73	3.65	6.33	59.86	3.69	6.44
6-F	97	Yell.-white microcryst.	P	255–255.5D				59.91	3.75	6.06
7-F	94	White needles	E	246D				59.77	3.72	6.45
8-F	93	Creamy needles	E	222–223D				59.93	3.56	6.40
		Bz-Fluoro-3-methyl-4-hydroxyquinolines								
5-F	96	White needles	I	>275	67.79	4.55	7.90	68.11	4.52	7.96
6-F	96	White prism.-needles	E	281–282				67.75	4.39	7.77
7-F	95	White prisms	E	288				67.89	4.47	7.83
8-F	92	White tablets	a	216–217				68.02	4.73	8.08
		Bz-Fluoro-3-methyl-4-chloroquinolines								
5-F	95	White leaflets	aM	70–71	61.39	3.61	7.16	61.16	3.99	7.65
6-F	92	White needles	Sk	57.5–58				61.45	3.52	7.39
7-F	94	White needles	aM	88.5–89				61.48	3.81	7.20
8-F	88	White needles	Sk	101–102				61.26	3.55	7.06
		Bz-Fluoro-3-methylquinoline derivatives Bz-Fluoro-3-methyl-4-(1′-methyl-4′-diethylaminobutylamino)-quinolines								
5-F	88	Bright yellow oil[g]		185–188/0.6[f]	71.88	8.89	13.24	72.14	9.02	12.93
6-F	80	Golden oil		160–162/0.1[f]				72.11	8.83	13.53
7-F	80	Bright yellow oil[h]		205–210/1[f]				72.07	9.31	12.98
8-F	83	Lemon oil		162–164/0.2[f]				72.13	8.89	13.30

[a] Not purified, as used for next step. [b] Legend: Ac = acetone, E = ethanol, I = propanol-2, M = methanol, P = propylene glycol, Sk = Skellysolve A, a = aqueous. [c] Uncorrected, °C. D = decomposes. [d] Yields obtained upon cyclization of crude azomethines (75–88% yields). [e] The yields of isomeric esters are those produced by the separation of crude mixtures, which were formed in 85–90% yields. [f] B. p., °C. (mm.). [g] Converted into the methane-*bis*-1,1′-(2-hydroxy-3-naphthoate) by precipitation from hydrochloric acid solution with the sodium salt of the organic acid; yellow powder, m. p. >300°. *Anal.* Calcd. for $C_{19}H_{28}FN_3 \cdot C_{23}H_{16}O_6 \cdot 2H_2O$: base, 42.79; H_2O, 4.86. Found: base, 43.34; H_2O, 5.23; SN 8798-S1. [h] As [g], yellowish powder, m. p. >300°. Found: base, 43.06; H_2O, 4.85; SN 8797-S1.

of the National Research Council, and the data have been tabulated.[13]

Experimental

Fluoroanilines.—The fluoronitrobenzenes were prepared from the corresponding nitroanilines by the method of Schiemann.[14,15] Conversion of the diazonium borofluorides, which were obtained in 92–99% yields, into the fluoronitrobenzenes was best accomplished by mixing the salts with sand before decomposition. The yield of pure *o*-fluoronitrobenzene was 11–16%; *m*-, 48–51%; *p*-, 40–49%. Neutral iron reduction[16,4c] of the nitro compounds led to yields of 72–83% of the corresponding fluoroanilines.

Ethyl α-ethoxalylpropionate and ethyl α-ethoxalylvalerate were prepared as described in previous contributions.[4a,12]

Bz-Fluoro-3-methylquinoline Series.—The general pattern of synthesis for the isomeric bz-fluoro-3-methylquinolines was that earlier described by us.[4] Separation of the 5/7-fluoro compounds, obtained from *m*-fluoroaniline, was accomplished by fractional crystallization from alcohol. The isomer which was the less soluble (designated as the 7-fluoro, see discussion) of higher m. p., was considerably more facile of purification. In Table I are the data relative to the several series. Distillation of all the 4-(4′-diethylamino-1′-methylbutylamino)-bz-fluoro-3-methylquinolines was tedious.

3,6,5/7-Trimethylquinoline Series.—3,4-Dimethylaniline[17] was employed in the preparation of the trimethylquinoline derivatives. The isomeric esters were fractionally crystallized from alcohol and each obtained pure with fair ease; the lower-melting isomer was the more soluble of the two. Unequivocal designation as to structures could not be made, as noted in the discussion. The data presented in Table II relate to the compounds of this series.

7-Chloro-4-(4′-diethylamino-1′-methylbutylamino)-quinaldine.—Only one compound was obtained from the reaction of *m*-chloraniline with ethyl acetoacetate after the method of Conrad and Limpach. An oxidation of the 4-hydroxy compound by permanganate (*cf.* ref. 4c) demonstrated that the chlorine was in position 7, as shown in Table III, wherein the several quinaldines are described.

5/7-Chloro-3-propylquinoline Series.—The use of ethyl α-ethoxalylvalerate[12] as the β-keto ester in the usual

---

[13] Wiselogle, editor, "Antimalarial Drugs, 1941–1945," Edwards Bros., Ann Arbor, Mich., 1946. All drugs identified by Survey Numbers (SN) in the files of the Antimalarial Survey office have been systematically tabulated in this work, together with the antimalarial activities.

[14] Schiemann and Pilarsky, *Ber.*, **62**, 3035 (1929).

[15] Ruddy, Starkey and Hartung, THIS JOURNAL, **64**, 828 (1942).

[16] West, *J. Chem. Soc.*, 494 (1925).

[17] Purchased from Chas. Pfizer and Co., Inc.

Table II

3,5,6- and 3,6,7-Trimethylquinoline Derivatives

Compound	Yield, %[a]	Appearance	Sol-vent[b]	M. p.[c]	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ethyl Trimethyl-4-hydroxyquinoline-2-carboxylates										
3,5,6-Trimethyl	45[d]	Yellowish prisms	aE	183–184	69.48	6.61	5.40	69.74	6.59	5.39
3,6,7-Trimethyl	48[d]	White needles	aE	224–225				69.48	6.67	5.69
Trimethyl-4-hydroxyquinoline-2-carboxylic Acids										
3,5,6-Trimethyl	91	Yellow microcryst.	P	250–251D	67.52	5.66	6.06	67.24	5.81	6.37
3,6,7-Trimethyl	95	White needles	P	263–264D				67.32	5.83	6.01
Trimethyl-4-hydroxyquinolines										
3,5,6-Trimethyl	89	Whitish prisms	E	267–268	76.97	7.00	7.48	76.86	6.94	7.58
3,6,7-Trimethyl	91	Pale yellow needles	aE	>280				76.80	7.25	7.21
Trimethyl-4-chloroquinolines										
3,5,6-Trimethyl	90	White needles	Sk	67–68	70.07	5.88	6.81	70.14	5.64	6.94
3,6,7-Trimethyl	85	Creamy platelets	aE	106–107				70.08	5.73	6.85
Trimethyl-4-(4′-diethylamino-1′-methylbutylamino)-quinolines										
3,5,6-Trimethyl	70	Yellow oil		186–190/0.6[e]	77.06	10.15	12.80	76.88	10.29	13.20
3,6,7-Trimethyl	76	White needles	Sk	79.5–80				77.23	10.45	13.07
Trimethyl-4-(4′-diethylamino-1′-methylbutylamino)-quinoline salts										
3,5,6-Trimethyl B[f]	95	Pale yellow needles	E-I	162–162.5	46.52[g]			46.40[g]	0.05[h]	
3,6,7-Trimethyl M[i]	99	Yellow microcryst.		>300	45.63[g]			42.0[g]	1.80[h]	

[a], [b] and [c] as in Table I. [d] Yields of esters from crude cyclizate, which resulted in 86–92% yield from the azomethine (formed in 80–90% yields). [e] B. p., °C. (mm.). [f] Di-(2-hydroxy-3-naphthoate), formed in alcohol-propanol-2; SN 10988. [g] Per cent. base. [h] Per cent. water. [i] Methane *bis*-1,1′-(2-hydroxy-3-naphthoate), precipitated; SN 10437.

Table III

Py-Alkyl-5/7-Chloroquinoline Derivatives

Compound	Yield, %[a]	Appearance	Sol-vent[b]	M. p.[c]	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ethyl 5/7-Chloro-4-hydroxy-3-propylquinoline-2-carboxylates										
5-Chloro	45[d,e]	Whitish needles	aE	170.5–171	61.34	5.49	4.77	61.18	5.33	4.80
7-Chloro	50[d,e]	White prisms	aE	218–218.5				61.27	5.46	4.93
5/7-Chloro-4-hydroxy-3-propylquinoline-2-carboxylic Acids										
5-Chloro	96	Yellow needles	Ac	185–185.5D	58.54	4.54	5.25	58.68	4.30	5.59
7-Chloro	94	Creamy white needles	aE	205D				58.60	4.56	5.43
5/7-Chloro-4-hydroxy-py-alkylquinolines										
2-Me-7-Cl	81[d]	Creamy needles	aE	315–316[n]	62.03	4.17	7.24	62.13	4.32	7.44
3-Pr-5-Cl	89	White platelets	aE		65.01	5.46	6.32	65.02	5.40	6.41
3-Pr-7-Cl	93	White prismatic needles	E	276–276.5				65.31	5.91	6.58
4-5/7-Dichloro-py-alkylquinolines										
2-Me-7-Cl	87	White prisms	Sk	103.5–104	56.87	3.34	6.63	56.69	3.60	6.47
3-Pr-5-Cl	88	Colorless liq., n^{25}_{D} 1.6122		116–117(0.4)[f,g]	60.02	4.62	5.83	60.26	4.79	5.72
3-Pr-7-Cl	90	White needles	Sk	52–52.5[h]				60.00	4.53	5.94
5/7-Chloro-4-(4′-diethylamino-1′-methylbutylamino)-py-alkylquinolines										
2-Me-7-Cl	75	Bright yellow oil		206–210(0.8)[f]	68.40	8.46	12.62	68.22	8.94	12.94
3-Pr-5-Cl	63	Golden oil		173–175(0.2)[f]	69.68	8.91	11.61	69.98	8.91	11.79
3-Pr-7-Cl	60	Orange-yellow oil		200–202(0.4)[f]				69.88	8.84	12.09
5/7-Chloro-4-(4′-diethylamino-1′-methylbutylamino)-py-alkylquinoline Salts										
2-Me-7-ClS[i]	71	White needles	aE-I	147.5–149	35.59[k]	3.29[l]		36.02[k]	3.23[l]	
3-Pr-S-Cl P[j]	*ca.* 90	Bright yell. needles	aE	219–220			3.42[m]			3.36[m]
3-Pr-7-Cl P[j]	*ca.* 90	Lemon yell. needles	E	218–219						3.34[m]

[a] to [f] as in Table I. [g] The picrate crystallized (alc.) as yellow needles, m. p. 213.5–214°. *Anal.* Calcd. for $C_{18}H_{14}Cl_2N_4O_7$: N, 11.94. Found: N, 11.80. [h] As [g] m. p. 218.5–219°. Found: N, 12.10. [i] Disulfate monohydrate, SN 7135. [j] Picrate. [k] Sulfuric acid. [l] Water. [m] Basic N (determined by $HClO_4$ titration). [n] Price, *et al.*,[11] give m. p. 313.5–315°.

synthesis left much to be desired, for the first steps were accompanied by many difficulties. Considerable gum formation during the pyrolytic cyclization was responsible for much of the tediousness involved in the separation of isomers by fractional crystallization. Since there was but slight success in use of the method employed with the related 3-methyl type (*cf.* ref. 4c), fractionation was accomplished from alcohol, or, alternating, alcohol and aqueous acetone. The less soluble of the fractions was the 7-chloro isomer, for the bz-chloro-4-hydroxy-3-propylquinoline-2-carboxylic acid produced by its hydrolysis was oxidized to 4-chloroanthranilic acid by alkaline permanganate.[4c] An inadequate amount of the desired 5- and 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-3-propylquinolines was obtained for screening as antimalarials, but all pertinent information relative to them and intermediates required is given in Table III.

Acknowledgement.—The authors are pleased to have had the advantage of advice and encouragement from Drs. C. M. Suter and J. S. Buck during the course of these investigations. The analytical staff of the Institute, under the direction of Mr. M. E. Auerbach, has shown great patience and care in carrying out the many determinations required. Mrs. N. P. Gorman and Mrs. E. J. Altier have rendered further valuable technical assistance.

Summary

A group of 4-(4′-diethylamino-1′-methylbutylamino)-quinolines has been prepared, including all possible bz-fluoro-3-methyl derivatives, and also 3,6,5/7-trimethyl, 7-chloro-2-methyl and the 5/7-chloro-3-propyl types.

RENSSELAER, N. Y. RECEIVED SEPTEMBER 13, 1947

[CONTRIBUTION FROM THE GEORGE WILLIAMS HOOPER FOUNDATION, UNIVERSITY OF CALIFORNIA, AND THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Paralytic Shellfish Poison. I. Occurrence and Concentration by Ion Exchange[1,2,3]

BY HERMANN SOMMER, ROBERT P. MONNIER, BYRON RIEGEL, D. WARREN STANGER, JAMES D. MOLD, DONALD M. WIKHOLM AND ELIZABETH SHANESY KIRALIS

The paralytic form of shellfish poisoning in man has been recognized for over a century as a clinical entity.[4] Shellfish become poisonous when they feed on the marine plankton organism, *Gonyaulax catenella* Whedon and Kofoid. This was established by Sommer and co-workers,[5] who showed: (1) that in the three-year period studied, there was a close correlation between the toxicity of shellfish and the number of *Gonyaulax catenella* per liter present in sea water; (2) that non-toxic bivalves kept in the laboratory became toxic when supplied with fresh sea water rich in this dinoflagellate; and (3) that the poison could be obtained directly from this plankton organism.

The California mussel, *Mytilus californianus* Conrad, has proved to be a better source of the poison, on a scale sufficient for chemical study, than the dinoflagellate. It has been estimated that the average mussel filters 38 liters of sea water a day to obtain its food supply of plankton.[5] Extensive beds of these mussels are found along the rocky Pacific coast of North America. From April to November selected beds along the coast 150 miles north and south of San Francisco were sampled semimonthly and the poison titer of the mussels determined. A large-scale collection was made when the poison content reached or exceeded 4000 MU. per 100-g. mussel.[6]

Daily collections can be made only during the last four or five days of the minus tide period, which occurs every two weeks with the new or full moon. Usually there is only one such period in the entire season during which the mussels are sufficiently toxic to warrant collection. In summer the lower low tide is at daybreak or shortly afterward. In the two-hour period when the beds were accessible, the mussels were pried loose from the rocks and carried up on the beach above tidewater. There they were sorted, washed and opened.[7] The "livers" or digestive glands were dissected out and preserved in acidified ethanol.

In the three-year period, 1944–46, a total of 4360 kg. of mussels containing 160×10^6 MU of poison was collected. The extraction of one of the many collections is shown in Table I. This collection was made south of Pedro Point, San Mateo County, California, on July 18, 1946.

---

[1] The work described in this paper was initiated under a contract between the Federal Security Agency and the University of California and Northwestern University. It was continued under a contract with the Chemical Corps, Camp Detrick, Frederick, Maryland.

[2] Since the mass poisoning in the San Francisco area in 1927, Dr. Karl F. Meyer, Director of the George Williams Hooper Foundation for Medical Research, University of California, has sponsored research on shellfish poison. He was responsible for renewed interest in the problem in 1944, when the contracts for further research in this field were made. The members of the Northwestern group are greatly indebted to Dr. Meyer for making the facilities of the Foundation available to them each summer during the collection period.

[3] The authors wish to thank Dorothy Butler, Ardath Clark Van Tuyl, Patricia Garbutt, Esther Kline and Ruth Nell for their technical assistance.

[4] (a) K. F. Meyer, H. Sommer and P. Schoenholz, *J. Preventive Med.*, **2**, 365 (1928); (b) H. Sommer and K. F. Meyer, *Arch. Path.*, **24**, 560 (1937).

[5] H. Sommer, W. F. Whedon, C. A. Kofoid and R. Stohler, *Arch. Path.*, **24**, 537 (1937).

[6] The mouse unit (MU.), or average lethal dose, is defined as the amount of mussel poison contained in 1.0 ml. of aqueous solution that, injected intraperitoneally into a 20-g. white mouse, will cause death in fifteen minutes. Directions for carrying out this bioassay, together with the tables for calculating the number of MU in the test solution from the weight of the mouse and the dying time, were furnished by H. Sommer to the other workers in this field. These tables are based on graphs[4b] recorded in the literature.

[7] Many of the people in the collecting party were members of the Hooper Foundation who volunteered their services. The authors are especially indebted to Lucile Foster, Florence Hockin, Vera Kreekis, Adelien Larson, Alma McDole, Ethel Meyer, Edward Sherry, Susanne Sommer and Richard Sommer.

TABLE I

EXTRACTION OF POISON FROM A COLLECTION OF TOXIC MUSSEL LIVERS

Collection

	Assay, MU./100-g. mussel,	Poison, 10^6 MU.
Weight of whole mussels,[a] kg. 240	5800	13.92
Volume of ground mussel liver,[b] ml.		
	MU./ml.	
11,600	860	9.98

Extraction

Extracts[c]	Volume, ml.	Total solids, g.	Toxicity, MU./mg.	Poison, 10^6 MU.
1	4,010	555	3.37	1.870
2	5,300	411	4.59	1.880
3	6,050	232	4.13	0.960
4	6,600	175	3.12	0.545
5	6,130	113	2.93	0.333
6	3,820	54	2.77	0.150
	31,910	1540	3.73 av.	5.738

[a] The livers were preserved in ethanol containing 4 ml. of concentrated hydrochloric acid per liter. [b] They were ground in a meat grinder and the *p*H of the *brei* was adjusted to approximately 4.5 by the addition of 60 ml. of concentrated acid. [c] Extract no. 1 was made by centrifuging the suspension of ground livers. Subsequent extracts were made in a similar manner after resuspending the residue in ethanol containing 2 ml. of concentrated hydrochloric acid per liter and stirring overnight. The final extracts were made by heating the suspension at 70° during the stirring.

Extracts of comparable toxicity were combined and divided into aliquot portions, each containing about 10^6 MU. of poison. Since the first extract of each day's collection contained large amounts of lipid material, it was advantageous to remove this by extraction with ether before proceeding further. With subsequent extracts it was immaterial whether defatting was done before or after decolorization. The ether extract usually contained less than 1000 MU. of poison.

Decolorization was carried out by adding 10–20 g. of active carbon (Nuchar C or XXX) to the extract and shaking. After standing overnight, the extract was filtered through a layer of the carbon on a Bücher funnel. The first portion of the filtrate was set aside and the remainder passed through a second lot of fresh carbon. This was continued until the desired degree of decolorization (dark red-brown to pale yellow) was attained. As much as 10% of the poison was lost due to irreversible adsorption or actual destruction. For this reason, the minimum weight of carbon (10–60 g.) was used and only partial decolorization carried out.

To remove a large portion of the ethanol, the decolorized extract was concentrated to 400–500 ml. With some extracts it was possible to improve the toxicity greatly by an additional step. The extract was concentrated *in vacuo* at 35–40° to a thin sirup By the very slow addition of absolute ethanol to the sirup, a white granular material was precipitated. This contained almost none of the poison and was in part taurine. However, the precipitate was often gummy and contained a large proportion of the poison. For this reason the step was omitted in most preparations.

The low concentration of the poison in the crude extract and its chemical and physical properties, insofar as they were known, determined the limited number of methods available for its purification. Evidence pointed to a minimum toxicity of 1 MU./0.001 mg.[8] for the purified poison. In a crude extract with a toxicity of 4–8 MU /mg. the poison would be present at most to the extent of 0.4–0.8%.

Mussel poison has been shown to be soluble in water, methanol, ethanol, glacial acetic acid and aqueous acetone.[4a] The effectiveness of these solvents for extracting the poison appeared to increase if small amounts of hydrochloric acid were added. The poison was insoluble in ether, chloroform, ethyl acetate, butanol and toluene. It could not be extracted from an aqueous alkaline solution by any of these solvents.

Studies were made of the effect of *p*H and temperature on the stability of the poison in aqueous solution as measured by its toxicity (Figs. 1 and 2). The results of these studies set further limits on the methods which might be used in purification. The decrease in toxicity with an increase in *p*H and in temperature showed that the poison must be handled in acid or, under certain conditions, in neutral solution and for all operations the temperature must be kept as low as possible.

Previous attempts to isolate the poison by precipitation with reagents, such as gold chloride, Reinecke salt, and phosphomolybdic, picric and rufianic acids, had been disappointing.[8] In general, either the compound, if it were formed, was too soluble to be obtained as a precipitate, or there was a loss of up to 100% in the toxicity of the poison, or the complex could be decomposed only by the use of alkali which destroyed the poison.

The isolation of betaine from a partially purified extract of mussel poison indicated that the properties of betaine and the poison were enough alike that the substances tended to accompany each other. This fact and the solubility behavior of the poison suggested that it might be a nitrogenous base.[4a] In an attempt to take advantage of the basic properties of the poison, ion exchange was tried as a method of concentration.[8] This proved to be highly successful and experimentally demonstrated the basic nature of the poison.

A commercial zeolite, sodium Permutit, was used by Sommer and Müller, but further studies[9] indicated that the barium compound was more

---

[8] H. Müller, *J. Pharmacol. Exptl. Therap.*, **53**, 67 (1935).

[9] R. P. Monnier, "Versuche zur Isolierung eines in *Mytilus californianus* enthaltenen Giftes," Thesis, Eidgen. Techn. Hochsch., Zurich, 1938.

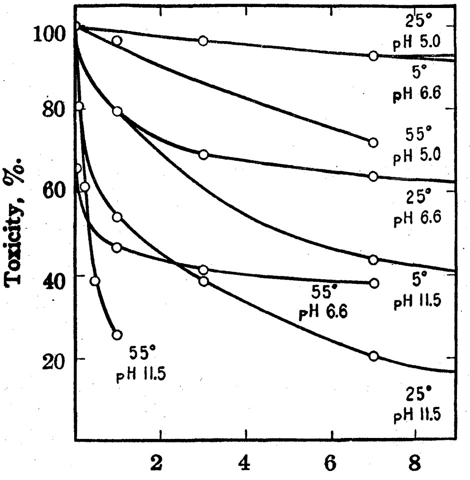


Fig. 1.—The effect of temperature and pH on the toxicity of mussel poison in aqueous solutions. No change in the toxicity of mussel poison in 3 N hydrochloric acid was observed at 55°; this was true also of an aqueous solution, pH 5.0 at 5°.

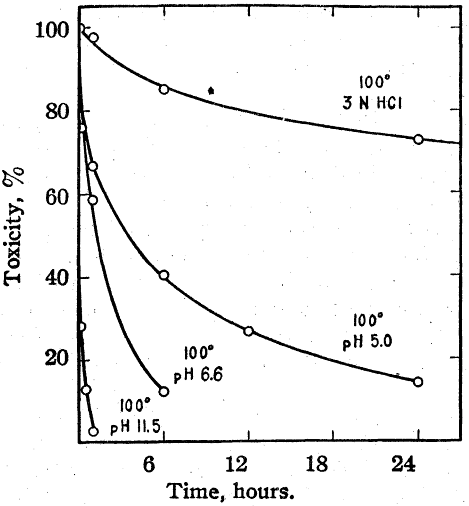


Fig. 2.—The effect of pH on the toxicity of mussel poison in aqueous solution at 100°.

suitable. The poison was adsorbed according to the equation

$$BaZ + BCl_2 \rightleftharpoons BZ + BaCl_2$$

where BaZ is barium Decalso (Permutit) and BCl_2, mussel poison hydrochloride. After the column had been well washed with water, the poison was eluted with a 20% solution of barium chloride. Concentration of the eluate and treatment with absolute ethanol removed most of the barium chloride.

The conditions for the concentration of mussel poison by ion exchange were determined by the properties of the poison and of the cation exchanger. The pH range of the poison extract for

TABLE II

CONCENTRATION OF MUSSEL POISON BY ION EXCHANGE

Preparation		1	2	3	4	5	6[b]
Starting material	Poison, 10^6 MU.	1.000	1.000	1.000	1.070	1.070	1.250
	Toxicity, MU./mg.	8.0	8.0	8.0	6.6	6.6	...
Decolorization	Weight of carbon, g.	60	60	10	20	20	200
	Poison, 10^6 MU.	1.020	0.759	0.895	0.994	1.090	1.250
	Toxicity, MU./mg.	10.1	7.6	7.2	6.3	7.1	...
Extraction with ether	Ether insoluble: Poison, 10^6 MU.	1.060	0.864	0.800	0.940	0.980	1.250
	Ether insoluble: Toxicity, MU./mg.	10.5	8.5	7.6	6.3	6.7	58.8
	Ether soluble poison, MU.	760	200	15,600	500	210	...
Adsorption on Decalso[a]	Decalso cation	barium	barium	barium	barium	sodium	barium
	Extract, pH	5.0	2.9	2.9	3.5	3.5	5.0
	Filtrate and washings, poison, 10^6 MU.	0.165	0.140	0.098	0.272	0.075	0.050
	Eluate: Poison, 10^6 MU.	0.557	0.591	0.633	0.547	0.633	1.200
	Eluate: Toxicity, MU./mg.	157	132	151	59.9	59.8	250
Poison recovered, %	Total	72.2	73.1	74.7	76.7	66.2	100.0
	Purified	55.7	59.1	63.3	51.1	59.2	96.0
$\frac{\text{Toxicity purified poison}}{\text{Toxicity starting material}}$		19.6	16.5	18.9	9.1	9.1	...

[a] A suspension of 1 kg. of commercial Decalso in water was evacuated to remove the entrapped air. The suspension was poured into a tube provided with a stopcock and a pad of absorbent cotton to form a column of Decalso 7 × 50 cm. It was washed with 3 liters of water, 3 liters of 2% acetic acid, 6 liters of water and 1.5 liters of a 20% aqueous solution of crystalline barium chloride ($BaCl_2 \cdot 2H_2O$). To convert the column from barium to sodium Decalso, it was treated with 2 liters of saturated sodium chloride solution and washed with water. The aqueous poison extract (1.5 liters) was passed through the column followed by 4 liters of wash water. The poison was eluted with 1.5 liters of a 20% solution of barium chloride. [b] The collection of mussels from which this extract was prepared had been made in 1936 at a time when the average mussel liver contained 10,000 mu. of poison. After decolorization, the extract was concentrated to a sirup and treated with 200 ml. of absolute ethanol which precipitated a white insoluble material containing no poison. The filtrate was treated with 1 liter of ether and placed in the cold room overnight. The ether was decanted and the gummy residue was dissolved in 1 liter of water. The pH was adjusted to 5.0 with 0.2 N barium hydroxide solution before adsorption on Decalso.

adsorption was limited by the fact that the poison is unstable in alkali and the Decalso becomes less stable as the acidity increases. In the early experiments, the *p*H of the extract was adjusted to 5.0 by the addition of 0.2 *N* barium hydroxide solution in the presence of ice (preparation 1, Table II). This introduced barium ions, which tended to drive the above reaction to the left by either preventing the adsorption of the poison or causing its elution. Later experiments showed that, within the limits 2.5–5.0, the *p*H of the extract is not a critical factor. A poison extract, within these limits, may be passed through the column without adjustment of the *p*H (preparation 2).

A comparison of preparations 2 and 3 shows that a decrease from 60 to 10 g. in the amount of carbon used for decolorization of the crude extract may actually increase the poison content and toxicity of the subsequent Decalso eluate. There was no improvement in the toxicity of the poison when the amount of wash water passed through the Decalso column was increased from 4 to 14 liters before its elution.

The amount of poison found in the filtrate and washings depends upon two factors. The first of these is the toxicity, which obviously is inversely proportional to the amount of inert material mixed with the poison. When an extract with a toxicity of 1.93 MU./mg. was passed through barium Decalso, 67.8% of the poison was found in the filtrate and washings; but when one with a toxicity of 27.5 MU./mg. was used, only 9.9% of the poison passed through. The second factor is the cation of the zeolite. After considerable experience had been gained in the use of barium Decalso as the ion exchanger, a second study was made of the properties of sodium Decalso. The change from the divalent barium to the monovalent sodium ion resulted in a decrease from 27.4% to 7.7% of the poison which passed into the filtrate and washings (preparations 4 and 5), and an increase in the recovery of purified poison.

Zeolites using cations other than sodium or barium were also investigated. Copper Permutit adsorbed the poison, which in turn could be eluted with potassium sulfate. It was found unsatisfactory, since the copper ions could be removed only by precipitation with hydrogen sulfide, and this resulted in a loss of about 40% of the poison. Tetramethylammonium Permutit adsorbed the poison quantitatively, but tetramethylammonium bromide was ineffective as an eluant. Concentrated potassium sulfate eluted the poison, but no great improvement in toxicity was obtained.

Lloyd's reagent adsorbs the poison almost quantitatively even in the presence of acid or alcohol. However, until recently it has not been possible to find a satisfactory eluant. This work, which is now in progress, will be reported later.

Synthetic resins prepared by the condensation of polyhydroxy phenols with formaldehyde[10] were investigated as cation exchangers for the concentration of the poison. The condensation product of phloroglucinol and formaldehyde adsorbed the poison, which could be eluted with dilute hydrochloric acid. Since the toxicity of the poison was not improved by this process, it was not further studied.

The following recommended procedure is based on the experience gained in the preparation of more than seventy-five mussel poison concentrates by ion exchange on Decalso. An aliquot portion of the crude extract containing 10^6 MU. of poison with a toxicity of 4–8 MU./mg. is partially decolorized with 10–60 g. of Nuchar. The filtrate is concentrated and extracted with ether to remove the lipids. These steps result in the loss of 10–20% of the poison. The solution of the poison is diluted to 1.5 liters with water and passed through a column containing 1 kg. of sodium Decalso. The Decalso is washed with 4 liters of water and the poison is eluted with 1.5 liters of a 20% barium chloride solution. Concentration of the eluate and extraction with alcohol furnishes a 50–70% yield of the poison with a toxicity of 70–140 MU./mg.

Summary

1. The collection of poison mussel livers and the preparation of the extract are described.

2. Studies show that the toxicity of the poison in aqueous solution decreases with an increase in *p*H and an increase in temperature.

3. The low concentration of the poison and its chemical and physical properties limit the methods available for its purification.

4. A procedure is described for the preparation of mussel poison concentrates by the use of ion exchange on barium or sodium Decalso. It is possible to obtain a 50–70% yield of the poison with a toxicity of 70–140 MU./mg., an enrichment of eighteen-fold.

5. Results obtained by varying the cation of the zeolite or by the use of synthetic resins have proved less satisfactory than those obtained by the method described.

SAN FRANCISCO, CALIF.
EVANSTON, ILLINOIS
RECEIVED JULY 25, 1947

---

(10) B. A. Adams and E. L. Holmes, *J. Soc. Chem. Ind. London*, **54**, 1T (1935).

[CONTRIBUTION FROM THE GEORGE WILLIAMS HOOPER FOUNDATION, UNIVERSITY OF CALIFORNIA, AND THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Paralytic Shellfish Poison. II. Purification by Chromatography[1]

BY HERMANN SOMMER, BYRON RIEGEL, D. WARREN STANGER, JAMES D. MOLD, DONALD M. WIKHOLM AND MARGARET B. MCCAUGHEY

Mussel poison concentrates prepared by ion exchange on Decalso[2] contain salts of other organic bases as well as inorganic salts. Sommer and Bendien[3] investigated the use of chromatography for further purification and found active carbon to be the most satisfactory adsorbent.

Preliminary tests were conducted to determine the optimum conditions for the chromatography. The results were accepted as the basis for all further work and corroborative tests have not been made using purer concentrates. Of the four carbons tested (Darco G-60, Norit A, and Nuchar C and XXX), Norit A appeared to be the most suitable. The mussel poison was not adsorbed completely from solutions much more dilute than 1.0 *N* in acid. Similarly, traces of ethanol in the extract caused a partial elution of the toxic material.

All of the succeeding runs were made by adsorbing the poison from 1.0 *N* hydrochloric acid solution. The mussel poison hydrochloride was retained by the carbon and the major portion of the inorganic as well as organic contaminants passed through at once. The use of distilled water to develop the chromatogram was sufficient to carry the poison through into the filtrate. The toxicity of the material in each fraction collected was calculated from the bioassay[4] and the determination of total solids. The most toxic fraction usually had a *p*H of about 2.3. The chromatography of a typical concentrate obtained by ion exchange on Decalso is described in Table I. Mussel poison hydrochloride with a toxicity greater than 3.3 MU./γ has been prepared by rechromatographing combined lots of material of high toxicity obtained from carbon columns. In this way the ash content of these samples has been reduced to 3–4%.

TABLE I

CHROMATOGRAM OF A TYPICAL DECALSO ELUATE[a]

Solvent	Volume, ml.	Poison recovered MU.	%	Total solids, g.	Toxicity, MU./γ
		Starting Material			
1 *N* HCl	100	612,000	100.0	5.1900	0.118
		Filtrates			
MeOH·HCl	20	<280		0.0008	
MeOH·HCl	15	<200		0.1615	
1 *N* HCl	50	<1,080		1.6454	
1 *N* HCl	25	<570		0.9078	
1 *N* HCl	25	810	0.1	.6434	0.0013
H_2O	25	1,670	0.3	.4211	.0040
H_2O	25	3,120	0.5	.2370	.0132
H_2O	25	43,200	7.1	.1432	.301
H_2O	40	238,000	38.9	.1659	1.44
H_2O	45	95,000	15.5	.0717	1.32
H_2O	50	18,800	3.1	.0457	0.410
H_2O	100	9,300	1.5	.0484	.192
H_2O	100	3,220	0.5	.0287	.112
MeOH·HCl	100	7,200	1.2	.2530	.0285
MeOH·HCl	100	<1,440		.0516	
		420,000	68.7	4.8252	

[a] The adsorbent was commercial acid-washed Norit A which was further digested with 10% hydrochloric acid. Treatment was repeated until a negative test for the ferric ion was obtained with 10% potassium ferrocyanide solution. The carbon was well washed with water and dried. A smooth suspension of 15 g. of the carbon in methanol containing 10 ml. of concentrated hydrochloric acid per liter was poured into a Pyrex column provided with a stopcock at the bottom and a cotton plug to support the carbon. The solvent was allowed to run through until level with the top of the adsorbent, and the amount remaining (38 ml.) was considered the hold-up of the carbon column (21 × 85 mm.). The column was operated under an air pressure of 125 cm. of water. The chromatogram was developed with distilled water. The final traces of material remaining on the column were eluted with the acidified methanol.

The use of dilute aqueous hydrochloric acid in place of acidified methanol in preparing the column for chromatography has little or no effect on the recovery of the poison. However, the rate of filtration of the water is more rapid in the latter type of column.

For crude mussel liver extracts with toxicities less than about 3.3 MU./mg., the concentration by ion exchange on Decalso proved unsatisfactory.[2] A method, which was suggested by the work of Sommer and Bendien,[3] was applied to this material with some success. This involved the direct chromatography of partially decolorized and defatted crude extracts on active carbon after removal of traces of ethanol by successive evaporations with water. It is possible to obtain fractions of mussel poison hydrochloride with toxicities greater than 1.0 MU./γ by this method (Table II). A decided advantage is that an over-all recovery of 60–80% is usually obtained. The poorer fractions may be rechromatographed for further purification. This method was not used for material of greater toxicity, since the Decalso procedure was less time-consuming and provided enriched poison concentrates in fairly good yield.

Since the preparation of the carbon for chromatography involved a rather lengthy procedure, it seemed advisable to attempt the repeated use

---

(1) The work described in this paper was done under a contract between the Chemical Corps, Camp Detrick, Frederick, Maryland, and the University of California and Northwestern University.

(2) H. Sommer, R. P. Monnier, B. Riegel, D. W. Stanger, J. D. Mold, D. M. Wikholm and E. S. Kiralis, THIS JOURNAL, **70**, 1015 (1948).

(3) W. M. Bendien and H. Sommer, *Proc. Soc. Exptl. Biol. Med.*, **48**, 715 (1941).

(4) The bioassay was carried out by the intraperitoneal injection of the poison into white mice. The mouse unit (MU) is the average lethal dose of poison that will kill a 20-g. mouse in fifteen minutes.

TABLE II

CHROMATOGRAPHIC FRACTIONATION OF CRUDE MUSSEL POISON EXTRACTS[a]

Solvent	Volume, ml.	Poison recovered MU.	Poison recovered %	Total solids, g.	Toxicity, MU./mg.
		Starting Material			
1 *N* HCl	500	410,000	100.0	20.0	20.5
		Filtrates			
MeOH·HCl	140				
1 *N* HCl	500	<11,400			
H_2O	248	2,820	0.7	0.166	1.70
H_2O	210	78,800	19.2	.546	144
H_2O	100	119,000	29.0	.125	952
H_2O	100	27,400	6.7	.096	284
H_2O	100	9,270	2.3	.087	107
H_2O	223	5,840	1.4	.120	48.9
H_2O	196	2,870	0.7		
H_2O	250	2,720	0.7		
H_2O	119	1,420	0.3		
MeOH·HCl	218	11,100	2.7		
		261,000	63.7		

[a] Acid-washed Norit A (60 g.) was used to prepare a 31 × 190 mm. column which had a hold-up of 138 ml.

of these columns. This provided some unexpected results. The used carbon gave a better return of eluted material as well as fractions of higher toxicity in most cases. However, after the passage of several lots through the same column or the use of very impure starting material, the column had to be discarded. A typical series of repeated runs with mussel poison prepared by ion exchange on Decalso is given in Table III. When crude material was chromatographed on a column of acid-washed Norit A which had been used once, a similar improvement in yield and enrichment was observed.

An experiment in which used carbon was reactivated by digestion with 10% hydrochloric acid indicated that it could be used again for chromatography of crude extracts with somewhat higher yields and greater enrichment than could be obtained with fresh acid-washed Norit A.

The adsorption behavior of mussel poison on acid-washed Norit A appears to be dependent upon the nature of the anion. Experiments in which solutions of mussel poison in 1.0 *N* hydrobromic, trichloroacetic and Reinecke acids were passed through columns of the active carbon provided widely varying results. The hydrobromide of the poison was found to be much more strongly adsorbed than the hydrochloride and was only eluted by acidified methanol. The trichloroacetate was not adsorbed under these conditions and passed through the column into the acid filtrate. The Reineckate was dissociated, the Reinecke acid being irreversibly adsorbed on the carbon and the poison reappearing as the hydrochloride in the eluate. None of these acids appeared

TABLE III

REPEATED CHROMATOGRAPHY OF MUSSEL POISON ON THE SAME COLUMN[a]

		Starting material[b] 1 *N* HCl	Hold-up MeOH·HCl	Acid filtrate 1 *N* HCl	Eluates							Total recov., %
					H_2O						MeOH·HCl	
					1	2	3	4	5	6		
1	Vol., ml.	25.0	8.0	25.0	11.0	9.0	12.5	15.0	20.0	25.0	25	
	*p*H				1.6	2.2	....	2.4	2.5	2.9		
	Poison, %	100.0	0.0	0.0	0.4	0.5	62.5	11.2		0.8	2.3	**77.7**
	Tox., MU./γ	0.0862			....	....	1.08	0.410		0.186		
2	Vol., ml.	25.0	7.0	25.0	10.0	10.0	10.0	10.0	10.0	30.0	25.0	
	*p*H				1.5	2.1	2.2	2.3	2.4	2.6		
	Poison, %	100.0	0.2	0.0	6.7	20.3	21.5	22.1	6.8	4.6	2.2	84.4
	Tox., MU./γ	0.0862			....	0.299	0.680		0.641	0.370		
3	Vol., ml.	25.0	7.0	25.0	10.0	10.0	10.0	11.5	25.0		25.0	
	*p*H				1.3	1.9	2.2	2.3	2.5			
	Poison, %	100.0	0.0	0.0	1.3	14.4	47.1	16.0	5.5		4.9	89.2
	Tox., MU./γ	0.0862			....	0.167	0.093	1.00	0.463			
4	Vol., ml.	25.0	9.0	23.0	11.0	10.0	11.5	12.0	25.0	25.0	50.0	
	*p*H				1.6	2.0	....	2.2	2.5	2.8		
	Poison, %	100.0	0.0	0.0	0.8	18.1	57.1	11.2	4.2		1.0	92.4
	Tox., MU./γ	0.437			....	0.268	0.926	0.451	0.225			
5	Vol., ml.	25.0	8.0	25.0	10.0	11.0	11.0	10.0	26.0	25.0	50.0	
	*p*H				1.2	....	....	2.5	2.7	2.9		
	Poison, %	100.0	0.0	0.8	15.6	28.8	28.7	15.3	4.5	0.4	1.5	95.6
	Tox., MU./γ	1.00			0.833	1.07	1.05	1.01	0.543	....		

[a] Three grams of acid-washed Norit A was used to prepare a 11.5 × 80 mm. column which had a hold-up of 9 ml.

[b] The starting material was a Decalso eluate containing 152,000 MU. with a toxicity of 86.2 MU./mg. This material was dissolved in 75 ml. of 1.0 *N* hydrochloric acid and divided into three portions of 25 ml. each for the first three runs. The fourth run was carried out on combined fractions with toxicities greater than 0.296 MU./γ from the first three runs, a total of 42,900 MU. (0.436 MU./γ). The starting material for the fifth run was made up of fractions with toxicities greater than 0.908 MU./γ from the first four runs, a total of 88,200 MU. (1.00 MU./γ).

to offer any advantage over hydrochloric acid for chromatography.

The recommended procedure for purifying mussel poison concentrates by chromatographic fractionation on acid-washed Norit A is based on experience gained from carrying out over one hundred chromatograms. Though it is difficult to obtain exactly duplicate results even with aliquots of the same material on columns prepared in an identical manner, the average total recovery of poison in chromatography is from 60–80%. The most toxic fraction of the eluate contains 30–50% of the poison. This fraction will often show an enrichment of as great as twenty-fold if the starting material is a concentrate obtained by ion exchange on Decalso and as great as seventy-five-fold if the starting material is a crude, partially decolorized mussel poison extract. Poison concentrates obtained from ion exchange on Decalso contain 50–70% of the poison in the crude extract and usually have a toxicity of 0.07–0.14 MU./γ. Chromatography of these eluates on acid-washed Norit A results in a recovery of 30–50% of this poison with a toxicity greater than 1 MU./γ. The over-all recovery of poison with a toxicity greater than 1 MU./γ, after purification by ion exchange on Decalso and subsequent chromatography on acid-washed Norit A, is 18–30%.

Summary

1. A procedure is described for the chromatographic fractionation of mussel poison concentrates on active carbon.

2. Repeated use of carbon columns for the chromatographic fractionation of mussel poison hydrochloride usually results in a better recovery of poison as well as in fractions of higher toxicity.

3. The adsorption behavior of mussel poison on active carbon varies widely with different anions.

4. By chromatography on Norit A of mussel poison concentrates obtained from ion exchange on Decalso, it is possible to obtain a 30–50% yield of twenty-fold enriched material with a toxicity greater than 1 MU./γ.

5. The chromatography of partially decolorized, defatted, crude mussel poison extracts on Norit A yields 30–50% of seventy-five-fold enriched material.

SAN FRANCISCO, CALIF.
EVANSTON, ILLINOIS

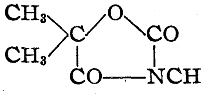
RECEIVED JULY 25, 1947

[CONTRIBUTION FROM ABBOTT LABORATORIES]

Some N-Alkyl-2,4-oxazolidinediones and their Anticonvulsant Properties

BY M. A. SPIELMAN AND GUY M. EVERETT

An earlier communication[1] has described the synthesis of some N-alkyl derivatives of 2,4-oxazolidinedione and their effect as analgesic agents. Subsequently, Everett and Richards[2] investigated the anticonvulsant properties of this type of compound, and as an outgrowth of their studies 3,5,5-trimethyl-2,4-oxazolidinedione under the trade name Tridione (I) has come into wide use in the treatment of petit mal epilepsy.[3] This paper presents results obtained in an expansion of the series.



I

The new N-alkyl-2,4-oxazolidinediones are much like those previously reported. They are liquids or low-melting solids, neutral in reaction and rapidly destroyed by strong aqueous alkali. They were synthesized along conventional lines as described below.

Experimental Part[4]

The parent 2,4-oxazolidinediones were prepared by the Stoughton method[5] in which an α-hydroxyester is condensed with urea by means of sodium ethoxide.

One α-hydroxyester is new. Methyl *n*-propyl ketone cyanhydrin on alcoholysis gave ethyl α-hydroxy-α-methylvalerate; b. p. 91–95° at 40 mm., n^{25}_{D} 1.4135. *Anal.* Calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.09. Found: C, 59.84; H, 9.88.

The following three new 2,4-oxazolidinediones were prepared by condensing the appropriate α-hydroxyester with urea.[5]

5-*n*-Propyl-2,4-oxazolidinedione boiled at 122–127° at 0.5 mm. After three crystallizations from ether–petroleum ether it formed thin blades which melted at 53–55°. *Anal.* Calcd. for $C_6H_9NO_3$: N, 9.80. Found: N, 9.63.

5-Isopropyl-2,4-oxazolidinedione boiled at 118–119° at 1.5 mm., n^{25}_{D} 1.4671. *Anal.* Calcd. for $C_6H_9NO_3$: N, 9.80. Found: N, 9.87.

5-Methyl-5-*n*-propyl-2,4-oxazolidinedione is a thick, colorless oil; b. p. 115–118° at 1 mm., n^{25}_{D} 1.4583. *Anal.* Calcd. for $C_7H_{11}NO_3$: N, 8.91. Found: N, 8.75.

N-Methylation was carried out with dimethyl sulfate as described before[1] except that the use of methanol as solvent gave more consistent yields.

Introduction of higher alkyls by reaction of silver salts with alkyl iodides[1] gave poor yields and the method was soon abandoned.[6] Better results were obtained by preparing the potassium salt of the 2,4-oxazolidinedione in Cellosolve (glycol monoethyl ether) and heating with the appropriate halide. Chlorides, bromides and iodides were substantially equivalent, although with iodides it was found best to add the halide slowly to the cooled solution or suspension of the salt.

---

(1) Spielman, THIS JOURNAL, **66**, 1244 (1944).

(2) Everett and Richards, *J. Pharmacol.*, **81**, 402 (1944).

(3) Lennox, *J. Am. Med. Assoc.*, **129**, 1069 (1945); Perlstein and Andelman, *J. Pediatrics*, **29**, 20 (1946).

(4) Microanalyses by E. F. Shelberg. Compound 7 was made by W. B. Brownell. We are indebted to A. H. Smith, Jr., for technical assistance.

(5) Stoughton, THIS JOURNAL, **63**, 2376 (1941).

(6) Hook, *Nature*, **160**, 610 (1947), in a note which has just come to our attention has shown that the silver salt method may lead to O-alkylation.

TABLE I

DERIVATIVES OF 2,4-OXAZOLIDINEDIONE

No.	3-Substituent	3,5-Substituents	M. p., °C.	B. p. °C.	Mm.	$n^{25}D$	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
1	C_2H_5	H, H		133–136[a]	32	1.4619	$C_5H_7NO_3$		
2	*n*-C_3H_7	H, H		142–147	32	1.4602	$C_6H_9NO_3$	9.78	9.60
3	*s*-C_5H_{11}	H, H		97–100	1.5	1.4585	$C_8H_{13}NO_3$	8.19	7.81
4	*i*-C_5H_{11}	H, H		157–162	35	1.4587	$C_8H_{13}NO_3$	8.19	8.16
5	C_2H_5	H, CH_3		140–145	60	1.4519	$C_6H_9NO_3$	9.78	9.67
6	$CH_2{=}CHCH_2$	H, CH_3		137–140	35	1.4688	$C_7H_9NO_3$	9.02	8.95
7	CH_3	H, C_2H_5		160–165	100	1.4567	$C_6H_9NO_3$	9.78	9.63
8	$C_6H_5CH_2$	H, CH_3	74–76				$C_{11}H_{11}NO_3$	6.83	6.65
9	CH_3	H, *n*-C_3H_7		99–101	3	1.4567	$C_7H_{11}NO_3$	8.92	8.89
10	CH_3	H, *i*-C_3H_7		118–119	18	1.4554	$C_7H_{11}NO_3$	8.92	8.92
11	CH_3	CH_3, *n*-C_3H_7		135–138	35	1.4498	$C_8H_{13}NO_3$	8.19	8.30
12	*n*-C_3H_7	CH_3, CH_3	47–48	120–124	28		$C_8H_{13}NO_3$	8.19	8.13
13	*s*-C_5H_{11}	CH_3, CH_3		142–147	50	1.4410	$C_{10}H_{17}NO_3$	7.05	7.02
14	$HOOCCH_2$	CH_3, CH_3	114–116				$C_7H_7NO_5$	7.49	7.47
15	$(C_2H_5)_2N(CH_2)_2$	CH_3, CH_3		108–110	1	1.4545	$C_{11}H_{20}N_2O_3$	12.28	12.07[b]

[a] Ahlquist, *J. prakt. Chem.*, 99, 45 (1919), gives 119.5° at 12 mm. [b] The hydrochloride melted at 192°. *Anal.* Calcd. for $C_{11}H_{21}ClN_2O_3$: N, 10.60. Found: N, 10.75.

Typically, to 100–150 cc. of Cellosolve in a 3-neck flask assembly was added 0.2 mole of the 2,4-oxazolidinedione and 13 g. of potassium hydroxide pellets with heating to effect solution. To the refluxing mixture 0.2 mole of the halide was added dropwise. Heating was continued one hour. The solution was cooled, filtered, and the solvent was removed under diminished pressure. The product was taken up in ether, washed with sodium bicarbonate solution, dried and distilled. Yields were 50% or better with primary halides and less with secondary halides. No individual reaction was studied extensively with the idea of obtaining maximum yield.

The 5,5-dimethyl-2,4-oxazolidinedione-3-acetic acid was prepared in 40% yield by refluxing the sodium salt of the 5,5-dimethyl-2,4-oxazolidinedione and sodium chloroacetate in water for sixteen hours with subsequent acidification. It was crystallized from benzene.

Physical properties and analyses are shown in Table I.

Pharmacology

The compounds were tested for their ability to suppress in mice the convulsions induced by Metrazole (pentamethylenetetrazole) or electroshock. The method was that described in the earlier work[2] and was considered adequate as a preliminary test for the two types of anticonvulsant activity. The compounds of the present series are low in toxicity and mildly depressing. They were administered in doses up to those producing ataxia, and it may be seen in Table II that only a few compounds have anticonvulsant activity and only at levels where ataxia was evident. The results are in contrast to those obtained from 3,5,5-trimethyl-2,4-oxazolidinedione (Tridione), 3,5-dimethyl-2,4-oxazolidinedione and 5-ethyl-3,5-dimethyl-2,4-oxazolidinedione which are particularly active against Metrazole, and which have been demonstrated in clinical trial to have anti-epileptic action against petit mal.

TABLE II

ANTICONVULSANT ACTIVITY IN MICE

No.	Dose, mg./kg.	Symptoms	Protection Metrazole	Protection Electroshock
1	1500	None	−	
2	400	Ataxia	+	+
3	200	Ataxia	−	−
4	200–800	Slight ataxia	−	+
5	400	Ataxia	−	−
6	100	Ataxia	−	−
7	400	Ataxia	+	−
8	400	Ataxia	−	−
9	200	Ataxia	−	−
10	200	Ataxia	−	−
11	400	Ataxia		−
12	200	Ataxia	−	−
13	800	Excitement	−	−
14	800	None	−	−
15	1000	None	−	−

An interesting observation in the series is that compound 13, 5,5-dimethyl-3-*s*-amyl-2,4-oxazolidinedione, is not depressing as are the other compounds but instead exerts a stimulating effect and at high levels produces convulsions. On the other hand, compound 15, which has the diethylaminoethyl group on the nitrogen atom and therefore might reasonably be expected to prove stimulating, is practically devoid of pharmacological activity.

Summary

A series of N-substituted derivatives of 2,4-oxazolidinedione has been prepared and tested for anticonvulsant activity. None has sufficient potency to be of therapeutic interest.

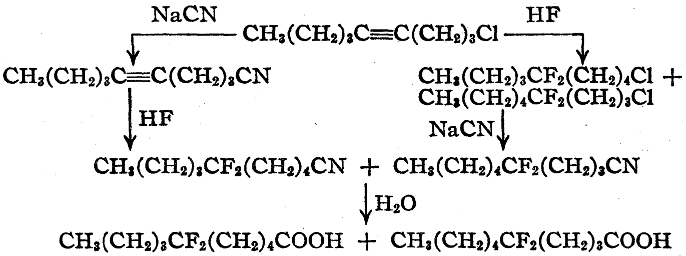
NORTH CHICAGO, ILLINOIS RECEIVED NOVEMBER 6, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

Synthesis and Reduction of Difluorodecanoic Acid Derivatives

BY MELVIN S. NEWMAN, MARY W. RENOLL[1] AND IRVING AUERBACH[1]

In this paper we describe the synthesis of 5,5- and 6,6-difluorodecanoic acids (mixture of isomers) and some reactions of their derivatives. The synthetic scheme is indicated below.



The starting compound, 1-chloro-4-nonyne, was best prepared by alkylation of 1-hexyne with 1-chloro-3-bromopropane using lithium amide in liquid ammonia. Of the two succeeding alternate paths, addition of hydrogen fluoride to the acetylenic nitrile proved superior.[2] In each case a mixture of isomeric difluoro compounds was obtained as was expected since the chloro or cyano groups were too far removed from the triple bond to cause directed addition. Because of the stability of the fluorinated compounds it is certain that CF_2 groups are present. The mixtures thus obtained were carried through to the corresponding difluoro acids, no attempt being made to separate pure individuals in any case.

Of particular interest are certain reduction reactions carried out in order to prepare the corresponding difluorodecanols. High pressure catalytic hydrogenation over copper chromite caused complete decomposition. Bouveault–Blanc reduction[3] was partly successful but considerable amounts of fluoride ion were detected in the reaction mixture. Reduction of the thiol esters by lithium aluminum hydride[4] gave the desired alcohol but the best method involved desulfurization of the thiol esters with Raney nickel.[5]

Experimental[6]

1-Chloro-4-nonyne.—Lithium amide, prepared in two liters of liquid ammonia from 42 g. (6 moles) of lithium, in presence of 1.8 g. of ferric nitrate nona-hydrate as catalyst, as described for sodamide by Greenlee and Henne[7] was treated with 492 g. (6 moles) of 1-hexyne[8] and then 946 g. (6 moles) of 1-chloro-3-bromopropane was added and allowed to react during fourteen hours.[9] Lithium amide, prepared and used *in situ*, was found to give higher yields of 1-chloro-4-nonyne than either sodium or potassium amide. After addition of 320 g. of ammonium chloride and subsequent evaporation of most of the ammonia, about 1500 ml. of water was added. Extraction with ether removed the organic product which was subsequently purified by fractional distillation. The yield of 1-chloro-4-nonyne boiling at 100–106° (23 mm.), $n^{20}D$ 1.4595, was 515.5 g. (54.2%). Approximately 180 g. of 1-hexyne was recovered, together with 51 g. of still residue.

4,4- and 5,5-Difluoro-1-chlorononane (Mixture of Isomers).—The addition of hydrogen fluoride to 1-chloro-4-nonyne was accomplished by adding a solution of 79 g. (0.5 mole) of 1-chloro-4-nonyne in 60 ml. of dry ether during one and three-fourths hours to a stirred mixture of 37 g. of dry ether and 83 g. (4.1 moles) of hydrogen fluoride in an ice-cooled stainless steel flask. After stirring for eight hours in the cold, the reaction mixture was poured on ice and extracted with ether. The ether extract was washed with 5% sodium hydroxide solution until free from acid and dried over calcium chloride. On distillation two fractions of incompletely fluorinated product were obtained: 37 g., b. p. 85–95° (11 mm.), $n^{20}D$ 1.4312; and 7 g., b. p. 95–105° (11 mm.), $n^{20}D$ 1.4297; together with 37.5 g. of heavy oil as still residue. The partly fluorinated material, 211 g., from a number of runs, was again treated with hydrogen fluoride (27 g.) at 0° as above, followed by stirring at room temperature overnight, to yield two fractions, 87 g., b. p. 87–92° (11 mm.), $n^{20}D$ 1.4232 and 84 g., b. p. 92–97° (11 mm.), $n^{20}D$ 1.4235. These completely fluorinated fractions were combined for conversion to the nitrile (see below). There was a still residue of 30.5 g. The pure chlorodifluorononane foams badly when redistilled.

Anal. Calcd. for $C_9H_{17}F_2Cl$: F, 19.1. Found: F, 19.7.

Increasing the time of contact of 1-chloro-4-nonyne with hydrogen fluoride (twenty-four hours) and allowing the temperature to rise to 7° during the latter part of this time (eight to twelve hours) afforded lower yields of fluorinated product and a larger amount of polymeric residue. The substitution of dimethyl or diisopropyl ether for ethyl ether as solvent gave slightly lower yields of fluorinated product.

5-Decynenitrile.—1-Chloro-4-nonyne (100 g., 0.63 mole) was refluxed, with stirring, with a solution of 123 g. of sodium cyanide in 175 ml. of water and one liter of ethanol for eighteen hours. After removal of nearly all of the alcohol under reduced pressure the residue was poured into water and extracted with ether. From the ether solution there was obtained 70 g. (74.5%) of 5-decynenitrile, b. p. 106–8° (5 mm.), $n^{20}D$ 1.4540.

5,5- and 6,6-Difluorodecanenitriles (Mixture of Isomers).—A solution of 202 g. (1.36 moles) of 5-decynenitrile in 140 ml. of ether was added to 268.5 g. (13.4 moles) of hydrogen fluoride in 106 g. of ether at 0° during two hours as described for 1-chloro-4-nonyne. The reaction flask was then placed in a vacuum-jacketed bath at 6° and stirring was continued for seventeen hours while allowing the temperature to rise to 18°. This was followed by four hours of stirring at 29°. From the washed and dried ether solution there was obtained 10 g. of fore-run, b. p. below 112° (5 mm.), 141 g. of incompletely fluorinated nitrile, b. p. 112–118° (5 mm.), $n^{20}D$ 1.4230, and 78 g. of crystalline still residue. A second treatment of 151 g. of

---

[1] B. F. Goodrich Company Research Associate of The Ohio State University Research Foundation.

[2] Compare Henne and Plueddeman, THIS JOURNAL, **65**, 587 (1943).

[3] Ziegler and Hechelhammer, *Ann.*, **528**, 114 (1937).

[4] Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947); Finholt, Bond and Schlesinger, *ibid.*, **69**, 1199 (1947).

[5] Jeger, *et al.*, *Helv. chim. acta*, **29**, 784 (1946).

[6] All fluorine analyses were carried out as described by Renoll, THIS JOURNAL, **68**, 1159 (1946).

[7] Greenlee and Henne, "Inorganic Syntheses," McGraw-Hill Book Company, New York, N. Y., 1946, Vol. II, p. 128.

[8] Purchased from the Farchan Laboratories, Cleveland, Ohio.

[9] Henne and Greenlee, THIS JOURNAL, **67**, 484 (1945).

the crude fluorinated nitrile in 85 ml. of ether with 160 g. (8 moles) of hydrogen fluoride in 65 g. of ether at 0°, followed by stirring for five hours at 25° gave a product consisting of 1 g. of fore-run, b. p. below 111.5° (5 mm.), $n^{20}D$ 1.4178, 135 g. of completely fluorinated nitrile, b. p. 111.5–118° (5 mm.), $n^{20}D$ 1.4145 and 15 g. of residue.

The crystalline still residue was hydrolyzed to difluorodecanoic acid by refluxing with potassium hydroxide in aqueous ethanol. From 176 g. of residue there was obtained 106 g. of acid.

1-Chloro-4,4- and 5,5-difluorononane mixture was converted to 5,5- and 6,6-difluorodecanenitrile mixture by sodium cyanide in 60% yield, as described for 1-chloro-4-nonyne. Approximately one-third of the starting material remained unreacted after twenty hours.

Difluorodecanoic Acid.—Hydrolysis of 265 g. (1.4 moles) of the nitrile by refluxing with a solution of 240 g. of potassium hydroxide in 1580 ml. of ethanol and 316 ml. of water, with stirring, for twenty-seven hours gave 274 g. (94%) of difluorodecanoic acid, b. p. 125–131° (2 mm.). When recrystallized from Skellysolve-B it melted at 44–46°, with softening at 40°.

Anal. Calcd. for $C_{10}H_{18}F_2O_2$: neut. equiv., 208; F, 18.3. Found: neut. equiv., 210; F, 18.4.

Taking into account the acid obtained by hydrolysis of the difluorodecanenitrile still residue (18%), the over-all yield of acid from 5-decynenitrile was 65%.

The **acid chloride** was prepared from the acid and excess thionyl chloride in 98% yield, b. p. 103–106° (4 mm.).

Ethyl Difluorodecanoate.—Esterification of 21 g. (0.1 mole) of difluorodecanoic acid with 25 ml. of ethanol in 150 ml. benzene, using *p*-toluenesulfonic acid as catalyst, gave 23 g. (97.4%) of ester, b. p. 107.5–108.5° (4 mm.), $n^{20}D$ 1.4126.

Reduction of Ethyl Difluorodecanoate.—Hydrogenation of 24 g. (0.1 mole) of ester over copper chromite catalyst (37 KAF)[10] in glass-lined equipment at 250° and 2500 lb. pressure resulted in almost complete decomposition of the ester.

A preliminary distillation of the Bouveault–Blanc[3] reduction product of 23 g. of ethyl ester separated 16 g. of material, b. p. 105–150° (3 mm.), and a small amount of still residue. Redistillation through a small helices-packed column gave 7 g. of 5,5- and 6,6-difluorodecanols (mixture of isomers),[11] b. p. 109–115° (5 mm.).

In order to identify the difluorodecanol, the phenylurethan, m. p. 73.6–74.2°, after recrystallization from Skellysolve-B, was prepared.[12]

Anal. Calcd. for $C_{17}H_{25}NO_2F_2$: F, 12.1. Found: F, 11.6.

Ethyl Thioldifluorodecanoate.—A solution of 120 g. (0.53 mole) of difluorodecanoyl chloride in 200 ml. of dry benzene and 100 g. (1.6 moles) of ethyl mercaptan was treated with 63 g. (0.78 mole) of pyridine in 100 ml. of dry benzene as described by Jeger.[5] The yield of ethyl thioldifluorodecanoate was 91 g. (68%), b. p. 118–121° (2 mm.). Thirty-one grams of difluorodecanoic acid was recovered.

***n*-Butyl Thioldifluorodecanoate.**—From 31 g. (0.14 mole) of difluorodecanoyl chloride, 50 g. (0.55 mole) of *n*-butyl mercaptan, 16.5 g. (0.21 mole) of pyridine, and 75 ml. of benzene there was obtained[5] 24 g. (88.9%) of *n*-butyl thioldifluorodecanoate, b. p. 125–130° (1.5 mm.).

Reductive Desulfurization of Ethyl and *n*-Butyl Thiol Esters.—(a) With Raney nickel[5]: Freshly prepared Raney nickel from 480 g. of Raney alloy[13] was washed by decantation several times with absolute ethanol and covered with 100 ml. of ethanol. A solution of 24–30 g. of the ester in 100 ml. of absolute ethanol was added slowly, with shaking, and agitation continued for one hour longer. Most of the supernatant liquid was decanted from the nickel through filter paper. The nickel residue was washed repeatedly with ethanol in a chromatographic adsorption tube plugged with cotton. The total volume of the combined ethanol solutions was about one liter. Because of foaming encountered in the removal of solvent by distillation, the alcohol solution was allowed to evaporate in an open dish at room temperature. The yield of difluorodecanol, b. p. 112–115° (5 mm.), was 15–18 g. (*ca.* 80%). There was no fore-run or residue in the distillation. It solidified at room temperature and had a pleasant odor.

Anal. Calcd. for $C_{10}H_{20}F_2O$: F, 19.6. Found: F, 18.9.

The reduction with Raney nickel is probably quantitative, but the removal of the last traces of product adsorbed on the nickel is most difficult.[5]

(b) With Lithium Aluminum Hydride: The preparation of lithium aluminum hydride and procedure for use as a reducing agent were as described.[4] A solution of 31 g. of mixed ethyl and butyl thiol esters in 50 ml. of dry ether was added to 50 ml. of an ether solution of lithium aluminum hydride containing 0.00136 mole of $LiAlH_4$ per ml. After removal of solvent, there was obtained 3.5 g. of fore-run, b. p. 103–110° (5 mm.), 17 g. of difluorodecanol, b. p. 110–115° (5 mm.), and 2.5 g. of still residue. All fractions had a mercaptan-like odor. It was obvious that by-products were formed in this reduction, in contrast to the complete absence of such substances in the Raney nickel reduction.

From 91 g. of ethyl thiol ester and 40 g. of *n*-butylthiol ester there was obtained a total of 78 g. (76%) of difluorodecanol by both reduction methods.

Summary

5,5- and 6,6-difluorodecanoic acids (mixture of isomers) have been synthesized from the corresponding nitrile which was formed by the addition of hydrogen fluoride to 5-decynenitrile. An alternate synthesis from 1-chloro-4,4- and 5,5-difluorononane (mixture of isomers) is described.

5,5- and 6,6-difluorodecanols (mixture of isomers) were prepared in good yield by Raney nickel reduction and by lithium aluminum hydride reduction of the ethyl thiol and *n*-butyl thiol esters.

COLUMBUS 10, OHIO RECEIVED MAY 26, 1947

---

[10] Connor, Folkers and Adkins, THIS JOURNAL, **54**, 1138 (1932).

[11] Referred to hereafter as difluorodecanol.

[12] Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 136.

[13] Mozingo, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1941, Vol. 21, p. 15.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

Fluorinated Derivatives of Ethane and Ethylene. VII

BY ALBERT L. HENNE AND ROBERT P. RUH

In the preparation of fluorinated derivatives of ethane and ethylene by conventional methods,[1] several hundred grams of various compounds have been available for purification. Physical measurements were thus made possible which are believed to be more precise than those in the literature and are claimed to be accurate to the extent shown by the significant decimals appearing in the table. Indications of high purity were: freezing ranges of about 0.1°; boiling points constancy of better than 0.1°; and atomic refractions for fluorine (AR_F) very close to 1.0.

In general, the literature values hover closely around those reported here; data which diverge widely are as follows: The boiling point of $CHCl{=}CF_2$ is $-17.7°$, and not "about $+2.4°$" as we erroneously reported[2] when we had only traces of this material. Next in importance is the correction for CCl_2FCF_3, previously reported[3] as "about $-2°$," and now found to be $+3.6°$; the former sample had been obtained from distillation heads of the industrial preparation of $CClF_2CClF_2$ and was found contaminated by some CF_3CClF_2; the present sample was synthesized from pure CCl_3CF_3.

Few freezing points appear in the literature. We are in contradiction with Booth[4] on the freezing point of $CClF{=}CCl_2$, which he gives as $-82°$ while we observed $-108.93°$, with a total range of less than 0.1°. We agree fully with Booth's boiling point, and we note in his paper that his freezing point was not determined by himself.

TABLE OF PHYSICAL CONSTANTS

	F. p., °C.	B. p., °C.	$t°$	$dt/4$	nt/D	MR	AR_F
$CH_2{=}CFCl$	−169	−24.0					
$CH_2{=}CF_2$		−84					
$CHCl{=}CF_2$	−138.5	−17.7					
$CHBr{=}CF_2$	−115.4	6.1	0.5	1.8175			
$CClF{=}CF_2$		−26.8					
$CCl_2{=}CClF$	−108.9	71.0	20.0	1.5460	1.4379	25.39	0.9
CH_2BrCF_2Br	− 61.3	93.2	20.0	2.2238	1.4456	26.84	1.0
$CClFBrCF_2Br$	− 72.9	93.1	20.0	2.2478	1.4278	31.63	1.0
CCl_2FCF_3	− 56.6	3.6					
CH_2ClCF_3	−105.5	6.93	0	1.389			
CH_2BrCF_3	− 93.9	26.3	20.0	1.7881	1.3331	18.75	1.0
CH_2BrCF_2Cl	− 75.8	68.4	20.0	1.8300	1.4018	23.86	1.0

Summary

Improved physical constants are listed for twelve fluorinated derivatives of ethane and ethylene.

COLUMBUS, OHIO RECEIVED JULY 23, 1947

---

[1] Henne in "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., p. 49.

[2] Henne and Ladd, THIS JOURNAL, **58**, 402 (1936).

[3] Locke, Brode and Henne, *ibid.*, **56**, 1726 (1934).

[4] Booth, *ibid.*, **55**, 2231 (1933).

[JOINT CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF SOUTH CAROLINA AND FROM HALOGEN CHEMICALS INC.]

Isomerization During Allylic Fluorination

BY A. M. WHALEY AND H. W. DAVIS

In the attempt to prepare $CCl_2{=}CClCHF_2$ (I) by the allylic fluorination of $CCl_2{=}CClCHCl_2$ (II) unexpected results were obtained. The fluorination was conducted in the usual way for allylic polychlorides[1] except that some antimony pentachloride was added. This was done to make sure that no material remained in the monofluoride stage. The boiling point of the above difluoride was predicted to be approximately 112°; however, the entire product distilled at about 53°. This material was found to be $CHCl{=}CClCF_3$ (III), the formation of which is explained by an allylic rearrangement during fluorination.

In order to determine if the antimony pentachloride was the isomerization agent, a fluorination was carried out using only antimony trifluoride. The product upon fractionation, yielded the following compounds: (III), 26%; $CHCl{=}CClCF_2Cl$ (IV), 21%; (I), 24%. There was also a small amount of material boiling at 150°, the predicted boiling point of $CCl_2{=}CClCHFCl$ (V). The course of the reaction is indicated by the following scheme:

$$\begin{array}{ccc}
CCl_2{=}CClCHCl_2 & \longrightarrow & (CHCl{=}CClCCl_3) \\
\downarrow & & \downarrow \\
CCl_2{=}CClCHFCl & & (CHCl{=}CClCFCl_2) \\
\downarrow & & \downarrow \\
CCl_2{=}CClCHF_2 & & CHCl{=}CClCF_2Cl \\
 & & \downarrow \\
 & & CHCl{=}CClCF_3
\end{array}$$

This experiment shows that even in the reaction with antimony trifluoride alone there is partial isomerization. Moreover, this isomerization becomes more complete as the reaction progresses. This was evidenced by the fact that the temperature of the reaction distillate was approximately 54° during the last part of the process.

This appears to be a novel case of rearrangement during allylic fluorination. It is of interest to note that it does not occur when compounds containing an allylic $—CCl_3$ group are fluorinated. For example, $CHCl{=}CClCCl_3$ (VI) is known to give (III)[1] and $CHCl{=}C(CH_3)CCl_3$ forms $CHCl{=}C(CH_3)CF_3$.[2] Hexachloropropene gives $CCl_2{=}CClCF_3$; however, in this case isomerization would not lead to a different product.

To study further the fluorination of allylic $—CHCl_2$ groups, $CHCl{=}CClCHCl_2$ (VII) was prepared by the method of Prins[3] and fluorinated. Only $CHCl{=}CClCHF_2$ (VIII) was found, but as in the case of hexachloropropene, even if rearrangement occurred, only one product would be formed.

The fluorination of $CCl_2{=}CHCHCl_2$ (IX) has been mentioned in the literature[4] with the formation of $CCl_2{=}CHCHF_2$ (X); however, the tetrachloroölefin actually obtained from the $CHCl_2CHClCHCl_2$ (XI) used as an intermediate is (VII)[3,5] and not (IX). Therefore, the difluoride reported to be (X) was in reality (VIII). Moreover, fluorination of (IX), if isomerization occurred as it does in the case of (II), would give $CHCl{=}CHCF_3$.

The rearrangement herein reported can be clarified by the mechanism

$$\begin{array}{ccl}
CCl_2{=}CClHCl_2 & \longrightarrow & CCl_2{=}CClC^*HCl + Cl^- \\
 & & \qquad\qquad\downarrow \\
 & & \qquad C^*Cl_2CCl{=}CHCl
\end{array}$$

This last then reacts with antimony trifluoride to form (III). The isomerization apparently occurs during the actual process of fluorination since no $CHCl{=}CClCCl_3$ (VI) was obtained when (II) was refluxed for one hour with antimony pentachloride. Generally, when it is possible for a $—CF_3$ group to form, one is obtained. Thus it is possible that the tendency to form the stable $—CF_3$ group is the driving force causing this allylic rearrangement. In any event, this isomerization represents a new method of preparation of $—CF_3$ groups. In our work at no time was there any evidence of the migration of a fluorine atom.

The physical constants, b.p. 186.7°, $n^{20}D$ 1.5333, obtained for our starting material (II), differed somewhat from those reported by Prins,[3] which were 183° and 1.5313, respectively. The structure of (II), however, could hardly be other than $CCl_2{=}CClCHCl_2$ since we prepared it from $CHCl_2CCl_2CHCl_2$, a compound which can only give one pentachloroölefin on dehydrochlorination. The presence of an allylic $—CHCl_2$ group was confirmed by the method of Prins,[3] the phenylhydrazone obtained having the same melting point as reported by that author. The above values were again found when (II) was made (a) from $CCl_3CHClCHCl_2$ formed by condensing $CHCl_3$ with $CHCl{=}CCl_2$ and (b) from the hexachloride fraction obtained in the chlorination of 1,2,3-trichloropropane.

That the properties of the material assumed to be (III) agreed with published values[1] was taken as sufficient proof of structure. Also, exhaustive chlorination in sunlight led to a compound melting at 109°, which agrees with the value reported for

---

(1) Henne, Whaley and Stevenson, THIS JOURNAL, **63**, 3478 (1941).

(2) Unpublished work, A. M. Whaley.

(3) Prins, *J. prakt. Chem.*, [2] **89**, 421 (1914).

(4) Henne, Alderson and Newman, THIS JOURNAL, **67**, 919 (1945).

(5) Gerding, Prins and Rijnders, *Rec. trav. chim.*, **65**, 165–167 (1946).

$CCl_3CCl_2CF_3$.[6] To prove the structure of (I), it was stirred at room temperature with excess sulfuric acid for six hours and poured in water. During the acid treatment hydrogen fluoride was evolved. An irritating oil was obtained which reacted with phenylhydrazine to give a hydrazone identical with that from (II), melting at 97–98°. The fluorinated material boiling at 97° is without doubt (IV) since its boiling point is 43° higher than that of (III). This is in agreement with the general change in boiling point caused by replacing a chlorine atom by an atom of fluorine in such groups.

Experimental

Fluorination of $CCl_2=CClCHCl_2$ (II) with Catalyst.—Ground antimony trifluoride, 537 g. (3 moles), was placed in a two-liter round-bottom flask surmounted by a 550-mm. air condenser. The top of this tube contained a thermometer and a bent tube connected to a water cooled downward condenser for distillation. A filter flask, containing about 200 ml. of concentrated hydrochloric acid and attached to the condenser with an adapter, served as a receiver. Fifteen milliliters of antimony pentachloride was added as catalyst. Then (II), 500 g. (2.35 moles), was added gradually from a dropping funnel, heat being applied at the same time. The reaction soon started and product distilled smoothly at 54°. Fresh olefin was added at the same rate at which product was removed. The distillate was washed three times with concentrated hydrochloric acid, once with dilute sodium hydroxide solution, dried and distilled to give 357 g., 92%, of (III), b. p. 53.7°.

Fluorination of (II) without Catalyst.—The apparatus was the same in this case as before. Ground antimony trifluoride, 970 g. (5.4 moles), was placed in the reaction flask, addition of 852 g. (4 moles) of (II) started and heat applied. The reaction was slow to start, rather strong heat being required. The distillate temperature at the start was 140° but it gradually went down, staying for awhile around 110°. During the addition of the last 300 g. of (II) the temperature was in the vicinity of 54°. The product was purified as before and distilled with the following results: 175 g., 26%, of (III), b. p. 53.7°; 157 g., 21%, (IV), b. p. 97°, n^{20}_{D} 1.4253; 179 g., 24%, (I), b. p. 114.4°, n^{20}_{D} 1.4452; 44 g. of material boiling from 115 to 180°.

Fluorination of $CHCl=CClCHCl_2$ (VII).—Two-hundred forty-eight grams (1.33 moles) of (VII) and 230 g. of ground antimony trifluoride (1.3 moles) reacted without catalyst as described above. The temperature of the distillate during the reaction was 100–110°. Purification gave 160 g., 82%, of (VIII), b. p. 89°, n^{20}_{D} 1.4150. The use of a small amount of antimony pentachloride as catalyst was found to hasten the reaction. However, when more than about 5 ml. of catalyst was used, the yield was decreased considerably.

Summary

The fluorination of two allylic polychlorides, $CCl_2=CClCHCl_2$ and $CHCl=CClCHCl_2$, has been studied. In the case of the first one, an isomerization leading to the formation of a $-CF_3$ group was observed. Two new compounds, $CHCl=CClCF_2Cl$ and $CCl_2=CClCHF_2$, are reported.

COLUMBIA, S. C. RECEIVED OCTOBER 8, 1947

---

[6] Henne and Whaley, THIS JOURNAL, **64**, 1158 (1942).

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

Reactions of Some Highly Chlorinated Unsaturated C_5 Hydrocarbons with Chlorine and Copper[1]

BY R. W. BOST AND J. A. KRYNITSKY[2]

In connection with a study of some highly chlorinated hydrocarbons, it was of interest to investigate some chlorination and coupling reactions of some polychlorinated unsaturated C_5 hydrocarbons which were used as intermediates in the preparation of hexachlorocyclopentadiene.[3]

Early work by Prins[4] showed that hexachloropropene can be made to add chlorine, in the presence of sunlight, to give almost quantitative yields of the octachloro compound. Later, McBee and co-workers[5,6] reported that the action of chlorine at high temperatures and pressures on polychloropentanes and heptanes results in a chlorinolysis with the formation of carbon tetrachloride, hexachloroethane, and a substance which was later shown to be octachlorocyclopentene. Recently, Prins[7] has reported that hexachlorocyclopentadiene reacts readily with chlorine to form octachlorocyclopentene yet octachloro-1,3-pentadiene (I) does not add the halogen but does give a small amount of hexachloroethane on continual exposure.

In this work, chlorinations of both octachloro-1,3-pentadiene (I) and 1,1,2,3,3,4,5,5,5-nonachloro-1-pentene (II) were carried out in the presence of direct sunlight. It was found that at temperatures of 100–130°, (I) undergoes a chlorinolysis reaction to form considerable amounts of hexachloroethane and carbon tetrachloride. However, at lower temperatures (36–52°), the extent of reaction was found to be much reduced and only small amounts of the chlorinolysis products were obtained. Experiments with (II) showed that this compound, like (I), is also cleaved through the action of chlorine to form hexachloroethane and *s*-heptachloropropane. With (II), however, reaction was found to proceed more rapidly than

---

[1] From a thesis presented by John A. Krynitsky to the Graduate School of the University of North Carolina, June, 1943, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. This work was done under a contract between the Naval Research Laboratory, Washington, D. C., and the University of North Carolina. Publication was delayed for security reasons.

[2] Present address: Naval Research Laboratory, Washington, D. C.

[3] Krynitsky and Bost, THIS JOURNAL, **69**, 1918 (1947).

[4] H. J. Prins, *J. prakt. Chem.*, **89**, 414–429 (1914).

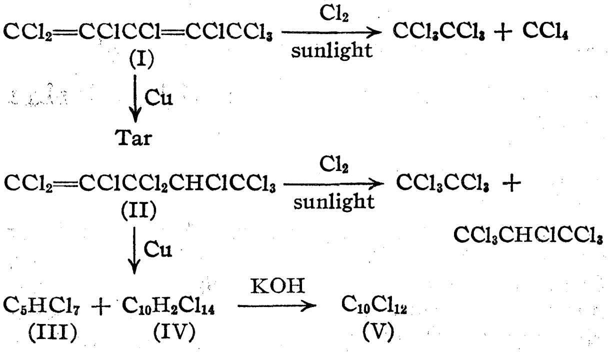
[5] McBee, Hass and Pierson, *Ind. Eng. Chem.*, **33**, 181–185 (1941).

[6] McBee, Hass and Bordenca, *ibid.*, **35**, 317–320 (1943).

[7] H. J. Prins, *Rec. trav. chim.*, **65**, 455–467 (1946).

with (I) and considerable amounts of hexachloroethane were obtained even at the lower temperatures (35–47°). In neither case was there any evidence of chlorine having been added to form the higher chlorinated pentanes.

Prins[4] found that certain compounds having chlorine atoms activated by a double bond undergo a coupling reaction when treated with an agent such as copper–bronze. Thus hexachloropropene yielded a compound C_6Cl_8 which is probably a perchloromethylenecyclopentene.[8] In the present work, this coupling reaction was extended to the compounds (I) and (II). When (I) was treated with equimolar quantities of freshly precipitated copper, a reaction took place with the evolution of heat. From this reaction mixture, no recognizable products were obtained except for a small amount of the starting (I). With (II), however, two definite compounds were obtained having the empirical formulas C_5HCl_7 (III) and $C_{10}H_2Cl_{14}$ (IV). (III) was found to react quantitatively with one mole of alcoholic potassium hydroxide while (IV) reacted with two moles. In the latter case, a compound $C_{10}Cl_{12}$ (V) was isolated. From their methods of formation and the quantitative reaction of (IV) with potassium hydroxide, (IV) is believed to be 3,4-bis-(α,β,β,β-tetrachloroethyl)-hexachloro-1,3,5-hexatriene and (V), 3,4-bis-(trichlorovinyl)-hexachloro-1,3,5-hexatriene.



Experimental

Action of Chlorine on Octachloro-1,3-pentadiene (I).—Into a 500-ml. quartz flask fitted with a gas inlet tube was placed 90 g. of (I). A slow stream of chlorine was admitted in the presence of direct sunlight for a total of thirty-two hours. During this period, the contents of the flask was maintained at 100–130° by means of an electric heater. Upon cooling, the reaction mixture turned to a semi-solid mass. This was found to be soluble in hot alcohol and was accordingly recrystallized three times from this solvent. There resulted 30 g. of a white crystalline material having a strong camphor odor, which was identified as being hexachloroethane by means of melting point, sublimation point and molecular weight determinations.

A later experiment was performed under similar conditions but employing ice-cooled traps to condense volatile products. Upon treatment of 90 g. of (I) with chlorine for seven hours, the traps were found to contain 17 g. of carbon tetrachloride which was identified by its boiling point, refractive index and density.

Action of Chlorine on 1,1,2,3,3,4,5,5,5-Nonachloro-1-pentene (II).—Into a flask, as above, was placed 90 g. of (II). Chlorine was admitted slowly in the presence of direct sunlight over a period of twenty-seven hours. During this addition, the temperature varied between 35 and 47°. The reaction mixture was transferred to a Claisen flask and distilled. A white, crystalline solid was noted to sublime and a total of 14 g. of this solid was collected at 30 mm. pressure in an ice-cooled receiver along with a small amount of a colorless liquid. No definite temperature could be obtained for the collection of this material. After removal of all solid, further distillation yielded fraction (a) 22 g., b. p. (4 mm.) 94–105° and fraction (b) 30 g., b. p. (3 mm.) 123–30°. Fraction (b) was identified as being recovered (II). Three recrystallizations of the solid material from alcohol gave a white crystalline compound which was identified as being hexachloroethane.

Inasmuch as fraction (a) was collected over a rather wide range, it was fractionated through a 50 cm. column of the Whitmore–Lux type packed with glass helices. There was obtained 10 g. of a colorless liquid b. p. (3–4 mm.) 93.2–93.5°. This was found to react quantitatively with 1 mole of alcoholic potassium hydroxide, proving it to contain one hydrogen. This together with molecular weight determinations showed it to have the molecular formula C_3HCl_7. Comparison with known unsymmetrical heptachloropropane showed the two compounds to be dissimilar. Since only one other structure is possible for a compound having this formula, the compound was concluded to be *s*-heptachloropropane: calcd. for C_3HCl_7: mol. wt. 285.2. Found: mol. wt. 290, 294 (titration with potassium hydroxide).

Reaction of (II) with Copper.—Into a flask fitted with a stirrer, thermometer and reflux condenser were placed 170 g. (0.45 mole) of (II) and 250 ml. of methanol. The temperature was raised to 60° and 29 g. (0.46 mole) of freshly precipitated copper was added in small portions, with stirring, over a period of two and one-half hours so as to maintain the temperature at 60–64°. The mixture was then refluxed overnight. After cooling, the material was washed three times with water. The organic layer contained a precipitate which was removed by filtration. Fractionation of the clear, dark amber, viscous filtrate through the Whitmore–Lux column yielded 34 g. of light golden (III) b. p. (1–2 mm.) 95–100° and a deep red resinous residue. (III) was found to react quantitatively with one mole of alcoholic potassium hydroxide showing it to contain one hydrogen. This and molecular weight determinations established its formula as being C_5HCl_7. Calcd. for C_5HCl_7: mol. wt., 309.2. Found: mol. wt., 285 (ebullioscopic), 303, 293 (titration with potassium hydroxide).

Two recrystallizations of the precipitate from carbon tetrachloride yielded 7 g. of white crystalline (needles) (IV) having a strong biphenyl-like odor and melting at 205–206°. (IV) was found to react quantitatively with two moles of alcoholic potassium hydroxide indicating the presence of two hydrogens. This together with the molecular weight determinations and analyses established its formula as being $C_{10}H_2Cl_{14}$. *Anal.* Calcd. for $C_{10}H_2Cl_{14}$: Cl, 80.27; mol. wt., 618.4. Found: Cl, 80.31, 80.57; mol. wt., 584 (ebullioscopic), 610, 622 (titration with potassium hydroxide).

Reaction of (I) with Copper.—When 91 g. (0.26 mole) of (I) was treated with 17 g. (0.27 mole) of copper under the conditions described above, a tarry reaction mixture was obtained. From this, no identifiable materials except for 23 g. of recovered (I) were obtained.

Reaction of (IV) with Potassium Hydroxide.—Five grams of (IV) dissolved in 30 ml. of hot carbon tetrachloride was treated with an excess of an alcoholic potassium hydroxide solution (approx. 0.35 *N*) to a strong permanent pink of phenolphthalein. The mixture was boiled on a steam-bath for five minutes and the excess base was neutralized carefully with dilute hydrochloric acid. Upon evaporation to one-half volume and cooling in an ice-bath, a white crystalline solid separated. Two

---

[8] Brederode, Gerding and Prins, *Rec. trav. chim.*, **65**, 184 (1946).

recrystallizations from carbon tetrachloride yielded 3 g. of white crystalline (V). (V) had practically no odor and melted at 113–113.5°. From analyses and molecular weight determinations, the formula of (V) was established as being $C_{10}Cl_{12}$.

Anal. Calcd. for $C_{10}Cl_{12}$: Cl, 78.00; mol. wt., 545.5. Found: Cl, 77.94; mol. wt., 537.

Summary

1. Octachloro-1,3-pentadiene (I) when treated with chlorine in the presence of direct sunlight at elevated temperatures undergoes chlorinolysis to yield hexachloroethane and carbon tetrachloride.
2. 1,1,2,3,3,4,5,5,5-Nonachloro-1-pentene (II) reacts as above but at lower temperatures to give hexachloroethane and *s*-heptachloropropane.
3. (II) reacts with copper to yield chiefly a dehalogenated product, C_5HCl_7 (III), and a smaller amount of a coupled product, $C_{10}H_2Cl_{14}$ (IV).
4. No definite products were obtained through the reaction of (I) with copper.
5. (IV) is dehydrohalogenated by potassium hydroxide to give $C_{10}Cl_{12}$ (V).
6. Structural formulas are suggested for compounds (IV) and (V).

CHAPEL HILL, NORTH CAROLINA

RECEIVED AUGUST 2, 1947

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE, AND THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

The Electric Moments of Some *p*-Substituted Phenyl Selenocyanates and Thiocyanates

BY TOD W. CAMPBELL AND MAX T. ROGERS

The electric moments of a series of *para* substituted phenyl thiocyanates and phenyl selenocyanates have been studied to obtain information concerning the nature of resonance in these compounds. None of the substances whose dipole moments are reported here have been measured previously, but values have been reported for phenyl thiocyanate,[1] *p*-chlorophenyl thiocyanate,[1] *p*-tolyl selenocyanate[2] and *p*-chlorophenyl selenocyanate[2] so that group moments may be calculated for the thiocyano- and selenocyano- groups in aromatic compounds.

Experimental Part

Materials

Benzene.—Baker C. P. benzene was dried over sodium and filtered before use, d^{25}_4 0.87344, n^{25}_D 1.4978.

***p*-Dimethylaminophenyl Thiocyanate and *p*-Aminophenyl Thiocyanate.**—These were prepared by the method of Brewster and Schroeder[3]: *p*-dimethylaminophenylthiocyanate, white needles, m. p. 75°; *p*-aminophenyl thiocyanate,[3a] m. p. 57°.

***p*-Dimethylaminophenyl Selenocyanate and *p*-Aminophenyl Selenocyanate.**[4]—These were prepared from cyanogen triselenide[5] and, respectively, dimethylaniline (m. p. product 105°) and aniline (m. p. of product 91–92°).

***p*-Nitrophenyl Thiocyanate and *p*-Nitrophenyl Selenocyanate.**—These were prepared from diazotized *p*-nitroaniline and, respectively, ferric thiocyanate (m. p. of product 133°) and potassium selenocyanate (m. p. of product 137–138°).[6]

***p*-Selenocyanophenyl Thiocyanate** was prepared from diazotized *p*-aminophenyl thiocyanate and potassium selenocyanate in a buffered solution.[7] The product melted at 111.5–112° after repeated recrystallization from a ligroin–benzene mixture.

***p*-Methoxyphenyl selenocyanate** was synthesized from diazotized anisidine and potassium selenocyanate. The product[8] melted at 65°.

Apparatus and Method

Electric moments were measured in benzene solution at 25° using a heterodyne-beat apparatus and technique previously described.[9] The experimental data and molar polarizations are shown in Table I; the derived values of the molar polarization at infinite dilution (P^{∞}), the molecular refraction, MR_D, and the dipole moment, are shown in Table II. The molecular refraction of each compound was obtained from the refractive indices of the solutions[2] (Table I) or, in the cases of *p*-aminophenyl selenocyanate and *p*-methoxyphenyl selenocyanate, from empirical atomic and group refractions.[10]

Discussion of Results

The observed dipole moments are compared in Table III with the vector sums of the moments of the substituents, assuming free rotation about single bonds. The group moments and angles used are: $C_{aromatic}$–H, 0.4 (assumed), 180°; C_{ar}–NO_2, 3.55, 0°; C_{ar}–NH_2,[11] 1.86, 143°; C_{ar}–$N(CH_3)_2$,[11] 1.98, 180°; C_{ar}–OCH_3,[11] 1.37, 119°; C_{ar}–SCN,[2] 3.36, 58°30′; C_{ar}–SeCN,[2] 3.83, 53°30′. (The angle is 0° when the negative end of the dipole is directed away from the ring.)

There is an increase in dipole moment when an electron donating group is *para* to the selenocyano or thiocyano group and this increment may be attributed to enhancement of resonance. The effect is greater with the dimethylamino group

---

[1] E. Bergmann, L. Engel and S. Sandor, *Z. physik. Chem.*, **B10**, 397 (1930).

[2] M. T. Rogers and T. W. Campbell, THIS JOURNAL, **69**, 2039 (1947).

[3] R. Q. Brewster and W. Schroeder, "Organic Syntheses," Vol. II, John Wiley and Sons, 1943, p. 574.

[3a] E. Söderbäck, *Ann.*, **419**, 217 (1919).

[4] F. Challenger, A. T. Peters and J. Halevy, *J. Chem. Soc.*, 1648 (1926).

[5] A. Verneuil, *Ann. chim. phys.*, [6] **9**, 328 (1886).

[6] H. Bauer, *Ber.*, **46**, 92 (1913).

[7] F. Challenger and A. T. Peters, *J. Chem. Soc.*, 1364 (1928).

[8] O. Behagel and M. Rollmann, *J. prakt. Chem.*, **123**, 336 (1929).

[9] M. T. Rogers and J. D. Roberts, THIS JOURNAL, **68**, 843 (1946).

[10] The group refractions of the —SCN and —SeCN groups were taken to be 13.4 and 18.0.

[11] Estimated from values of various *para* disubstituted benzene derivatives in the literature using principally the *p*-chloro-, *p*-fluoro- and *p*-methyl- compounds.

TABLE I
DIELECTRIC CONSTANTS, DENSITIES, REFRACTIVE INDICES AND POLARIZATIONS IN BENZENE AT 25°

f_2	ϵ	$n^{25}D$	d	P_2
p-Aminophenyl thiocyanate				
0.001464	2.328		0.87422	588.3
.001578	2.333		.87434	591.6
.001808	2.343	1.4982	.87431	600.9
.002521	2.369	1.4984	.87474	587.3
.004182	2.432	1.4988	.87561	576.2
p-Dimethylaminophenyl thiocyanate				
0.001325	2.334		0.87410	712.4
.002818	2.402	1.4987	.87483	699.7
.003788	2.447	1.4988	.87530	697.0
.006030	2.549	1.4991	.87626	682.3
.007456	2.614	1.4993	.87710	672.6
.007979	2.637	1.4997	.87737	669.7
p-Nitrophenyl thiocyanate				
0.002205	2.303	1.4983	0.87517	241.0
.004283	2.329	1.4988	.87672	230.4
.005624	2.350	1.4991	.87780	235.9
.007304	2.373	1.4992	.87911	236.3
.009116	2.400	1.4995	.88049	237.7
.010934	2.423	1.5000	.88188	223.6
p-Aminophenyl selenocyanate				
0.001147	2.316		.87471	584.3
.001315	2.322		.87438	591.9
.001624	2.335		.87511	591.1
.002078	2.352		.87530	591.2
p-Dimethylaminophenyl selenocyanate				
0.001008	2.318		0.87453	703.7
.001974	2.363		.87535	704.6
.002205	2.376		.87555	721.7
.002792	2.399	1.4982	.87628	694.3
.003869	2.449	1.4987	.87726	692.7
.004228	2.465	1.4987	.87761	689.9
p-Methoxyphenyl selenocyanate				
0.001645	2.317		0.87511	437.0
.002421	2.341		.87599	450.2
.005249	2.420		.87879	441.8
p-Nitrophenyl selenocyanate				
0.000993	2.290		0.87402	309.2
.001852	2.306	1.4983	0.87518	311.5
.003631	2.339	1.4989	.87746	307.7
.005651	2.379	1.4992	.88012	311.1
.007567	2.417	1.4995	.88237	313.5
.010602	2.477	1.5000	.88632	311.8
p-Selenocyanophenyl thiocyanate				
0.003598	2.358		.87790	384.9
.005198	2.392	1.4989	.88011	370.4
.009200	2.486	1.5000	.88500	370.1

than with the amino group and is least with the methoxy group. The enhancement is larger for the thiocyano than for the selenocyano group for the same *para* substituent; thus, the increment (1.0) observed for *p*-dimethylaminophenylthiocyanate is almost as large as found for *p*-nitrodimethylaniline (1.35).

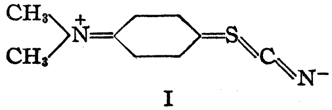
TABLE II
MOLAR REFRACTIONS, MOLAR POLARIZATIONS AND DIPOLE MOMENTS

Substance	MR_D	P_∞	μ (Debye)
p-Aminophenyl thiocyanate	47.0	592	5.16
p-Dimethylaminophenyl thiocyanate	54.0	720	5.70
p-Nitrophenyl thiocyanate	46.0	243	3.10
p-Aminophenyl selenocyanate	43.0	600	5.22
p-Dimethylaminophenyl selenocyanate	57.0	708	5.64
p-Methoxyphenyl selenocyanate	48.1	450	4.42
p-Nitrophenyl selenocyanate	50.5	312	3.58
p-Selenocyanophenyl thiocyanate	55.4	385	4.02

TABLE III
OBSERVED AND CALCULATED ELECTRIC MOMENTS OF SOME DISUBSTITUTED BENZENES

Compound X⬡Y X	Y	$\mu_{obs.}$	$\mu_{calcd.}$	$\mu_{obs.} - \mu_{calcd.}$
NH_2	SCN	5.22	4.51	0.71
$N(CH_3)_2$	SCN	5.70	4.71	.99
NH_2	SeCN	5.16	5.02	.14
$N(CH_3)_2$	SeCN	5.64	5.25	.39
OCH_3	SeCN	4.40	4.42	− .02
NO_2	SCN	3.10	3.38	− .28
NO_2	SeCN	3.58	3.34	.24
SCN	SeCN	4.02	4.23	− .21

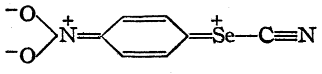
It is unlikely that the larger increments, at least, could be accounted for by a widening of the angles alone since the angle of the dimethylamino group is already small (or zero) and we would not expect a large change in the angle C_{ar}–SCN. It seems more likely that structures such as I are somewhat stabilized in the molecules with a strong electron-receiving group (–SCN or –SeCN) *para* to a strong electron-donating group (–$N(CH_3)_2$, NH_2, OCH_3) and contribute to a small extent to the ground state of the molecule. Since the charge separation is large such structures have a large effect on the dipole moment.



I

Selenium might be expected to be able to expand its octet more easily than sulfur since it belongs to a higher period; however, structures such as I appear to be less important in the selenocyanates, probably because of the smaller tendency of selenium to form multiple bonds.

The thiocyanate and selenocyanate groups might also act as electron donating groups and the increment observed for *p*-nitrophenyl selenocya-



II

nate could be due to a small contribution of structures such as II; this explanation is made doubtful by the observed decrement in the case of *p*-nitrophenyl thiocyanate.

An alternative explanation of the observed increments might be that they arise from an abnormally large vibration polarization[12] such as is found in *p*-dinitrobenzene. The large increments observed here and, especially, the large differences between the thio- and selenocyanates suggests that these are principally resonance effects.

---

(12) L. E. Sutton, *Annual Reports Chem. Soc.*, **37**, 36 (1940).

Summary

The electric moments of some *para* substituted phenylthiocyanates and phenylselenocyanates have been measured in benzene solution at 25°; the substituents used were the amino, dimethylamino, nitro, and methoxyl groups. A rather large enhancement of resonance is observed when the thiocyano- and, to a smaller extent, the selenocyano- group is *para* to an electron-receiving group. The results have been briefly discussed in terms of resonance.

RECEIVED OCTOBER 3, 1947

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

Properties of Polymers as Functions of Conversion. IV. Composition Studies of Rubber-like Copolymers[1]

BY F. T. WALL, R. W. POWERS,[2] G. D. SANDS[3] AND G. S. STENT

It is generally recognized that the products obtained at different stages of conversion in a polymerization reaction will exhibit wide variations in chemical and physical properties. For example, the intrinsic viscosity can show changes of several hundred per cent.,[4] and the molecular weight can likewise vary several fold.[5] In the case of copolymers, the composition of the product, which is generally different from that of the reaction mixture, can also change during the conversion.

Numerous copolymer systems have been investigated from a composition standpoint by Mayo,[6] Alfrey[7] and others. For bulk and solution polymerizations, relatively simple theories have been devised for the compositional relationships,[6a,7a,8] but for emulsion systems, the situation is much more complicated. A considerable amount of experimental work, however, has been done on emulsion copolymerizations. For example, Meehan[9] studied the GR-S system in some detail and observed that the styrene content varied from 17 to 25% in the course of a reaction when the initial charge was 25% styrene. Fordyce and Chapin[10] also have investigated several emulsion systems. The investigations here reported deal with the dependence of composition on conversion for a number of rubber-like copolymers other than GR-S.

Theory

During recent years considerable thought has been given to the theoretical aspects of the compositional relationships in copolymers.[6a,7a,8] These theories ultimately give rise to a basic differential equation governing the relative rates of disappearance of the monomers. This differential equation, which is valid for single phase polymerizations, is

$$\frac{dM_1}{dM_2} = \frac{M_1(r_1M_1 + M_2)}{M_2(M_1 + r_2M_2)} \qquad (1)$$

where M_1 and M_2 equal the number of moles of unreacted monomer and the parameters r_1 and r_2 represent the ratios of certain specific reaction rate constants for the chain growth steps.[11] The general validity of equation (1) has been established by many experiments, although it is not obvious that it should be valid for emulsion reactions. However, it will be seen later that an equation of the same type does empirically agree with the observations for many emulsion systems, although considerable doubt can be raised as to its full validity in some cases. Actually it is possible to derive such an equation for emulsion systems by making certain assumptions such as the following:

(1) It is first supposed that the reaction does not take place in the oil phase of the emulsion. (If the reaction occurs in the oil phase, then equation (1) would be expected to hold right off and the present discussion would be irrelevant except for the perturbing effect of the monomer solubility in water.)

(2) Secondly, it is assumed that the amount of monomeric material in the actual reaction environment (supposed not to be the oil phase) repre-

---

[1] This investigation was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program (first reported in March, 1941).

[2] Present address: Cryogenic Laboratory, Ohio State University, Columbus 10, Ohio.

[3] Present address: Chemical and Physical Research Laboratories, Firestone Tire and Rubber Company, Akron 17, Ohio.

[4] F. T. Wall, R. W. Powers, G. D. Sands and G. S. Stent, THIS JOURNAL, **69**, 904 (1947).

[5] F. T. Wall and L. F. Beste, *ibid.*, **69**, 1761 (1947).

[6] (a) F. R. Mayo and T. M. Lewis, *ibid.*, **66**, 1594 (1944); (b) T. M. Lewis, F. R. Mayo and W. F. Hulse, *ibid.*, **67**, 1701 (1945).

[7] (a) T. Alfrey and Goldfinger, *J. Chem. Phys.*, **12**, 205 (1944); (b) T. Alfrey and J. G. Harrison, Jr., THIS JOURNAL, **68**, 299 (1946).

[8] F. T. Wall, *ibid.*, **66**, 2050 (1944).

[9] E. J. Meehan, *J. Polymer Sci.*, **1**, 318 (1946).

[10] R. G. Fordyce and E. C. Chapin, THIS JOURNAL, **69**, 581 (1947).

[11] T. Alfrey, F. R. Mayo and F. T. Wall, *J. Polymer Sci.*, **1**, 581 (1946).

sents only a small fraction of the total monomer present.

(3) Finally it is postulated that the distribution of monomers between the oil and reaction phases is subject to the ideal solution laws. This is equivalent to assuming that the ratio of the reactants in the oil phase is proportional to (but not necessarily equal to) their ratio in the reaction phase. Although we speak of "reaction phase," it must be understood that the reaction may take place in the neighborhood of some interface or in soap micelles as well as in a distinct phase of the system.

In accordance with the above assumptions, the desired relationship can readily be derived. Letting M_1 and M_2 represent the total amounts of the monomers, and letting M'_1 and M'_2 equal the amounts in the reaction phase, we can write the following differential equation for the relative rates of disappearance of the two monomers

$$\frac{\mathrm{d}M_1}{\mathrm{d}M_2} = \frac{M'_1(r_1M'_1 + M'_2)}{M'_2(M'_1 + r_2M'_2)} \qquad (2)$$

According to the ideal solution laws

$$\frac{M'_1}{M'_2} = k\,\frac{M_1}{M_2} \qquad (3)$$

it being assumed that M'_1 and M'_2 are very small compared to M_1 and M_2. Substituting the above relationship (3) into the differential equation (2), we find

$$\frac{\mathrm{d}M_1}{\mathrm{d}M_2} = \frac{M_1(kr_1M_1 + M_2)}{M_2(M_1 + r_2/kM_2)} = \frac{M_1(r'_1M_1 + M_2)}{M_2(M_1 + r_2'M_2)} \qquad (4)$$

where $r'_1 = kr_1$ and $r'_2 = r_2/k$. This equation has the same form as the basic relationship valid for single phase polymerizations, except that r_1 and r_2 are respectively multiplied and divided by the distribution coefficient k. The above derivation suggests that the copolymerization equation might be applicable to emulsion systems even if the polymerization occurs outside the oil phase. Accordingly the results here reported will be interpreted on that basis. To emphasize the fact that the copolymerization parameters for emulsion systems are not necessarily ratios of specific reaction rate constants, they will be represented as primed quantities (r'_1 and r'_2). Of course if the reaction occurs in the oil phase, this distinction is unnecessary.

Partial Conversion Composition

In earlier publications[4,5] the concept of partial conversion properties of polymers was introduced using intrinsic viscosities and molecular weights as examples. At this time it is appropriate to define what we shall mean by the partial conversion composition of a copolymer. If $\bar{F}_i$ represents the average weight fraction of monomer i in the copolymer, then the partial conversion composition, $\bar{\bar{F}}_i$ will be given by the relationship

$$\bar{\bar{F}}_i = \bar{F}_i + W\frac{\mathrm{d}\bar{F}_i}{\mathrm{d}W} \qquad (5)$$

where W is the weight conversion. Taking account of the definitions of $\bar{\bar{F}}_i$ and W, it can be shown from (5) that

$$\bar{\bar{F}}_1 = \frac{m_1\mathrm{d}\mathbf{M}_1}{m_1\mathrm{d}\mathbf{M}_1 + m_2\mathrm{d}\mathbf{M}_2} \qquad (6)$$

where $\mathbf{M}_1$ and $\mathbf{M}_2$ are the molecular weights of the monomers. It is evident that $\bar{\bar{F}}_i$ represents the composition of the copolymer increment which forms at any given instant during the reaction. Assuming the validity of differential equation (4), this can be rewritten as

$$\bar{\bar{F}}_1 = \frac{\mathbf{M}_1M_1(r'_1M_1 + M_2)}{\mathbf{M}_1r'_1M_1^2 + (\mathbf{M}_1 + \mathbf{M}_2)M_1M_2 + \mathbf{M}_2r'_2M_2^2} \qquad (7)$$

Experimental Section

The polymerizations studied include butadiene with 2,5-dichlorostyrene, with *p*-chlorostyrene, with acrylonitrile, and with 1-cyanobutadiene. Using dodecyl mercaptan as a modifier and Procter and Gamble SF Flakes as the emulsifying agent, these copolymerizations were carried out for various initial charges. In every case, potassium persulfate was the catalyst used.

The polymerizations were carried out in 12 and 28-ounce beverage bottles fitted with special self-sealing caps. During the polymerizations the reaction bottles were immersed in a water-bath maintained at 50 ± 0.02°, and were rotated end-over-end at the rate of 20 revolutions per minute. Samples of the latex were removed at various times by means of a brass syringe, the needle of which was inserted into the latex through the self-sealing bottle cap.[12] The polymers were coagulated by adding the latex dropwise to absolute ethanol with vigorous mechanical stirring.

To check the validity of the sampling technique, a special experiment was conducted using butadiene with 2,5-dichlorostyrene. In this experiment the composition of a very high conversion sample obtained from a 12-ounce bottle, from which several samples had been removed in the course of the reaction, was compared with the composition of a polymer formed in a 4-ounce bottle from which no low conversion samples had been taken. The experiment was carried out for three different initial monomer ratios, *i. e.*, 85/15, 60/40, and 40/60 by weight. As long as the final percentage conversion was the same, no significant composition differences were observed between the products obtained in the two different ways. This suggests that the sampling technique is truly representative; if unrepresentative samples had been removed, the effect would have been evident in the composition of the final product.

The following materials were used in these studies: 1. Butadiene: Phillips "Research Grade" 1,3-butadiene was used throughout the investigation. 2. 2,5-Dichlorostyrene: This material was obtained from the Monsanto Chemical Company. It was redistilled immediately before use, as were all other liquid monomers employed in this investigation. At a pressure of 1–2 mm., it boiled between 57 and 58°. 3. *p*-Chlorostyrene: The *p*-chlorostyrene used in this study was obtained from the Dow Chemical Company and boiled at 114° at 6 mm. pressure. 4. Acrylonitrile: Redistilled Eastman "Practical Grade" acrylonitrile was used for this investigation. At atmospheric pressure, it was distilled at 77°. 5. 1-Cyanobutadiene: This chemical consisted mostly of the *trans*-isomer and was obtained from the Organic Division at the University of Illinois. It distilled at 49° under a pressure of 31 mm. 6. *n*-Dodecyl Mercaptan: Very pure *n*-dodecyl mercaptan was prepared by the Organic Division at the University of Illinois by the hydrolysis of

---

[12] R. L. Frank, C. E. Adams, J. R. Blegen, R. Deanin and P. V. Smith, *Ind. Eng. Chem.*, **39**, 887 (1947).

n-dodecylisothiouronium chloride prepared from pure *n*-dodecyl bromide. The boiling range of this mercaptan was 127–129° at 9 mm., and the material was believed to be 99.5% pure.

Two samples from each batch of latex removed from the reactor were used to determine the conversion by a method of total solids. The composition of the copolymers of butadiene with chloro-substituted styrenes was determined by chlorine analyses. These analyses were accomplished by fusing the copolymer samples with sodium and titrating the chloride formed with silver nitrate, using the amperometric technique of Laitinen and Kolthoff.[13] The compositions of butadiene–acrylonitrile copolymers were determined by nitrogen analyses carried out by a macro-Kjeldahl method.[14]

Discussion and Analysis of Results

Each monomer pair investigated will be considered separately, with each set of data, calculations, and conclusions treated as a unit. In every case, butadiene will be considered the first monomer of the pair and will be given the subscript "1."

To determine the copolymerization parameters for butadiene with 2,5-dichlorostyrene, three different monomer ratios were used. These ratios were 85/15, 70/30, and 50/50 parts of butadiene to parts of 2,5-dichlorostyrene by weight. Samples were taken from the polymerization bottle at intervals corresponding roughly to 10, 20, 30, and 40% conversion. As indicated earlier, the conversions were determined in duplicate, whereas the compositions were measured either in triplicate or duplicate for each sample. The results for this system are given in Tables I-A, I-B, and I-C. From a knowledge of the composition as a function of conversion, it is possible to determine the copolymerization parameters.

Theoretically, a single run with analyses corresponding to several conversions should suffice to determine the parameters. In practice, however, it is much better to use each of several different initial charging ratios to make the calculations. The procedure finally adopted was the following: The logarithm of the amount of unreacted butadiene was plotted against the logarithm of the amount of unreacted comonomer. It was found empirically that these plots gave straight lines, at least for moderate conversions. Taking the initial slope of such a line, one obtains a relationship between the two parameters, r'_1 and r'_2. Letting the slope of the log plot equal m, it is readily seen that

$$m = \frac{d \ln M_1}{d \ln M_2} = \frac{r'_1 M_1 + M_2}{M_1 + r'_2 M_2} \qquad (8)$$

Evidently if one has experimental data for two different initial charging ratios, one can calculate r'_1 and r'_2 from the two simultaneous equations of

TABLE I-A

Initial charge in 12-oz. bottle:
68.0 g. butadiene
12.01 g. 2-5-dichlorostyrene
0.2814 g. dodecyl mercaptan
140.0 g. 3% solution of P. & G. SF Flakes
8.0 ml. 3% solution of $K_2S_2O_8$

Reaction time, hr.	Fractional conversion		Weight fraction of dichlorostyrene in polymer	
0	0		..	
1.9	0.131 .131	0.131	0.2546 .2554 .2570	0.2557
3.2	.227 .233	.230	.2434 .2436	.2435
4.4	.304 .304	.304	.2335 .2369	.2352
5.7	.361 .364	.362	.2244 .2293 .2293	.2277

TABLE I-B

Initial charge in 12-oz. bottle:
56.0 g. butadiene
24.02 g. 2,5-dichlorostyrene
0.2789 g. dodecyl mercaptan
140.0 g. 3% solution of P. & G. SF Flakes
8.00 ml. 3% solution of $K_2S_2O_8$

Reaction time, hr.	Fractional conversion		Weight fraction of dichlorostyrene in polymer	
0	0		..	
1.5	0.131 .133	0.132	0.4181 .4226 .4251	0.4219
2.5	.240 .241	.240	.4081 .4110 .4147	.4113
3.5	.338 .343	.340	.4014 .4028 .4083	.4042
4.5	.440 .450	.445	.3860 .3900 .3947	.3902

TABLE I-C

Initial charge in 12-oz. bottle:
40.0 g. butadiene
39.99 g. 2,5-dichlorostyrene
0.2772 g. dodecyl mercaptan
140.0 g. 3% solution of P. & G. SF Flakes
8.00 ml. 3% solution of $K_2S_2O_8$

Reaction time, hr.	Fractional conversion		Weight fraction of dichlorostyrene in polymer	
0	0		..	
1.1	0.154 .154	0.154	0.5874 .5878 .5906 .5925	0.5896
1.7	.275 .276	.276	.5734 .5794 .5795	.5774
2.4	.417 .419	.418	.5736 .5742 .5797	.5758
3.1	.544 .547	.546	.5614 .5630 .5657 .5678	.5641

---

(13) H. A. Laitinen and I. M. Kolthoff, *J. Phys. Chem.*, **45**, 1079 (1941).

(14) The authors are indebted to Dr. H. A. Laitinen and his group for these analyses.

type (8) involving the two m's. To get an indication of the experimental error, at least three runs were always made, and the best over-all value for the parameters was selected. The procedure adopted was to plot r'_1 *versus* r'_2 and note the points of intersection for the three (or more) lines so plotted. After inscribing a circle in the triangle resulting from three such lines, one can take the center of that circle to determine the best set of values for the parameters. For purposes of illustration, the graphs will be given for the butadiene–2,5-dichlorostyrene system (Figs. 1–2), but similar plots will not be included for all the other pairs investigated. The procedure employed here differs from that used by Mayo and Lewis,[6a] who used the integrated form of the equation instead of the differential form.

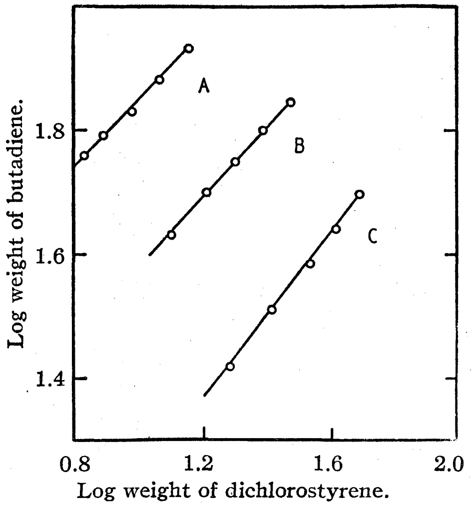


Fig. 1.—Log weight butadiene *vs.* log weight dichlorostyrene for determining values of m. Curves labeled A, B and C correspond to data in Tables 1-A, I-B and I-C.

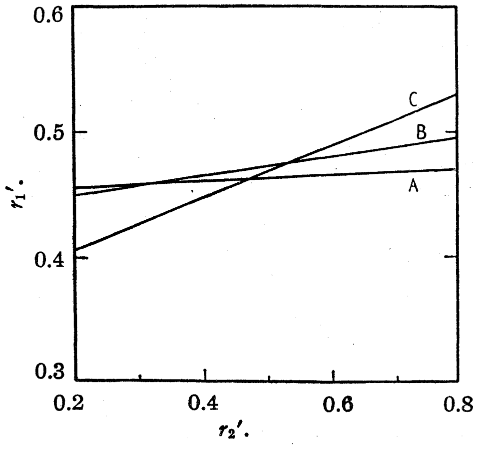


Fig. 2.—Plot for determining copolymerization parameters for dichlorostyrene–butadiene system. Lines A, B and C correspond to data in Tables I-A, I-B and I-C.

The parameters r'_1 and r'_2 were each found to equal 0.46 for butadiene with 2,5-dichlorostyrene. This suggests that the system butadiene with 2,5-dichlorostyrene can form an azeotropic copolymer[8] of composition 75 parts 2,5-dichlorostyrene to 25 parts of butadiene by weight (this is a one-to-one molar ratio). To test this prediction, an experiment was carried out with that initial charge. The results are given in Table II. It will be observed that the composition was indeed very constant over a wide range of conversion, justifying the theory in this connection.

Table II

Initial charge in 12-oz. bottle	60.92 g.	2,5-dichlorostyrene
	19.1 g.	butadiene
	0.2832 g.	dodecyl mercaptan
	140.0 g.	3% solution of P. & G. SF Flakes
	8.00 ml.	3% solution of $K_2S_2O_8$

Reaction time, hr.	Fractional conversion		Weight fraction of dichlorostyrene in polymer	
0.5	0.032 .42	0.037	0.7743 .7788	0.7766
1.1	.286 .290	.288	.7766 .7766 .7795	.7784
1.6	.519 .524	.522	.7742 .7782 .7790	.7772
6.0	.946 .950	.948	.7489 .7502	.7496

The validity of the theory was further tested by carrying out a special experiment involving a 3 to 1 weight charging ratio of butadiene with 2,5-dichlorostyrene, and comparing the observed compositions with those calculated using the parameters obtained from the experiments described earlier. The results are shown in Fig. 3, which gives the calculated average and partial conversion compositions together with the observed average compositions. Bearing in mind the fact that the parameters were determined by completely independent experiments not involving use of any of the points included in Fig. 3, it is

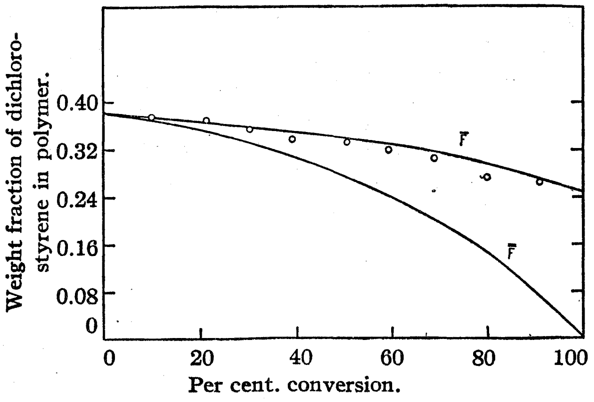


Fig. 3.—Predicted ($\bar{F}$) and partial conversion ($\bar{\bar{F}}$) compositions of dichlorostyrene in copolymer with butadiene together with experimental average compositions (indicated by circles).

clear that the theory agrees well with observation. It will be noted that although the composition of the charge was only 25% (by weight) of the substituted styrene, the partial conversion composition was initially 38%. This figure falls off with conversion, finally ending up at zero.

Butadiene and *p*-chlorostyrene were polymerized for charging ratios of 80/20, 60/40, and 40/60, butadiene to the substituted styrene, by weight. The results for this system are given in Tables III-A, III-B, and III-C. The values for r'_1 and r'_2 were found to be 1.07 and 0.42, respectively.

Butadiene and acrylonitrile were copolymerized in the weight ratios 85/15, 75/25, and 65/35. The data for these polymerizations are compiled in Tables IV-A, IV-B, and IV-C. The values of the parameters r'_1 and r'_2 appear to be 0.4 and -0.1. The negative value found for r'_2 is of course meaningless as far as the theory is concerned. Nevertheless, the agreement for the several compositions was excellent, as seen in Fig. 4, demonstrating that the copolymerization equation may have only empirical significance for emulsion systems. The negative value in the case of the acrylo-

TABLE III-A

Initial charge in 12-oz. bottle
16.01 g. *p*-chlorostyrene
64.0 g. butadiene
0.2827 g. dodecyl mercaptan
140.0 g. 3% solution of P. & G. SF Flakes
8.00 ml. 3% solution of $K_2S_2O_8$

Reaction time, hr.	Fractional conversion		Weight fraction of *p*-chlorostyrene in polymer	
0				
2.5	0.149	0.150	0.1820	0.1824
	.152		.1829	
4	.252	.254	.1835	.1859
	.256		.1858	
			.1885	
5.5	.356	.356	.1933	.1933
	.356			
7	.481	.482	.1878	.1892
	.484		.1906	

TABLE III-B

Initial charge in 12-oz. bottle
31.97 g. *p*-chlorostyrene
48.0 g. butadiene
0.2781 g. dodecyl mercaptan
140.0 g. 3% solution of P. & G. SF Flakes
8.00 ml. 3% solution of $K_2S_2O_8$

Reaction time, hr.	Fractional conversion		Weight fraction of *p*-chlorostyrene in polymer	
0	0			
2	0.188	0.190	0.3597	0.3620
	.192		.3617	
			.3647	
3	.300	.300	.3681	.3693
	.301		.3705	
4.2	.458	.463	.3627	.3632
	.468		.3637	
5	.541	.543	.3690	.3699
	.545		.3708	

TABLE III-C

Initial charge in 12-oz. bottle
48.01 g. *p*-chlorostyrene
32.0 g. butadiene
0.2759 g. dodecyl mercaptan
140.0 g. 3% solution of P. & G. SF Flakes
8.00 ml. 3% solution of $K_2S_2O_8$

Reaction time, hr.	Fractional conversion		Weight fraction of *p*-chlorostyrene in polymer	
0				
1.5	0.218	0.219	0.5326	0.5345
	.220		.5364	
2.2	.485	.487	.5596	.5607
	.489		.5617	
4.2	.696	.706	.5654	.5684
	.716		.5670	
			.5728	

TABLE IV-A

Initial charge in 28-oz. bottles
30.09 g. acrylonitrile
170.0 g. butadiene
0.6970 g. dodecyl mercaptan
350.0 g. 3% solution of P. & G. SF Flakes
20.00 ml. 3% solution of $K_2S_2O_8$

Reaction time, hr.	Fractional conversion		Nitrogen in polymer, %		Weight fraction of acrylonitrile in polymer
1	0.209	0.210	5.62	5.64	0.2136
	.212		5.65		
2	.390	.392	5.27	5.31	.2011
	.394		5.35		
2.8	.518	.518	4.79	4.85	.1837
	.519		4.92		
3.5	.654	.654	4.56	4.58	.1735
	.655		4.61		
13.7	.983	.986	3.79	3.81	.1443
	.988		3.83		

TABLE IV-B

Initial charge in 28-oz. bottle
50.02 g. acrylonitrile
150.0 g. butadiene
0.7575 g. dodecyl mercaptan
350.0 g. 3% solution of P. & G. SF Flakes
20.00 ml. 3% solution of $K_2S_2O_8$

Reaction time, hr.	Fractional conversion		Nitrogen in polymer, %		Weight fraction of acrylonitrile in polymer
0.5	0.156	0.158	7.93	7.94	0.3008
	.160		7.95		
0.9	.266	.268	7.58	7.60	.2879
	.269		7.62		
1.3	.394	.396	7.55	7.56	.2864
	.398		7.57		
1.8	.528	.528	7.22	7.24	.2742
	.529		7.25		
2.5	.688	.688	6.88	6.92	.2621
	.688		6.95		
3.3	.829	.831	6.69	6.73	.2549
	.833		6.77		
5.0	.949	.949	6.37	6.41	.2428
	.949		6.45		
18.3	1.00	1.00	6.14	6.14	.2330
	1.00		6.15		

Table IV-C

Initial charge in 28-oz. bottle	69.90	g. acrylonitrile
	130.0	g. butadiene
	0.6994	g. dodecyl mercaptan
	350.0	g. 3% solution of P. & G. SF Flakes
	20.00	ml. 3% solution of $K_2S_2O_8$

Reaction time, hr.	Fractional conversion		Nitrogen in polymer, %		Weight fraction of acrylonitrile in polymer
0.2	0.030 .032	0.031	9.54	9.54	0.3614
.5	.178 .180	.179	9.40 9.43	9.42	.3568
.8	.518 .524	.521	9.05 9.19	9.12	.3455
1.0	.631 .634	.632	..		....
9.0	1.00 1.00	1.00	9.03 8.99	9.01	.3413

nitrile copolymer is doubtless due to the appreciable water-solubility of the nitrile, which would render invalid one of the basic assumptions that went into the derivation of the emulsion equation.

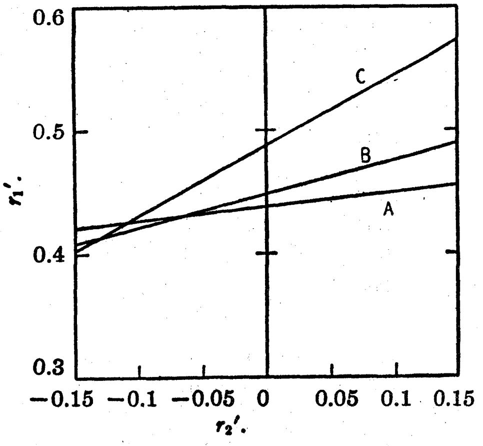


Fig. 4.—Plot for determining copolymerization parameters for acrylonitrile–butadiene system. Lines A, B and C correspond to data in Tables IV-A, IV-B and IV-C.

Butadiene was polymerized with 1-cyanobutadiene in emulsion using weight ratios of 75/25, 60/40, and 40/60, and the results are given in Tables V-A, V-B, and V-C. In this case r'_1 was found to be -0.08, although a value 0 would probably be satisfactory; r'_2 was found to have a value of 1.7. This implies that butadiene cannot grow onto a free radical whose last member is a cyanobutadiene unit, although a cyanobutadiene can add onto a butadiene. Accordingly, the first polymer to form will be abnormally high in cyanobutadiene, but as soon as that monomer is depleted, the consumption of butadiene increases. This strange behavior also manifests itself in the conversion *versus* time curve (Fig. 5). The initial rate of conversion is found to be very high, but after about 25% reaction, the rate falls off considerably.

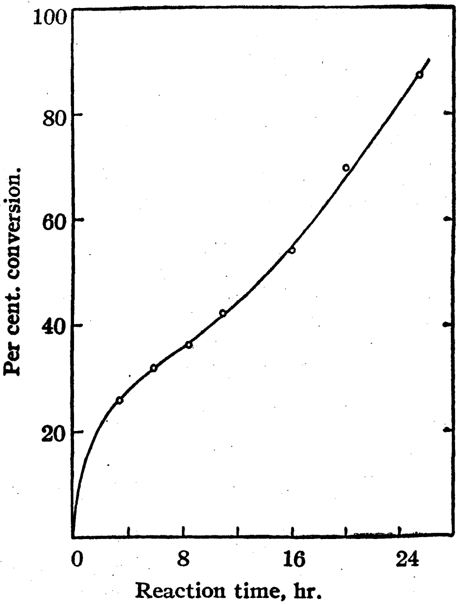


Fig. 5.—Conversion *vs.* reaction time for cyanobutadiene–butadiene copolymer (data in Table V-A).

The experimental results given above demonstrate empirically the validity of the basic copolymerization equation. Theoretically it was shown that the equation might be expected to hold whether the polymerization occurs in the oil or in the aqueous phase. Therefore the experimental observations here reported do not prove which phase the reaction occurs in. As a matter of fact, Fordyce and Chapin[10] have suggested that the oil phase is the seat of the reaction in the case of styrene copolymerized with acrylonitrile. To arrive at a similar conclusion here, it would be

Table V-A

Initial charge in 28-oz. bottle	50.03	g. cyanobutadiene
	150.0	g. butadiene
	1.007	g. dodecyl mercaptan
	350.0	g. 3% solution of P. & G. SF Flakes
	20.00	ml. 3% solution of $K_2S_2O_8$

Reaction time, hr.	Fractional conversion		Nitrogen in polymer, %		Weight fraction of cyano-butadiene in polymer
3.5	0.259 .261	0.260	11.03 11.38	11.20	0.6325
6	.319 .321	.320	10.82 10.83	10.82	.6110
8.5	.362 .363	.362	10.20 10.43	10.32	.5828
11	.410 .411	.410	9.87 10.02	9.94	.5613
16	.539 .545	.542	7.70 7.76	7.73	.4365
20	.697 .698	.698	5.88 5.99	5.94	.3354
25.5	.871 .876	.874	4.79 4.79	4.79	.2705

TABLE V-B

Initial charge in 12-oz. bottle
- 31.98 g cyanobutadiene
- 48.0 g butadiene
- 0.4511 g. dodecyl mercaptan
- 140.0 g. 3% solution of P. & G. SF Flakes
- 8.00 ml. 3% solution of $K_2S_2O_8$

Reaction time hr.	Fractional conversion		Nitrogen in polymer, %		Weight fraction of cyano-butadiene in polymer
4.5	0.409	0.410			
	.410				
6	.443	.446	12.08	12.12	0.6844
	.449		12.15		
8	.491	.494	11.69	11.72	.6618
	.496		11.76		
10	.543	.544	11.12	11.12	.6279
	.546		11.13		
25.5	.951	.951	7.74	7.77	.4388
			7.80		

TABLE V-C

Initial charge in 12-oz. bottle
- 47.92 g. cyanobutadiene
- 32.0 g. butadiene
- 0.4256 g. dodecyl mercaptan
- 140.0 g. 3% solution of P. & G. SF Flakes
- 8.00 ml. 3% solution of $K_2S_2O_8$

Reaction time, hr.	Fractional conversion		Nitrogen in polymer, %		Weight fraction of cyano-butadiene in polymer
0					
4	0.474	0.478	13.54	13.60	0.7680
	.483		13.66		
5.5	.625	.626	13.01	13.07	.7381
	.627		13.13		
7	.690	.693	12.77	12.77	.7211
	.696		12.77		
8	.730	.730	12.68	12.70	.7172
	.730		12.73		
25.5	.913	.918	11.06	11.09	.6266
	.922		11.12		

necessary to have more data than are available at present.

Summary

Copolymerizations of butadiene with various other monomers have been carried out in emulsion systems. It is found that the copolymerization equations of Mayo and others have empirical validity for all of the systems examined. The equations are also believed to be theoretically significant in most cases, an exception being butadiene with acrylonitrile. The anomalous results obtained for that pair are attributed to the high solubility of acrylonitrile in water.

URBANA, ILLINOIS RECEIVED AUGUST 9, 1947

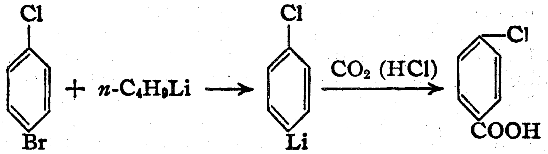
[CONTRIBUTION FROM LOS ALAMOS SCIENTIFIC LABORATORY]

The Application of the Halogen–Metal Interconversion Reaction to Syntheses with Isotopic Carbon[1]

BY ARTHUR MURRAY, III, W. W. FOREMAN AND WRIGHT LANGHAM

The extensive application of the halogen–metal interconversion reaction to a wide variety of aryl halides has resulted in the preparation of organometallic compounds having additional functional groups.[2a,b,c,d]

Because of the rapidity of the reaction, the halogen–metal interconversion between an alkyllithium compound and an aryl halide is uniquely suited to the preparation of organolithium compounds with additional functional groups. As an example, *p*-chlorobromobenzene and *n*-butyllithium react to give a 90% yield of *p*-chlorophenyllithium in ten minutes.[2a] Subsequent carbonation results in the formation of the corresponding carboxylic acids according to the reaction.



The use of isotopic carbon in biological studies is complicated by the relatively small quantities of isotope available and by the unavoidable high dilution of the isotope when introduced into biological systems. In order to conserve isotopic carbon and to achieve maximum specific activity required for certain investigations, we have adapted the halogen–metal interconversion reaction to the micro synthesis of certain compounds of biological significance.

p-Aminobenzoic acid, labelled with C^{14} in the carboxyl group, was prepared by an adaptation of the reaction of Gilman and Stuckwisch.[3a,b] The *p*-aminophenyllithium derivative[4] was isolated and washed free of *n*-butyllithium before carbonation with gaseous $C^{14}O_2$.

---

(1) This paper is based on work performed under contract W-7405-Eng-36 with the Atomic Energy Commission at the Los Alamos Scientific Laboratory of the University of California.

(2) (a) Gilman, Langham and Moore, THIS JOURNAL, **62**, 2327 (1940); (b) Langham, Brewster and Gilman, *ibid.*, **63**, 545 (1941); (c) Gilman, Langham and Willis, *ibid.*, **62**, 346 (1940); (d) Gilman and Gainer, *ibid.*, **69**, 1946 (1947).

(3) (a) Gilman and Stuckwisch, *ibid.*, **63**, 2844 (1941); (b) Gilman and Stuckwisch, *ibid.*, **64**, 1007 (1942).

(4) This compound is believed to be *p*-$LiC_6H_4N(Li)_2$. C. G. Stuckwisch, private communication.

Good yields of carboxyl-labelled nicotinic acid were obtained by the method of Gilman and Spatz,[5] when the reaction was scaled down to the millimole level and adapted to carbonation with gaseous carbon dioxide.

Experimental

Apparatus and General Procedure.—A compact vacuum system was designed and constructed as outlined in Fig. 1. The total volume of the system was kept at a minimum. The apparatus was attached at (V) to an oil pump by means of a three-way stopcock that permitted independent evacuation of both main sections of the system. A source of dry carbon dioxide and oxygen-free nitrogen was attached to the system at (N).

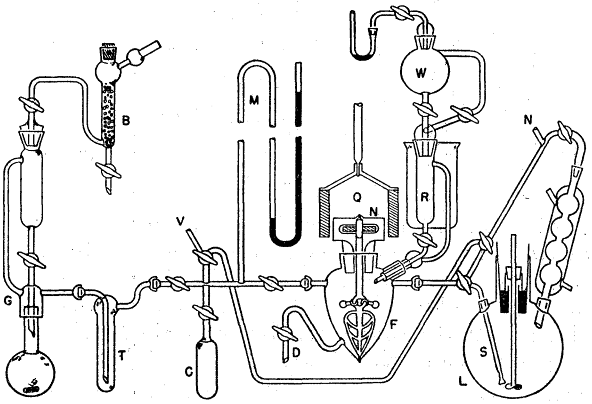


Fig. 1.—Apparatus for the preparation and gaseous carbonation of organolithium compounds.

After evacuation isotopic carbon dioxide was prepared in generator (G) by slowly adding outgassed concentrated sulfuric acid to isotopic barium carbonate. The stopcock involved was lubricated with a paste of paraffin and mineral oil. Quantitative evolution of carbon dioxide was attained by warming the acid and stirring by means of a magnet and glass encased iron core. The gas was passed through a trap (T), immersed in a Dry Ice–acetone bath, and condensed in storage bulb (C) by means of liquid air. Any non-condensable gas was pumped off.

The required volume of *n*-butyllithium[2a] solution (assayed before every run by the differential titration method of Gilman and Haubein[6]) was transferred from the preparation flask (L) to the calibrated cone-shaped reaction flask (F) which had been previously evacuated, flamed and swept out with nitrogen gas. The transfer was made by applying a positive pressure of nitrogen, thus forcing the solution through a filter of glass wool in siphon (S). The addition tube (R), equipped with an outside jacket for a Dry Ice–acetone cooling mixture, was filled with the aryl halide in ether solution. This solution was added to the *n*-butyllithium in flask (F) which had been filled with nitrogen. Moderate stirring was achieved by means of a vacuum-tight glass-enclosed magnetic induction stirrer (N) motivated by two motor-driven permanent bar magnets (Q). In cases where the aryllithium compound was washed free of excess *n*-butyllithium, a siphon (D) controlled by a stopcock was used for drawing off supernatant liquid into an evacuated flask immersed in a freezing bath. Wash ether was stored over sodium wire in reservoir (W) and was added through the addition tube (R).

Before carbonation the reaction flask (F) was cooled to −80°, and pumped down to the vapor pressure of ether. The storage bulb (C) was then warmed and carbonation effected by opening the stopcock connecting the bulb with the reaction flask (F). The absorption of carbon dioxide was followed by observing the fall in pressure on the manometer (M). Rapid stirring of the reaction mixture facilitated the absorption of the gas. When the pressure became constant, the reaction mixture was alternately frozen solid with liquid air and then thawed several times. Unabsorbed gas was then distilled back into the storage bulb (C) and nitrogen was admitted to the reaction flask. The addition tube (R) was quickly filled with dilute acid. The mixture was hydrolyzed while still cold by adding the dilute acid from (R) to the well stirred solution. Any liberated carbon dioxide was frozen back into the storage bulb (C) from which it was recovered, at convenience, by sweeping out the system with nitrogen through the absorption column (B).

***p*-Aminobenzoic Acid.**—To 23.8 mM. of *n*-butyllithium in 29 ml. of ether was added 4.74 mM. of vacuum dried *p*-bromoaniline in 8 ml. of ether. The *p*-bromoaniline was added over a five-minute period, and the reaction mixture cooled during the addition. Stirring was continued at room temperature for one and one-half hours after the bright yellow precipitate of the aryllithium compound first appeared. This precipitate began to form in twenty to ninety minutes, depending upon the age of the *n*-butyllithium. The yields were unaffected by varying the reaction time from one to three hours. The *p*-aminophenyllithium was washed several times with anhydrous ether. The supernatant liquors were siphoned off under nitrogen into an evacuated flask immersed in a Dry Ice–acetone mixture (the dry *p*-aminophenyllithium derivative is explosive in contact with air[4]). Carbonation was effected with 1.029 mM. of carbon dioxide (2 millicuries of C^{14}) of which 32.5% was recovered. The reaction mixture was hydrolyzed with 8 ml. of 6 *N* hydrochloric acid. The strongly acidic reaction mixture was transferred to a modified Soxhlet and continuously extracted with ether for eight hours. The ether phase was discarded. The aqueous phase was made strongly alkaline with potassium hydroxide and again extracted for eight hours. The aqueous phase was then adjusted to *p*H of 3 and the *p*-aminobenzoic acid extracted with ether (sixteen hours). The crude yield of product was 32.8% based on the barium carbonate or 48.2% based on the carbon dioxide absorbed in the reaction. Recrystallization from water gave 35 mg. of colorless needles (m. p. 184–185°). The final product had a specific activity of approximately 30 million disintegrations per minute per mg.

Similar experiments with 1.01–1.59 mM. of ordinary carbon dioxide consistently gave yields of 31.3–38.5%. Ether extraction was found to be superior to the formation of the copper and silver salts for isolating the small amounts of product.

3-Pyridine-carboxylic Acid (Nicotinic Acid).—To 1.63 mM. of *n*-butyllithium in 2.76 ml. of ether cooled to −35° was added, over a four-minute period, 2.44 mM. of redistilled 3-bromopyridine in 5 ml. of ether (also cooled to −35°). Carbonation was effected after one minute, with 0.81 mM. of isotopic carbon dioxide (one millicurie of activity, 160.8 mg. barium carbonate) at −80°. The reaction mixture was quickly hydrolyzed with 3 ml. of 2.5 *N* nitric acid. The acid phase was placed in a modified Soxhlet and continuously extracted with ether (three to four hours), then made alkaline and re-extracted (four to six hours). The crude product was then isolated by adjusting the aqueous phase to *p*H of 3 and continuing the extraction for twenty-four to forty-eight hours. The yield of crude material was 62.4% based on the weight of barium carbonate or 70.3% based on carbon dioxide absorbed. Vacuum sublimation and recrystallization from methanol yielded 30 mg. of colorless powder, m. p. 225–228° (authentic purified specimen m. p. 228–229°). The specific activity of the purified material was approximately 16 million disintegrations per minute per mg.

By the above methods, two different experiments were carried out with 10.6 and 10.4 mM. of C^{13}O$_2$[7] (approx. 6 isotopic per cent. C^{13}) and the same ratio of reagents used

---

[5] Gilman and Spatz, This Journal, 62, 446 (1940).

[6] Gilman and Haubein, *ibid.*, 66, 1515 (1944).

[7] The BaC^{13}O$_3$ was kindly supplied by Dr. Howard W. Bond of the National Institute of Health.

above. The combined reaction mixtures gave a crude yield of 81.9%. Purification by means of the silver salt gave 55.4% of pure acid (m. p. 227–229°).

Acknowledgment.—We gratefully acknowledge the assistance of Dr. Henry Gilman in whose laboratory one of the authors spent several days becoming acquainted with the latest techniques of handling organolithium compounds. We also acknowledge helpful suggestions from Dr. C. G. Stuckwisch.

Summary

The halogen–metal interconversion reaction between the appropriate aryl halide and *n*-butyllithium has been applied on a one millimole scale to the preparation of *p*-aminobenzoic and nicotinic acids marked in the carboxyl groups with C^{14}. These biologically important compounds have been prepared with extremely high specific activities.

Nicotinic acid containing approximately 6 isotopic per cent. of C^{13} in the carboxyl group was also prepared by the same procedure.

LOS ALAMOS, NEW MEXICO RECEIVED JULY 29, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Some Systems of Silicon Halides with Dioxane

BY S. M. SCHOLASTICA KENNARD[1] AND P. A. MCCUSKER

Molecular compounds of dioxane with inorganic halides, in dioxane solution and in the crystalline state, have been the subject of previous studies in these laboratories[2,3] and elsewhere.[4]

Most of these molecular compounds, whose dielectric properties have been studied in solution, appear to be formed as a result of coördination between dioxane and the central atom of the halide. It has been further observed that those halides which coördinated strongly with dioxane in solution also formed relatively stable crystalline complexes. Since silicon tetrachloride gave no evidence of coördination with dioxane in solution, it was considered of interest to determine whether any solid molecular compounds would be formed between silicon tetrahalides and dioxane. For this reason a study was made of the solid–liquid equilibria in silicon tetrahalide–dioxane systems. Dielectric constant and density data were also obtained for silicon tetrabromide in solution. During the course of this work it became desirable to obtain melting point–composition data for the cyclohexane–dioxane system.

Experimental

Preparation and Purification of Materials.—Dioxane was purified as described previously.[2] Silicon tetrabromide was prepared by passing bromine in a stream of nitrogen over granular silicon, in a vertical, 24 mm. Pyrex tube electrically heated. The exothermic reaction was maintained, with slight heating, by a rapid flow of bromine over the heated silicon. Under carefully controlled conditions silicon tetrabromide, essentially free of bromine, was distilled out of the reaction tube. Purification was effected by shaking with mercury and several distillations in a 4 ft. glass helix-packed distilling column. The final product boiled at 154° and was further purified by fractional freezing. The purity was established by separating into two fractions each melting sharply at 5.4°. The melting point reported by Pohland[5] for highly purified silicon tetrabromide is 5.2–5.3°. Silicon tetrachloride was prepared by a similar procedure and purified by fractional distillation. C. P. cyclohexane was refluxed over phosphorus pentoxide and fractionally distilled.

Determination of Melting Points.—Temperatures were measured with a calibrated tenth-degree mercury thermometer. The apparatus for the determination of the melting points was designed for convenience and rapidity in obtaining data. A motor-actuated reciprocating glass ring stirrer surrounded the bulb of the thermometer immersed in the liquid. The system contained a side arm through which measured volumes of liquid could be added from a buret. A thin rubber finger was used to connect the stirring rod and its glass shaft and permitted the complete exclusion of moisture. In a typical determination, a measured volume of liquid was run into the apparatus and a cooling bath placed around the tube. The liquid was cooled and stirred slowly so as to obtain considerable undercooling. In all this work undercooling of from 5 to 10° was readily obtained. The undercooling is an essential feature of this method of determining melting points. By intermittent application of a bath, held at about 10° below the expected melting point, and control of the rate of stirring, sufficient undercooling could be obtained to cause separation of a large quantity of solid in finely divided form. When solid separated, the bath was removed and the mixture allowed to warm up while being vigorously stirred. With finely divided solid and rapid stirring equilibrium between solid and liquid was closely approached. The equilibrium temperature was taken as the point of visible clarification of the mixture and this temperature checked by observation of the increased rate of temperature rise. In all cases these two readings checked within the precision of the thermometer, and numerous checks demonstrated the reproducibility of the data. Subsequent addition of measured volumes of a second component enabled a considerable number of determinations to be made with one original charge. Warming curves were obtained in a similar manner, temperature–time readings being taken during the warming and vigorous stirring of the mixture, after considerable solid had separated.

Dielectric Constants and Densities.—These were determined as previously described.[2] The molar refraction for silicon tetrabromide was computed from the density and refractive index data of Pohland[5] and this value used for the electron polarization. Ten per cent. of the electron polarization was taken as the value for the atomic polarization. The method of Hedestrand[6] was used for calculat-

---

[1] Sister M. Scholastica, C.S.C. Present address: St. Agnes Convent, Los Angeles, California.

[2] Lane, McCusker and Curran, THIS JOURNAL, **64**, 2076 (1942).

[3] Kelley and McCusker, *ibid.*, **65**, 1307 (1943).

[4] Rheinboldt, Luyken and Schmittmann, *J. prakt. Chem.*, **148**, 81 (1937).

[5] Pohland, *Z. anorg. allgem. Chem.*, **201**, 265 (1931).

[6] Hedestrand, *Z. physik. Chem.*, **B2**, 428 (1929).

ing the electric moment. Measurements of dielectric constants and densities were made at 25.0°.

Results and Discussion

I. The Silicon Tetrabromide–Dioxane System.—The melting point–composition data for this system are listed in Table I and plotted in Fig. 1. The stable eutectic mixture contains 39.5 mole % dioxane and melts at −11.4°. When pure silicon tetrabromide was undercooled 5° or more a metastable crystalline form frequently separated. This was sufficiently less opaque than the stable form to be readily recognized although the smallness and instability of the crystals did not permit further characterization. In some cases the metastable form would persist until it melted sharply at 2.3°. In other cases, transformation to the stable form melting at 5.4° would occur suddenly. When solutions of composition between pure silicon tetrabromide and the eutectic mixture were undercooled, the stable form of silicon tetrabromide usually separated. Frequently, however, the metastable form separated and persisted until liquefaction was complete. In some instances, after separation of the metastable form, a sudden transition to the stable, higher melting form would occur. Some typical warming curves illustrating the three different modes of behavior are given in Fig. 2. The curve for the melting point obtained when metastable silicon tetrabromide was the solid phase is shown as a broken line in Fig. 1.

It may be observed that there is an approximately constant difference in the melting points when the two different forms separate, over a range of composition. The metastable eutectic mixture melts at 13.5°.

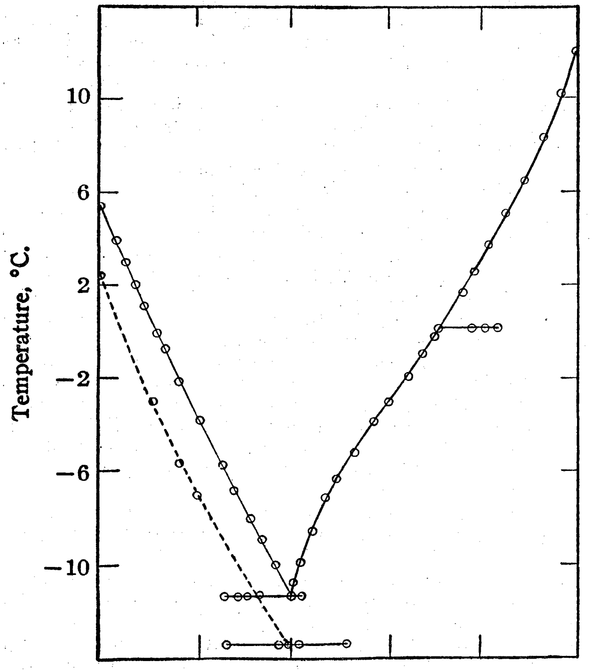


Fig. 1.—Melting point–composition diagram for the silicon tetrabromide–dioxane system.

TABLE I

MELTING POINTS OF SILICON TETRABROMIDE–DIOXANE SOLUTIONS

Mole % Dioxane	M. p., °C. Stable	M. p., °C. Metastable	Eutectic, °C. Stable	Eutectic, °C. Metastable	Mole % Dioxane	M. p., °C.
0.0	5.4	2.3			43.2	−8.6
0.7	4.7				44.5	−8.0
2.4	3.9				46.6	−7.2
3.2	3.7				48.3	−6.5
4.5	2.9				50.6	−6.0
6.8	2.0				52.5	−5.4
8.4	1.2	− 2.0			52.9	−5.2
10.0	0.4	− 3.2			54.6	−4.5
11.1	0.0				56.4	−4.0
12.5	− 0.8	− 4.2			57.9	−3.6
16.3	− 2.2	− 5.8			59.9	−3.1
18.9	− 3.6				61.2	−2.7
19.8	− 3.9	− 7.1			63.9	−2.0
25.0	− 5.8			−13.5	64.8	−1.6
25.2	− 6.1				66.9	−1.1
25.5	− 6.3		−11.4		68.9	−0.3
27.0	− 6.9				70.6	0.1
28.5	− 7.4				73.5	0.9
29.3	− 7.7		−11.4		75.5	1.7
31.1	− 8.2	−11.1	−11.4		77.4	2.3
32.8	− 9.2				79.1	3.0
33.0	− 9.0				80.8	3.6
33.6	− 9.3				82.4	4.3
35.8	−10.1		−11.4	−13.5	86.4	6.9
36.7	−10.4			−13.5	88.0	5.6
36.9	−10.6				89.2	6.3
38.2	−11.1		−11.4		90.9	7.5
38.7	−11.2		−11.4	−13.5	92.6	8.2
39.6	−10.8				96.6	10.0
40.4	−10.7			−13.5	97.3	10.4
41.0	− 9.9				99.6	11.5
42.2	− 9.6		−11.4		100.0	11.8

The silicon tetrabromide–dioxane system is a simple eutectic giving no evidence of strong interaction between the two components except for a slight but definite change of curvature between 60 and 80 mole % dioxane.

Some carefully obtained warming curves for mixtures between 77 and 85 mole % dioxane revealed a reproducible temperature halt in the region 79–83 mole % dioxane. Some representative data from these warming curves are plotted in Fig. 3. A maximum temperature halt shows up at 80 mole % dioxane with temperature halts of shorter duration at neighboring compositions. This behavior is commonly interpreted as due to the existence of a molecular compound with incongruent melting point. Thus the existence of a 1:4 complex between silicon tetrabromide and dioxane is indicated by the warming curve results.

Dielectric Constant and Density Data.—The dielectric constants and densities of dilute solu-

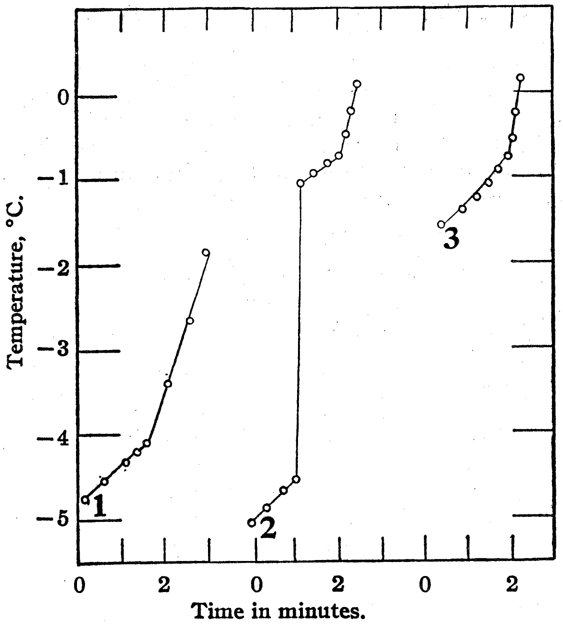


Fig. 2.—Warming curves for 12.5% dioxane in silicon tetrabromide: (1) separation and complete melting of metastable form; (2) separation of metastable form and transformation to stable form before complete melting; (3) separation of stable form.

tions of silicon tetrabromide in dioxane and in carbon tetrachloride were measured and are listed in Table II.

TABLE II

DIELECTRIC CONSTANTS AND DENSITIES FOR SILICON TETRABROMIDE SOLUTIONS AT 25°

C_2	ϵ	d
	Dioxane solutions	
0.0000	2.208	1.0279
.0106	2.220	1.0545
.0190	2.226	1.0756
.0300	2.234	1.1030
	Carbon tetrachloride solutions	
.0000	2.2300	1.5856
.0122	2.2356	1.6035
.2190	2.2389	1.6177

The calculated polarization and electric moments are listed in Table III.

TABLE III

POLARIZATIONS AND ELECTRIC MOMENTS OF SILICON TETRABROMIDE

Solvent	$P_E + A$	$P_{2\infty}$	μ
Dioxane	44.66	51.15	0.55 ± 0.09
Carbon tetrachloride	44.66	45.20	.00 ± .10

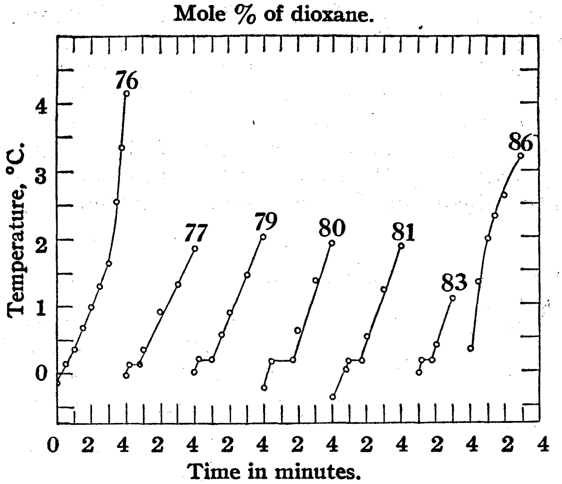


Fig. 3.—Warming curves for some silicon tetrabromide–dioxane solutions.

The value obtained for the electric moment of silicon tetrabromide in carbon tetrachloride is the expected zero value for the tetrahedral structure indicated by electron diffraction,[7] and Raman spectra studies.[8] The value for the electric moment in dioxane is small but is significantly different from zero. A slight but definite electronic interaction between dioxane and silicon tetrabromide is probably responsible for this small moment. The composition of the unstable crystalline compound between silicon tetrabromide and dioxane, indicated by the warming curve data, suggests that interaction at higher temperatures in the same molecular ratio would lead to a zero moment since the moment vectors would cancel. The small electric moment observed for silicon tetrabromide in dioxane is not sufficient evidence to assume extensive interaction between the halide and dioxane in the liquid state. It may, however, indicate a diminished tendency for such interaction with the symmetrical 1:4 complex being partly dissociated.

Measurements of the densities of solutions of silicon tetrabromide in dioxane were made over the whole range of composition. The results obtained are listed in Table IV.

TABLE IV

DENSITY DATA FOR SILICON TETRABROMIDE–DIOXANE

Volume % dioxane	d^{25}_4	Volume % dioxane	d^{25}_4
0.00	2.7715	71.72	1.5141
16.06	2.4853	75.54	1.4483
25.12	2.3236	79.63	1.3770
42.62	2.0184	82.35	1.3312
53.01	1.8380	87.98	1.2342
64.11	1.6457	100.00	1.0279
68.49	1.5703		

Plotting of the density against volume fraction gives a straight line and shows no abnormal change in density at 80 mole per cent. dioxane. This is evidence that no appreciable concentration of the 1:4 complex persists in the liquid state at 25.0°.

---

(7) Spitzer, Howell and Schomaker, THIS JOURNAL, **64**, 62 (1942).

(8) Trumpy, *Z. physik*, **68**, 675 (1931).

II. The Cyclohexane–Dioxane System.—While few solid–liquid equilibrium diagrams are available in the literature for systems containing dioxane, the system with water has been investigated.[9,10] In this system a considerable change occurs in the curvature of the liquids at approximately the same temperature as observed in the silicon tetrabromide–dioxane system. Since molecular interaction is probable between the highly polar water and dioxane, comparable data were sought for a substance which should be completely inert to dioxane. Cyclohexane was chosen for this purpose, since its melting point was convenient and its geometric similarity to dioxane would minimize steric factors influencing the composition of the solid phase. The melting point data for this system are listed in Table V and diagrammed in Fig. 4.

TABLE V

MELTING POINTS OF CYCLOHEXANE–DIOXANE SOLUTIONS

Mole % dioxane	M. p., °C.	Mole % dioxane	M. p., °C.
0.0	6.5	41.7	−3.1
4.5	1.2	48.2	−2.0
8.7	−2.6	49.6	−1.6
12.9	−6.5	56.2	−0.8
16.1	−8.9	59.2	−0.4
19.3	−11.0	60.2	−0.3
22.3	−8.9	66.7	0.9
25.3	−7.7	72.7	2.3
27.6	−7.0	76.7	2.9
31.8	−5.7	81.5	4.4
35.6	−4.5	86.5	6.0
35.8	−4.7	91.5	7.7
37.5	−4.0	95.9	9.7
39.5	−3.7	100.0	11.8

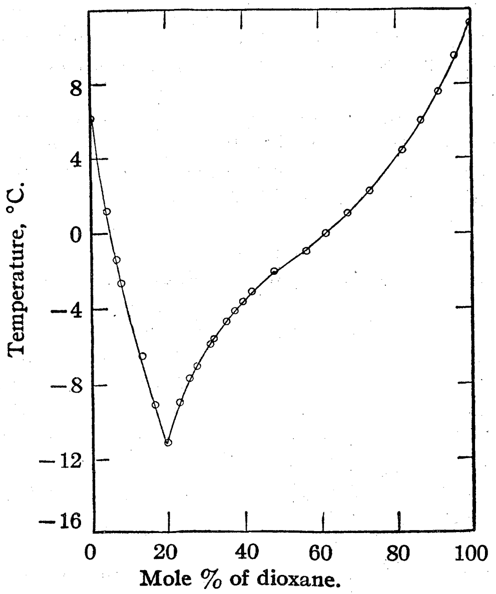


Fig. 4.—Melting point–composition diagram for the cyclohexane–dioxane system.

This system gives a eutectic at −11.1° containing 19 mole % dioxane. The same type of curvature change in the liquidus appears in this system as in the silicon tetrabromide–dioxane and water–dioxane systems, and in the same approximate temperature range, −1° to +2°.

TABLE VI

MELTING POINTS OF SILICON TETRACHLORIDE–DIOXANE SOLUTIONS

Mole % dioxane	M. p., °C.	Mole % dioxane	M. p., °C.
18.1	−11.9	62.0	1.3
22.0	−9.8	62.4	1.2
24.9	−8.3	62.5	1.2
28.2	−7.0	64.0	1.6
30.6	−6.0	64.2	1.8
34.0	−4.9	66.4	2.1
38.0	−3.9	67.4	2.2
42.2	−2.9	70.3	2.8
44.5	−2.2	72.4	3.3
47.8	−1.7	73.8	3.7
48.8	−1.4	74.6	3.9
51.9	−0.8	77.0	4.5
52.7	−0.7	80.0	5.3
54.7	−0.3	82.2	6.0
57.0	0.0	84.0	6.6
57.5	.3	88.2	7.8
59.5	.4	90.1	8.6
59.9	.7	92.0	8.9
60.4	.7	93.4	9.3
61.8	.8	94.5	9.6

III. The Silicon Tetrachloride–Dioxane System.—For the purpose of comparison, a portion of the solid–liquid equilibrium diagram for silicon tetrachloride–dioxane was worked out.

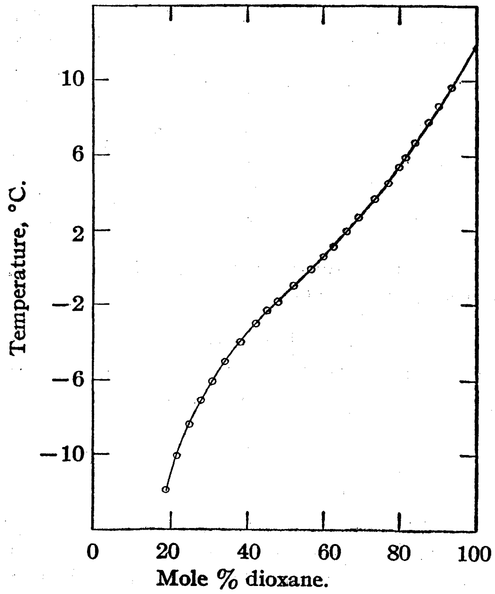


Fig. 5.—Melting point–composition diagram for a portion of the silicon tetrachloride–dioxane system.

---

(9) Gillis and Delaunois, *Rec. trav. chim.*, **53**, 186 (1934).

(10) Hovorka, Schaeffer and Dreisbach, THIS JOURNAL, **58**, 2264 (1936).

The selected portion includes all compositions at which molecular compound formation might reasonably be expected to occur. The melting point data for this system are listed in Table VI and are diagrammed in Fig. 5.

An examination of the diagram shows a considerable degree of similarity with the silicon tetrabromide and cyclohexane systems with dioxane. No stable compound is indicated and the same type of curvature change occurs in the liquidus at about the same temperature.

Previous determinations[2] of the electric moment of silicon tetrachloride in dioxane gave zero value. If the small moment obtained for silicon tetrabromide in dioxane is attributed to an electronic interaction between the halogens and the donor oxygens of dioxane, the zero value of the moment for silicon tetrachloride in dioxane would indicate a lessened tendency for such interaction. Attempts to obtain reproducible warming curves for silicon tetrachloride–dioxane solutions in the neighborhood of 80 mole % dioxane were unsuccessful.

Summary

1. Melting point–composition diagrams for the systems of silicon tetrabromide, silicon tetrachloride and cyclohexane with dioxane have been determined.

2. A metastable form of solid silicon tetrabromide, m. p. 2.3°, has been observed.

3. Thermal analysis of the system silicon tetrabromide–dioxane indicates the existence of an unstable 1:4 complex.

4. A characteristic curvature change in the liquidus for several systems containing dioxane was found to occur at approximately 0°.

5. Dielectric constant and density data indicate a small degree of electronic interaction between silicon tetrabromide and dioxane. The electric moment of silicon tetrabromide in carbon tetrachloride was found to be 0.0.

NOTRE DAME, IND. RECEIVED NOVEMBER 20, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Phenyl and Ethoxy Silicon Isocyanates

BY GEORGE S. FORBES AND HERBERT H. ANDERSON

This paper describes two complete series of new mixed silicon isocyanates. The phenyl silicon isocyanates were prepared from phenylchlorosilanes and silver isocyanate, and the three ethoxy silicon isocyanates from ethoxychlorosilanes and silver isocyanate.

Preparation of Phenyl Silicon Isocyanates.—In the usual manner,[1] each phenylchlorosilane was changed into the corresponding isocyanate through reaction with an excess of silver isocyanate; the yields varied from 75 to 90%. All three phenyl silicon isocyanates were distilled at 3 mm. pressure through a plain column 4 mm. i. d. and 300 mm. long. Triisocyanate, collected from 101 to 102°; diisocyanate, 142–143°; monoisocyanate, 177.5–178.5°.

Physical Properties and Analyses of Phenyl Silicon Isocyanates (see Table I).—Dynamic vapor pressure measurements were made on each of the three compounds—six values on the triisocyanate, five on the diisocyanate and four on the monoisocyanate. Frozen phenyl silicon triisocyanate melted over the range −50 to −20°, approximately. Possibly two solid forms were present; diphenyl silicon diisocyanate supercooled to −70°, but formed a crystalline solid of sharp m. p. after addition of a small clay chip to promote crystallization; triphenyl silicon isocyanate supercooled less than 20°. Needless to say, vigorous stirring was essential in obtaining melting points. When shaken with water, the triisocyanate hydrolyzed slowly at first and then with increasing speed; the diisocyanate hydrolyzed at a moderate rate only, even with vigorous shaking; the monoisocyanate, however, hydrolyzed very slowly, if at all. Analyses employed the Dumas method for nitrogen, combustion for carbon and hydrogen, and the hydrolysis and ignition of the triisocyanate to obtain silica as the end-product. Calcd. for $(C_6H_5)Si(NCO)_3$: Si, 12.2; C, 46.8; H, 2.2. Found: Si, 12.3; C, 47.1; H, 2.3. Calcd. for $(C_6H_5)_2Si(NCO)_2$: N, 10.5; H, 3.8. Found: N, 10.8; H, 3.5. Calcd. for $(C_6H_5)_3Si(NCO)$: N, 4.6; H, 5.0. Found: N, 4.4; H, 5.3 The observed molecular weights in camphor solution were 212, 250 and 290, respectively, corresponding to the calculated values 231, 266 and 301.

Preparation of Ethoxy Silicon Isocyanates.—Methanol reacts with silicon isocyanate to produce methoxy silicon isocyanates,[2] the boiling points of which are 15° apart; however, the reaction between ethanol and silicon isocyanate yields products difficultly separable. It was much easier to obtain the desired products from the ethoxychlorosilanes. Ethoxytrichlorosilane, prepared from tetrachlorosilane and ethanol, boiled at 102.1° at 758 mm.[3]; diethoxydichlorosilane boiled at 137.4–137.6° at 754 mm.[3] Triethoxychlorosilane boiled from 154 to 157°,[4] even upon repeated distillation on a plain column 4 mm. i. d., 125 cm. long; apparently redistribution limited the purity of the sample. Following the general method,[1] a solution of the individual ethoxychlorosilane in benzene was heated with a 30% excess of silver isocyanate for thirty minutes at 90°, and then filtered with washing of the silver salts; benzene was removed by distillation at atmospheric pressure. The middle fraction of ethoxy silicon triisocyanate boiled at 178.5° uncor. at 764 mm. with little variation; that of diethoxy silicon diisocyanate boiled at 174.8–174.9° uncor. at 760 mm. in a column without spiral or packing, and 4 mm. i. d. and 50 cm. long.

Triethoxy silicon isocyanate could not be purified by distillation alone; the main contaminant was probably diethoxy silicon diisocyanate, the boiling point of which is only 2.5° higher, and the minor contaminant was the more easily removed ethyl orthosilicate (tetraethoxysilane). The first preparation showed a b. p. of 173.5°, d^{20}_4 1.025 and n (index of refraction) 1.3933, leading to R (molar refraction, n^2 formula) 47.82 ml., none of which agreed with values interpolated in the series. A product of apparently higher purity was next obtained by treatment of the above material with ethanol in excess. Prob-

---

[1] Forbes and Anderson, THIS JOURNAL, **62**, 761 (1940).

[2] Forbes and Anderson, *ibid.*, **66**, 1703 (1944).

[3] Peppard, Brown and Johnson, *ibid.*, **68**, 70 (1946), reported 101.5–102.0°, 136.0–136.5° and 156.0–156.5°, respectively, at 760 mm.

TABLE I

PHENYL SILICON ISOCYANATES

Compound		$Si(NCO)_4$[1]	$(C_6H_5)Si(NCO)_3$	$(C_6H_5)_2Si(NCO)_2$	$(C_6H_5)_3Si(NCO)$	$Si(C_6H_5)_4$
B. p., °C.		185.6	251.9 ± 1°	319.6 ± 1°	372.0 ± 1°	428[b]
M. p., °C.		26	Indefinite	22.9 ± 0.3°	95.0 ± 1°	233[b]
d^{20}_4		1.442[a]	1.273	1.188	....	..
Index of refraction, 20°, ±0.0010		1.4610	1.5210	1.5675	....	..
Molar refraction, ml.	Found	37.29	55.45	73.3	....	..
	Calcd.	......	55.40	73.5		
Constants in vapor pressure equation	A	9.0198	8.6663	8.6683	8.3234	..
	$-B$	2816	3038	3421	3511	..
Heat of vaporization, calcd., kcal.		12.9	13.9	15.7	16.1	..
Trouton constant		26.5	26.4	26.5	24.9	..

[a] Calculated from density at 25°. [b] Lewis and Newkirk, THIS JOURNAL, **69**, 701 (1947).

TABLE II

PROPERTIES OF ETHOXY SILICON ISOCYANATES

Compound		$(C_2H_5O)_4Si$	$(C_2H_5O)Si(NCO)$	$(C_2H_5O)_2Si(NCO)_2$	$(C_2H_5O)Si(NCO)_3$	$Si(NCO)_4$
B. p., °C.		165.5[a]	172.9 ± 0.5	175.4 ± 0.5	179.6 ± 0.5	185.6 ± 0.5
Index of refraction at 20° ±0.0005		1.3862[b]	1.3922	1.4046	1.4251	1.4610
d^{20}_4		0.933[a]	1.015 ± 0.004	1.108	1.236	1.442[c]
Molar refraction, ml.	Found	52.05[d]	48.2	44.71	41.06	37.29
	Calcd.	...	48.36	44.67	40.98	....
Vapor pressure constants	A	...	8.2179	8.2577	8.4374	9.0198
	$-B$	...	2380	2411	2515	2816
Heat of vaporization, calcd., kcal.		...	10.9	11.0	11.5	12.9
Trouton constant		...	24.4	24.6	25.4	26.5

[a] Average of acceptable published data. [b] Solana and Moles, *C. A.*, **27**, 1252 (1933). [c] Estimated from d^{25}_4 1. 434. [d] Bygden, *Z. physik. Chem.*, **90**, 243 (1915).

ably the diethoxy impurity was thus converted into the desired triethoxy compound. As shown below, the diisocyanate is destroyed by alcohol or water more rapidly than is the monohalide. Eighteen milliliters of absolute ethanol was added to 90 g. of triethoxysilicon isocyanate, over a period of forty minutes, and then unchanged ethanol was removed by distillation; after further purification, the triethoxy derivative was found to have the analyses given below and the following physical properties: b. p. 172.9°, d^{20}_4 1.015, n 1.3922, R, 48.19 ml. A second similar treatment with ethanol produced a sample of b. p. 172.8°, d^{20}_4 1.009, n 1.3917 and R 48.41. A third treatment with ethanol followed by shaking with a moderate amount of 0.06 M sodium hydroxide, drying and repurification resulted in a product of b. p. 173.2°, d^{20}_4 1.003, n 1.3902 and R 48.51 ml. When values of d^{20}_4 and of n were graphed for the series from silicon tetraisocyanate to tetraethoxysilane exclusive of the triethoxy compound, the curves were quite smooth and predicted the following values: d^{20}_4 1.013 ± 0.005, n 1.3921 ± 0.0003. Corresponding data, as yet unpublished, for the methyl silicon isocyanates, and for the methyl silicon isothiocyanates, also lie on smooth curves. It was concluded that the product of boiling point 172.9°, obtained through a single treatment with ethanol, was the purest of the four.

Analyses of Ethoxy Compounds.—Carbon and hydrogen were obtained by combustion, and the Dumas method was used for nitrogen. Calcd. for $(C_2H_5O)_3Si(NCO)$: C, 41.0; H, 7.3; N, 6.8. Found: C, 40.8; H, 7.4; N, 6.7. Calcd. for $(C_2H_5O)_2Si(NCO)_2$: C, 35.6; H, 5.0; N, 13.9. Found: C, 36.0; H, 4.9; N, 13.6. Calcd. for $(C_2H_5O)Si(NCO)_3$: C, 30.1; H, 2.5; N, 21.1. Found C, 29.8; H, 2.6; N, 21.2. The molecular weights observed by the Dumas method were 208, 206 and 205 respectively, corresponding to calculated values of 205, 202 and 199.

Physical Properties of Ethoxy Silicon Isocyanates (See Table II).—Dynamic vapor pressure measurements, made on the day of final purification and using calibrated thermometers, served for calculations of heats of vaporization. The vapor pressure equations fit eighteen observed points with an average deviation of three mm. Swarts' rule of linear progression[4] of boiling points predicts 170.5, 175.5 and 180.6° for the new isocyanates, in reasonable agreement with observed values. All were colorless liquids. Densities were taken using a special 2-ml. micropycnometer. Rates of hydrolysis decreased strikingly from silicon isocyanate to tetraethoxysilane.

Summary

Each of the three phenylchlorosilanes and also each of the three ethoxychlorosilanes yielded the corresponding new isocyanate upon treatment with silver isocyanate. Triphenylsilicon isocyanate, $(C_6H_5)_3Si(NCO)$, boiled at 372°; diphenylsilicon diisocyanate, $(C_6H_5)_2Si(NCO)_2$, at 320°; phenylsilicon triisocyanate, $(C_6H_5)Si(NCO)_3$, at 252°; triethoxysilicon isocyanate, $(C_2H_5O)_3Si(NCO)$, at 172.9°; diethoxysilicon diisocyanate, $(C_2H_5O)_2Si(NCO)_2$, at 175.4°; ethoxysilicon triisocyanate, $(C_2H_5O)Si(NCO)_3$, at 179.6°.

Densities, refractive indices, molar refractions and vapor pressure equations were determined.

Substitution of phenyl or of ethoxy groups progressively decreases rates of hydrolysis of the isocyanate groups present.

CAMBRIDGE, MASSACHUSETTS

RECEIVED SEPTEMBER 9, 1947

---

[4] Swarts, *Bull. soc. chim.*, **35**, 1557 (1924).

CONTRIBUTION FROM THE RADIATION LABORATORY AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

Some Exchange Experiments Involving Hexacyanoferrate(II) and Hexacyanoferrate(III) Ions[1]

BY ROY C. THOMPSON[2]

Exchange reactions involving the following pairs of ions have been investigated using radioactive iron: hexacyanoferrate(II) and hexacyanoferrate (III) ions, iron(III) and hexacyanoferrate(III) ions, iron(III) and hexacyanoferrate(II) ions, iron(II) and hexacyanoferrate(II) ions, and iron (II) and hexacyanoferrate(III) ions. The exchange of activity between hexacyanoferrate(II) and hexacyanoferrate(III) ions can be accomplished by an oxidation–reduction reaction involving only the transfer of an electron. The other reactions investigated require the exchange of an atom between molecules.

Most of these exchange reactions were previously investigated by Kennedy, Ruben and Seaborg, who also studied the exchange between iron (II) and iron(III) ions. The results of this earlier investigation were referred to in a review article by Seaborg,[3] but the details of the work have not been published. The experiments reported here will confirm the absence of any detectable exchange in the case of the atomic interchanges studied. However, complete and rapid exchange was observed in the case of the hexacyanoferrate (II)–hexacyanoferrate(III) ion pair, whereas Kennedy, *et al.*, detected no exchange in this case.

Experimental

The radioactive iron employed as tracer was a mixture of the beta-emitting $^{59}_{26}$Fe of forty-seven day half-life[4] and the four year $^{55}_{26}$Fe which decays by orbital electron capture.[5] These isotopes were prepared by bombardment of an iron plate with 22 Mev. deuterons obtained from the 60 inch cyclotron of the University of California.

A sample of potassium hexacyanoferrate(II) containing radioactive iron was synthesized by addition of a solution of active iron(II) chloride to a saturated solution of potassium cyanide. The product was purified by crystallization from ethanol–water mixtures. Active potassium hexacyanoferrate(III) was synthesized by oxidation of active potassium hexacyanoferrate(II) with chlorine and purified by crystallization from ethanol–water mixtures.

Hexacyanoferrate(II)-Hexacyanoferrate(III) Exchange.—Equal volumes of 0.2 *M* solutions of active potassium hexacyanoferrate(II) and inactive potassium hexacyanoferrate(III) were mixed and samples taken from this mixture at intervals of from one minute to five days after mixing. The *p*H of this mixture was 8.1 as measured with a Beckman *p*H meter. A solution of cerium(III) nitrate was added to the samples immediately after removal from the mixture, which resulted in the selective precipitation of the hexacyanoferrate(II) ion as $KCeFe(CN)_6$.[6] This precipitate was separated by centrifugation, washed, slurried onto platinum plates and the radioactivity measured with a bell-type Geiger tube having a 3 mg./sq. cm. mica window. The supernatant solution and washings were combined, evaporated on platinum plates and also counted. Of the activity recovered in these two fractions, an average of 56% was found in the hexacyanoferrate(II) precipitate and the remainder in the hexacyanoferrate(III) supernatant solution. The range of values observed in six determinations over a five-day interval was 53 to 60%. From 87 to 94% of the initial activity was recovered in each experiment.

The experiment was then repeated, starting with active potassium hexacyanoferrate(III) and inactive potassium hexacyanoferrate(II). Practically identical results were obtained with an average of 58% of the total recovered activity being found in the potassium cerium(III) hexacyanoferrate(II) precipitate. The *p*H of the exchange mixture in this case was 7.3.

The exchange between 0.1 *M* solutions of hexacyanoferrate(II) and hexacyanoferrate(III) ions was also studied in 1.0 *M* hydrochloric acid and in 0.05 *M* sodium hydroxide solutions, and the exchange between 0.009 *M* solutions of hexacyanoferrate(II) and hexacyanoferrate (III) ions was studied in neutral solution. In all of these cases complete exchange was observed within one minute after the time of mixing.

Cerium(III) ion was chosen to effect the separation of hexacyanoferrate(II) and hexacyanoferrate(III) ions after experiments had shown iron(III) ion to be unsatisfactory for this purpose. The addition of iron(III) ion to a mixture of hexacyanoferrate(II) and hexacyanoferrate(III) ions resulted in the precipitation of more than 75% of the radioactivity regardless of whether this activity was added in the form of hexacyanoferrate(II) or hexacyanoferrate(III) ion. Because cerium was employed in its more stable oxidation state and because essentially identical results were obtained in approaching the equilibrium from both directions it can be assumed that the presence of cerium does not induce an exchange.

Iron(III)-Hexacyanoferrate(III) Exchange.—A mixture 0.07 *M* in active potassium hexacyanoferrate(III) and 0.14 *M* in inactive iron(III) chloride was allowed to stand in the dark at room temperature for six days. Iron (III) hydroxide was then precipitated from the mixture by addition of 0.5 *M* sodium hydroxide. The iron(III) hydroxide precipitate was completely inactive.

Iron(III)-Hexacyanoferrate(II) Exchange.—Excess inactive iron(III) chloride solution was added to 0.05 ml. of a 0.2 *M* solution of active potassium hexacyanoferrate(II). The precipitate was separated by centrifugation, washed and allowed to stand in the dark at room temperature for six days. The precipitate was then converted to iron(III) hydroxide by addition of 0.5 *M* sodium hydroxide and the product was separated, washed and the radioactivity measured. The iron(III) hydroxide was found to be completely inactive.

Iron(II)-Hexacyanoferrate(II) and Iron(II)-Hexacyanoferrate(III) Exchange.—In similar experiments, no exchange was observed between iron(II) and hexacyanoferrate(II) ions, and none between iron(II) and hexacyanoferrate(III) ions.

Discussion

The rapid electronic exchange between hexacyanoferrate(II) and hexacyanoferrate(III) ions is not surprising since exchange has been observed in all cases in which pairs of ions differing only in electronic charge have been studied, *e. g.*, iron

---

[1] This paper is based on work performed under contract number W-7405-Eng-48, with the Manhattan Project, in connection with the Radiation Laboratory, University of California.

[2] Present address: Department of Chemistry, University of Texas, Austin.

[3] Seaborg, *Chem. Rev.*, **27**, 199 (1940).

[4] Livingood and Seaborg, *Phys. Rev.*, **54**, 51 (1938).

[5] Livingood and Seaborg, *ibid.*, **55**, 1268 (1939).

[6] Banerjee, *J. Indian Chem. Soc.*, **6**, 259 (1929).

(II) and iron(III) ions,[3] lead(II) and lead(IV) acetates,[7] manganese(II) and manganese(III) (oxalate complex) ions,[8] thallium(I) and thallium (III) ions,[9] manganate and permanganate ions,[10] and mercury(I) and mercury(II) ions.[11]

Kennedy, Ruben and Seaborg studied the hexacyanoferrate(II)–hexacyanoferrate(III) equilibrium from only one direction, by mixing active hexacyanoferrate(II) and inactive hexacyanoferrate(III) ions followed by precipitation of the hexacyanoferrate(II) ion with iron(III) chloride.[12] This fact no doubt accounts for their erroneous conclusion, since it was demonstrated in the present investigation that a satisfactory separation of hexacyanoferrate(II) from hexacyanoferrate(III) could not be obtained by precipitation with iron(III) chloride.

The fact that in the present investigation slightly more than 50% of the radioactivity was precipitated with the potassium cerium(III) hexacyanoferrate(II) is clearly due to partial coprecipitation of the hexacyanoferrate(III) ion and not due to incomplete exchange, since an essentially equal excess activity was present in the precipitate regardless of whether the active iron was originally added as hexacyanoferrate(II) or hexacyanoferrate(III) ion.

The failure to observe any atomic exchange between iron(III) and hexacyanoferrate(III) ions, iron(III) and hexacyanoferrate(II) ions, iron (II) and hexacyanoferrate(III) ions and iron(II) and hexacyanoferrate(II) ions adds to our knowledge of the nature of the various compounds formed between these ions. It is now certain that the two kinds of iron atoms which enter into the formation of such compounds as iron(III) hexacyanoferrate(III), iron(II) hexacyanoferrate(II), iron(III) hexacyanoferrate(II), etc., do not occupy equivalent positions in the compound, nor do they exchange positions with each other.

The structures of substances such as $KFeFe(CN)_6$ have been the subject of X-ray analyses by Keggin and Miles.[13] The iron atoms were found to occupy the corners of a single cubic lattice, each being linked with its six neighboring iron atoms by —CN— groups extending along the edges of the cube. Potassium ions and water molecules are contained within these cubes. This structure was further elucidated by the magnetic susceptibility measurements of Davidson and Welo.[14] These data show that, in effect, half of the iron atoms are diamagnetic and the other half are paramagnetic, which Pauling[15] has interpreted to mean that half of the iron atoms are bonded by essentially covalent links (presumably to six surrounding carbon atoms) and half (presumably those surrounded by nitrogen atoms) are held by ionic bonds. We may now add that the iron–carbon bonds which are present in the hexacyanoferrate (II) and hexacyanoferrate(III) ions are not broken in the solid precipitate and remain intact when the precipitates are decomposed by the addition of dilute sodium hydroxide.

Acknowledgments.—The author wishes to express his indebtedness to Professor G. T. Seaborg who suggested the problem, to Dr. J. G. Hamilton under whose direction the cyclotron bombardment of the iron was performed, and to Mr. R. C. Lilly who effected the initial purification of the iron tracer.

Summary

1. An exchange of electrons between hexacyanoferrate(II) and hexacyanoferrate(III) ions in neutral solution, 1.0 *M* hydrochloric acid, and 0.05 *M* sodium hydroxide has been observed to occur within the time interval required for separation of the ions (one minute).

2. No exchange of iron atoms was observed between any of the following pairs of ions: iron (III) and hexacyanoferrate(III), iron(III) and hexacyanoferrate(II), iron(II) and hexacyanoferrate(II), and iron(II) and hexacyanoferrate (III).

RECEIVED AUGUST 18, 1947

---

[7] Hevesy and Zechmeister, *Z. Elektrochem.*, **26**, 151 (1920).

[8] Polissar, THIS JOURNAL, **58**, 1372 (1936).

[9] Majer, *Z. physik. Chem.*, **A179**, 51 (1937).

[10] Libby, THIS JOURNAL, **62**, 1930 (1940).

[11] Nahinsky and Ruben, unpublished work.

[12] Seaborg, private communication.

[13] Keggin and Miles, *Nature*, **137**, 577 (1936).

[14] Davidson and Welo, *J. Phys. Chem.*, **32**, 1191 (1928).

[15] Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 111.

CONTRIBUTION NO. 1147 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

The Coulometric Titration of Arsenic by Means of Electrolytically Generated Bromine and an Amperometric End-point

BY ROLLIE J. MYERS AND ERNEST H. SWIFT

Introduction

A method and apparatus for the determination of thiodiglycol has been described by Sease, Niemann and Swift.[1] This method involved passing a known constant current for a measured time between two platinum electrodes (called the "generator electrodes") immersed in an acetic acid solution containing a soluble bromide, thus at a constant rate generating bromine which oxidized the thiodiglycol. The end-point was obtained by noting the increase in current, caused by excess bromine, between a second pair of platinum electrodes (called the "indicator electrodes") which had a small potential difference impressed across them. The method was developed as part of a war project and time was not available for a detailed study. However, the results obtained, together with the rapidity of the method and the simplicity and cheapness of the apparatus, appeared to justify further investigations in order to establish the accuracy of the method, to obtain a better understanding of certain of the phenomena observed, and to determine the applicability of the method to other constituents. As a part of these investigations a study of the titration of arsenious acid has been made and the results obtained are presented below.

Experimental

Chemicals.—One formal sulfuric acid solutions were prepared from "Reagent Grade" concentrated acid. Immediately after dilution these solutions were found to contain up to 10^{-8} equivalent per milliliter of reducing material; after standing for a day or longer this quantity diminished by 50 to 90%.

Two formal sodium bromide solutions were prepared from "Reagent Grade" material; no reducing material was found present.

Bureau of Standards arsenious oxide was used after being dried for one hour at 115°. Stock 0.005 formal solutions were prepared by dissolving 500 mg. of the oxide in 10 ml. of water containing 1 g. of Reagent Grade sodium hydroxide, then acidifying the solution with 25 ml. of the one formal sulfuric acid and diluting to 500 ml. These solutions were kept for not more than five days.

The laboratory distilled water was found at times to contain as much as 10^{-8} equivalent per milliliter of an oxidizing agent, thought to be chlorine, which could be removed by boiling. A stock of water free of oxidizing agent was used throughout the work.

Apparatus.—The titration cell is outlined in Fig. 1, a basic diagram of the apparatus is shown in Fig. 2, and the details of the electrical circuits are shown in Fig. 3.

The Titration Cell.—The various components of the cell are arranged to give the greatest mechanical strength and to permit the maximum stirring with the minimum fluctuation of solution level; oscillations of the solution level cause variation of the indicator current. Under the conditions of these experiments, changes in the relative positions of the indicator anode and cathode caused no significant difference in the sensitivity of the indicator system. For reasons discussed below the cathode guard shown in Fig. 1 was used to prevent most of the generated hydrogen from being swept into the solution. The small hole in the side of this guard permits sufficient circulation to prevent solution from being trapped in the guard. The amount of hydrogen passing into the solution can be controlled by vertical adjustment of the electrode.

A Cenco variable speed stirrer was used. In order to stabilize the sensitivity of the indicator system the stirrer speed was adjusted by means of a stroboscopic disc consisting of two perpendicular white stripes on a black background illuminated by a fluorescent light or a small neon bulb; a stirrer speed of 1800 r.p.m. was used.

The Indicator System.—All electrodes were made from 0.003 inch platinum foil; the sizes are shown in Fig. 1.

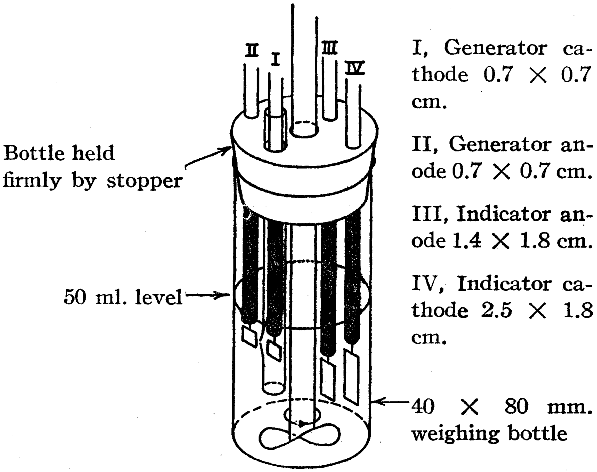


Fig. 1.—Titration cell.

The applied potential difference across the indicator electrodes was usually 200 millivolts. The switch S-8 controlling the sensitivity of the microammeter, M-2, was left in the "high" sensitivity position except in the case of a badly over-run end-point. The switch S-1 was used to short the electrodes during preliminary treatment and storage; otherwise they were found to develop a potential difference.

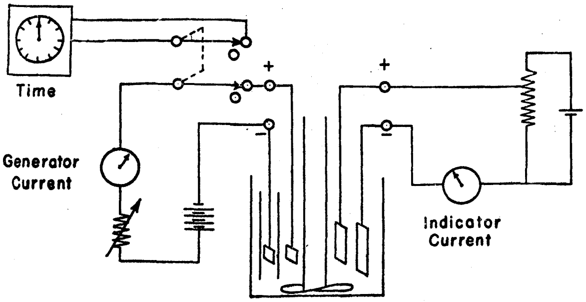
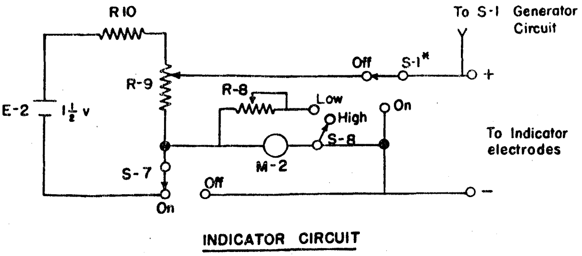


Fig. 2.—Basic diagram of electrical circuits.

---

(1) John Sease, Carl Niemann and Ernest H. Swift, *Anal. Chem.*, **19**, 197 (1947).



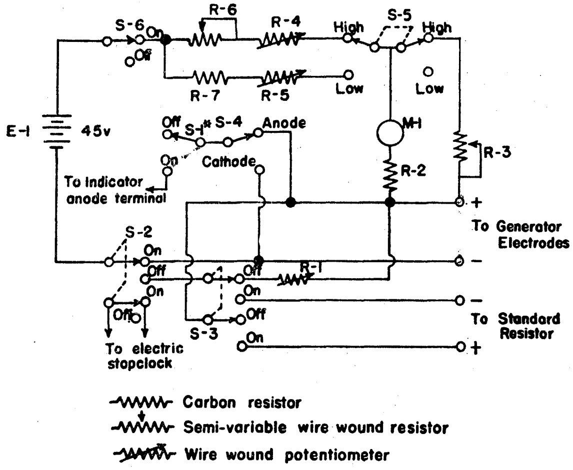


Fig. 3.—Details of generator circuit: *S-1 indicator ganged with S-1 generator: S-1, S-2, S-3, S-5, DPDT radio toggle switches; S-4, S-6, S-7, S-8, SPDT radio toggle switches; M-1 Weston meter, model 301, 0–1 milliampere; M-2 Weston meter, model 301, 0–50 microamperes; E-1 Burgess battery 2308 45v.; E-2 Burgess battery 4F4 1.5v.; R-1 3000Ω, R-2 600Ω2w, R-3 350Ω10w, R-4 1500Ω, R-5 15,000Ω, R-6 5000Ω10w, R-7 45,000Ω2w, R-8 2000Ω10w, R-9 100Ω10w, R-10 240Ω2w.

The indicator anode size is not important. The sensitivity of the indicator system depends linearly on the size of the cathode.

The Generator System.—The switch S-5 provides for "high" and "low" bromine generating rates of approximately 10 and 1 milliamperes, respectively, corresponding to 10^{-7} and 10^{-8} equivalent per second. The generating rate could be adjusted within a reproducibility of ±0.05% by making use of a fixed point near the 10 milliampere calibration on the scale of meter M-1; calibrations over a ten minute period were found to agree to within ±0.1%. With batteries in good condition the current through a fixed resistance would normally remain constant to within ±0.1% over a ten minute period.

Because of temperature and other variations the current value for a specific setting was checked every ten minutes by setting the calibration switch, S-3, to the "on" position and measuring the potential across a standard 200 ohm resistance by means of a potentiometer.

The switch controlling bromine generation, S-2, was ganged so that a Standard Electric Time Co., model S-10, time clock, calibrated to one-tenth second was started and stopped with the generation current.

Resistance R-1 was provided so that between consecutive titrations and during the "warm up" period the current through the meter and battery would be the same as during a titration; this resistance has to be adjusted to correspond to the generation rate. Resistance R-2 was provided so that the contact resistance of switch S-5 had little effect on the resistance in shunt with milliammeter, M-1; switch S-5 has to be of better quality than the other switches.

Accuracy of Standards and Measurements.—The absolute accuracy of the current determination was dependent upon the accuracy of the standard resistor and the standard cell used. The resistance was a 200 ohm coil from a Leeds and Northrup no. 4716 resistance decade, rated by the manufacturer as ±0.05%.[2] The standard cell used was checked against a Weston standard cell which had been calibrated by the U. S. Bureau of Standards; however, during the period of its use the value of the cell changed 1 millivolt. Therefore the uncertainty in the current determination was ±0.1%. The error in the potentiometer readings should have been less than ±0.1%.

The errors in the preparation of the solutions and in the volumetric measurements involved are believed to be less than ±0.1%.

The value used for the faraday was 96,500 coulombs.

Procedure.—When not in use the electrodes are immersed in a solution prepared from 5 ml. of 1 *F* sulfuric acid, 5 ml of 2 *F* sodium bromide and 40 ml of water; the switch S-1 should be in the "on" position. This procedure minimizes changes in the sensitivity of the indicator electrodes and the development of potential differences between them.

First the apparatus is allowed to equilibrate for ten minutes with S-6 and S-7 on, with S-2 and S-3 off, with S-5 set for the appropriate rate, and with R-1 set to the approximate cell resistance for that rate. (After this period the voltage of the generator battery should have become constant and the reading of M-1 stable.) Then before use after a period of storage the electrodes are treated as follows: With switch S-1 on, the generator switch S-2 is turned on for an arbitrary time of nine seconds (at either rate); during this time the treatment selector switch, S-4 is turned to the "cathode" position for three seconds and to the "anode" position for six seconds.

Because the sensitivity of the indicator electrodes tends to change, end-point correction measurements are then made. These values are obtained by generating bromine in the titration medium, at the rate to be used in the titration, for five periods (one or five seconds each for the high or low rate, respectively) and noting the microammeter reading when the needle becomes stable after each of these periods. The stirrer speed should be checked after each period. Two series of such measurements are made. These readings should agree within 3 microamperes at currents of 40 microamperes. Each reading should be stable for twenty seconds and at 40 microamperes momentary fluctuations of the needle should not exceed 1 microampere. With proper reagents the initial current, zero generation time, should not exceed 1 microampere. After completion of each of the end-point correction measurements the indicator electrodes are again treated in the anode position for five seconds as directed above. In Figure 4 the data obtained from a series of three such measurements made on the low generation rate have been plotted in order to show the reproducibility of the measurements and the linearity of the current–time curve. At the high generation rate the end-point correction time is of the order of 1% of the titration time, therefore if the indicator system is reproducible to within ±10%, the uncertainty introduced into the titration should not exceed ±0.1%.

The switch S-3 is then turned on and the desired setting of M-1 calibrated for its exact current value. This calibration should be made every ten minutes or at the end of every titration.

The titrations were made by pipetting the arsenite solu-

---

(2) Not until after the termination of this investigation did a resistance standard become available, a Wolff potentiometer calibrated to within 0.01%. The 200 ohm. coil was then checked against this standard, and was found to be 0.06% low. Since this correction opposed a possible hydrogen current correction, mentioned later, of 0.1% or less, the uncorrected value of 200.0 ohms was used in the calculations.

tion into the titration cell, which contained 5 ml. of 1 *F* sulfuric acid and 5 ml. of 2 *F* sodium bromide, and then diluting the solution to 50 ml. Generation at the appropriate rate is then begun and continued until the first sign of a definite decrease or increase in the indicator current. If the indicator current is less than 2 microamperes, generation is continued until it becomes greater than this value. The indicator current at the end-point should be less than 40 microamperes for the high generation rate and less than 20 microamperes for the low rate. The end-point correction in seconds is obtained by interpolation between the values obtained from the end-point correction measurements.

After each titration the indicator electrodes are treated as was done after the end-point correction measurements, use being made of the titrated solution.

Discussion of the Method

Limitations.—The predominant reaction at the generator anode is the oxidation of bromide to bromine, and at the cathode the reduction of hydrogen ion. One would predict that the method as described would be limited in application to substances which do not establish reversible electrode potentials, otherwise there would be appreciable reduction at the generator cathode of the oxidation product and also the possibility of significant current flow through the indicator system throughout the titration. Also, the assumption is made that the oxidation of hydrogen gas at the generator anode is not a significant factor in the total current through the generator circuit. The results obtained show that in the solution used the arsenic in the quinquepositive state is inert to the generator cathode and to both indicator electrodes. The possibility of extending the method to substances which establish reversible electrode potentials by isolating the generator cathode and by modifications of the end-point procedure is being investigated.

Indicator Current Phenomena.—In solutions 0.1 *F* in sulfuric acid, 0.2 *F* in sodium bromide and varying from 5 to 50 $\times 10^{-7}$ *F* in bromine, this bromine concentration corresponding to indicator currents of from 5 to 50 microamperes, the predicted indicator electrode reactions could be represented as

$$\text{Cathode}\quad Br_2 + 2e^- = 2Br^-$$
$$\text{Anode}\quad 2Br^- - 2e^- = Br_2$$

Making use of a saturated calomel cell and salt bridge, measurements were made (under the conditions of an end-point correction measurement) of the potentials of the generator cathode, generator anode, and of an independent platinum electrode immersed in two such solutions. The values obtained are summarized in Table I.

TABLE I

POTENTIALS OF THE INDICATOR ELECTRODES

Indicator current, microamperes	Potential difference (volts) of indicator electrode *vs.* S. C. E. cathode	anode	Potential difference (volts) of solution. *vs.* S. C. E.
11	0.50	0.71	0.70
30	.53	.73	.71

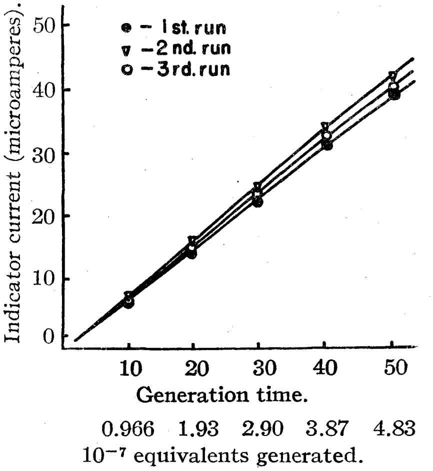


Fig. 4.—Reproducibility of end-point correction measurements: solutions prepared from 5 ml. of 1 *F* sulfuric acid and 5 ml. of 2 *F* sodium bromide diluted to 50 ml.; titrated on the low rate at 0.932 milliampere: ●, first run; ▽, second run; ○, third run.

It appears that the indicator current in the system described is limited by the diffusion of bromine to the cathode. The following formula for such a diffusion current has been derived by Laitinen and Kolthoff[3] with the aid of Fick's law

$$i = (AD/l)\, nFc$$

Here i is the diffusion current, A is the area of the electrode, D is the diffusion constant for the diffusing substance, l is the thickness of the diffusion layer, n is the number of electrons involved, F is the Faraday, and c is the concentration of the diffusing substance in solution.

From this formula it can be seen that an increase in the area of the cathode should increase the bromine diffusion current. This was observed by Sease, Niemann and Swift.[1] Also the current should be a linear function of the bromine concentration, and Fig. 4 shows this to be true. Also one would expect that stirring the solution would decrease the thickness of the diffusion layer, thereby increasing the sensitivity.

Laitinen and Kolthoff[4] used a rotating microcathode (at 600 r. p. m.) with a total surface area of 0.047 sq. cm. and obtained a sensitivity of 1.77 microamperes/10^{-5} mole of Br_2/liter. Using a cathode with a total surface area of 9.0 sq. cm. and the stirring means described we obtain a sensitivity of 1.0 microamperes/10^{-7} mole of Br_2/liter.

The Effect of Hydrogen Gas.—In the apparatus used by Sease, Niemann and Swift[1] the hydrogen produced at the generator cathode was swept into the solution. During a titration the indicator current was found to increase slowly, and before the end of a two-hundred second

---

[3] H. A. Laitinen and I. M. Kolthoff, *J. Phys. Chem.*, **45**, 1061 (1941).

[4] H. A. Laitinen and I. M. Kolthoff, *ibid.*, **45**, 1079 (1941).

titration the current would have become 10–30 microamperes. Shortly before the equivalence point of the titration the current would begin to decrease, would reach zero, reverse direction and temporarily a meter reading below zero would be obtained; then after a few seconds the meter reading would increase rapidly. This decrease and reversal are hereinafter called the **Current Decrease** and the **Current Reversal.**

If hydrogen is bubbled into a solution such as is used for end-point corrections the indicator current will rise, apparently because of oxidation of hydrogen gas at the indicator anode and simultaneous reduction of hydrogen ion at the indicator cathode. However, when bromine generation is started the current will behave as described above. The data from two such experiments are illustrated in Fig. 5.

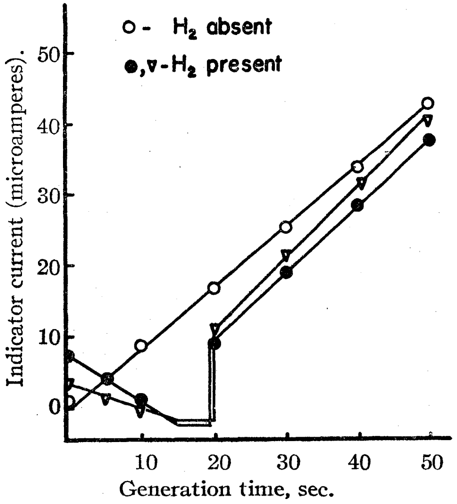


Fig. 5.—The effect of hydrogen gas on end-point correction measurements: solution prepared from 5 ml. of 1 *F* sulfuric acid and 5 ml. of 2 *F* sodium bromide diluted to 50 ml. The hydrogen was bubbled into the solution till the current indicated at zero time was obtained, then bromine was generated in five to ten second intervals and the value of the current read five to fifteen seconds after termination of generation. Portions of curves between ten and twenty seconds describe the general behavior of the meter during this period. Generation rate was 0.90 milliampere.

It is evident from the figure that if hydrogen were present at the end-point, and the normal end-point correction made, the titration would give high results. This is illustrated by the titration graph shown in Fig. 6.

A series of titrations was run (as illustrated in Fig. 6) in which the hydrogen produced at the generator cathode was allowed to pass into the solution. When the normal end-point correction was used the results were 1% too high; when nitrogen was bubbled into the solution to eliminate the dissolved hydrogen, the few measurements made were within 0.3%. The use of nitrogen was not investigated further, since by the use of the cathode shield satisfactory results and certain advantages were obtained.

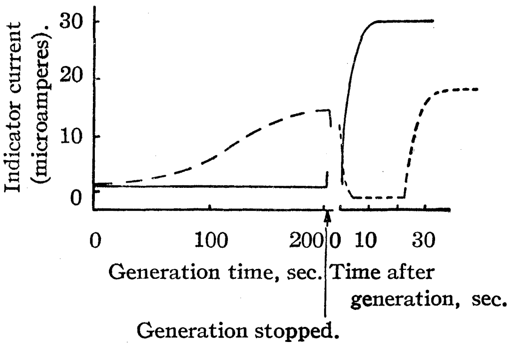


Fig. 6.—Titration characteristics with and without hydrogen present: the solid line represents a titration in which hydrogen was excluded from the solution; the dashed line represents a titration in which hydrogen was allowed to accumulate. The flat portion of the dashed curve represents time during which the meter needle is held fixed below zero by reversal of current. Solution was prepared from 5 ml. of 1 *F* sulfuric acid, 5 ml. of 2 *F* sodium bromide, and 10 ml. of 2×10^{-3} *N* arsenite solution diluted to 50 ml.; generation rate, 9.65 milliamperes.

Since the area of the generator anode is approximately one fifth that of the indicator anode, and the maximum concentration of hydrogen in the solution is obtained only near the end-point, it has been assumed that the error caused by oxidation of hydrogen at the generator anode is relatively small.

Current Decrease.—Kolthoff and Miller[5] have described the action of the polarograph in a solution exhibiting what they term a "mixed potential." Solutions containing hydrogen and bromine have been found to have such a potential, and the explanation advanced by Kolthoff and Miller for the current–voltage phenomena with a single electrode system can be applied to our two electrode system. According to this explanation the time of zero current should correspond to equal quantities of hydrogen and bromine diffusing to an electrode in the solution.

In Figure 5 the measurements obtained from end-point correction experiments with and without hydrogen are plotted. It is seen there that the number of equivalents per second of hydrogen diffusing to the anode can be calculated by the initial indicator current, and at zero current the amount of bromine which has been generated would in the absence of hydrogen, cause a diffusion current which is represented by the normal end-point correction curve. On this normal curve, this current would represent the number of equivalents per second of bromine diffusing to the cathode at the time of zero current. In Table II such values are calculated for the amount of hydrogen and bromine arriving at 1 sq. cm. of electrode surface per second at zero current for different values of initial hydrogen current.

---

[5] I. M. Kolthoff and C. S. Miller, THIS JOURNAL, **62**, 2171 (1940).

TABLE II

THE EFFECT OF HYDROGEN GAS

I_{H_2}[a] microamperes	N_{H_2}[b] 10^{-11} eq.	I_{Br_2}[c] microamperes	N_{Br_2}[d] 10^{-11} eq.
1.8	0.37	3.0	0.35
4.0[e]	0.83	7.9	0.91
4.3	0.90	7.8	0.90
5.0	1.1	8.3	0.95
7.4[e]	1.5	9.3	1.1
13.0	2.7	21.0	2.4
15.0	3.1	18.0	2.1

[a] I_{H_2}, initial hydrogen current. [b] N_{H_2}, equivalents of hydrogen arriving at 1 sq. cm. of anode per second for I_{H_2}. [c] I_{Br_2}, bromine current at time of zero current if no hydrogen were present. [d] N_{Br_2}, equivalents of bromine arriving at 1 sq. cm. of cathode per second for I_{Br_2}. [e] Note: I_{H_2} of 4.0 and 7.4 are taken from Fig. 5, other values are from unpublished measurements.

It can be seen that at the lower values of hydrogen current, when the rate at which the hydrogen leaves the solution is small, the calculated values of bromine and hydrogen which arrive at an electrode are approximately equal at the time of zero current.

Current Reversal.—In the upper portion of Fig. 7 the potential of the indicator cathode *versus* a saturated calomel half cell is shown during generation of bromine with and without hydrogen being initially present in the solution.

As would be expected, during the period of current decreases and current reversal there is a great change in the potential of the indicator electrodes and of the solution. If because of a local condition about one of the indicator electrodes the potential of that electrode were to lag or lead the potential of the other electrode during this change, a transient condition could exist whereby the potential between the indicator electrodes could be greater than the applied potential, thus causing a reversal of current.

During hydrogen diffusion current, before the addition of bromine, hydrogen is being produced at the indicator cathode and being removed at the indicator anode. One might expect then that at the time of zero current, when equal quantities of bromine and hydrogen are arriving at the anode, there would be an adsorbed layer of hydrogen on the indicator cathode. A cell would then be established in opposition to the applied potential, and could cause a current reversal until this hydrogen was removed. Thereafter bromine predominates at the cathode and the current behaves essentially as during bromine generation in the absence of hydrogen.

It is of interest to note that the number of equivalents of hydrogen which would be discharged to cause the current reversal as illustrated in Fig. 6 would be about 4 × 10^{-10} equivalent. A monomolecular layer of hydrogen on the 9.0 sq. cm. cathode, assuming one hydrogen molecule per 10 Å.^{2}, would amount to 3.0 × 10^{-8} equivalent.

Titration of Arsenite Solutions.—In Table III are shown the data collected from a series of titrations of arsenious acid solutions in which there was no guard tube over the generator cathode and in which the hydrogen evolved was allowed to pass freely into the solution. The error is in all cases positive and is attributed to the hydrogen effect discussed above.

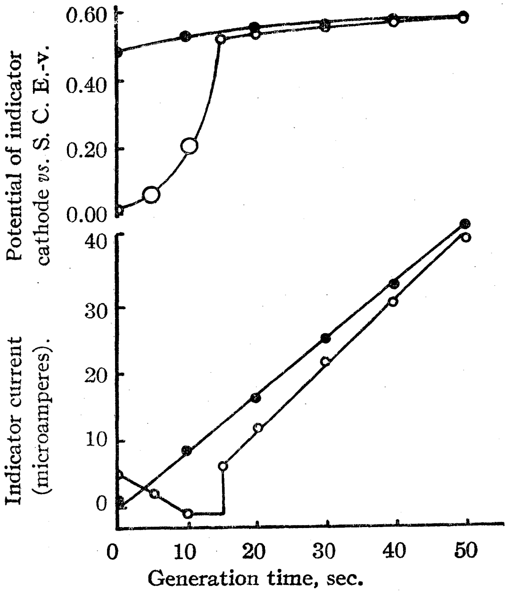


Fig. 7.—Change of potential of indicator cathode during generation (with and without hydrogen): solution prepared from 5 ml. of 1 *F* sulfuric acid and 5 ml. of 2 *F* sodium bromide, diluted to 50 ml.; generation rate, 0.90 milliampere: ●, hydrogen absent; ○, hydrogen present.

TABLE III

TITRATIONS OF ARSENITE SOLUTIONS (NO GUARD TUBE OVER GENERATOR CATHODE)

The arsenious acid was added to 5 ml. of 1 *F* sulfuric acid and 5 ml. of 4 *F* potassium bromide, then the volume was adjusted to 50 ml. In all cases current decrease and current reversal were obtained; the indicator current at the beginning of current decrease varied from 20–40 microamperes.

Expt.	Generation time, sec.	Generator current, milliamperes	End-point correction, sec.	Arsenic, micrograms Taken	Arsenic, micrograms Found	Arsenic, micrograms Error
Ia	199.8	9.77_0	6.4	726.3	733.4	7.1
Ib	198.3	9.77_0	5.0	726.3	733.0	6.7
IIa	249.7	9.68_0	3.5	919.1	925.0	5.9
IIb	249.1	9.68_0	3.0	919.1	924.6	5.5
IIIa	392.2	9.72_0	3.6	1452.5	1466.1	13.6
IIIb	390.6	9.72_0	3.0	1452.5	1462.3	9.8

A series of titrations was run using the apparatus with the guard shown in Fig. 1 around the generator cathode. During a two-hundred second titration the cathode guard permitted sufficient hydrogen to pass into the solution to give an indicator current of about 1.2 microamperes just before the end-point. This hydrogen diffusion current was adequate to give a small decrease and a distinct current reversal. Since on the high rate bromine is being generated at such a rate as to cause an indicator current rise of 10 microamperes per second after passing the equivalence-point it was decided that the current reversal, especially for an inexperienced operator, was a convenient end-point indication, and at times resulted in a smaller end-point correction.

From the above discussion of the current decrease, it is seen that 1.2 microamperes of hydrogen diffusion current would correspond to a decrease of 2.2 microamperes in the bromine diffusion current at the end-point. For a two-hundred second titration this would be a correction of −0.10%. Since the accuracy of the standards is of this magnitude, this correction was not used. Therefore, in the calculation of the values of arsenic found shown in Table IV no hydrogen correction was made.

TABLE IV

TITRATIONS OF ARSENITE SOLUTIONS (GUARD TUBE OVER GENERATOR CATHODE)

The arsenious acid was added to 5 ml. of 1 *F* sulfuric acid and 5 ml. of 2 *F* sodium bromide, then the volume was adjusted to 50 ml.

Generation time, sec.	Generator current, milli-amperes	End-point corrn., sec.	Arsenic found, micrograms	Error
Solution I—860.3 micrograms of arsenic taken				
227.1	9.81_0	1.3	859.7	−0.6
226.5	9.82_0	0.9	859.9	− .4
227.0	9.83_5	1.7	860.0	− .3
227.1	9.83_5	1.8	860.0	− .3
			Average 859.9	−0.4
Solution II—800.0 micrograms of arsenic taken				
210.4	9.82_5	0.7	799.7	−0.3
210.5	9.82_5	0.7	800.1	.1
211.0	9.82_0	1.0	800.4	.4
210.5	9.82_0	0.6	800.0	.0
			Average 800.1	0.1

In order to demonstrate the general accuracy of the method, another series of titrations was run. In this case the first member of each set was an unknown for the operator. The operator knew only that the end-point would not occur during the first thirty seconds of the titration period. This allowed him to correct for the initial fluctuations in the generator current. Two operators were used, one of the authors (RM) and an inexperienced operator. (We are indebted to Mr. W. S. Wooster for making these determinations.)

A good current reversal was obtained, in the titrations made on the high rate which were longer than one-hundred seconds; those made on the low rate gave no current reversal. The results of this series of determinations are tabulated in Table V. An inspection of this table shows that the absolute error appears to be independent of the amount of arsenic being determined, that the maximum deviation is about 1 microgram, and the average deviation is 0.5 microgram.

TABLE V

TITRATIONS OF ARSENITE SOLUTIONS (GUARD TUBE OVER GENERATOR CATHODE)

The arsenious acid was added to 5 ml. of 1 *F* sulfuric acid and 5 ml. of 2 *F* sodium bromide, then the volume was adjusted to 50 ml.

Expt.	Operator	Generation time, sec.	Generator current, milli-amperes	End-point corrn., sec.	Arsenic, micrograms Taken	Arsenic, micrograms Found	Error
Ia	M	252.3	9.83_5	0.4	960.4	961.6	1.2
b		252.3	9.83_5	0.7	960.4	960.4	0.0
c		252.2	9.83_5	0.5	960.4	960.8	0.4
IIa	W	211.8	9.80_5	1.4	800.4	800.7	0.3
b		210.9	9.80_5	0.6	800.4	800.3	−0.1
c		210.9	9.80_5	1.0	799.7	798.8	−0.9
IIIa	W	112.1	9.82_5	2.9	416.5	416.4	−0.1
b		109.7	9.82_5	0.4	416.5	416.8	0.3
c		110.5	9.82_5	1.2	416.5	416.8	0.3
IVa	M	85.3	9.83_0	1.5	320.6	319.7	−0.9
b		86.4	9.83_0	2.3	320.6	320.9	0.3
c		85.7	9.83_0	1.8	320.6	320.1	−0.5
Va	W	247.2	0.930	7.6	86.2	86.5	0.3
b		247.3	0.930	8.0	86.2	86.4	0.2
c		253.0	0.930	12.1	86.2	87.0	0.8
VIa	W	175.8	0.930	6.1	60.4	61.3	0.9
b		175.0	0.930	6.4	60.4	60.9	0.5
VIIa	M	103.8	0.930	6.3	34.5	35.2	0.7
b		102.8	0.930	6.1	34.5	34.9	0.4

Summary

A coulometric method is described for the determination of approximately 30–1000 microgram quantities of tripositive arsenic. The arsenic is oxidized by electrolytically generated bromine, and an amperometric method is used for the determination of the end-point. The accuracy of this amperometric method has been improved by limiting the amount of hydrogen passing into the solution from the generator cathode. The causes of the decrease and reversal of the indicator current near the equivalence-point have been investigated.

PASADENA, CALIFORNIA RECEIVED AUGUST 20, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Preparation of Aluminum Di-Soaps[1]

BY GEROULD H. SMITH,[2] HAROLD H. POMEROY, CHARLES G. MCGEE AND KAROL J. MYSELS[3]

The existence of mono-, di- and tri-aluminum soaps has been in question for a decade. Extreme opinions on the subject have been set forth. Lawrence[4] maintains that the mono-, di- and tri-soaps of aluminum all exist and exhibit a similar behavior. He has asserted that the tri-soap is most easily prepared. Indeed a so-called tri-soap has long been an article of commerce. On the other hand, Eigenberger and Eigenberger–Bittner[5] obtained none of these soaps but only a basic compound intermediate between mono- and di-soaps, and a still more basic sorption compound. Alexander[6] suggested that only the mono-soap exists; McBain and McClatchie[7] were unable to prepare aluminum tri-palmitate even under the most anhydrous conditions. The third equivalent of fatty acid could always be immediately extracted as such by an anhydrous solvent, leaving a di-soap. Even the di-soap was partially hydrolyzed by moisture or aqueous media. Ostwald and Riedel[8] also found that precipitation from aqueous solution resulted in an aluminum di-soap. Markowicz[9] had earlier reported that aluminum palmitate, prepared in an aqueous medium, was such an aluminum dipalmitate.

In the present work the region in the immediate neighborhood of the di-soap has been explored thoroughly, that of the tri- and mono-soap less intensively. It is concluded that di-soaps such as dilaurate, $AlOHL_2$, definitely exist as chemical entities, and that the existence of the tri-soaps, AlL_3, AlP_3 and $AlStr_3$, remains unproven and improbable. On the basis of work not recorded here and of subsequent work by C. G. McGee, it is concluded that polymerized mono-soaps approximating such empirical formulas as $Al(OH)_2L$ also exist. This will be published separately.

Addition of aqueous solution of potassium soaps to an excess of aqueous solution of aluminum chloride leads to the formation of a *di-soap*. However, this is usually associated with 20–30% of free or loosely bound fatty acid which is extractable with anhydrous solvents, leaving the di-soap.

When the extraction is carried out with highly dried acetone at 20°, the first few hundred cc. of acetone used per gram of soap removed practically all the excess of fatty acid above the di-soap, showing that the excess of acid was partly free and partly merely sorbed. Only in the case of the stearate, where the stearic acid is but little soluble at 0° was the extraction slower. Further exhaustive extraction with 5 or 6 liters of acetone per gram removed very little further acid. However, extraction at 53° definitely caused further removal of acid below the di-soap which could be accounted for by hydrolysis due to the irreducible trace of water in the dried acetone. Further moisture increased the rate and amount of extraction.

Extraction of aluminum stearate with boiling anhydrous isoöctane yielded a clear jelly of aluminum distearate, $Al(OH)Str_2$, with ash value of 8.74%; calcd. 8.52%.

The present paper deals with dilaurate, distearate, dioleate, dicyclohexane carboxylate, and dinaphthenate.

Materials

Baker's C.P. Reagent grade aluminum chloride hexahydrate and potassium hydroxide were used. Lauric and stearic acids were obtained from the Eastman Kodak Company and were found to have neutralization numbers of 279.4 and 198, respectively (calcd., 277.5 and 197.3). Potassium soaps were prepared by mixing carbonate-free solutions of potassium hydroxide and fatty acid in methanol. They precipitated in a fine, white, flocculent state and filtered easily. They were washed with portions of methanol, and then with acetone to purify and dry the soap. Final drying was carried out over phosphorus pentoxide in an evacuated desiccator. The dried soaps were white, light and powdery. Kahlbaum potassium oleate was used directly.

Procedure

After numerous tests, the following standardized procedure was developed. A 2% freshly prepared aqueous solution of potassium soap was slowly added to a 1.5% solution of aluminum chloride with vigorous agitation in a blender provided with an electrically heated jacket. The amount of aluminum chloride present (in the ratio of one mole aluminum chloride to one mole potassium soap, each 0.00775 *m* in the case of stearate) was approximately twice that necessary for the complete precipitation of all the fatty acid as aluminum disoap. Under these conditions, a precipitate formed which contained all of the fatty acid either as free or loosely bound molecular fatty acid or as aluminum soap, while the mother liquor contained the chlorides of aluminum and potassium.

The precipitate was washed with water in the blender, and filtered until the filtrate gave no turbidity with a silver nitrate solution. The soap was finally dried to constant weight over phosphorus pentoxide. This was the "unextracted" soap. Extraction at 0° with acetone dried over Drierite (calcium sulfate), or with dried isoöctane at room temperature, frees the aluminum soap from all free and loosely bound acid, leaving an "extracted" soap of nearly the theoretical composition of aluminum disoap.

Samples of all aluminum soaps, both extracted and unextracted, were ashed at 900–1000°, duplicate results on a given sample agreeing within 0.04%. The ash was calculated as aluminum oxide, since it was repeatedly found

---

[1] Study conducted under contract OEMsr-1057 between Stanford University and the Office of Emergency Management, recommended by Division 11.3 of the National Defense Research Council, reported in P.B. 5885, and supervised by Professor J. W. McBain.

[2] Present address: Union Oil Company of California, Oleum.

[3] Present address: University of Southern California, Los Angeles.

[4] Lawrence, *J. Inst. Petroleum*, **31**, 312 (1945).

[5] Eigenberger and Eigenberger–Bittner, *Kolloid Z.*, **91**, 287 (1940).

[6] Reports to Division 11.3 N. D. R. C.

[7] McBain and McClatchie, *J. Phys. Chem.*, **36**, 2567 (1932).

[8] Ostwald and Riedel, *Kolloid Z.*, **69**, 185 (1934).

[9] Markowicz, *Farben-Ztg.*, **34**, 326, 414, 503 (1928).

to be free from water-soluble salts. Some of the aluminum soaps were also analyzed by decomposing with excess of strong acid, titrating the excess, and also determining the liberated fatty acid. Conditions of mixing and stirring have no appreciable effect on the properties of the resulting soap, nor does varying concentration of the reactants.

Aluminum Dilaurate, $AlOHL_2$.—The precipitation of aluminum laurate when carried out at 25–30° resulted in free-floating flocs that were readily filtered and washed. However, temperatures above 40° resulted in a sticky aluminum soap that on cooling became hard and brittle, necessitating grinding to permit satisfactory washing. The ash content of the dried extracted aluminum soap varied but little with the temperature of precipitation from room temperature to the boiling point, and was close to 11.56–11.62% as compared with a theoretical value[10] of 11.49 for the dilaurate, $Al(OH)L_2$, whereas that of a monolaurate, $Al(OH)_2L$, would be 19.6%. The pure aluminum dilaurate melted between 195 and 197°.

A composition much closer to the theoretical (ash contents 11.56-11.62%) was obtained if extraction was conducted so as to minimize hydrolysis, *e. g.* Soxhlet extraction with isoöctane at room temperature, or with acetone at 0°, or rapid washing in a fritted glass funnel with 80 cc. of acetone per gram of salt. The product obtained by this last method contained 89.3% of lauric acid by titration (theory 90.5) melted over a range of one degree centigrade at 193–196° and was used for most of subsequent studies.[11]

When 0.4 equivalent excess of potassium hydroxide was added to the potassium laurate used for precipitation, the ash of the resulting extracted soap was 12.4%, only about 0.8% higher than before.

Aluminum Distearate, $AlOHStr_2$.—Aluminum stearate precipitated at temperatures from 0° up to about 50–60° usually formed soft and slow-filtering sludges. However, samples prepared at a higher temperature separated easily as coagula from the clear aqueous medium. The dried aluminum soap from batches precipitated at temperatures below 50–60° was flaky and compact, whereas higher temperatures resulted in light, powdery and very finely divided aluminum soaps. The composition of extracted aluminum stearate depends largely on the temperature of precipitation; the ash content is constant at 9.55% between 0 and 40°, but then decreases linearly with temperature to 100° where it is within 0.1 to 0.15% of the theoretical value for the ash of distearate, 8.38%; the ash of monostearate would be 14.86%. The distearate melts between 175 and 177°.

Aluminum Dioleate, $AlOHOl_2$.—Dry unextracted aluminum oleate was an orange-tan, granular powder at 0–5° which became gummy when the free oleic acid was allowed to melt. The extracted soap was in the form of small friable granules, with no definite melting point. Like laurate, temperature of precipitation had but little effect on the composition of the extracted oleate. It remained close to 8.64% ash as compared with 8.42%, the theoretical value for $Al(OH)Ol_2$.

Aluminum Dicyclohexanecarboxylate, $Al(OH)(C_6H_{11}COO)_2$.—Cyclohexanecarboxylic acid (Eastman Kodak Company) differs from fatty acids in being somewhat water soluble and some part of the original precipitate of the free or loosely bound acid is removed when washing with water. The extracted, white, powdery, odorless product had an ash content of 16.95%; Calcd. for $Al(OH)(C_6H_{11}COO)_2$: 17.09%. It is insoluble and apparently inert in water, acetone, ethyl alcohol, and diethyl ether. A slight tendency toward swelling occurs in *n*-amyl alcohol, diisobutylene, cyclohexane and dioxane. It swells to a gel in carbon tetrachloride and toluene. It exhibits a remarkable thermal stability, showing no decomposition upon prolonged heating at 360° in a sealed, evacuated glass tube; but at about 450° it melts with decomposition.

Aluminum Naphthenates.—Several samples of aluminum naphthenate were prepared from purified samples of commercial naphthenic acids of different molecular weights. The sodium soaps of the naphthenic acids were prepared and then washed exhaustively with acetone. This removed most of the color and residual oil. Following this treatment, the aluminum soaps were prepared in the usual manner. Some fractionation of the original impure naphthenic acids occurs as a result of the drastic acetone extraction of the sodium naphthenates. As determined from the extracted ash value and the neutralization value of the acids freed from the finished soap, the white powdery products had a composition corresponding to about $^1/_3$ dinaphthenate and $^1/_3$ mononaphthenate.

Summary

Aluminum dilaurate, dicyclohexanecarboxylate, moderately pure dioleate, distearate and a product intermediate between dinaphthenate and mononaphthenate were prepared by aqueous precipitation, followed by thorough extraction with dried isoöctane or acetone. The original precipitates, at least of the first three, are aluminum di-soaps, together with free or loosely bound molecular fatty acid.

STANFORD UNIVERSITY, CALIFORNIA

RECEIVED SEPTEMBER 16, 1947

---

[10] The "theoretical" compositions of all soaps in this paper are based on the actual molecular weight of the fatty acid used.

[11] J. W. McBain, K. J. Mysels, *et al*, *J. Gen. Physiol.* **30**, 159 (1946); *J. Coll. Sci.*, **2**, 265 (1947); **2**, 375 (1947); *J. Phys. Coll. Chem.*, **51**, 963 (1947); *Trans. Far. Soc.*; and unpublished work.

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

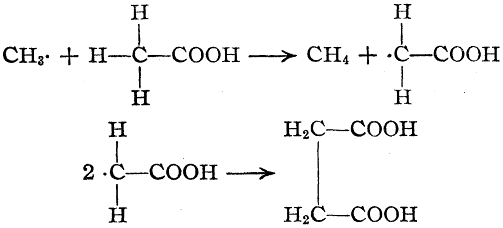
Reactions of Atoms and Free Radicals in Solution. XII. The Addition of Bromo Esters to Olefins

BY M. S. KHARASCH, P. S. SKELL AND PAUL FISHER

Introduction

Investigation of the additions of a number of substances to olefins has demonstrated that some of these additions proceed by a free radical chain reaction. Among the reactions observed, are radical-induced polymerizations or copolymerizations, and additions of the following types of atoms and free radicals[1]: $Br\cdot$,[(a)] $RS\cdot$,[(b)] $\cdot SCH_2COOH$,[(c)] $HO_3S\cdot$,[(d)] $Cl_3C\cdot$, $Br_3C\cdot$, $Cl_2BrC\cdot$, $Br_2HC\cdot$,[(e)] $C_2H_5OCOCCl_2\cdot$,[(f)] $Cl_2P\cdot$,[(g)] $Cl_3Si\cdot$,[(h)] $(C_6H_5)_3C\cdot$[(k)]. The present paper deals with the free radical chain reactions involved in the additions of various bromo esters to olefins.

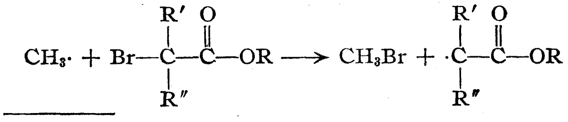
Addition of Bromo Esters to Olefins.—It has been shown that a free methyl radical, generated in solution by the thermal decomposition of diacetyl peroxide, abstracts an α-hydrogen atom from carboxylic acids,[2a] esters, nitriles,[2c] ketones,[2b] etc. Where carboxylic acids are used, the products of the reaction[2a] are methane and a free carboxylic acid radical, which then dimerizes to the corresponding succinic or substituted succinic acid



$$CH_3\cdot + H{-}\overset{H}{\underset{H}{C}}{-}COOH \longrightarrow CH_4 + \cdot\overset{H}{\underset{H}{C}}{-}COOH$$

$$2\,\cdot\overset{H}{\underset{H}{C}}{-}COOH \longrightarrow \begin{array}{l} H_2C{-}COOH \\ \;| \\ H_2C{-}COOH \end{array}$$

The method cited for producing free carboxymethyl radicals or free carbalkoxymethyl radicals cannot, however, be used to study the reactions of these free radicals with olefins because olefins successfully compete with the acid or the ester for the free methyl radical. The same type of free carbalkoxymethyl radical is however produced when a free methyl radical acts on an α-bromo ester.



$$CH_3\cdot + Br{-}\overset{R'}{\underset{R''}{C}}{-}\overset{O}{\overset{\|}{C}}{-}OR \longrightarrow CH_3Br + \cdot\overset{R'}{\underset{R''}{C}}{-}\overset{O}{\overset{\|}{C}}{-}OR$$

Since an α-bromine atom in an α-bromo carboxylic ester is more susceptible to attack by a free methyl radical than is an α-hydrogen atom of an ester[3] or any hydrogen atom in an aliphatic olefin, it should be possible, by using α-bromo esters, to generate free ester radicals in olefinic solvents and to study their reactions with those solvents.

When a small amount of diacetyl peroxide (5-10 mole per cent.) is decomposed in a solution of octene-1 in ethyl bromoacetate a good yield of ethyl γ-bromocaprate and a small quantity of methyl bromide are obtained. The reaction presumably takes place according to the following scheme:

$$CH_3\cdot + BrCH_3COOC_2H_5 \longrightarrow CH_3Br + \cdot CH_2COOC_2H_5 \quad (1)$$

$$n\text{-}C_6H_{13}CH{=}CH_2 + \cdot CH_2COOC_2H_5 \longrightarrow n\text{-}C_6H_{13}\dot{C}HCH_2CH_2COOC_2H_5 \quad (2)$$

$$n\text{-}C_6H_{13}\dot{C}HCH_2CH_2COOC_2H_5 + BrCH_2COOC_2H_5 \longrightarrow n\text{-}C_6H_{13}CHBrCH_2CH_2COOC_2H_5 + \cdot CH_2COOC_2H_5 \quad (3)$$

Step (1) is the initiating step. Steps (2) and (3) constitute a self-sustaining chain reaction; hence the number of condensations per free methyl radical is relatively large.

The requisites for such a self-sustaining chain reaction are as follows: (a) the free carboxylic ester radical and the olefin must be so constituted that they can condense rapidly (step 2); otherwise the concentration of the radical increases to the point where dimerization becomes a successfully competitive chain-breaker; (b) the nature of the bromo ester and the new radical produced by the addition of the free carboxylic ester radical to the olefin must be such as to permit the rapid transfer of a bromine atom from the former to the latter (step 3).

The type of condensation reaction described yields (as end-products) substituted γ-bromo esters. It has been successfully applied to bromo esters (both straight-chain and branched), and to α-bromo dicarboxylic esters, but it fails with β-bromo esters. The reason for this failure is that the bromine atom in the β-position is but little affected by the carbalkoxy group; hence this atom is so strongly bound that condition (b) is not fulfilled.

Branching of the carbon skeleton of the ester in the neighborhood of the position α to the carbalkoxy group shortens the chain length of the condensation reactions. Thus, under comparable conditions α-bromoisobutyric and α-bromoiso-

---

(1) (a) Kharasch, Englemann and Mayo, *J. Org. Chem.*, **2**, 288, 400, 577 (1937). (b) Kharasch and Mayo, THIS JOURNAL, **55**, 2491 (1933); Jones and Reid, *ibid.*, **60**, 2452 (1938); Kharasch, Nudenberg and Graham, unpublished work; (c) Kharasch, Read, and Mayo, *Chemistry and Industry*, **57**, 752 (1938); (d) Kharasch, May and Mayo, *J. Org. Chem.*, **3**, 175 (1938); (e) Kharasch, Jensen and Urry, *Science*, **102**, 128 (1945); Kharasch, Jensen and Urry, THIS JOURNAL, **68**, 154 (1946); Kharasch, Jensen and Urry, *ibid.*, **69**, 1100 (1947); Kharasch, Reinmuth and Urry, *ibid.*, **69**, 1105 (1947); (f) Kharasch, Urry and Jensen, *ibid.*, **67**, 1626 (1945); (g) Kharasch, Urry and Jensen, *ibid.*, **67**, 1864 (1945); (h) Sommer, Pietrusza and Whitmore, *ibid.*, **69**, 188 (1947); (k) Marvel, Dec and Corner, *ibid.*, **67**, 1855 (1945).

(2) (a) Kharasch and Gladstone, *ibid.*, **65**, 15 (1943); (b) Kharasch, McBay and Urry, unpublished work; (c) Kharasch, Smith and Urry, unpublished work.

(3) It is noteworthy that in the α-chlorinated acetic esters the chlorine atom is less active than the α-hydrogen atoms.

valeric esters give poorer yields of condensation products than do the corresponding esters of the normal acids. If the amount of diacetyl peroxide is increased, the yield of the condensation product (formed from the bromo ester) increases. This fact indicates that some chain-breaking reaction operates with greater efficiency in the additions of branched free radicals to olefins than it does in the additions of the corresponding normal free radicals.

The question therefore arises whether this chain-breaking mechanism is a failure to meet condition (a) or a failure to meet condition (b). In order to obtain evidence on this point a number of experiments were carried out. It is to be borne in mind that octene-1 and the esters of α-bromoacetic acid, when treated as described, give good yields of γ-bromo capric esters per unit of peroxide used; whereas octene-1 and the esters of bromoisobutyric acid give poor yields of γ-bromo-α,-α-dimethylcapric esters. If diacetyl peroxide is decomposed in an octene-1 solution of a mixture of ethyl α-bromoacetate and methyl α-bromoisobutyrate, then the following results are to be anticipated. If the bromine atom in the bromoacetic ester is more easily attacked by the secondary alkyl free radical (step 3) than is the bromine atom in the bromoisobutyric ester then the chain should be carried mostly by the bromoacetate; here the predominant product should be ethyl γ-bromocaprate and this product should be obtained in good yield per unit of peroxide used. On the other hand, if the bromine atom in the isobutyric ester is more easily attacked, then the chain should be carried mostly by the bromoisobutyrate; here the predominant product should be methyl γ-bromo-α,α-dimethylcaprate and this product should be obtained in poor yield. Actually the reaction product, when converted to a lactone by distillation at 150° is principally a poor yield of α,α-dimethyl-γ-caprolactone. Even with an (undetected) impurity of 10% of γ-caprolactone in the reaction product, this result would still indicate that the bromine atom in the α-bromoisobutyrate is at least eight times as easily attacked by secondary alkyl radicals (step 3) as is the bromine atom in the bromoacetate.

The experiment just described shows clearly that the α-bromoisobutyric ester complies with condition (b) even better than does the bromoacetic ester. Hence the poor yields obtained from the α-bromoisobutyrate must be due to inadequate compliance (on the part of this ester) with condition (a). Supporting this conclusion is the fact that when the α-bromoisobutyric esters alone are added to olefins (under the condition stated) the reaction products always contain considerable quantities of tetramethylsuccinic esters. This result is exactly what would be predicted on the basis of the experiment cited. The free radical produced from α-bromoisobutyric ester (step 1) adds so slowly to the olefin that it accumulates in the solution to the point where dimerization effectively competes with the addition reaction.

Competition experiments similar to those already cited were carried out to determine the relative reactivities of the bromine atoms in ethyl bromoacetate and ethyl α-bromo-*n*-butyrate. The condensation product was converted to the lactone, which proved to be a mixture of 45 mole per cent. of γ-caprolactone and 55 mole per cent. of α-ethyl-γ-caprolactone. This difference, (10%), is only slightly greater than the experimental error of the method. Hence, it may be concluded that, toward a secondary free alkyl radical, the bromine atom in ethyl α-bromo-*n*-butyrate is only slightly more reactive than the bromine atom in ethyl bromoacetate. This result taken in conjunction with those already mentioned shows that, if only one hydrogen atom in bromoacetic ester is replaced by an alkyl radical, the reactivity of the bromine atom is but slightly increased. On the other hand, substitution of both hydrogen atoms by alkyl radicals greatly increases the reactivity of the bromine atom.

The nature of the alcoholic alkyl radical in the ester is not critical, so long as this radical contains no chain-breaking substituent. When tertiary butyl α-bromopropionate is condensed with octene-1, the yield of condensation product is only slightly less than that obtained from the corresponding ethyl ester. In general, methyl esters appear to give slightly better yields than do ethyl esters; but, so far, there is no evidence to show whether the ethyl group exerts a chain-breaking effect by virtue of its active α-hydrogen atom or whether it exerts a steric influence.

Varying the structure of the olefinic component has demonstrated that straight-chain aliphatic olefins with either terminal or non-terminal double bonds, participate successfully in the chain reaction. When styrene or ethyl acrylate are used under comparable conditions they yield products of moderate molecular weight rather than 1:1 condensation products. Judging from the ease with which these olefins undergo radical-induced polymerization, there can be little doubt that in the reactions tested condition (a) is fulfilled. Neither compound, however, fulfills condition (b) for the free radicals which they produce ($C_6H_5\underset{\cdot}{C}HCH_2CH_2COOC_2H_5$ and $C_2H_5OCO\underset{\cdot}{C}HCH_2CH_2COOC_2H_5$, respectively) have so little ability to abstract a bromine atom from a molecule of α-bromo ester that they cannot continue the reaction chain. On the other hand, these radicals can add to other molecules of styrene or ethyl acrylate and thus produce polymers. This latter type of reaction is of only slight importance when straight-chain aliphatic olefins are employed because (1) these olefins are not reactive enough to polymerize and (2) the radical produced from either of these (by addition of a free ester radical) is so reactive that it readily removes a bromine atom from the α-bromo ester to continue the chain. But, even with these aliphatic olefins, there is always a small amount of residue left after removal of the 1:1 condensation product. This residue is probably a 2:1 condensation product formed as follows

$$R\underset{\cdot}{C}HCH_2CH_2COOC_2H_5 + RCH{=}CH_2 \longrightarrow RCHCH_2\underset{\cdot}{C}HRCH_2CH_2COOC_2H_5$$

$$R\underset{\cdot}{C}HCH_2CHRCH_2CH_2COOC_2H_5 + BrCH_2COOC_2H_5 \longrightarrow RCHBrCH_2CHRCH_2CH_2COOC_2H_5 + \cdot CH_2COOC_2H_5$$

The γ-bromo esters prepared in this study have been successfully converted to the corresponding γ-lactones both by alkaline hydrolysis followed by lactonization, and by direct thermal decomposition at 150–180°. This latter treatment results in the rapid formation of a γ-lactone and an alkyl bromide. Most of the γ-lactones hereafter described are new compounds; it was however possible to establish the identities of γ-valerolactone and γ-caprolactone by comparison with authentic samples of these compounds.

As a synthetic method, the free radical addition of an α-bromo ester to an olefin is a simple one-step reaction which lengthens the carbon chain by two carbon atoms and simultaneously introduces a bromine atom in position gamma to the carboxyl group. The bromo compounds thus formed are not readily accessible by any other preparative method.

The over-all reaction where the double bond in the olefin is terminal may be formulated as

$$BrCR_1R_2COOCH_3 + R_3CH{=}CH_2 \longrightarrow R_3CHBrCH_2CR_1R_2COOCH_3$$

where the R's are either hydrogen atoms or alkyl groups.

Experimental

The choice of the procedure to be used (as hereafter described) for the addition of bromo esters to olefins was governed by the physical properties of the olefin used. For gaseous olefins, a Pyrex pressure apparatus fitted with pressure stopcocks was employed; where the olefin was a liquid at the reaction temperature, no special equipment was needed.

It was found most convenient to add the diacetyl peroxide (dissolved in a small amount of bromo ester) in small portions (over a period of three to six hours) to a mixture of the olefin and the bromo ester contained in a flask held at a temperature of approximately 90°. When gaseous olefins were used, the bromo ester (held at 90°) was saturated with the olefin under a pressure of 40–55 pounds per square inch, absolute. The reactions were not markedly exothermic when the ratio of the reactants was as described. An inert atmosphere was maintained throughout all the reactions. Previous to the addition of the peroxide, air was always removed from the apparatus by flushing either with nitrogen or with the gaseous olefin.

Most of the addition products studied were stable when distilled *in vacuo* at pressures of 0.1–1.0 mm. However, in the cases of the α-bromoisobutyrates, α-bromoisovalerates, bromomalonate, and bromosuccinate, some decomposition was noticed when the γ-bromo ester addition products were distilled in ordinary vacuum apparatus. The low values for the bromine content of some of the products (see Table I) are probably due to thermal decomposition of the γ-bromo esters to form the corresponding γ-lactones, by the elimination of ethyl or methyl bromide. In several of the experiments, molecular distillation was used: here the bromine values and the saponification equivalents were satisfactory. To demonstrate the homogeneity of the condensation products the distillates were collected in many small fractions. The product was considered pure when both the boiling point and the index of refraction of successive fractions were constant. The following are typical procedures.

Addition of Ethyl Bromoacetate to Octene-1.—A solution of 27.4 g. (0.244 mole) of octene-1 in 160 g. (0.96 mole) of ethyl bromoacetate was treated with 3.1 g. (0.0254 mole) of diacetyl peroxide in 6.8 g. (0.041 mole) of ethyl bromoacetate. To isolate the addition product, the unreacted starting materials were removed by distillation at 20 mm. pressure. Distillation of the residue yielded 37 g. of ethyl γ-bromocaprate boiling at 93–94° (0.2 mm.), $n^{20}D$ 1.4599. There was 1.6 g. of high-boiling residue.

Addition of Ethyl Bromoacetate to Propylene.—To 173 g. (1.03 mole) of ethyl bromoacetate which was kept saturated with propylene at 90° and 45 lb./sq. in. (absolute), was added (over a period of five hours) 1.8 g. (0.015 mole) of diacetyl peroxide dissolved in 8.0 g. (0.048 mole) of ethyl bromoacetate. The apparatus was vented three times during the addition of the peroxide to eliminate carbon dioxide. Distillation of the residue left after recovering unchanged ethyl bromoacetate yielded 22 g. of ethyl γ-bromo-*n*-valerate boiling at 103–104° (22 mm.), $n^{20}D$ 1.4553. There was 1.5 g. of high-boiling residue.

Formation of γ-Caprolactones from Ethyl γ-Bromocaprate. Proof of the Structure of Ethyl γ-Bromocaprate.—Ethyl γ-bromocaprate (19.0 g., 0.0681 mole) was refluxed at 160–180° for two hours, during which time the external pressure was maintained at 55 mm. Volatile materials evolved during the pyrolysis were caught in a liquid nitrogen trap. Distillation of the residue gave 9.6 g. of γ-caprolactone (83% yield), b. p. 84° (0.2 mm.), $n^{20}D$ 1.4489.

Anal. Calcd. for $C_{10}H_{18}O_2$: saponification equivalent, 170. Found: sapon. equiv., 170.7; Br, 0.00.

This lactone was converted to the *p*-toluidide of γ-hydroxycapric acid,[4] m. p. 133.4–134°. A sample of γ-caprolactone, made by the method of Fittig and Schneegans,[5] gave a *p*-toluidide, which melted at 133.5°. The mixture of the two toluidides melted at 133–134°. In the liquid nitrogen trap there was collected 6.1 g. of material which proved to be ethyl bromide, b. p. 38°, contaminated with hydrogen bromide. This ethyl bromide was further identified by conversion to ethyl mercuric bromide (m. p. 193°).[6]

In the distillation of the reaction mixture, 2.0 g. of a low-boiling fraction was collected. This material which gave a positive test for unsaturation when treated with a carbon tetrachloride solution of bromine, may possibly consist of unsaturated esters or acids formed by elimination of hydrogen bromide from the ethyl γ-bromocaprate during the heating period. The appearance of unsaturated material also accounts for the presence of hydrogen bromide in the cold trap.

In all cases the γ-bromo esters were converted to lactones by pyrolysis at 150–180°.

Proof of the Structure of Ethyl γ-Bromo-*n*-valerate.—The structure of the addition product, ethyl γ-bromo-*n*-valerate, obtained by the addition of ethyl bromoacetate to propylene, was proved in the following manner. A mixture of 10.6 g. of the addition product, 20 g. of sodium hydroxide and 30 cc. of water was heated under reflux for five hours. During this period the reaction mixture became homogenous. The solution was acidified with dilute hydrochloric acid, and then extracted with ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. After the ether had been removed from the extract, a colorless liquid was obtained by distillation (4.0 g., b. p. 70° (6 mm.); $n^{20}D$ 1.4328). This substance was identified as γ-valerolactone (80% yield)

---

[4] Koelsch and Tenenbaum, THIS JOURNAL, **55**, 3049 (1933).

[5] Fittig and Schneegans, *Ann.*, **227**, 79 (1885).

[6] Shriner and Fuson, "Identification of Organic Compounds," 2nd edition, p. 158.

Table I

Experimental Data of Addition Reactions[c, d]

Bromo ester, moles	Olefin, moles	Peroxide, moles	Addition product
Ethyl bromoacetate (1.00)	Octene-1 (0.244)	(0.025)	Ethyl γ-bromocaprate
Ethyl α-bromopropionate (1.02)	Octene-1 (.265)	(.019)	Ethyl α-methyl-γ-bromocaprate
t-Butyl α-bromopropionate (0.726)	Octene-1 (.196)	(.044)	*t*-Butyl α-methyl-γ-bromocaprate
Ethyl α-bromo-*n*-butyrate (1.05)	Octene-1 (.25)	(.014)	Ethyl α-ethyl-γ-bromocaprate
Ethyl α-bromoisobutyrate (0.838)	Octene-1 (.178)	(.022)	Ethyl α,α-dimethyl-γ-bromocaprate
Methyl α-bromoisobutryate (0.739)	Octene-1 (.258)	(.027)	Methyl α,α-dimethyl γ-bromocaprate
Ethyl α-bromo-(d) isovalerate (0.521)	Octene-1 (.132)	(.027)	Ethyl α-isopropyl-γ-bromocaprate
Methyl α-bromoisovalerate (0.676)	Octene-1 (.206)	(.024)	Methyl α-isopropyl-γ-bromocaprate
Dimethyl bromosuccinate (0.437)	Octene-1 (.089)	(.012)	Methyl α-carbomethoxy-γ-bromocaprate
Diethyl bromomalonate (0.40)	Octene-1 (.44)	(.012)	Ethyl α-carbethoxy-γ-bromocaprate
Ethyl bromoacetate (0.786)	Propylene 45 psia[b]	(.040)	Ethyl α-bromovalerate
Ethyl α-bromopropionate (0.602)	Propylene 45 psia[b]	(.025)	Ethyl α-methyl-γ-bromovalerate
Ethyl α-bromoacetate (0.807)	Butene-2 45 psia[b]	(.029)	Ethyl β-methyl-γ-bromovalerate
Ethyl α-bromopropionate (0.656)	Isobutylene 45 psia[b]	(.015)	Ethyl α,γ-dimethyl-γ-bromovalerate
Ethyl α-bromopropionate (0.944)	Styrene (.25)	(.023)	Styrene polymer
Ethyl α-bromopropionate (1.01)	Ethyl acrylate (.253)	(.019)	Acrylate polymer

by converting it to the amide of γ-hydroxy-*n*-valeric acid, m. p. 49–50°, according to the method of Boorman and Linstead.[7] The melting point of this derivative and the melting point of a mixture with the amide from an authentic sample of γ-valerolactone was 49–50°. For purposes of comparison, γ-valerolactone (b. p. 70–71° (6 mm.), $n^{20}\text{D}$ 1.4328) was prepared by the reduction of levulinic acid according to the method of Schuette and Thomas.[8]

γ-Valerolactone, 20.0 g., was converted into ethyl γ-bromo-*n*-valerate by dissolving it in 50 cc. of absolute ethanol and saturating the solution with hydrogen bromide at a temperature of 5°. The solution was allowed to stand for twenty-four hours at room temperature and was then resaturated with hydrogen bromide. After an additional twelve hours of standing at room temperature, an equal volume of water was added to the solution. The heavy organic layer which separated was extracted with ether, washed with dilute sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Distillation of the residue through a 15-inch column packed with helices yielded pure ethyl γ-bromo-*n*-valerate, b. p. 78° (9 mm.) $n^{20}\text{D}$ 1.4552, identical in all its properties with the ethyl bromoacetate–propylene addition product.

Anal. of the synthetic sample. Calcd. for $C_7H_{13}O_2Br$: Br, 38.2. Found: Br, 38.3.

Boorman and Linstead[9] report for ethyl γ-bromo-*n*-valerate, b. p. 105–107° (20 mm.), $n^{20}\text{D}$ 1.4533. This last figure is not in agreement with the observations here recorded. When the lactone was saturated with hydrogen bromide only once (instead of twice as above), the product was a mixture the constituents of which could not be separated by distillation through the packed column. This mixture had the following physical properties: b. p. 63–69° (6 mm.), $n^{20}\text{D}$ 1.4460–1.4520.

Tetramethylsuccinic Acid from the Reaction of Methyl α-Bromoisobutyrate with Octene-1.—By distillation of the product of the reaction between methyl α-bromoisobutyrate and octene-1 (see Table I), a low-boiling fraction, 2.6 g., b. p. 40–95° (0.3 mm.) was separated. This fraction was saponified by refluxing it for one-half hour with an excess of alcoholic sodium hydroxide solution. All solvents were removed by distillation *in vacuo*. The residue was believed to be a mixture of the dry sodium salts of γ-hydroxyisobutyric acid, γ-hydroxy-α,α-dimethylcapric acid and tetramethylsuccinic acid. The dry material was treated with 30 cc. of hot anhydrous ethyl alcohol in order to dissolve all the salts except the salt of the dicarboxylic acid. The insoluble residue was collected on a filter, and added to 5 cc. of water, the solution was carefully acidified with sulfuric acid, and extracted with 15 cc. of ether. The ethereal solution was dried with anhydrous sodium sulfate, and the ether was then removed by evaporation. The white granular residue, 0.45 g., was washed well with ligroin and collected on a filter. The solid thus obtained melted at 190–192°; sublimation *in vacuo* did not raise its melting point. This melting point showed no depression when the material was mixed with an authentic sample of tetramethylsuccinic acid melting at 192°. The reported melting point of tetramethylsuccinic acid is 200°.[10] However, it has been found that this melting point varies from 180 to 200°, depending upon the rate at which the sample is heated. This variation is due to the partial formation of the anhydride.

Isolation and Identification of Methyl Bromide from the Reaction of α-Bromo Esters with Octene-1.—Methyl bromide was isolated and identified as a product in the condensations of octene-1 with dimethyl bromosuccinate, ethyl α-bromopropionate, or ethyl α-bromoisovalerate when these reactions were started by the decomposition of small amounts of diacetyl peroxide.

In the experiment with dimethyl bromosuccinate described in Table I, 0.012 mole of diacetyl peroxide was used for the initiation of the free radical chain. The methyl bromide was isolated by attaching a Dry Ice–ether trap to the reflux condenser of the reaction vessel. All volatile materials evolved during the addition of the peroxide solution were caught in this trap. At the conclusion of the reaction, the Dry Ice–ether was replaced by liquid nitrogen and the entire system was evacuated to 0.1 mm. The material collected in the trap was distilled into a vacuum line, weighed and identified by its molecular weight and vapor pressure. The molecular weight found was 92.4; that calculated for methyl bromide is 95. The vapor pressure at Dry Ice–ether temperature was 6.5 mm.; that reported[11] for methyl bromide is 5 mm. at −80.6°, and 10 mm., at −72.8°. The amount of methyl bromide isolated was 0.29 g. (0.0031 mole).

Reaction of Ethyl β-Bromopropionate with Octene-1.—Ethyl β-bromopropionate (188 g., 1.04 moles) was treated with 28 g. of octene-1 (0.25 mole) in the presence of 2.2 g. of diacetyl peroxide (0.019 mole). Removal of the unreacted starting materials left 4.0 g. of high-boiling residue. The compound formed under these conditions is diethyl α-bromo-α'-methylsuccinate. This reaction will be discussed in a subsequent publication.

---

[7] Boorman and Linstead, *J. Chem. Soc.*, 578 (1933).

[8] Schuette and Thomas, This Journal, **52**, 3010 (1930).

[9] Boorman, Linstead and Rydon, *J. Chem. Soc.*, 575 (1933).

[10] Auwers and Meyer, *Ber.*, **23**, 300 (1890).

[11] Stull, *Ind. Eng. Chem.*, **39**, 517 (1947).

TABLE I (*Continued*)

Addition product B. p., °C.	Mm.	n^{20}_D	Br Found (calcd.)	Sapn. eq. Found (calcd.)	Yield	Lactone B. p. °C.	Mm.	n^{20}_D	Sapn. eq. Found (calcd.)	Yield
93–94	0.2	1.4599	28.88 (28.67)	142.6 (139.5)	57.0%	84	0.2	1.4489	170.7 (180.0)	48%
92	0.1	1.4570	26.92 (27.30)	148.2 (146.5)	77.0%	73–74	.02	1.4460	184.9 (184.0)	64%
						73–74	.02	1.4460	185.0 (184.0)	49%
108	0.6	1.4576	25.80 (26.05)	152.5 (153.5)	62.0%	114	.4	1.4480	193.7 (198.0)	47%
[a]		1.4572	23.13 (26.05)	168.0 (153.5)	11.7 g.					
98–102	0.3	1.458	20.16 (27.30)		22.2 g.	83–84	.3	1.4436	198.2 (198.0)	24%
[a]		1.4592	23.53 (24.92)	164.8 (160.5)	13.7 g.					
84–85	0.03	1.4608	25.83 (26.05)	154.1 (153.5)	46.0%	[a]		1.4508	210.0 (212.0)	41%
[a]		1.4669	23.29 (23.73)	112.6 (112.3)	83.0%					
[a]		1.4572	21.82 (22.80)	119.8 (117.0)	74.0%	[a]		1.4504	121.2 (121.0)	58%
82–83	8	1.4552	38.23 (38.2)	104.5 (104.5)	28.5 g.	70	6	1.4328		11 gr.
82–84	9.5	1.4521	32.16 (35.80)	112.2 (111.5)	18.0 g.					
70–71	4	1.4588	35.27 (35.87)	12.2 (111.5)	19.2 g.	91–92	8	1.4346	114.2 (114.0)	10 gr.
69–70	4	1.4520	33.84 (33.80)	124.4 (118.5)	103. g.					

[a] These products were molecularly distilled. [b] The amount of olefin added was not determined. [c] The over-all yield is based upon the amount of olefin used. [d] These reactions were heated between 70–80°.

Competition Experiments. (A) **Methyl α-Bromoisobutyrate *versus* Ethyl Bromoacetate.**—A mixture of 49.2 g. of ethyl bromoacetate, 57.1 g. of methyl α-bromoisobutyrate and 10.8 g. of octene-1 was heated for fourteen hours at 88°, in the presence of 1.1 g. of diacetyl peroxide. After distillation of the unreacted materials, the residue, upon distillation at reduced pressure, gave 6.5 g. of a material which contained 9.65% bromine. This material was heated at 150–180° for two hours to convert it to the lactone. Upon distillation at reduced pressure a material was collected which had an index of refraction of 1.4436 at 20°.

Anal. Calcd. for $C_{10}H_{18}O_2$: saponification equivalent, 170. Calcd. for $C_{12}H_{22}O_2$: saponification equivalent, 198. Found: sapn. equiv., 197, 202.

(B) **Ethyl α-Bromo-*n*-butyrate *versus* Ethyl Bromoacetate.**—A mixture of 50.8 g. of ethyl bromoacetate (304 mmoles), 59.7 g. of ethyl α-bromo-*n*-butyrate (306 mmoles), and 11.6 g. of octene-1 (104 mmoles) was heated for fourteen hours at 83° in the presence of 1.18 g. of diacetyl peroxide (10 mmoles). After distillation *in vacuo* of the unreacted materials, a residue (23.9 g.) was obtained. This residue was a mixture of the two possible γ-bromo esters. To convert these γ-bromo esters to the lactones, the material was heated at 150–180° for three hours, and then subjected to distillation at reduced pressure (b. p. 73–75° (0.02 mm.), n^{20}_D 1.4488).

Anal. Calcd. for $C_{10}H_{18}O_2$: saponification equivalent, 170. Calcd. for $C_{12}H_{22}O_2$: saponification equivalent, 198. Found: saponification equivalent, 184.6, 186.3.

Preparation of α-Substituted γ-Caprolactones.—These substances were prepared by the addition of the appropriate α-bromo esters to octene-1; in each instance the reaction product was distilled *in vacuo* to obtain the α-substituted γ-bromocaprate formed. When these γ-bromocaprates were refluxed for two hours at 160–180°, alkyl halides were evolved, and α-substituted γ-caprolactones were formed. These lactones were then distilled at reduced pressures. By following this procedure

1. α,α-Dimethyl-γ-caprolactone was obtained from methyl α-bromoisobutyrate and octene-1.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.7; H, 11.1. Found: C, 72.3; H, 11.0.

2. α-Carbethoxy-γ-caprolactone was obtained from diethyl α-bromomalonate and octene-1.

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.4; H, 9.12. Found: C, 63.8; H, 9.0.

3. α-Isopropyl-γ-caprolactone was obtained from methyl α-bromoisovalerate and octene-1.

Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.5; H, 11.3. Found: C, 73.0; H, 11.4.

TABLE II

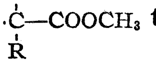
PHYSICAL CONSTANTS OF BROMO ESTERS USED

Bromo ester	Boiling point °C.	Mm.	n^{20}_D
Ethyl α-bromoacetate	58–59	15	1.4489
Ethyl α-bromopropionate	58	16	1.4461
Ethyl α-bromobutyrate	63	12	1.4479
t-Butyl α-bromopropionate	62.2	15	1.4392
Ethyl α-bromoisobutyrate	59.9	18	1.4438
Methyl α-bromoisobutyrate	52.2	21	1.4509
Methyl α-bromoisovalerate			1.4530
Ethyl α-bromoisovalerate	73–74	12	1.4496
Dimethyl bromosuccinate	61	3	1.4630
Diethyl bromomalonate	123	20	1.4521
Methyl α-bromoisovalerate	64–65	11	1.4530
Ethyl α-bromopropionate	69.7	15	1.4578

Acknowledgment.—The authors are grateful to Mr. P. Silverman for the preparation of some of the starting products used, and to Mr. I. S. Bengelsdorf for the analyses reported in this paper.

Summary

Good yields of γ-bromo esters are formed by free-radical chain reactions between aliphatic olefins and α-bromo carboxylic esters. These reactions involve the addition of radicals of the



$\cdot\overset{R}{\underset{R}{C}}\text{—COOCH}_3$ type to the double bond. The chain is initiated by the thermal decomposition of diacetyl peroxide. The mechanism and necessary requisites for the chain reaction are discussed.

CHICAGO, ILLINOIS RECEIVED AUGUST 18, 1947

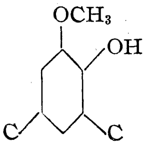
[CONTRIBUTION FROM THE NORTHERN RESEARCH LABORATORY[1]]

Interpretation of Lignin. I. The Synthesis of Gymnosperm Lignin

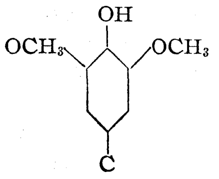
BY ALFRED RUSSELL[2]

Lignin, from whatever source it is obtained, is an amorphous material with none of the usual criteria of purity. It cannot be assumed to have a constant composition since it seems to undergo changes easily. It is a plant product without definite character and is probably best described as the residual plant structural material after carbohydrates, coloring matters, waxes, resins and the like have been removed. The fission products are in harmony with a simple structure of the familiar 2-phenylbenzopyran type but it is impossible for lignin to be a single such unit. It is certain that lignin in the plant is sensitive enough to undergo some structural change during the process of extraction. The alteration may be minor when extraction is carried out with nondestructive solvents, such as alcohols containing traces of mineral acids, but it is impossible to ignore the likelihood that the use of strong mineral acids, aqueous alkalies and alkaline bisulfites may cause extensive structural changes. This has been recognized by a few workers who have tried to look on the process of extraction as a reaction to which unaltered lignin is exposed and of which the material extracted represents the product. There is general evidence in favor of this idea in the fact that totally inert solvents will not dissolve lignin.

The available evidence indicates that there are two varieties of lignin both largely aromatic in character. As significant cleavage products one variety (from gymnosperms) gives, on degradation, only derivatives of catechol-2-methyl ether (guaiacol) with carbon atoms attached in the -4- and -6- positions (I); and the other (from angiosperms) gives the same derivatives of catechol-2-methyl ether and of pyrogallol-1,3-dimethyl ether with a carbon atom attached in the -5- position (II).

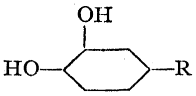


I

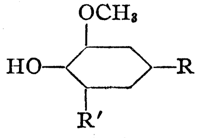


II

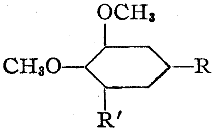
As examples of the cleavage products of a typical gymnosperm, those of spruce lignin, the most exhaustively examined one, may be described (a) alkali fusion gives protocatechnic acid (III, R = CO_2H) and catechol (III, R = H); (b) methylation with dimethyl sulfate and alkali followed by oxidation with potassium permanganate, gives veratric acid (V, R′ = H, R = CO_2H), isohemipinic acid (V, R = R′ = CO_2H) and veratrole (V, R = R′ = H) and dehydrodiveratric acid; (c) treatment of sulfonated lignin with alkali at 160° gives vanillin (IV, R′ = H, R = CHO), acetovanillone (IV, R′ = H, R = $COCH_3$) and guaiacol (IV, R = R′ = H); (d) dry distillation gives guaiacol (IV, R = R′ = H), vanillic acid (IV, R′ = H, R = CO_2H) and eugenol (IV, R′ = H, R = $CH_2CH{=}CH_2$); (e) zinc dust distillation gives guaiacol (IV, R′ = R = H) and 4-*n*-propylguaiacol (IV, R′ = H, R = *n*-C_3H_7); (f) Oxidation with nitrobenzene gives vanillin-5-carboxylic acid (IV, R = CHO, R′ = CO_2H) and vanillin (IV, R = CHO, R′ = H). It is clear from these cleavage products that the changes (VI) → (VII) → (VIII) occur readily.



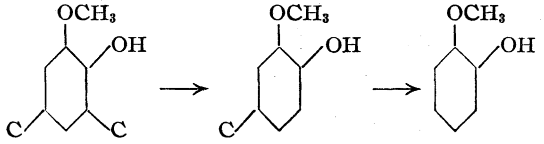
(III)



(IV)



(V)



(VI) (VII) (VIII)

The occurrence among lignin degradation products of small amounts of formaldehyde, methanol, acetic acid and the like has little significance. Decomposition of any carbon chain will rise to similar products. It is significant, however, that there is no report of a simple fission product containing more than two carbon atoms (the products of hydrogenation of hydrogenolysis are, naturally, excluded).

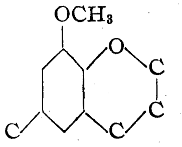
Now, referring to the lignin from gymnosperms, it has to be inferred that one or both of the carbon atoms free in the skeleton (I) must be joined to at least one other carbon atom. The occurrence of an oxygen atom in (I) in the *ortho* position to an attached carbon atom and the absence of typical free phenolic hydroxyl groups in this lignin makes the benzopyran structure almost inevitable, hence, (I) may be expanded to (IX). Specific examples of such a structure among natural products are common. The occurrence of 4-*n*-propyl-

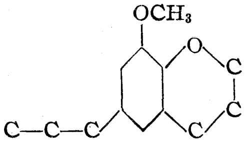
---

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

[2] Chemist, Industrial Chemical Section, Agricultural Residues Division.

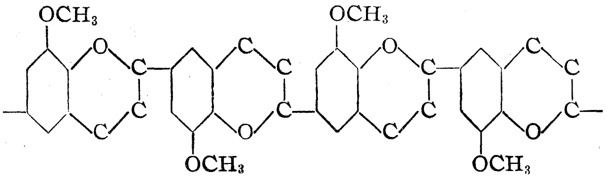
guaiacol (IV, R = H, R = n-C_3H_7) and similar compounds as cleavage products of this lignin under certain conditions means that the skeleton (IX) must be expanded to (X) to explain the occurrence of a three-carbon chain *para* to the hydroxyl group in such cleavage products.


IX


X

Few, if any, common natural products have very complicated structures. Consequently the elaborations proposed by Cross and Bevan,[3] Fuchs,[4] Pavolini,[5] Schrauth,[6] and the meticulous detail of the structure proposed by Brauns[7] have little to recommend them.

It is much more likely, as has long been supposed in a general way, that lignin (in this case, that from gymnosperms) is composed of a series of n-propylbenzene units. If this, as most likely, is true, then referring to the skeleton (X), the three carbon atoms in the chain *para* to the pyranose oxygen must be the three carbon atoms of a *second* pyranose ring. This implies a continuing structure of the type (XI).


XI

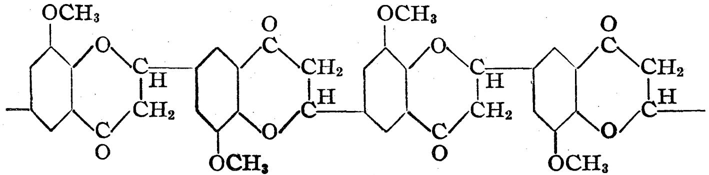
With other suggested structures, one, not dissimilar to the above, but containing methyl furan rings has been tentatively put forward by Erdtman and, separately, by Freudenberg, and Hibbert has come close to advocating a benzopyran unit structure.

To account for the hydrogen and oxygen content of the lignin under consideration, the skeletal structure (XI) must be completed by adding an oxygen atom and three hydrogen atoms to each pyran ring. The most plausible way to do this, by analogy with other plant products, such as flavanones, flavones, and flavonols is to make it the poly-8-methoxydihydrobenzopyrone (XII).

This material is available synthetically by the following steps: vanillin mono-acetate (XIII), by Fries rearrangement, will give 2-hydroxy-3-methoxy-5-formyl acetophenone (XIV). This will undergo easy condensation polymerization (aldolization, loss of water—Claisen condensation) to give (XV) which, in turn, will cyclicize to the product required. Under most conditions (XV) and (XI) will be in equilibrium.

The intermediate ketoaldehyde (XIV) is sufficiently reactive that, in any conditions under which it is formed, the final product (XII) is likely to result at once. By Fries rearrangement of vanillin monoacetate, then, the product (XII) is likely to be obtained with no intermediates.

The properties of the product (XII) should be entirely analogous to those recorded for lignin. The carbonyl group would not be very typical and lignin does not give satisfactory carbonyl derivatives. Enolization would be easy and this, with the easily opened pyranose ring and the possible occurrence of a hydrated form, would give a series of enolic derivatives. The hydrogens of the methylene group in the cyclic form would be rather reactive; consequently, halogens would substitute more easily in this form than add to the enol form. Lignin, again, undergoes a substitution rather than an addition reaction with halogens. Moreover, the product (XII) would have to give the same cleavage products as the lignin from gymnosperms.


(XII)

The synthesis described has been carried out and the synthetic material, apart from being somewhat darker in color, has the same qualitative properties as those recorded for spruce lignin and, where direct comparison has been made, with those observed for a specimen of "alkali" lignin obtained from the saccharification processing of corncobs. The solubility characteristics are the same; like lignin, the synthetic material is soluble in aqueous alkali, ethanol, acetone and dioxane; insoluble in dilute mineral acids, water, ether, hydrocarbons and halogenated solvents. Parallel to the solubility of unaltered natural lignin in alkaline bisulfites, the synthetic product is soluble in aqueous sodium bisulfite. In all probability this corresponds to the formation of a stable sulfonic acid by the familiar 1,4-addition process to the open chain form.

The synthetic material suspended on paper pulp and treated in succession with chlorine, aqueous sulfur dioxide, and aqueous sodium sulfite gives the pink color characteristic of lignin specimens. For purposes of comparison the test was run simultaneously on a specimen of alkali lignin from the saccharification processing of corncobs. Moreover, dispersed on filter paper, the synthetic material gives the pink color typical of lignin with

---

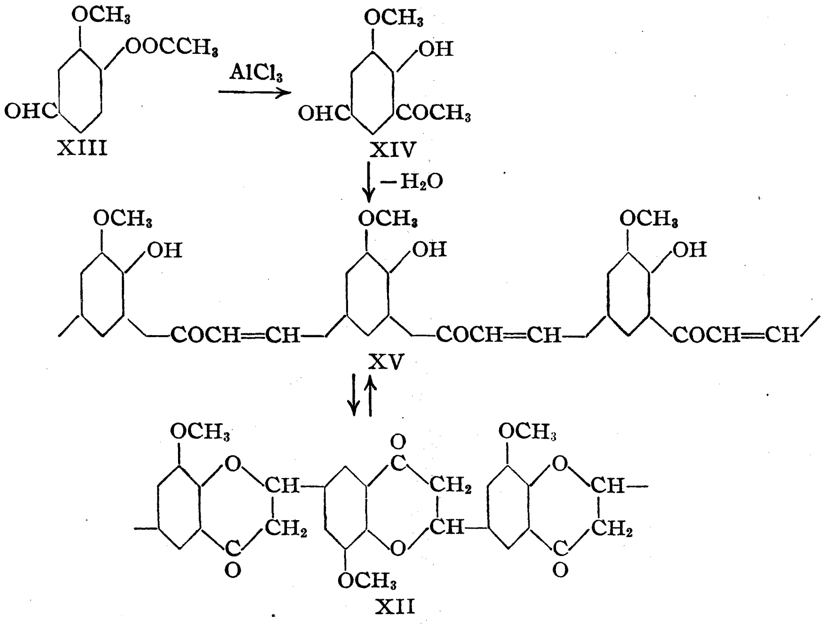
(3) Cross and Bevan, *Ber.*, **26**, 2520 (1893).

(4) Fuchs, *Z. angew. Chem.*, **44**, 111 (1931).

(5) Pavolini, *Industria Chemica*, **6**, 1367 (1931).

(6) Schrauth, *Z. angew. Chem.*, **36**, 149 (1923).

(7) Brauns, Report to Second Southwest Chemurgic Clinic, National Farm Chemurgic Council, Mimeographed Circular No. 483, Oklahoma City, Oklahoma, June 3, 1946.



phloroglucinol dissolved in 12% aqueous hydrochloric acid.

There never has been any way of measuring the purity or degree of alteration of any lignin specimen or derivative. Consequently no recorded experiment could ever be repeated exactly, using the synthetic product for comparison purposes. The synthetic material must give the same recognizable simple cleavage products as gymnosperm lignin. Apart from such simple products, lignin does not give derivatives that can be positively identified. It may be methylated, acetylated and so on but the reactions must be regarded as stepwise since the analytical values of the products vary continuously. However, so many methylations, acetylations, and the like have been carried out that the *maximum* values on record should correspond rather closely to those for total reaction. Indeed, it is obvious that such maxima are the only values to which any meaning may be attached.

Apart from an anticipated low methoxyl value (aluminum chloride is an effective demethylating agent) and consequent lowering of hydrogen content, the analytical values for the synthetic material are close enough to the range reported for gymnosperm lignins and to the calculated range for the monomer ($C_{10}H_{10}O_4$) and the polymer ($C_{10}H_8O_3$).

Many "acetyl" values are on record for the acetylated lignin from gymnosperms and the maximum is 27.2%. Acetylation of the synthetic material with acetic anhydride gives a product having an "acetyl" content of 29.5%. Two acetyl groups for each monomeric residue is the maximum number that could be introduced and this would correspond to an acetyl content of 30.9%. It is evident that the triacetate implied by the open-chain formula is most improbable since the carbonyl oxygen, in this form, is chelated with the hydrogen of the phenolic hydroxyl group and, furthermore, the same carbonyl group forms part of a stable, total crossed conjugated system. The diacetate formed is the geminal diacetate of the pyranose form.

Like the acetylation, the methylation of lignin appears to be a continuous process. The maximum value reported for "methoxyl" is 32.4% corresponding to the calculated (32.3%) value for two methoxyl groups in each monomeric residue and implying the methylation of one free hydroxyl group in each. By exhaustive treatment with dimethyl sulfate and alkali, the synthetic material gives a methylated product containing 29.6% of "methoxyl."

It is, of course, very evident that the alkaline conditions of methylation and the acid conditions of acylation favor, respectively, the open and closed ring forms.

Reports on halogenation experiments indicate that the maximum halogen content of chlorinated spruce lignin is about 38%. This corresponds to the introduction of three chlorine atoms into each monomeric residue in the polymer (requires: Cl, 38.1%). There have been few attempts to brominate lignins and not enough figures are on record for comparison. However, bromination of the synthetic material with excess bromine in acetic acid in the presence of iodine gives a product containing about 57% of the halogen. For three bromines in each monomeric residue the calculated value is 58.1%. In a word, three hydrogen atoms in each monomeric residue may be replaced by halogens. The replaceable hydrogens are, of course, the active ones in the pyranose ring. Halogenation values then for spruce lignin and the synthetic material are in good agreement.

Although experimental verification might be difficult, it is worth recording that the methoxyl values for methylated spruce lignin sulfonic acid (20.7–25.4%) are in agreement with the calculated value for the synthetic material having two methoxyl groups and one sulfonic acid group for each monomeric residue (22.8%).

Again, although its significance is obscure, a Klason lignin determination run on the synthetic material gave a value of 85.7%. A simultaneous determination run on a purified specimen of alkali lignin from the saccharification processing of corncobs gave a value of 88.3%.

Finally, although in the ordinary way the comparison of two analytical values obtained from amorphous materials provides questionable evidence of constitution; in each instance quoted in this particular case it is impossible for the repeated coincidence of *three* values to be fortuitous. There cannot be anything casual about such repeated agreements. When the additional evidence of what is, under the circumstances, an unambiguous synthesis, and the same fission products with, almost complete qualitative identity is taken into account, the matter must be considered reasonably well established.

Experimental[8]

Vanillin Monoacetate.—Vanillin (15.2 g., 1 mole) was dissolved in dry pyridine (40 cc.) and acetyl chloride (10 g., 1.25 mole tech. grade) added portionwise over ten minutes with occasional shaking. The hot orange-colored reaction mixture was heated on the steam-bath for thirty minutes. The somewhat-cooled reaction mixture was poured into ice and water, the precipitate collected, washed (water) and recrystallized from dilute ethanol (charcoal); slender white needles, m. p. 77–78°, yield 62%.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.8; H, 5.15; "OMe," 15.9; "CH_3CO," 22.16. Found: C, 61.6; H, 5.18; "OMe," 15.88, 15.98; "CH_3CO," 22.2, 22.8, 22.8.

Fries Rearrangement of Vanillin Monoacetate into Poly-8-methoxydihydrobenzopyrone.—Vanillin monoacetate (9.7 g., 1 mole) was dissolved in anhydrous nitrobenzene (50 g.) and dry aluminum chloride (13.3 g., 2 mole) added portionwise with shaking. The temperature rose and as addition proceeded the straw-colored reaction mixture became very dark and viscous. After all the aluminum chloride had been added the reaction mixture was heated to 93–100° (oil-bath temperature) for two hours. The cooled reaction mixture was treated with sufficient dilute hydrochloric acid and the nitrobenzene removed by steam distillation. The dark-colored, resinous residue was collected and washed with water. It could not be crystallized and was reprecipitated several times from solution in ethanol by cold, very dilute hydrochloric acid. The flocculent, near-gelatinous, light-brown precipitate was collected and dried and formed a dark-brown (almost black), brittle solid. After nearly complete drying (six days at 23 mm. over potassium hydroxide) the material was no longer totally soluble in ethanol or acetone. It could not easily be reduced to a powder because of its electrical properties.

Anal. Calcd. for $C_{10}H_8O_5$: C, 68.2; H, 4.55; "OMe," 17.6. Calcd. for $C_{10}H_{10}O_4$: C, 61.8, H, 5.15; "OMe," 15.9. Found: C, 65.9, 66.0; H, 4.35, 4.44; "OMe," 9.96, 9.95. Lignin recorded: C, 62–64; H, 5–6; "OMe," 15–17.

Acetylation of Poly-8-methoxydihydrobenzopyrone.—Poly-8-methoxydihydrobenzopyrone (1 g.) was dissolved in acetic anhydride (5 cc.) and the solution boiled for two hours. The reaction mixture was decomposed with water and the brown precipitate collected. It was insouble in ethanol and was precipitated several times from solution in acetone with ice water. Finally, it was collected and dried (at least six days, 23 mm., potassium hydroxide). The "acetyl" value corresponds to two acetyl groups for each monomeric residue.

Calcd.: "OAc," 30.9. Found: "OAc," 29.4, 29.5.

Methylation of Poly-8-methoxydihydrobenzopyrone.—Poly-8-methoxydihydrobenzopyrone (1 g.) was dissolved (heat) in aqueous sodium hydroxide (20 cc., 10%). Dimethyl sulfate (6 g.) was added portionwise with shaking at about 70°. Then with heating and shaking, more dimethyl sulfate (12 g.) was added portionwise and the reaction mixture kept hot and alkaline by addition, from time to time, of aqueous sodium hydroxide (20%). In about ninety minutes a considerable amount of alkali-insoluble material had separated. This was collected after dilution with water, washed and reprecipitated several times from solution in acetone with water. The finely divided precipitate was very hard to handle. It was dried (six days, 23 mm., potassium hydroxide).

Anal. Calcd.: (two "OMe" groups for each monomeric residue) "OMe," 32.3. Found: "OMe," 29.3, 29.6.

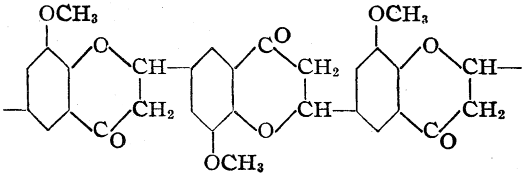
Bromination of Poly-8-methoxydihydrobenzopyrone.—Poly-8-methoxydihydrobenzopyrone (1 g.) was suspended in glacial acetic acid (25 cc.), a crystal of iodine and bromine (10 cc.) added. The reaction mixture was heated at 90° for ten hours, diluted with water (200 cc.) and the dark-red, finely-divided precipitate collected, washed three times with water and reprecipitated twice with water from solution in ethanol. The finely-divided dark-orange colored, flocculent precipitate was collected and dried (six days, 23 mm., potassium hydroxide).

Anal. Calcd.: (for three bromines for each monomeric residue) Br, 58.1. Found: Br, 56.3, 57.4.

Summary

The existence of at least two varieties of lignin appears to be definitely established. One of these is associated with gymnosperms and gives, as significant fission products, only derivatives of catechol monomethyl ether (guaiacol). The other is associated with angiosperms and gives, as significant cleavage products, the same derivatives of catechol monomethyl ether and some derivatives of pyrogallol-1,3-dimethyl ether. The possible occurrence of other varieties of lignin giving other fission products is not excluded.

Examination of the analytical evidence accumulated over the past, some seventy years, excludes the improbable elaborate formulas previously proposed and what appears to be a reasonable structure has been advanced. It is concluded from a study of the existing evidence that the lignin from gymnosperms is a poly-8-methoxydihydrobenzopyrone (XII). The lignin from angiosperms is likely constituted in the same way but with pyrogallol-1,3-dimethyl ether groups terminally, or otherwise, attached. The pyrogallol-1,3-dimethyl ether nuclei could not form part of a continuing chain as in (XII) unless the migration of a methyl group occurs during degradation. However, such nuclei could form part of the open chain form and a "mixed" chain is easily visualized.



XII

The proposed polymeric structures may not be absolutely correct and may need some modification later but it is in harmony with the known facts and with such plausible suggestions as have been made in the past. It is a cyclized condensation polymer of 2-hydroxy-3-methoxy-5-formyl-

---

[8] All analyses are micro determinations by Mr. Van Etten and Mrs. Wiele of this Laboratory.

acetophenone and is available in a single step by Fries rearrangement of vanillin monoacetate.

A polymeric material having its proposed structure has been synthesized and properties found not to differ qualitatively or, quantitatively from those recorded for spruce lignin. Solubility characteristics and general behavior are identical and it may be methylated, acetylated and halogenated (brominated) in the same fashion giving entirely analogous derivatives. The methoxyl content is noticeably lower than the calculated values but aluminum chloride is a good demethylating agent, and the introduction of free phenol groups could easily be responsible for the darker color.

PEORIA, ILLINOIS RECEIVED AUGUST 13, 1947

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Methyl 2,4:5,6-Dimethylene-D-gluconate

BY C. L. MEHLTRETTER, R. L. MELLIES AND C. E. RIST

In an attempt to prepare polyesters of 2,4:3,5-dimethylene-D-gluconic acid by heating the methyl ester (I)[2] *in vacuo*, there was obtained by sublimation a mixture of compounds from which a new methyl dimethylene gluconate was isolated in 22% yield. This compound has now been shown to be methyl 2,4:5,6-dimethylene-D-gluconate (II). It is apparent from structures (I) and (II) that a methylene cyclic acetal rearrangement has occurred from carbons 3,5 to 5,6 of the gluconic acid chain. Cyclic acetal rearrangements were observed by Hibbert and his associates[3] who found that isomeric methylene, benzylidene and *p*-nitrobenzylidene cyclic acetals of glycerol were readily interconverted in the presence of hydrogen chloride. More recently Hann, Maclay and Hudson[4] have reported a cyclic acetal shift in the benzoylation of α-diacetone dulcitol.

The separation of the methyl dimethylene gluconate (II) from unchanged methyl 2,4:3,5-dimethylene-D-gluconate (I) and other products was effected by fractional crystallization of the sublimate mixture from methanol. The purified product, which melted at the same temperature as methyl 2,4:3,5-dimethylene-D-gluconate (152°), formed a crystalline amide and a crystalline tosyl derivative. The new product gave a specific rotation of −14.4° in methanol, as compared to +13.3° for methyl 2,4:3,5-dimethylene-D-gluconate. Efforts to establish the presence of a primary or secondary alcohol group in the methyl dimethylene gluconate by subjecting the tosylated compound to iodination by the Oldham and Rutherford[5] procedure gave only anomalous results.

The removal of a methylene group from the methyl dimethylene gluconate (II) would provide a monomethylene acetal, the structure of which if known would aid considerably in establishing the structure of the original ester. Hudson and Hann and their associates[6] have shown that the controlled acetolysis of a number of methylene sugar alcohol acetals by an acetic anhydride–acetic acid solution containing 1 to 2% sulfuric acid results in the preferential cleavage of certain methylene acetal linkages. Those formed through primary hydroxyl groups are readily cleaved. Where two secondary alcoholic acetal linkages are involved, such as in 2,4:3,5-dimethylene-D-sorbitol, the 2,4-methylene acetal ring is the more stable to acetolysis.

The acetolysis reaction was first applied to methyl 2,4:3,5-dimethylene-D-gluconate (I) to ascertain whether it would proceed according to rule. A crystalline substance was produced which was presumed to be methyl 3-acetoxymethyl-5,6-diacetyl-2,4-methylene-D-gluconate (IV). Catalytic removal of the acetyl and acetoxymethyl groups of this compound with sodium methoxide and reaction of the crude product with methanol–ammonia gave crystalline 2,4-methylene-D-gluconamide (V). The structure of the latter compound was established by the oxidative degradation of the product obtained by saponification of (IV) to 2,4-methylene-xylotrihydroxyglutaric acid. This substance was esterified and isolated as the methyl ester[7] (VII). Thus the acetolysis of methyl 2,4:3,5-dimethylene-D-gluconate results in the cleavage of only the 3,5-methylene cyclic acetal linkage as was found to be the case with 2,4:3,5-dimethylene-D-sorbitol.[6]

When analogous reactions were carried out with the methyl dimethylene gluconate, 2,4-methylene-D-gluconamide was again produced. This fact not only is evidence that the methyl dimethylene gluconate contains a 2,4-methylene acetal linkage but it also limits its structure to methyl 2,4:3,6-dimethylene-D-gluconate or methyl 2,4:5,6-dimethylene-D-gluconate (II). Conclusive proof for the latter structure was obtained from a study of

---

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

[2] Mehltretter, Mellies, Rist and Hilbert, THIS JOURNAL, **69**, 2130 (1947).

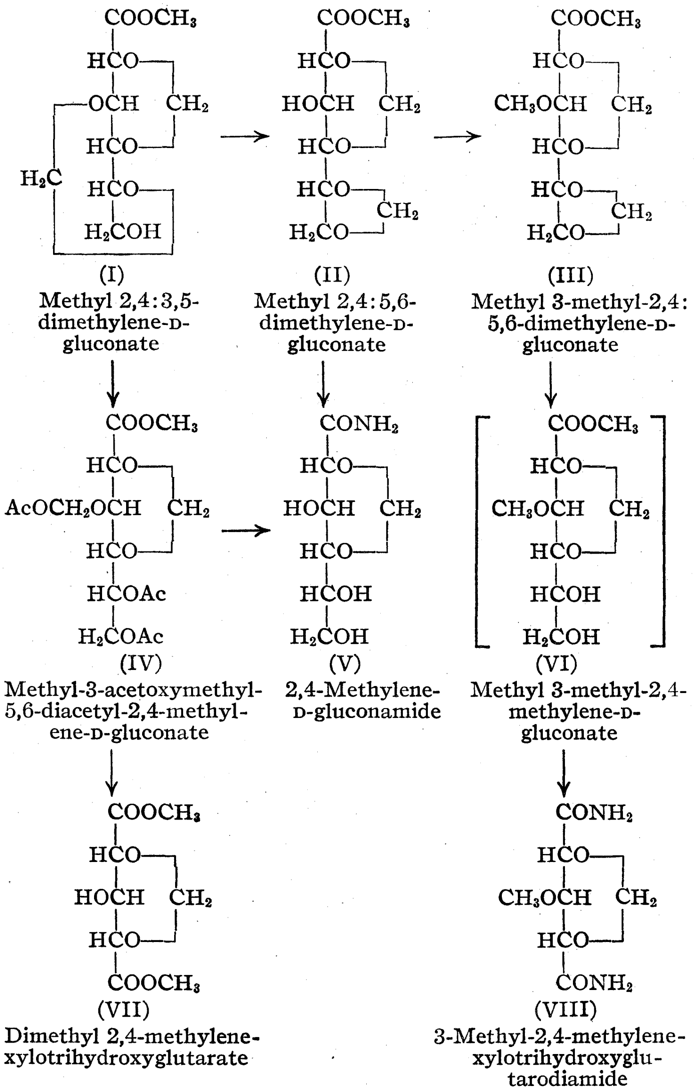
[3] Hill, Whelan and Hibbert, *ibid.*, **50**, 2235 (1928); Hibbert and Carter, *ibid.*, **50**, 3120, 3376 (1928).

[4] Hann, Maclay and Hudson, *ibid.*, **61**, 2432 (1939).

[5] Oldham and Rutherford, *ibid.*, **54**, 336 (1932); Ness, Hann and Hudson, *ibid.*, **66**, 1901 (1944).

[6] Ness, Hann and Hudson, *ibid.*, **65**, 2215 (1943); **66**, 665 and 670 (1944); Hann, Wolfe and Hudson, *ibid.*, **66**, 1898 (1944).

[7] Jones and Wiggins, *J. Chem. Soc.*, 382, 364 (1944).



(I) Methyl 2,4:3,5-dimethylene-D-gluconate

(II) Methyl 2,4:5,6-dimethylene-D-gluconate

(III) Methyl 3-methyl-2,4:5,6-dimethylene-D-gluconate

(IV) Methyl-3-acetoxymethyl-5,6-diacetyl-2,4-methylene-D-gluconate

(V) 2,4-Methylene-D-gluconamide

(VI) Methyl 3-methyl-2,4-methylene-D-gluconate

(VII) Dimethyl 2,4-methylene-xylotrihydroxyglutarate

(VIII) 3-Methyl-2,4-methylene-xylotrihydroxyglutarodiamide

the methyl ether of the methyl dimethylene gluconate (III). Acetolysis of this crystalline derivative, followed by saponification, gave a sirupy product which was oxidized with alkaline permanganate solution at 5 to 10°. The resulting acid was esterified with methanol and after treatment with methanol–ammonia yielded the diamide of 3-methyl-2,4-methylenexylotrihydroxyglutaric acid (VIII).[7] This substance could have been derived only from methyl 2,4:5,6-dimethylene-D-gluconate (II) by the series of reactions used.

Experimental

Isolation of Methyl 2,4:5,6-Dimethylene-D-gluconate (II).—Twenty grams (0.085 mole) of methyl 2,4:3,5-dimethylene-D-gluconate (I)[2] was heated for seven hours in a sublimation apparatus at 1 mm. pressure and a bath temperature of 150°. The sublimate, which consisted of both crystalline and oily substances, weighed 11.8 g. Recrystallization from methanol gave 4.4 g. (22%) of methyl 2,4:5,6-dimethylene-D-gluconate as colorless needles: m. p. 151–152°; $[\alpha]^{25}D$ −14.4° (*C*, 4.3; methanol). The melting point of a mixture of this compound with methyl 2,4:3,5-dimethylene-D-gluconate (m. p. 152–153°) was approximately 125°.

Anal. Calcd. for $C_9H_{14}O_7$: C, 46.2; H, 6.0; OCH_3, 13.3. Found: C, 46.2; H, 6.2; OCH_3, 13.4.

2,4:5,6-Dimethylene-D-gluconamide.—A 0.45-g. (0.002 mole) sample of methyl 2,4:5,6-dimethylene-D-gluconate was dissolved in 50 ml. of methanol which had been saturated with ammonia at 0°. After the solution had remained at 5 to 10° for five days it was concentrated *in vacuo* to dryness. The crude product was recrystallized from ethanol, giving 0.35 g. (83%) of 2,4:5,6-dimethylene-D-gluconamide as fine needles; m. p. 168–169°; $[\alpha]^{25}D$ +52.3° (*C*, 1.3; water).

Anal. Calcd. for $C_8H_{13}O_6N$: C, 43.8; H, 6.0; N, 6.4. Found: C, 44.1; H, 5.8; N, 6.4.

Methyl 3-Tosyl-2,4:5,6-dimethylene-D-gluconate.—To a solution of 5.85 g. (0.025 mole) of methyl 2,4:5,6-dimethylene-D-gluconate in 80 ml. of dry pyridine was added 5.50 g. (0.029 g. mole) of *p*-toluenesulfonyl chloride. After the mixture had remained at room temperature for four days it was poured into 500 ml. of ice water. The crystalline substance that precipitated (6.5 g., 67%) melted at 90–91°. After recrystallization from methanol, colorless prisms of methyl 3-tosyl-2,4:5,6-dimethylene-D-gluconate were obtained; m. p. 91–92°; $[\alpha]^{25}D$ −35.7° (*C*, 2.2; acetone).

Anal. Calcd. for $C_{16}H_{20}O_9S$: C, 49.5; H, 5.2; S, 8.3; OCH_3, 8.0. Found: C, 49.5; H, 5.1; S, 8.0; OCH_3, 7.9.

Samples of the tosylated compound upon treatment with an acetone solution of sodium iodide at 100° for two and for four hours gave, respectively, 50% and 57% of sodium *p*-toluenesulfonate. However, when the tosyl derivative was refluxed for two hours with an acetic anhydride solution of sodium iodide, 98% of sodium *p*-toluenesulfonate was obtained. A considerable quantity of free iodine was liberated in these reactions, and no desoxyiodo-derivative could be isolated.

Acetolysis of Methyl 2,4:3,5-Dimethylene-D-gluconate (I).—To 4.7 g. (0.02 mole) of methyl 2,4:3,5-dimethylene-D-gluconate was added an ice-cold acetolyzing solution consisting of 35 ml. of acetic anhydride, 15 ml. of acetic acid and 1 ml. of concentrated sulfuric acid. The resulting mixture was allowed to stand at 0° for forty-five minutes and then was agitated at room temperature for fifteen minutes to dissolve the ester completely. The solution was poured upon 400 g. of crushed ice and nearly neutralized to litmus by the addition of 70 g. of sodium bicarbonate. The white crystalline product was removed by filtration and washed with ice water. After recrystallization of the crude product from ethanol, 1.0 g. of methyl acetoxymethyl diacetyl methylene D-gluconate (probably methyl 3-acetoxymethyl-5,6-diacetyl-2,4-methylene-D-gluconate) (IV) was obtained as elongated hexagonal plates; m. p. 95–96°.

A further yield of 2.6 g. of product was obtained from the mother liquor; m. p. 95–96°. The total yield of methyl acetoxymethyl diacetyl methylene D-gluconate was 3.6 g. (48%).

Anal. Calcd. for $C_{15}H_{22}O_{11}$: C, 47.6; H, 5.9; OCH_3, 8.2. Found: C, 47.6; H, 5.7; OCH_3, 8.3.

Oxidation of the Saponified Acetolysis Product of Methyl 2,4:3,5-Dimethylene-D-gluconate.—To 12.6 g. (0.033 mole) of methyl acetoxymethyl diacetyl methylene D-gluconate obtained by acetolysis of methyl 2,4:3,5-dimethylene-D-gluconate was added 500 ml. of a solution which contained 21.1 g. (0.067 mole) of barium hydroxide octahydrate. The latter solution was added in portions at 60° over a one-hour period so that saponification occurred gradually under conditions of low alkalinity. The barium salt was decomposed with the calculated amount of dilute sulfuric acid and the barium sulfate removed by filtration. Concentration of the filtrate *in vacuo* gave 7.0 g. of crude 2,4-methylene-D-gluconic acid as a colorless sirup. A solution of this sirup in 200 ml. of water containing 5 g. of potassium hydroxide was cooled to 5° to 10° in an ice-bath. To the stirred mixture was added a solution of 14 g. of potassium permanganate in 250 ml. of water over a period of thirty minutes. Two grams more of permanganate was introduced and the mixture stirred at 10° for one hour. Excess permanganate was destroyed with ethanol, and the manganese dioxide that had precipitated was separated by centrifugation. The clear supernatant liquor was made slightly acid to litmus with sulfuric acid and concentrated *in vacuo* to dryness. The residue was suspended in 300 ml. of methanol and 3 ml. of concentrated sulfuric acid was added with stirring. The potassium sulfate that precipitated was removed, and the solution was refluxed for seven hours. After neutralizing the sulfuric acid with barium carbonate and removing the barium sulfate by filtration the clear filtrate was concentrated *in vacuo* until crystallization occurred. The crude crystals weighed 3.8 g. and melted at 175°. Recrystallization from water gave 2.0 g. of dimethyl 2,4-methylene-xylotrihydroxyglutarate (VII); m. p. 204°; $[\alpha]^{25}\text{D}$ 0°.

Anal. Calcd. for $C_8H_{12}O_7$: C, 43.7; H, 5.5; OCH_3, 28.2. Found: C, 43.7; H, 5.3; OCH_3, 28.1.

A further quantity of product (1.5 g., m. p. 203–204°) was obtained from the original mother liquor. The diamide of 2,4-methylene-xylotrihydroxyglutaric acid was prepared from the methyl ester and melted at 286° with decomposition. The melting points of these substances agree with the values recorded by Jones and Wiggins.[7]

Acetolysis of Methyl 2,4:5,6-Dimethylene-D-gluconate (II).—A solution of 4.7 g. (0.02 mole) of methyl 2,4:5,6-dimethylene-D-gluconate in 50 ml. of an ice-cold acetolyzing mixture (35 ml. of acetic anhydride, 15 ml. of acetic acid and 1 ml. of concentrated sulfuric acid) was allowed to stand at 0° for thirty minutes and then poured into 400 ml. of ice water. The solution was neutralized to slight acidity with 70 g. of sodium bicarbonate and extracted with chloroform. The dried chloroform solution was concentrated *in vacuo* to a nearly colorless sirup (5.0 g.) which would not crystallize. The product was presumed to be methyl 5-acetoxymethyl-3,6-diacetyl-2,4-methylene-D-gluconate. In a subsequent experiment this acetolysis product was converted to crystalline 2,4-methylene-D-gluconamide by the action of methanol–ammonia.

2,4-Methylene-D-gluconamide (V). (a) From the Acetolysis Product of Methyl 2,4:3,5-Dimethylene-D-gluconate.—To 1.90 g. (0.005 mole) of methyl acetoxymethyl diacetyl methylene D-gluconate obtained by acetolyzing methyl 2,4:3,5-dimethylene-D-gluconate was added 30 ml. of chloroform. After the addition of 3 ml. of 0.2 *N* sodium methylate solution the mixture was allowed to stand at 0° for nineteen hours and was then concentrated *in vacuo* to dryness. The residue was extracted with hot ethanol and the extract concentrated to a colorless sirup (1.05 g.). A solution of 0.70 g. of this sirup in 30 ml. of methanol–ammonia was allowed to stand at 5 to 10° for two days. Concentration of the solution to dryness *in vacuo* and recrystallization of the residue from 90% ethanol gave 0.40 g. (60%) of 2,4-methylene-D-gluconamide as colorless fine needles; m. p. 195–196°; $[\alpha]^{25}\text{D}$ +55.8° (*C*, 2.1; water).

Anal. Calcd. for $C_7H_{13}O_6N$: C, 40.6; H, 6.3; N, 6.8. Found: C, 40.7; H, 6.2; N, 6.8.

It was found that methyl acetoxymethyl diacetyl methylene D-gluconate, on direct treatment with methanol–ammonia, was deacetylated and converted to 2,4-methylene-D-gluconamide.

(b) From the Acetolysis Product of Methyl 2,4:5,6-Dimethylene-D-gluconate.—To 1.0 g. of the sirup obtained from the acetolysis of methyl 2,4:5,6-dimethylene-D-gluconate was added 40 ml. of methanol which had been saturated with ammonia at 0°. After the mixture was allowed to remain at 5 to 10° for forty hours, it was concentrated *in vacuo* to dryness. The residue was recrystallized from ethanol and gave 0.3 g. of 2,4-methylene-D-gluconamide; m. p. 195–196°; $[\alpha]^{25}\text{D}$ +55.7° (*C*, 2.1; water). The melting point of this compound was not depressed when it was mixed with a sample of 2,4-methylene-D-gluconamide prepared from the acetolysis product of methyl 2,4:3,5-dimethylene-D-gluconate.

Methyl 3-Methyl-2,4:5,6-dimethylene-D-gluconate (III).—A solution of 7.8 g. (0.033 mole) of methyl 2,4:5,6-dimethylene-D-gluconate in 25 ml. of hot methanol was added to 80 ml. of methyl iodide. The resulting mixture was stirred vigorously and refluxed for six hours with 12 g. of silver oxide, the latter being added in portions over a four-hour period. The silver salts were filtered off and extracted with hot methanol and the combined filtrate and washings concentrated *in vacuo* to dryness. The dry reaction product was suspended in 70 ml. of methyl iodide and methylated again with the aid of 10 g. of silver oxide. After two more methylations in this manner 6.3 g. of crude crystalline product was isolated. Recrystallization from ethanol gave 4.8 g. (58%) of methyl 3-methyl-2,4:5,6-dimethylene-D-gluconate as long fine needles; m. p. 124–125°; $[\alpha]^{25}\text{D}$ −6.5° (*C*, 1.5; water).

Anal. Calcd. for $C_{10}H_{16}O_7$: C, 48.4; H, 6.5; OCH_3, 25.0. Found: C, 48.3; H, 6.5; OCH_3, 25.2.

Oxidation of the Saponified Acetolysis Product of Methyl 3-Methyl-2,4:5,6-dimethylene-D-gluconate.—A solution of 4.20 g. (0.017 mole) of methyl 3-methyl-2,4:5,-6-dimethylene-D-gluconate in 50 ml. of an acetolyzing mixture (35 ml. acetic anhydride, 15 ml. of acetic acid and 1 ml. of concentrated sulfuric acid) was allowed to remain at 0° for thirty minutes and then diluted with 400 ml. of ice water. The resulting solution was then neutralized with 75 g. of sodium bicarbonate, extracted with chloroform, and the dried chloroform solution concentrated *in vacuo* to a sirup (6.8 g.). This crude reaction product was presumed to be methyl 3-methyl-5-acetoxymethyl-6-acetyl-2,4-methylene-D-gluconate. The 6.8 g. of sirup was saponified at 60° with a solution of 11.30 g. (0.036 mole) of barium hydroxide octahydrate in 250 ml. of water. The barium salt was treated with the calculated amount of sulfuric acid and the barium sulfate that precipitated was removed by filtration. After concentrating the clear filtrate *in vacuo*, 2.2 g. of a nearly colorless sirup was obtained which presumedly was 3-methyl-2,4-methylene-D-gluconic acid.

For the oxidation all of the sirup was dissolved in a solution of 1.2 g. of potassium hydroxide in 50 ml. of water. The mixture was stirred and cooled to 5 to 10° and a solution of 5 g. of potassium permanganate in 90 ml. of water was introduced slowly over a thirty-minute period. Stirring was continued for thirty minutes after which the excess permanganate was destroyed with ethanol. The precipitated manganese dioxide was removed and washed with hot water by centrifugation. The supernatant solutions were combined and made slightly acid to litmus with sulfuric acid. The residue obtained by concentrating this solution *in vacuo* was suspended in 200 ml. of methanol and 3 ml. of concentrated sulfuric acid was added with stirring. Potassium sulfate precipitated and was removed and washed with methanol by centrifugation. The supernatant solution and washings were combined (500 ml.) and refluxed for ten hours. The sulfuric acid was then neutralized with barium carbonate, the barium sulfate removed, and the clear solution concentrated *in vacuo* to dryness. The residue was allowed to stand at 5 to 10° for two days with 200 ml. of methanol–ammonia. After concentrating this solution to dryness *in vacuo* the crude product was recrystallized twice from 80% ethanol. The yield of purified 3-methyl-2,4-methylene-xylotrihydroxyglutarodiamide was 0.3 g.; m. p. 305–306° (dec.); $[\alpha]^{25}\text{D}$ 0°. Jones and Wiggins[7] reported a melting point of 295° for this compound. An authentic sample prepared by their procedure[7] was found to melt at 305–306° (dec.).

Acknowledgment.—The authors are indebted to C. H. Van Etten of the Analytical and Physical Chemical Division of this Laboratory for performing the microanalyses.

Summary

A new methyl dimethylene gluconate has been isolated from the sublimate mixture obtained by heating methyl 2,4:3,5-dimethylene-D-gluconate *in vacuo* at 150°. The structure of the new diacetal has been shown to be methyl 2,4:5,6-dimethylene-D-gluconate. The rearrangement of a six-membered methylene acetal ring to a five-membered ring has thus been demonstrated.

The application of the procedure of Hudson and Hann and their associates[6] for the limited acetolysis of the methylene acetals of sugar alcohols to methyl 2,4:3,5-dimethylene-D-gluconate and methyl 2,4:5,6-dimethylene-D-gluconate has resulted in further confirmation of the relative stability of the 2,4-methylene acetal linkage to acetolysis.

PEORIA, ILLINOIS RECEIVED NOVEMBER 14, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY OF THE AMERICAN UNIVERSITY OF BEIRUT]

Sulfanilamide Derivatives Containing Urea, Thiourea or Hydrazide Groupings

BY EVA NIEMIEC[1]

Urea has been used in therapy along with sulfanilamides, its alleged effect being to counteract the action of *p*-aminobenzoic acid. It appeared of interest to prepare sulfanilamides containing urea or related groupings and study their bacteriostatic effects.

In the preparation of sulfanilamidourea (I) and sulfanilamidothiourea (II) from acetylsulfanilyl chloride and the appropriate semicarbazide hydrochloride (condensed in the presence of aqueous sodium acetate), deacetylation was accomplished by boiling for three hours in aqueous alcoholic hydrochloric acid solution. Alkaline hydrolysis causes liberation of ammonia; even ten hours of boiling with concentrated hydrochloric acid results only in partial hydrolysis.

(I) p-$H_2NC_6H_4SO_2NHNHCONH_2$
(II) p-$H_2NC_6H_4SO_2NHNHCSNH_2$
(III) p-$H_2NCH_2C_6H_4SO_2NHNHCONH_2$
(IV) p-$CH_3CONHC_6H_4SO_2NHNH_2$
(V) p-$CH_3CONHC_6H_4SO_2NHNHCOC_6H_5$
(VI) p-$CH_3CONHC_6H_4SO_2NHNHCOCH_3$
(VII) p-$CH_3CONHC_6H_4SO_2NHN(COCH_3)_2$
(VIII) p-$H_2NC_6H_4SO_2NHNH_2$

Marfanil or homosulfanilamide is interesting because its bacteriostatic action is not counteracted by *p*-aminobenzoic acid; its urea derivative (III) was prepared as above. Sulfanilylhydrazides should be available by either (1) treatment of acetylsulfanilyl chloride with the hydrazide, or (2) acylation of N^4-acetylsulfanilylhydrazine (IV), and hydrolysis at the N^4-position. Haslewood[2] prepared sulfanilylbenzhydrazide using the first method. Since acethydrazide is difficult to prepare, the second method was employed in this work. N^4-Acetylsulfanilylhydrazine[3] was prepared in good yield by grinding hydrazine dihydrochloride in a mortar with dry acetylsulfanilyl chloride and crystalline sodium carbonate.

If N^4-acetylsulfanilylhydrazine is treated in pyridine solution with one mole of benzoyl chloride, N^4-acetylsulfanilylbenzhydrazide[2] (V) is obtained; this yields sulfanilylbenzhydrazide on alkaline hydrolysis. Excess benzoyl chloride gives a product which appears to be a mixture of the mono- and dibenzhydrazide. This is in agreement with the experience of McFadyen and Stevens.[4] Acetylsulfanilylhydrazine in pyridine can be converted into either N^4-acetylsulfanilacethydrazide (VI) or the diacetate VII. When either product is subjected to acid hydrolysis[3] with 12 *N* hydrochloric acid or even with 6 *N* or 3 *N* hydrochloric acid, all acetyl groups are split off and only sulfanilylhydrazine[3] (III) is obtained.

Studies of the bacteriostatic properties of these compounds by Miss Aida Djanian at the Department of Bacteriology of this University indicate that sulfanilamidourea and 4-homosulfanilamidourea are superior to sulfathiazole in their inhibitory action upon *Clostridium welchii*, *Cl. tetani*, *Cl. sporogenes*, and *Cl. chauvei*. Sulfanilamidourea and sulfanilamidothiourea are approximately one-tenth as active against *Streptococcus viridans* as sulfathiazole, whereas homosulfanilamidourea has no inhibitory effect.

Experimental[5]

N^4-Acetylsulfanilamidourea.[6]—A mixture of 5 g. of semicarbazide hydrochloride, 10.5 g. of dry acetylsulfanilyl chloride, and 30 g. of crystalline sodium acetate is thoroughly ground in a mortar with a few cc. of water. The thick paste is then transferred with the minimum amount of water and heated for thirty minutes at 60°. After cooling the product is filtered, washed, and crystallized from boiling water, in which it is not very soluble; needles, m. p. 223–224° with decomposition, yield 6 g.

---

(1) Part of a Master's thesis submitted to the American University of Beirut, 1946.

(2) Haslewood, *Biochem. J.*, **35**, 1307 (1941).

(3) Curtius and Stoll, *J. prakt. Chem.*, **112**, 1117 (1926).

(4) Compare McFadyen and Stevens, *J. Chem. Soc.*, p. 584 (1936).

(5) All melting points are uncorrected.

(6) After the completion of these experiments, Roth and Degering, THIS JOURNAL, **67**, 126 (1945), reported the preparation of this compound in comparable yield in pyridine solution

Anal. Calcd. for $C_9H_{12}N_4O_4S$: N, 20.58. Found: N, 20.41, 20.05.

Sulfanilamidourea (I).—N^4-Acetylsulfanilamidourea (6.0 g.) is refluxed for three hours with 21 cc. of concentrated hydrochloric acid (density 1.19) and 70 cc. of 95% alcohol. The crystals that separate on cooling are filtered and neutralized with sodium carbonate to litmus. The needles that separate on cooling are recrystallized from boiling water; m. p. 229° with decomposition; yield 4.5 g.

Anal. Calcd. for $C_7H_{10}N_4O_3S$: C, 36.51; H, 4.38; N, 24.34. Found: C, 37.1, 37.2; H, 4.6, 4.7; N, 24.25, 24.20.

N^4-Acetylsulfanilamidothiourea.[6]—A mixture of 5 g. of thiosemicarbazide, 13 g. of acetylsulfanilyl chloride, and 23 g. of crystalline sodium acetate is allowed to react as described for the urea derivative; needles (from water), m. p. 186°; yield 2 g.

Anal. Calcd. for $C_9H_{12}N_4O_3S_2$: C, 37.49; H, 4.20; N, 19.43. Found: C, 37.1, 36.8; H, 4.6, 4.9; N, 19.0, 18.8.

Sulfanilamidothiourea (II).—The hydrolysis is carried out exactly as described for the urea derivative; needles (from water) m. p. 224–225° with decomposition.

Anal. Calcd. for $C_7H_{10}N_4O_2S_2$: C, 34.13; H, 4.09; N, 22.75. Found: C, 34.45, 34.30; H, 4.3, 4.3; N, 23.0, 23.2.

N^4-Acetyl-4-homosulfanilamidourea.—A mixture of 7 g. of N-acetyl-4-homosulfanilyl chloride,[7] 7 g. of semicarbazide hydrochloride, and 20 g. of crystalline sodium acetate is treated as described for the lower homolog. The product is crystallized from boiling water, in which it is quite soluble; rods, m. p. 193–194° with decomposition; yield 5 g. The air-dried product contains 1 mole of water of crystallization, which is removed by drying in vacuum over phosphorus pentoxide at 100°.

Anal. Calcd. for $C_{10}H_{14}N_4O_4S \cdot H_2O$: N, 18.41. Found: N, 18.5, 18.2.

4-Homosulfanilamidourea Hydrochloride (III).—One gram of N^4-acetyl-4-homosulfanilamidourea is refluxed for eight to nine hours with concentrated hydrochloric acid and 56 cc. of absolute alcohol. On cooling the hydrochloride separated in the form of clusters melting at 225–226° with decomposition; yield 0.7 g.

Anal. Calcd. for $C_8H_{13}N_4O_3SCl$: N, 19.96. Found: N, 19.8, 19.9.

N^4-Acetylsulfanilylhydrazine (IV).—Hydrazine dihydrochloride (5 g.), dry acetylsulfanilyl chloride (12 g.), and crystalline sodium carbonate (28 g.) are ground in a mortar. The reaction is marked by a strong evolution of gas. When the gas stops evolving a few cc. of water is added and the reaction mixture is left for one hour at room temperature. The product is filtered, washed with water, and crystallized from 500 cc. of boiling water; plates, m. p. 183–184° with decomposition. Prolonged boiling results in decomposition of the product.

Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 41.9, 42.1; H, 4.9, 5.3; N, 18.2, 18.4.

N^4-Acetylsulfanilylbenzhydrazide (V).—N^4-Acetylsulfanilylhydrazine (1 g.) is dissolved in a minimum amount of dry pyridine. The solution is cooled and treated slowly with 0.5 cc. of benzoyl chloride. After standing for twenty-four hours at room temperature the pyridine is removed *in vacuo*. The residue is treated with dilute hydrochloric acid and the precipitate is collected and crystallized three times from water or alcohol; m. p. 219–220° with decomposition; yield 0.5 g. It shows no depression with Haslewood's product.

N^4-Acetylsulfanilylmonoacethydrazide (VI).—To a cooled solution of 3 g. of N^4-acetylsulfanilylhydrazine in dry pyridine, 0.93 cc. of acetyl chloride is slowly added. After standing for twenty-four hours and after evacuation of the pyridine, the residue is treated with dilute hydrochloric acid and kept for several hours in the icebox. The product is filtered and crystallized twice from water; m. p. 204–205° with decomposition.

Anal. Calcd. for $C_{10}H_{13}O_4N_3S$: N, 15.49. Found: N, 15.79, 15.68.

N^4-Acetylsulfanilyldiacethydrazide (VII).—N^4-Acetylsulfanilhydrazine (3 g.) in pyridine is treated without cooling with acetic anhydride (3 cc.). The procedure is the same as for the monoacethydrazide; needles (from water), m. p. 191–192° with decomposition.

Anal. Calcd. for $C_{12}H_{15}N_3O_5S$: C, 46.00; H, 4.83; N, 13.41. Found: C, 45.8, 46.1; H, 4.8, 4.6; N, 13.6, 13.3.

Summary

Sulfanilamidourea, sulfanilamidothiourea, and 4-homosulfanilamidourea were prepared and tested for bacteriostatic activity.

A simplified method for the preparation of N^4-acetylsulfanilylhydrazine is described. The latter compound can be used for the preparation of sulfanilylbenzhydrazide and of N^4-acetylsulfanilyl-mono- and diacethydrazide. Acid hydrolysis of the last two compounds yields sulfanilylhydrazine.

BEIRUT, LEBANON RECEIVED AUGUST 28, 1947

---

[7] Bergeim and Braker, THIS JOURNAL, 66, 1459 (1944).

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE EVANS RESEARCH AND DEVELOPMENT CORPORATION]

Esters of Dithiodiglycolic Acid

BY JOHN F. MULVANEY, JAMES G. MURPHY AND RALPH L. EVANS

The esters of dithiodiglycolic acid reported here were prepared as a part of the general program of research in these laboratories on compounds reacted to thioglycolic acid and its derivatives.

Although the methyl[1] and ethyl[1,2] esters of dithiodiglycolic acid were described many years ago, to our knowledge only one other ester, namely, the dimethylaminoethyl ester,[3] has been reported during the intervening years.

Claesson prepared the ethyl ester by direct esterification of the dithio acid with alcohol, using dry hydrogen chloride as a catalyst. As noted by Price and Twiss the ester that Claesson obtained was impure. These authors[1] prepared the dimethyl and diethyl esters by electrolysis of the Bunte salts prepared from ethyl or methyl bromoacetate and sodium thiosulfate.

In a later report[4] these same authors describe the preparation of the dimethyl ester by the oxidation of the Bunte salt with iodine.

All the esters reported here were prepared by direct esterification of dithiodiglycolic acid with the corresponding alcohol. The usual acid catalyst, sulfuric acid, benzene- or toluenesulfonic acid, was used. Several of the esters were also prepared by oxidation of the corresponding ester of thioglycolic acid with the hydrogen peroxide. The average yield of crude ester was about 95%. The physical properties of the liquid esters were determined on the middle fraction of a doubly distilled product. All esters were distilled in presence of a slow stream of nitrogen.

Dithiodiglycolic acid was prepared by the oxidation of thioglycolic acid with hydrogen peroxide, or by the reaction of chloroacetic acid with sodium polysulfide. It was recrystallized from ethylene dichloride or from a mixture of benzene and ethyl acetate (9:1), m. p. 106–107° (uncor.).

In general 0.5 mole of dithiodiglycolic acid was refluxed with 1.0–1.1 moles of the alcohol in the presence of 150 cc. of toluene or benzene and 2 g. of benzene- or toluenesulfonic acid. The vapors were condensed and the lower layer of the benzene–water azeotrope was separated in a Dean–Stark trap. Esterification was generally completed in thirty minutes to two hours. The solution of the ester was washed with 5% bicarbonate solution and water, dried over anhydrous sodium sulfate, and then distilled in vacuum.

The tetra-, hexa- and octadecyl esters separated when the reaction mixture was cooled. The cyclohexyl ester crystallized after the toluene was removed.

All liquid esters are colorless when pure and are practically odorless. They are immiscible with water but soluble in most organic solvents.

TABLE I

ESTERS OF DITHIODIGLYCOLIC ACID $(SCH_2COOR)_2$

R	B. p. °C.	Mm.	$n^{25}D$	d^{25}_{25}	M_D Calcd.	M_D Obs.	% Sulfur Calcd.	% Sulfur Found
n-Propyl	104–6	0.1	1.4903	1.1380	67.9	67.6	24.07	24.26
i-Propyl	91–3	.1	1.4838	1.1240	67.9	67.7	24.07	23.85
n-Butyl	121.5–122.5	.1	1.4870	1.1018	77.1	76.8	21.77	22.44
i-Butyl	112–114	.1	1.4839	1.0936	77.1	76.9	21.77	22.41
n-Octyl	202–207	.5	1.4780	1.0096	114.1	114.0	15.77	15.72
n-Dodecyl[b]			1.4769	0.9687	151.0	151.3	12.36	12.42
n-Tetradecyl	34.5–35[a]						11.15	11.22
n-Hexadecyl	44.0–44.5[a]						10.16	9.98
n-Octadecyl	52.0–52.5[a]						9.33	9.33
Methylcellosolve	150–154	0.3	1.4990	1.2337	71.2	71.0	21.49	21.76
Cyclohexyl	55–56[a]						18.50	18.15

[a] Melting points, uncor. [b] Precipitated as an oil from petroleum ether by methanol.

Summary

Eleven new esters, seven liquids and four solids, of dithiodiglycolic acid have been prepared and some of their physical properties determined.

250 EAST 43RD STREET
NEW YORK 17, N. Y.

RECEIVED NOVEMBER 8, 1947

---

(1) T. S. Price and D. F. Twiss, *J. Chem. Soc.*, 1645–1653 (1908).

(2) Claesson, *Ber.*, **14**, 411 (1881).

(3) J. M. Gulland, M. W. Partridge and S. S. Randall, *J. Chem. Soc.*, 419–425 (1940).

(4) T. S. Price and D. F. Twiss, *ibid.*, 1489–1491 (1909).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Carcinogenic Hydrocarbons. 9,11-Dimethylbenz[*a*]anthracene and 8,9,11-Trimethylbenz[*a*]anthracene

BY BYRON RIEGEL AND JOHN G. BURR, JR.[1]

The possibility that some tumors may arise from abnormal steroid metabolism has stimulated a search for the carcinogenic agents. A plausible substance is 3,5-dimethylcholanthrene, the synthesis of which is described in the second paper of this series. The positions of interest in this hydrocarbon are C-5, where the steroid side chain would appear, and C-3, where the C-20 methyl group of the steroid side chain appears. To test this hypothesis further, the cumulative effect of methyl groups in the corresponding 9 and 11 positions[2] of the benz[*a*]anthracene system was investigated. The parent hydrocarbons selected are of varying carcinogenic activity so that any coupling effect by the addition of methyl groups in the 9 and 11 positions should be clearly evident. Two hydrocarbons that would best demonstrate this effect are 9,11-dimethylbenz[*a*]anthracene (I) and 8,9,-11-trimethylbenz[*a*]anthracene (II).

These two hydrocarbons (I and II) have been prepared by a new method, which incorporates certain features of the Cook and Robinson synthesis of 11-methylbenz[*a*]anthracene[3] and of the Bachmann and Chemerda synthesis of 10-methylbenz[*a*]anthracene.[4] 3-Acetylphenanthrene (III) was condensed with diethyl succinate under the conditions of the modified Stobbe reaction, as developed by Johnson and his co-workers.[5] The yield of the half ester (IV) obtained in this reaction was found to depend upon the concentration of potassium *t*-butoxide in the solvent *t*-butyl alcohol, and to be nearly independent of the duration of heating or the excess of diethyl succinate. The use of a solution of potassium *t*-butoxide in *t*-butyl alcohol nearly saturated at the boiling point gave a 72% yield of the half ester (IV). The lactone (V) was produced in 70% yield by repeated hydrolysis of IV with a boiling mixture of acetic and hydrobromic acids. This lactone (V) was reduced to the corresponding γ-(3-phenanthryl)-valeric acid by several agents. Clemmensen reduction of the lactone produced the acid in 62–85% yields with a quantitative recovery of unreduced lactone. Catalytic reduction gave a 95% yield of the acid. The most convenient reducing agent, as determined by the results of the ensuing cyclization, was a mixture of iodine and red phosphorus in glacial acetic acid. In all of these experiments, the substituted valeric acid was obtained as an oil, although it has been reported[4] as a solid melting at 75–77°. Cyclization of this non-crystalline acid, however, produced the known[4] 8-keto-11-methyl-8,9,10,11-tetrahydrobenz[*a*]anthracene (VI) in a 72–97% yield.

The ketone (VI) when condensed with methyl oxalate by the usual procedure[4] gave a quantitative yield of the glyoxalate (VII), which was decarbonylated by heating with powdered soft glass to the β-ketoester (VIII). The sodium salt of the keto ester was refluxed with methyl iodide, and the resulting methyl keto ester was repeatedly hydrolyzed with a boiling mixture of acetic and hydrochloric acids. 8-Keto-9,11-dimethyl-8,9,-10,11-tetrahydrobenz[*a*]anthracene (IX) was thus obtained in a 75% yield from the ketone (VI), as colorless needles melting at 169–170°.

Reduction of this ketone (IX) with aluminum isopropoxide, and subsequent dehydration (through an intermediate 8-chloro compound) of the carbinol, led to 9,11-dimethyl-10,11-dihydrobenz[*a*]anthracene (X) which was obtained as colorless massive plates melting at 70–71°. The aromatization of X was accomplished by the Linstead solution method.[6] 9,11-Dimethylbenz[*a*]-anthracene (I) forms colorless plates which melt at 154–154.5°.

The ketone (IX) was refluxed with an excess of methylmagnesium iodide, and the resulting carbinol (XI) was then heated with 5% palladium–charcoal at 300° to give the 8,9,11-trimethylbenz-[*a*]anthracene (II) which was isolated (63% overall yield from IX) from the fusion mass as yellowish plates melting at 201–203.5°.

Samples of these hydrocarbons have been sent to Dr. M. J. Shear, of the National Cancer Institute, for biological testing.

Experimental[7]

Stobbe Half Ester (IV).—A solution of 10.6 g. of potassium (cleaned and weighed under kerosene) in 150 ml. of anhydrous *t*-butyl alcohol was prepared by heating. This solution was mixed with 73.5 g. of diethyl succinate and 46.0 g. of 3-acetylphenanthrene[8] (m. p. 69–72°). The flask containing this mixture was repeatedly evacuated and filled with nitrogen, and the solution then refluxed for five hours in a nitrogen atmosphere. The warm solu-

---

[1] Eastman Kodak Fellow, 1946–1947. Present address: Department of Chemistry, Miami University, Oxford, Ohio.

[2] The system of numbering used here is that recommended by "The Ring Index," Reinhold Publishing Corp., New York, N. Y., 1940, p. 381. Many of the previous investigators have named such compounds as derivatives of anthracene instead of benzanthracene.

[3] J. W. Cook and A. M. Robinson, *J. Chem. Soc.*, 505 (1938).

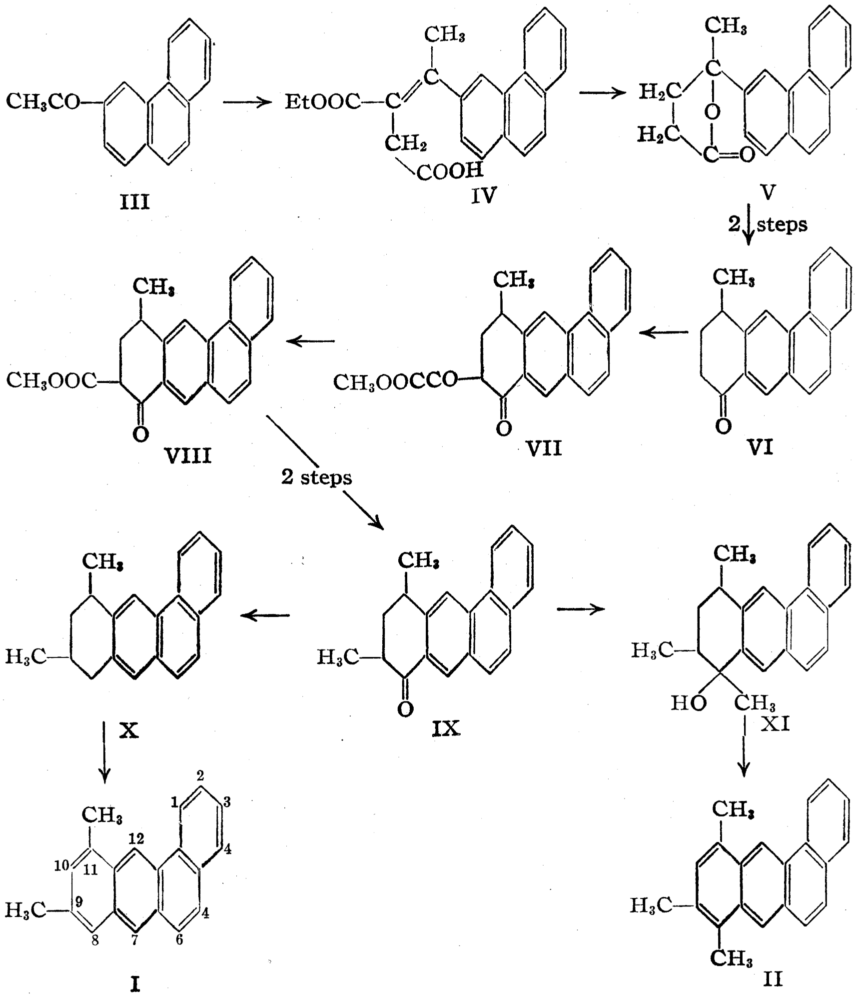
[4] W. E. Bachmann and J. M. Chemerda, *J. Org. Chem.*, **6**, 36 (1941).

[5] W. S. Johnson, A. Goldmann and W. P. Schneider, THIS JOURNAL, **67**, 1357 (1945).

[6] R. P. Linstead, A. F. Millidge, S. L. S. Thomas and A. L. Walpole, *J. Chem. Soc.*, 1146 (1937).

[7] All melting points were taken on a Fischer–Johns apparatus. Microanalyses by Patricia Craig and Nelda Mold, Northwestern University.

[8] Prepared by the method of E. Mosettig and J. van der Kamp, THIS JOURNAL, **52**, 3704 (1930), as modified by W. E. Bachman and C. H. Boatner, *ibid.*, **58**, 2097 (1936).



tion was hydrolyzed with dilute hydrochloric acid, and organic solvents removed by distillation. The viscous product was dissolved in ether and the half ester extracted from the ether with dilute ammonium hydroxide. Acidification of the alkaline solution precipitated the half ester. From 85 g. of 3-acetylphenanthrene was obtained 98.5 g. (72%) of the half ester (IV) as a dark, clear, very viscous oil. The neutral material obtained by evaporation of the ether was crystallized from methanol and unreacted ketone (III) recovered as yellow needles, m. p. 64–67°.

Employment of a more dilute solution of potassium *t*-butoxide lowers the yield of half ester to 42–45% with proportionate recovery of the ketone (III).

γ-(3-Phenanthryl)-valerolactone (V).—A suspension of 98.5 g. of the half ester (IV) in a mixture of 95 ml. of water, 188 ml. of 48% hydrobromic acid, and 285 ml. of glacial acetic acid was refluxed for six and one-half hours. The product of this reaction was a brown sandy solid which weighed 80.1 g. This solid was dissolved in chloroform, decolorized, and the solution concentrated and diluted with a large volume of ether. The lactone (V) crystallized (38.7 g.) as pale tan plates. The material remaining in solution was recovered and hydrolyzed with an acid mixture of the same composition and quantity as used originally. In this way, an additional 14.5 g. of the lactone was obtained, making a total yield of 53.2 g. (70%). Two crystallizations of this solid from chloroform–ether gave colorless needles melting at 150–151°.

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.6; H, 5.80. Found: C, 82.2; H, 5.92.

γ-(3-Phenanthryl)-valeric Acid. A.—To reduce the lactone (V), 18.64 g. of it with a mixture of 250 ml. of glacial acetic acid, 15 g. of red phosphorus, 5 g. of iodine, and 5 ml. of water was heated to boiling for six hours. This solution was filtered through sintered glass, and poured into two liters of water containing a little sodium bisulfite. The precipitated product was dissolved in ether–benzene, and the acid extracted from this solution with 10% potassium carbonate. The alkaline extract was acidified and the acid taken up in ether. Evaporation of the ether gave the acid as a clear brown viscous liquid weighing 18.86 g. (100%). When 38.7 g. of the lactone was reduced with the same quantities of reagents, 18.3 g. of the acid was obtained, and 20.0 g. of pure lactone was recovered. The reduction of 34 g. of the lactone with double the above quantities of reagents produced the acid in 84% yield, with recovery of 13% of lactone. The acid was identified by cyclization to the known 8-keto-9-methyl-8,9,10,11-tetrahydrobenz[*a*]anthracene (VI), as described below.

B. A 1.14-g. sample of the lactone was reduced by the use of 26 g. of amalgamated zinc, 20 ml. of water, 50 ml. of concentrated hydrochloric acid and 30 ml. of toluene. The reaction mixture was refluxed vigorously for forty-eight hours; during the first eight hours, 10-ml. portions of concentrated hydrochloric acid were added hourly. After cooling, the reaction mixture was diluted with water and ether and worked up essentially as described in A. A yield of 0.98 g. (85%) of acidic material was obtained. Crystallization of the neutral fraction from chloroform–ether gave 0.21 g. (18%) of recovered lactone melting at 150–151°. On other runs the modified Clemmensen reduction did not give as consistent yields as the first method.

C. To a solution of 1.0 g. of the lactone in 50 ml. of glacial acetic acid containing 1.0 ml. of sulfuric acid was added 0.10 g. of palladium–charcoal catalyst. This solution was shaken with hydrogen at an initial pressure of 33.5 lb. At the end of four hours the catalyst was separated by filtration and most of the acetic acid removed under reduced pressure. The residue was poured into water and the precipitated oil extracted with ether and benzene. From the organic solution was obtained 0.95 g. (95%) of acidic material as a yellow viscous liquid. It was cyclized to the ketone in a nearly quantitative yield.

8-Keto-11-methyl-8,9,10,11-tetrahydrobenz[*a*]anthracene (VI).—γ-(3-Phenanthryl)-valeric acid (18.86 g.) was dissolved in 100 ml. of benzene, and converted to the acid chloride with 19 g. of phosphorus pentachloride. The acid chloride was cyclized with 20 ml. of stannic chloride; after the bright orange crystalline complex had stood for one-half hour, it was hydrolyzed with a mixture of ice, hydrochloric acid, and ether. The product of this reaction was 16.0 g. (91.5%) of brown prisms. It was crystallized from ethanol–benzene to give 13.8 g. (79%) of shining tan crystals which melted at 126–130°. A sample of this ketone was dissolved in benzene, passed through alumina, and then crystallized from ethanol–benzene.

It then formed massive pale yellow prisms melting at 129–130.5° (lit.[4] 130–131.5°). The yield of crude ketone varied from 72–97%, depending upon the source of the acid.

The **oxime** crystallizes from alcohol as massive colorless plates melting at 192–193° (dec.).

Anal. Calcd. for $C_{19}H_{17}ON$: N, 5.09. Found: N, 4.88.

8-Keto-11-methyl-8,9,10,11-tetrahydrobenz[*a*]anthracene-9-glyoxalate (VII).—A mixture of 13.8 g. of the ketone (VI), the dry sodium methoxide from 2.21 g. of sodium, and 11.3 g. of dimethyl oxalate was dissolved in 500 ml. of dry benzene by shaking and gentle warming. After standing at room temperature for nine and one-half hours, the deep red solution was hydrolyzed with 100 ml. of water and the product extracted with 2% sodium hydroxide. The alkaline solution was acidified and the crude glyoxalate obtained as a clear deep red gum weighing 18.68 g. (100%). This gum crystallized on standing overnight. A portion was dissolved in acetone, decolorized with Nuchar and the first crop of crystals was again crystallized from ethanol. The glyoxalate forms pale chartreuse leaflets melting at 122–123.5° and gives a dark-brown color with alcoholic ferric chloride.

Anal. Calcd. for $C_{22}H_{18}O_4$: C, 76.3; H, 5.23. Found: C, 76.7; H, 5.57.

8-Keto-11-methyl-9-carbomethoxy-8,9,10,11-tetrahydrobenz[*a*]anthracene (VIII).—A mixture of 18.68 g. of the glyoxalate and 10 g. of powdered glass was heated at 180–190° for forty-five minutes at which time the evolution of gas had ceased. The keto-ester was extracted with benzene and crystallized from benzene–methanol to give 6.80 g. of brown prisms and 8.42 g. of an orange oil. Both fractions were suitable for the next step. A portion of the solid (in benzene solution) was passed through alumina, and crystallized from dioxane–methanol to give light tan prisms melting at 121–122.5°. It gives a green color with alcoholic ferric chloride.

Anal. Calcd. for $C_{21}H_{18}O_3$: C, 79.2; H, 5.71. Found: C, 79.7; H, 5.85.

8-Keto-9,11-dimethyl-8,9,10,11-tetrahydrobenz[*a*]anthracene (IX).—To a solution of sodium methoxide, prepared from 0.4 g. of sodium and a mixture of 5 ml. of methanol and 25 ml. of benzene, was added 2.50 g. of the crystalline keto ester (VIII). A pasty green solid precipitated. The solution was refluxed with 5 ml. of methyl iodide (a second 5-ml. portion was added after two hours) overnight. Volatile substances were stripped out by distillation, and the residue was taken up in benzene and passed through alumina. In some runs, the pink precipitate of sodium iodide formed in the reaction clogged the alumina column, so the suspension was filtered first. The methyl keto ester was obtained from the eluate as 2.72 g. (100%) of a yellow viscous oil. When cruder keto ester was methylated, the yield dropped to 84–89%.

The methyl keto ester (33.4 g.) was decarbomethoxylated by refluxing it for five hours with a mixture of 300 ml. of glacial acetic acid and 300 ml. of concentrated hydrochloric acid. The solvents were slowly distilled under reduced pressure, and the red granular residue (28.7 g.) was crystallized from benzene–methanol. The ketone, IX (19.5 g.), was obtained as pinkish needles. The material remaining in solution was recovered and refluxed with 200 ml. of the acid mixture. An additional 4.2 g. of the ketone was so produced. The total yield was 23.7 g. (75%); m. p. 169–172°. One crystallization from benzene–methanol, after treatment with Nuchar, gave a product which separated as colorless needles and melted at 169–170°.

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.6; H, 6.61. Found: C, 87.5; H, 6.77.

The **oxime** crystallized in long silky needles from ethanol and melted at 220–220.5°.

Anal. Calcd. for $C_{20}H_{19}ON$: N, 4.84. Found: N, 4.89.

8-Hydroxy-9,11-dimethyl-8,9,10,11-tetrahydrobenz[*a*]anthracene.—Aluminum isopropoxide was prepared from 1.4 g. of aluminum wire and 190 ml. of dry isopropyl alcohol. Three grams of the ketone (IX) was dissolved in this solution, and isopropyl alcohol distilled out slowly. After 115 ml. of the alcohol had distilled during seven hours, a negative test for acetone was obtained in the distillate. Hydrolysis of the residual solution gave 3.19 g. of the carbinol as an oily solid.

9,11-Dimethyl-10,11-dihydrobenz[*a*]anthracene (X).—A rapid stream of dry hydrogen chloride was passed into a chilled solution of 3.19 g. of the above carbinol in 50 ml. of benzene containing 2.3 g. of calcium chloride. After twenty minutes the hydrogen chloride flow was stopped and the reaction mixture filtered through a sintered glass funnel. The solvent was evaporated and the residue heated *in vacuo* on a steam-bath. It evolved hydrogen chloride vigorously. The residue was sublimed at 1 mm., and the white solid sublimate crystallized from ethanol containing a few drops of water. The dihydrodimethyl hydrocarbon (X) was obtained as colorless, massive plates (1.44 g.) m. p. 68–70°. One crystallization from absolute ethanol raised the melting point to 70–71°.

Anal. Calcd. for $C_{20}H_{18}$: C, 93.0; H, 7.02. Found: C, 92.8; H, 6.76.

9,11-Dimethylbenz[*a*]anthracene (I).—To a solution of 1.06 g. of the dihydrodimethyl hydrocarbon (X) in 35 ml. of mesitylene was added 0.19 g. of 5% palladium–charcoal, and the resulting mixture was heated to vigorous boiling in a stream of carbon dioxide. The evolved gases were collected in a nitrometer. During three hours and twenty minutes, 110 ml. of hydrogen was collected. The product obtained from this reaction was crystallized from ethanol–benzene to give 0.75 g. of colorless plates melting at 154–155°. One crystallization from ethanol gave a product melting at 154–154.5°.

Anal. Calcd. for $C_{20}H_{16}$: C, 93.7; H, 6.29. Found: C, 93.7; H, 6.39.

The **picrate** crystallized from alcohol as deep red-brown needles which melted at 191–192°.

Anal. Calcd. for $C_{20}H_{16}\cdot C_6H_3O_7N_3$: N, 8.7. Found: N, 8.5.

The **trinitrobenzene complex** crystallized from alcohol as long thin orange needles which melted at 188–190°.

Anal. Calcd. for $C_{20}H_{16}\cdot C_6H_3O_6N_3$: N, 9.0. Found: N, 8.7.

8,9,11-Trimethylbenz[*a*]anthracene (II).—To a solution of methylmagnesium iodide prepared from 3.4 g. of methyl iodide and 0.67 g. of magnesium in 40 ml. of ether was added a solution of 1.64 g. of the ketone (IX) in 50 ml. of benzene. The reaction mixture was refluxed for one and one-half hours. The carbinol obtained after hydrolysis was a clear, amber, viscous liquid (2.29 g.). It was mixed with 200 mg. of 5% palladium–charcoal, protected with a nitrogen atmosphere, and during a one-hour period the temperature was gradually raised to 310°. The product was extracted from this melt and crystallized from benzene. There was obtained 1.02 g. (63%) of yellowish plates; m. p. 196–201°. A portion of this substance was crystallized twice more from ethanol–benzene, passed (in benzene solution) through an alumina column, and finally crystallized again from ethanol–benzene. 8,9,11-Trimethylbenz[*a*]anthracene thus purified has a melting point of 201–203.5°, and forms large regular faintly yellow diamond-shaped plates.

Anal. Calcd. for $C_{21}H_{18}$: C, 93.3; H, 6.71. Found: C, 93.5; H, 6.67.

The **picrate** crystallized as fine red-brown needles which melted at 190–191°.

Anal. Calcd. for $C_{21}H_{18}\cdot C_6H_3O_7N_3$: N, 8.4. Found: N, 8.3.

The **trinitrobenzene derivative** crystallized as orange micro-needles which melted at 199–200°.

Anal. Calcd. for $C_{21}H_{18}\cdot C_6H_3O_6N_3$: N, 8.7. Found: N, 8.5.

Summary

1. 9,11-Dimethylbenz[*a*]anthracene and 8,9,-11-trimethylbenz[*a*]anthracene have been prepared by an improved synthesis for benz[*a*]anthracene derivatives.

EVANSTON, ILLINOIS RECEIVED AUGUST 15, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

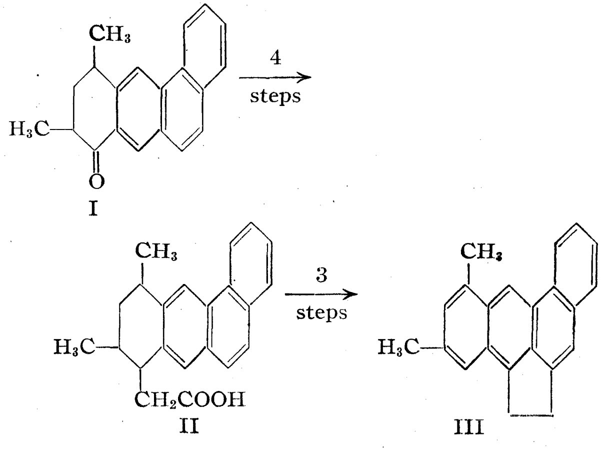
Carcinogenic Hydrocarbons. 3,5-Dimethylcholanthrene[1]

BY BYRON RIEGEL, JOHN G. BURR, JR.,[2] MICHAEL A. KUBICO AND MARVIN H. GOLD[3]

Since the preparation of methylcholanthrene from desoxycholic acid,[4] and from cholic acid[5] by a series of reactions whose types are known to occur in the animal body, it has been a natural speculation[6] that some tumors may be caused by carcinogenic agents produced by an abnormal metabolism of sterols or bile acids. The formation of substituted cholanthrenes from steroids requires a ring closure between the steroid side chain and ring C of the nucleus. The residue of the side chain will then occupy the 5 position in cholanthrene, and the C-20 methyl group of the steroid will be at the 3 position of cholanthrene (present system of numbering[7]). To date, 3,5-dialkylcholanthrenes have not been prepared and tested for carcinogenic activity. The biological reasons for desiring such information are obvious.

The first member of this series, 3,5-dimethylcholanthrene (III), has been prepared by general methods already recorded in the literature[8] for the preparation of substituted cholanthrenes. The starting material was 8-keto-9,11-dimethyl-8,9,10,11-tetrahydrobenz[a]anthracene (I).[9] By means of a Reformatsky reaction followed by dehydration, hydrogenation, and saponification, the ketone (I) was transformed into 9,11-dimethyl-8,9,10,11-tetrahydrobenz[a]anthryl-8-acetic acid (II). Cyclization of this acid by the action of stannic chloride upon the acid chloride produced a viscous liquid ketone which after reduction and dehydrogenation gave 3,5-dimethylcholanthrene. The action of liquid hydrogen fluoride upon the acid gave two products, one of which was an acetone-soluble viscous liquid, and the other (35%) was an acetone-insoluble substance crystallizing in bright yellow needles with a melting point of 267–270°. The physical properties and analysis of this substance conform well with those expected for 1-keto-3,5-dimethylcholanthrene. It is evident that extensive dehydrogenation has occurred, presumably by hydrogen transfer during the cyclization, although the low hydrogen content found in the acid indicates the possibility that dehydrogenation occurred in an earlier step. At the time this experimental work was performed, the extent of the dehydrogenation was not suspected, and both the non-crystalline and the crystalline cyclization products were combined, after reduction of the keto group, and carried through to 3,5-dimethylcholanthrene which was obtained in fair yield from the mixture.

The reduction of the ketonic material was accomplished by the Martin modification of the Clemmensen reduction.[10] The reduction products from both the solid and the oily ketone were combined. Two methods were used for aromatization of this material: (1) the Linstead liquid phase method[11] which gave pure 3,5-dimethylcholanthrene (III) but in poor yield, and (2) the heating of the crude tetrahydro hydrocarbon with palladium–charcoal at 300°. This last method was distinctly superior, giving the 3,5-dimethylcholanthrene (III) in a 51% yield.



From ethanol or ethanol–acetone 3,5-dimethylcholanthrene crystallized as orange-yellow needles melting at 183–184°, but from acetone alone, it crystallized either as diamond-shaped plates or

---

[1] From the Ph. D. Theses by Michael A. Kubico, 1943, and John G. Burr, Jr., 1947.

[2] Eastman Kodak Fellow, 1946–1947. Present address: Department of Chemistry, Miami University, Oxford, Ohio.

[3] Anna Fuller Fund Research Associate, 1940–1942.

[4] H. Wieland and E. Dane, *Z. physiol. Chem.*, **219**, 240 (1933).

[5] L. F. Fieser and M. S. Newman, THIS JOURNAL, **57**, 961 (1935).

[6] J. W. Cook and G. A. D. Haslewood, *Chemistry and Industry*, **52**, 758 (1933); *J. Chem. Soc.*, 428 (1934).

[7] A. M. Patterson and L. T. Capell, "The Ring Index," Reinhold Publishing Corp., New York, N. Y., 1940, p. 437.

[8] (a) J. W. Cook and G. A. D. Haslewood, *J. Chem. Soc.*, 767 (1935); (b) E. Bergman and O. Blum-Bergmann, THIS JOURNAL, **59**, 1573 (1937); (c) W. E. Bachmann, *J. Org. Chem.*, **3**, 434 (1938); (d) W. E. Bachmann and J. M. Chemerda, *ibid.*, **6**, 50 (1941).

[9] B. Riegel and J. G. Burr, Jr., THIS JOURNAL, **70**, 1070 (1948).

[10] E. L. Martin, *ibid.*, **58**, 1438 (1936).

[11] R. P. Linstead, A. F. Millidge, S. L. S. Thomas and A. L. Walpole, *J. Chem. Soc.*, 1146 (1937).

stout rods all having the same melting point alone or admixed. An acetone or alcohol solution of the hydrocarbon has a strong violet fluorescence. When 3,5-dimethylcholanthrene is dissolved in concentrated sulfuric acid, a rose colored solution with a yellow fluorescence is formed. The hydrocarbon was characterized[12] by means of its ultraviolet absorption spectrum. The curve for this exhibits the maxima characteristic of the benz[*a*]-anthracene system which show a bathochromic shift of 30–40 Å. units when compared to positions of the maxima of cholanthrene (Table I). The same shift has been observed for the two methyl groups in 3,11- and 4,11-dimethylcholanthrene (Table I).

TABLE I

MAXIMA IN THE ULTRAVIOLET ABSORPTION SPECTRA OF CHOLANTHRENES (λ IN Å. UNITS) AND CORRESPONDING INTENSITIES (LOG E_M); SOLVENT, ETHANOL

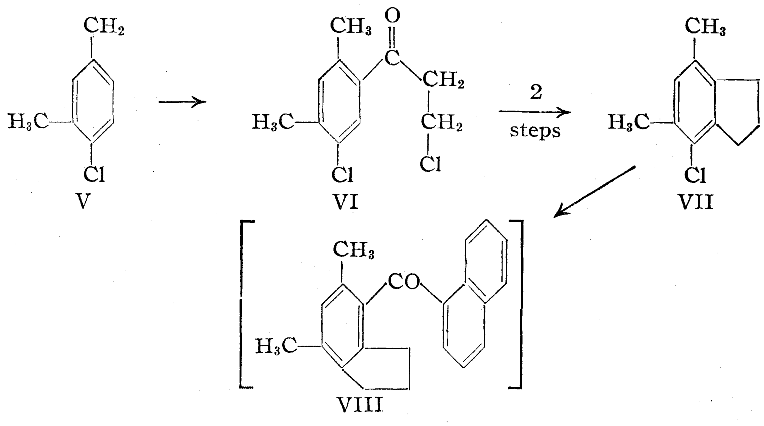
Cholanthrene and dimethyl derivatives	A	B	C	D	E	F
Cholanthrene[a]	2615	2740	2845	2950	3280	3420
	4.6	4.6	4.8	4.9	3.6	3.8
4,11-Dimethyl[12]	2635	2780	2882	2985	3310	3445
	4.64	4.63	4.78	4.82	3.69	3.80
3,11-Dimethyl[12]	2610	2768	2868	2983	3255	3430
	4.65	4.65	4.89	4.98	3.69	3.85
3,5-Dimethyl	2650	2770	2880	3000	3300	3460
	4.60	4.55	4.81	4.94	3.63	3.80

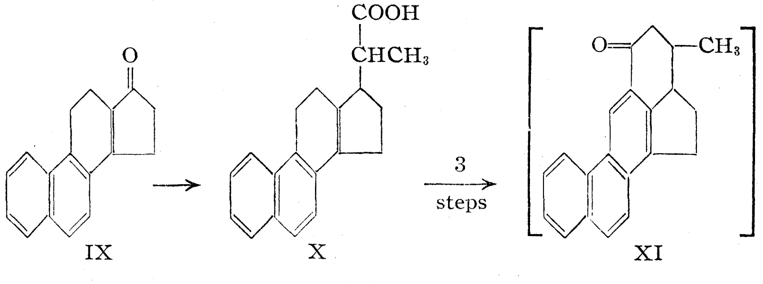
[a] L. F. Fieser and E. B. Hershberg, THIS JOURNAL, 60, 940 (1938).

The method which has been most widely used for the preparation of substituted cholanthrenes is the Elbs pyrolysis of the appropriately substituted naphthoylhydrindenes.[13] In spite of the fact that pyrolysis of the ketone (VIII) could yield two possible isomers, caused by ring closure to either the *o*-methyl group or the *o*-methylene group, several efforts were made to prepare this substance with the aim of pyrolyzing it to 3,5-dimethylcholanthrene (III). By the chlorination of xylene,[14] 4-chloro-1,3-dimethylbenzene (V) was prepared. A Friedel–Crafts condensation of this compound with β-chloropropionyl chloride should produce theoretically three different isomeric chlorodimethyl-β-chloropropiophenones. Two of these possible isomers, *i. e.*, where substitution has taken place at the 5 or 6 positions of the 4-chloro-1,3-dimethylbenzene (V), would give the same and desired hydrindene (VII) after cyclization and Clemmensen reduction of the chlorodimethylhydrindones. One of these isomers, tentatively assigned the structure written as VI, was obtained as a sharp melting crystalline product. It gave a high yield (94%) of chlorodimethylhydrindone on ring closure with concentrated sulfuric acid. The chlorine atom in VII proved so highly hindered that a negligible yield of VIII was obtained by condensation of the lithium derivative with α-naphthonitrile. Attempts to exchange the chlorine atom in 4-chloro-5,7-dimethylhydrindene (VII) for a cyano group and then condense the resulting 4-cyano-5,7-dimethylhydrindene with α-naphthylmagnesium bromide were likewise fruitless.

An alternative path was sought in the reaction of 3′-keto-3,4-dihydro-1,2-cyclopentenophenanthrene (IX) with ethyl α-bromopropionate. It was planned to extend the side chain of the resulting acid (X) by the Arndt–Eistert procedure and then by aromatization and cyclization to arrive at the ketone (XI). 3,5-Dimethylcholanthrene could be derived from this ketone (XI) by an obvious series of reactions. However, the reaction of the ketone (IX) with ethyl α-bromopropionate gave a product which could not be characterized either as the ester or as the free acid.

Several other synthetic schemes were also explored but with less success than those described. Samples of 3,5-dimethylcholanthrene have been submitted to Dr. M. J. Shear, National Cancer Institute, and Dr. A. M. Seligman, for biological testing.





---

(12) L. F. Fieser and D. M. Bowen, THIS JOURNAL, 62, 2103 (1940).

(13) L. F. Fieser and A. M. Seligman, *ibid.*, 58, 2482 (1936).

(14) O. Jacobsen, *Ber.*, 18, 1761 (1885).

Experimental[15]

9,11-Dimethyl-8,9,10,11-tetrahydrobenz[*a*]anthryl-8-acetic Acid (II).—On warming a mixture of 2.0 g. of 8-keto-9,11-dimethyl-8,9,10,11-tetrahydrobenz[*a*]-anthracene,[9] 3 ml. of ethyl α-bromoacetate, 0.2 g. of iodine, 4.0 g. of 20-mesh zinc (thoroughly cleaned and dried), 20 ml. of dry ether and 20 ml. of dry benzene, a brisk spontaneous reaction set in. When the reaction subsided (fifteen minutes), the solution was refluxed for three hours, and hydrolyzed with dilute hydrochloric acid. The aqueous layer was extracted three times with ether, then the combined organic solutions were dried and concentrated. The deep red residue was warmed gently *in vacuo* and dissolved in a mixture of 30 ml. of dry alcohol and 20 ml. of dry benzene containing some anhydrous sodium sulfate. Dry hydrogen chloride was passed into the solution (chilled in an ice-bath) for one-half hour. The chloro compound was recovered by diluting the solution with water and extracting with ether. The ether solution was washed with dilute potassium carbonate solution, dried, and the solvent was removed. Dehydrohalogenation was effected by distilling the dark residue under two microns pressure at a bath temperature of 140–190°. The distillation was carried out very slowly to minimize a persistent tendency to bump. The light amber viscous distillate weighed 2.43 g. (98%). On one larger run, the distillation was stopped when 14.0 g. (78%) of the unsaturated ester had distilled during a period of one-hundred forty-four hours at 10^{-4} mm. (bath at 115–120°). In this case the still residue was a dark stiff glass which weighed 5.46 g. (31%).

The unsaturated ester (2.43 g., 0.0071 mole) was hydrogenated in absolute ethanol, using 0.34 g. of platinum oxide. During one and three-quarters hours, it absorbed 136 ml. of hydrogen at 27° (78% of the theoretical). This same hydrogen uptake was observed in a number of runs which varied in size. The saturated ester was obtained as a viscous yellow liquid. It was saponified in a nitrogen atmosphere with alcoholic potassium hydroxide. The alkaline solution was diluted with water, extracted with ether and acidified. The acid (II) precipitated as light yellow flakes and crystals which weighed 2.04 g. (87%) after filtering and air-drying. In other runs, yields as high as 95% were observed, based on the dimethyl ketone (I). A portion of the acid was crystallized once from ethanol, then from methanol, and was obtained as colorless needles which melted at 192.5–194°.

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 83.0; H, 6.96. Found: C, 83.3; H, 6.30.

1-Keto-3,5-dimethylcholanthrene.—The acid (II), 11.36 g. (including 3.06 g. of non-crystalline material), was cyclized by dissolving it in about 150 g. of anhydrous liquid hydrogen fluoride contained in a copper beaker surrounded by an ice-bath. After evaporation of the hydrogen fluoride, the residue was washed with water and with a solution of potassium carbonate, then triturated with acetone. The resulting solid was suspended in boiling benzene which was cooled slightly and diluted with ether. The solid product (yellow-brown crystals) was separated by filtration and crystallized twice from chloroform and twice from benzene. It was very difficultly soluble in both solvents, as well as acetone. The ketone forms brilliant yellow needles melting at 267–270°, and it gives a precipitate when heated with alcoholic 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{22}H_{16}O$: C, 89.2; H, 5.40. Found: C, 89.6; H, 5.57.

The **oxime** crystallized from chloroform as fluffy yellow needles which darkened at 245° and decomposed without melting at 254–258°.

Anal. Calcd. for $C_{22}H_{17}ON$: N, 4.50. Found: N, 4.42.

A total of 4.7 g. of this solid ketone was obtained. The acetone-soluble fraction composed 8.75 g. of a stiff red-brown oil. This was considered to be the tetrahydro ketone.

The solid ketone (3.5 g.), and the oily ketone (8.75 g.) were dissolved separately in 34-ml. portions of glacial acetic acid. To each of these solutions was added 50 ml. of toluene, 34 ml. of water, 200 ml. of concentrated hydrochloric acid, and 65 g. of amalgamated mossy zinc. The solutions were refluxed for forty-eight hours; 150 ml. of concentrated hydrochloric acid was added in 50-ml. portions at twelve-hour intervals. From each of these experiments, when worked up, was obtained a deep red gum. During the work-up, 1.3 g. of acidic material was recovered, presumably uncyclized (II). The products were combined, giving 10.1 g. of hydrocarbon.

3,5-Dimethylcholanthrene (III). A.—A 2-g. sample of the above product was dissolved in 50 ml. of *p*-cymene (terpene-free), 0.15 g. of 5% palladium–charcoal added and the solution heated to brisk boiling in a stream of carbon dioxide. The gases were collected in a nitrometer. In all, 202 ml. of inert gas (uncorrected for blank) were obtained during several days. The product recovered from this solution was an amber viscous substance (1.46 g.) which could not be made to crystallize. It was distilled under 4 microns pressure (bath at 140–170°). The 0.90 g. of light orange distillate (a viscous liquid) was crystallized from ethanol–benzene, giving 0.30 g. of orange-yellow needles, m. p. 170–173°. 3,5-Dimethylcholanthrene, after three crystallizations from ethanol–acetone, formed pale orange-yellow needles melting at 183–184°.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.6; H, 6.45. Found: C, 93.4; H, 6.49.

B. Another sample of the Clemmensen product, 10.1 g., was heated with 1.50 g. of 5% palladium–charcoal at 300–310° for forty minutes. A brisk evolution of gas occurred at 285–310°. The cooled melt was repeatedly extracted with benzene; and the benzene solution, after filtering, was concentrated. The solution was diluted with an equal volume of ethanol, decolorized, and filtered. The filtrate gave 2.2 g. of yellow-brown plates, m. p. 175–179°. The mother liquors were evaporated to dryness and the residue triturated with boiling ethanol. An additional 2.7 g. of crystalline hydrocarbon was thus obtained. The ethanol solution deposited 0.5 g. of hydrocarbon, making a total yield of 5.5 g. (51%). The crude hydrocarbon was decolorized in acetone solution, then a benzene solution of it passed through alumina. The material recovered from the eluate was crystallized from acetone. A total of 3.28 g. of shining yellow-brown plates was obtained, which melted at 179–181°. A mixture of this material with the needle form of the hydrocarbon showed no depression of the melting point; it crystallized from ethanol as needles.

3,5-Dimethylcholanthrene forms a **picrate**, m. p. 179–180°, which dissociates when recrystallized from ethanol.

Anal. Calcd. for $C_{22}H_{18}\cdot C_6H_3N_3O_7$: N, 8.22. Found: N, 8.22.

The **trinitrobenzene derivative** forms massive dull red needles from ethanol, which melt at 189–190°.

Anal. Calcd. for $C_{22}H_{18}\cdot C_6H_3N_3O_6$: N, 8.48. Found: N, 8.24.

The **trinitrofluorenone derivative** crystallizes as blue microneedles, melting at 252–255°.

A Beckmann spectrophotometer was used for observation of the ultraviolet spectrum. The hydrocarbon, weighed on a microbalance, was dissolved in absolute ethanol, and the solution diluted accurately to a concentration of 0.0025 mg./ml.

β-(α-Naphthoyl)-propionic Acid.—The intermediate used for the preparation of compound (IX) was 1-keto-1,2,3,4-tetrahydrophenanthrene. Several methods were investigated for the preparation of this intermediate because it is a laborious task. One of the possible starting materials for its synthesis is β-(α-naphthoyl)-propionic acid. The following new method for the preparation of this starting material was explored. A benzene solution of di-α-naphthylcadmium (prepared by the general method

---

[15] All melting points were taken on a Fischer–Johns apparatus. Microanalyses are by Patricia Craig and Nelda Mold, Northwestern University.

of Cason and Prout[16] from 20.7 g. of α-bromonaphthalene and 9.7 g. of anhydrous cadmium chloride) reacted with 16.5 g. of carbomethoxypropionyl chloride. The crude ester isolated from this reaction was a pale yellow oil boiling at 184–188° (1 mm.). It was saponified with alcoholic potassium hydroxide, giving 10.2 g. (45%) of the free acid which after one crystallization from dilute ethanol melted at 133–134° (lit.[17] 132–133°).

This acid was also prepared by the customary[17] acylation of naphthalene with succinic anhydride, using tetrachloroethane as solvent in place of nitrobenzene.

Reaction between 3'-Keto-3,4-dihydro-1,2-cyclopentenophenanthrene (IX)[18] and Ethyl α-Bromopropionate.—A mixture of 2.20 g. of the ketone (X) (m. p. 214–216°), 2.09 g. of ethyl α-bromopropionate, 5 g. of thoroughly cleaned and dried 20-mesh zinc, 0.10 g. of iodine, 70 ml. of benzene, and 30 ml. of toluene was refluxed for four and one-half hours. The iodine color faded immediately, and the pale yellow solution became orange as the reaction progressed. Two additions of 2.5 g. of zinc were made at forty-five minute intervals, and 1.90 g. of bromoester was added after one and one-half hours. The neutral material isolated from this reaction was distilled in high vacuum; and the distillate, after numerous fruitless attempts at crystallization, was saponified with alcoholic potassium hydroxide. The acidic material so obtained was 2.52 g. (93%) of a very viscous liquid, which could not be made to crystallize. Only a small fraction of it was volatile in a high vacuum. When this reaction was carried out in ether-benzene solution, the ketone (IX) was recovered almost quantitatively.

Chloro-*m*-dimethyl-β-chloropropiophenone (VI).—Aluminum chloride, 72 g., was added in portions to a solution of 36 g. of β-chloropropionyl chloride and 40 g. of 4-chloro-1,3-dimethylbenzene[14] (b. p. 187–194° (760 mm.)) in 145 ml. of carbon disulfide. The addition required two to three hours. Stirring was continued overnight, and the reaction then heated briefly to 45°. The mixture was hydrolyzed, and the solvent layer after drying was distilled (keeping the temperature below 60°). The residue crystallized on chilling; it weighed 67.5 g. Trituration of this solid with methanol gave 20.7 g. of slightly yellow solid, m. p. 84–87°, suitable for cyclization. Seven crystallizations of this solid from petroleum ether produced the β-chloroketone (VI) with a melting point of 93–93.5°.

Anal. Calcd. for $C_{11}H_{12}OCl_2$: C, 57.1; H, 5.24. Found: C, 57.2; H, 5.32.

***x*-Chloro-*m*-dimethylhydrindone.**—A solution of 19 g. of the crude crystalline β-chloroketone (VI) in 50 ml. of benzene was slowly run into 150 ml. of concentrated sulfuric acid at 105–120°, with rapid stirring. The mixture was stirred for twenty minutes, then poured onto cracked ice. The precipitated solid, 15 g. (93.5%), when recrystallized once from methanol melted at 110–111°.

The non-crystalline substance recovered from the methanol washings above was cyclized separately. An additional 8 g. of hydrindone was so obtained.

Anal. Calcd. for $C_{11}H_{11}OCl$: C, 67.8; H, 5.70. Found: C, 67.8; H, 5.77.

4-Chloro-5,7-dimethylhydrindene (VII).—The chlorohydrindone, 10 g., was reduced by the Martin modification of the Clemmensen procedure.[10] The hydrindene was isolated as a colorless liquid, 8.67 g. (94%), which boiled at 126–129° (12 mm.); d^{26} 1.116; $n^{19}\text{D}$ 1.5549.

Anal. Calcd. for $C_{11}H_{13}Cl$: C, 73.1; H, 7.25. Found: C, 73.0; H, 7.15.

Attempts to Condense the Hydrindene (VII) with α-Naphthonitrile.—A mixture of 3.77 g. of the hydrindene (VII), 30 ml. of absolute ether and 0.32 g. of lithium metal cut into tiny pieces was refluxed and stirred in a nitrogen atmosphere for twenty-four hours. Although some of the lithium remained unreacted, 3.19 g. of α-naphthonitrile dissolved in 40 ml. of dry benzene was added and reflux with stirring continued for three hours. The material obtained from hydrolysis of the reaction mixture was refluxed with alcoholic hydrochloric acid, then distilled under reduced pressure. A large amount of the hydrindene (VII) was recovered and a very small amount of high boiling material. When di-*n*-butyl ether was used as the solvent for this reaction, 2.0 g. of the hydrindene required nineteen hours to react with 0.19 g. of lithium metal. However, treatment of the solution with 1.69 g. of the nitrile resulted in almost quantitative recovery of both starting materials.

Summary

1. 3,5-Dimethylcholanthrene has been prepared from 8-keto-9,11-dimethyl-8,9,10,11-tetrahydrobenz[a]anthracene and characterized by means of its ultraviolet spectrum. This dimethylcholanthrene has a second methyl group in the same position that would be occupied by the steroid side chain.

2. Attempts to prepare 3-naphthoyl-5,7-dimethylhydrindene, with the intention of pyrolyzing this ketone to 3,5-dimethylcholanthrene, were unsuccessful. Apparently the two *ortho* groups offer too much hindrance for the preparation of the ketone.

3. The Reformatsky reaction of 3'-keto-3,4-dihydro-1,2-cyclopentenophenanthrene with ethyl α-bromopropionate gave a product which could not be characterized.

EVANSTON, ILLINOIS

RECEIVED AUGUST 15, 1947

---

[16] J. Cason and F. S. Prout, THIS JOURNAL, **66**, 46 (1944).

[17] L. F. Fieser and M. A. Peters, *ibid.*, **54**, 4347 (1932).

[18] Prepared by the method of W. S. Johnson and J. W. Petersen, *ibid.*, **67**, 1366 (1945).

[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

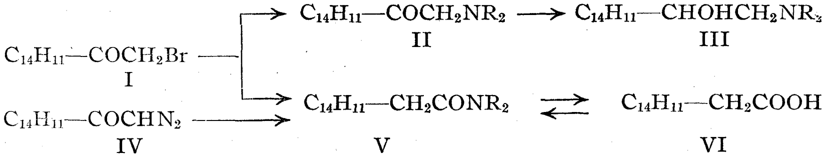
Studies in the Anthracene Series. V. A Novel Rearrangement in the Reaction of Halomethyl Ketones with Secondary Amines

BY EVERETTE L. MAY AND ERICH MOSETTIG

This investigation was undertaken with the purpose of synthesizing, for biological testing, alkamines in which the chain —$CHOHCH_2NR_2$ is attached to the *meso* position of 9,10-dihydroanthracene.

When 9-ω-bromoacetyl-9,10-dihydroanthracene (I) was allowed to react with secondary aliphatic amines, the expected amino ketones (II) were formed in yields of 30–40%. In addition, the isomeric 9-(9,10-dihydroanthryl)-acetamides (V) were obtained in yields of 40–50%.[1] It appears that a rearrangement has taken place similar to that of diazomethyl ketones to the corresponding homo-acid amides in the presence of amine and catalyst.[2]

The amides of type V proved to be exceedingly resistant to hydrolysis, but prolonged acid treatment ultimately gave the acid VI from which V ($R = C_2H_5$) was resynthesized. It was also obtained from 9,10-dihydro-9-anthroic acid in the Arndt–Eistert procedure *via* the diazomethyl ketone IV. A few attempts to convert IV directly to an amino ketone of type II failed. The amino ketones II ($R = C_2H_5$, C_3H_7, C_5H_{11}) were readily hydrogenated (platinum oxide) to the corresponding amino alcohols (III).



$C_{14}H_{11}$ = 9-(9,10-dihydroanthracyl), R = C_2H_5, C_3H_7, C_5H_{11}

Fig. 1.

In the course of this work we developed two convenient methods for the preparation of 9,10-dihydro-9-anthroic acid.[3] In the first, 9-cyanoanthracene[4] was saponified to the acid amide, which was reduced with hydriodic acid and phosphorus to the corresponding dihydro amide. Hydrolysis of the latter gave the acid in a yield of 82%, based on nitrile (70% based on anthracene). Secondly, reduction of 9-anthroic acid with sodium amalgam gave the dihydro acid in a yield of 80%. Reduction of 9-anthroic acid with hydriodic acid and phosphorus led to the desired acid in a yield of only 20%.

The amino alcohols III (R—C_2H_5, C_5H_{11}) were ineffective in blood-inoculated *gallinaceum* malaria.[5]

Acknowledgment.—The microanalyses were carried out by the microanalytical Laboratory of this Institute under the direction of C. A. Kinser. We are indebted to H. George Latham, Jr., for technical assistance.

Experimental[6]

9-Anthramide.—A mixture of 18.8 g. of 9-cyanoanthracene,[4] 17 g. of potassium hydroxide, 10 cc. of water and 75 cc. of ethylene glycol monoethyl ether (Cellosolve) was refluxed for two and one-half hours and diluted with water to give 20.5 g. of amide, m. p. 212–215°. It crystallized from aqueous ethanol in pale yellow needles, m. p. 215–216°.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.4; H, 5.0. Found: C, 81.4; H, 5.3.

9,10-Dihydro-9-anthroic Acid.[3] (a) **From 9-Anthramide.**—A mixture of 20.5 g. of 9-anthramide, 5.6 g. of red phosphorus, 14 cc. of 57% hydriodic acid and 150 cc. of acetic acid was refluxed for seven hours, filtered hot, and diluted with twice its volume of water. The precipitate was washed with water and refluxed for two hours with 120 cc. of acetic acid and 60 cc. of concentrated hydrochloric acid. After dilution to 450 cc. with water and ice-cooling, the acid was collected and digested with an excess of dilute, boiling sodium carbonate. Filtration and acidification of the filtrate gave 17 g. (82%) of the dihydro acid of m. p. 199–202°.

(b) **By Sodium Amalgam Reduction of 9-Anthroic Acid.**—To a stirred mixture of 8.8 g. of 9-anthroic acid,[7] 2.4 g. of sodium carbonate and 100 cc. of water was added during forty-five minutes 200 g. of 2.5% sodium amalgam. The temperature was kept at 10°. After an additional ninety minutes the solution was decanted, treated with decolorizing carbon (Norit), filtered hot, and acidified; yield of acid 7.3 g., m. p. 201.5–203.5°.

N,N-Diethyl-9,10-dihydro-9-anthramide.—A mixture of 0.5 g. of 9,10-dihydro-9-anthroic acid and 1 cc. of thionyl chloride was refluxed for one hour and evaporated to dryness *in vacuo*. The residue, in dry ether, was treated slowly with 1 cc. of diethylamine. After filtration, the filtrate was evaporated to dryness to give a residue which crystallized from aqueous ethanol in long prisms of m. p. 99.5–100.5°; yield 0.5 g. (81%).

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.7; H, 7.6. Found: C, 81.5; H, 7.9.

9,10-Dihydro-9-anthroylguanidine (NIH 2932).[8]—To a stirred, ice-cooled mixture of 2 g. of guanidine hydrochloride, 2.1 g. of sodium hydroxide, 4 cc. of water and 4 cc. of acetone was added during thirty to forty minutes 4 g. of 9,10-dihydro-9-anthroyl chloride[3] in 16 cc. of acetone. After an additional one-half hour of stirring at

---

[1] Amide V ($R = C_2H_5$) was also obtained from 9-ω-chloroacetyl-9,10-dihydroanthracene. Piperidine, the only heterocyclic amine allowed to react with I, gave the homo-acid amide in a yield of only 15%.

[2] "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 38.

[3] See Paper IV of this series, May and Mosettig, THIS JOURNAL **70**, 688 (1948).

[4] Fieser and Hartwell, *ibid.*, **60**, 2555 (1938).

[5] Coatney and Cooper, unpublished results.

[6] All melting points given are uncorrected.

[7] For a convenient preparative method for 9-anthroic acid see the following paper of this series.

[8] This compound was found to be inactive in avian malaria. Compounds tested are designated by an NIH number.

room temperature, the mixture was diluted with water. The precipitate was recrystallized from ethanol to give 2.2 g. (50%) of rods, m. p. 200–201.5° (d.).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.4; H, 5.7. Found: C, 72.3; H, 5.6.

N,N-Diethyl-9,10-dihydro-9-anthrylacetamide (V, R = C_2H_5).—A mixture of 5.0 g. of I,[3] 5 cc. of diethylamine, and 40 cc. of dry ether was shaken for one-half hour (slight cooling is necessary at first), diluted with about 20 cc. of ligroin (b. p. 30–60°) and cooled in ice to give 4.4 g. of precipitate which, when digested with water, yielded 2.2 g. (45%) of amide, m. p. 133–135°. It crystallized from methanol in long prisms of m. p. 134–135°.

Anal. Calcd. for $C_{20}H_{23}NO$: C, 81.9; H, 7.9; N, 4.8. Found: C, 81.4; H, 7.8; N, 4.7.

9-(2-Diethylamino-1-oxoethyl)-9,10-dihydroanthracene (II, R = C_2H_5) **Picrate.**—The filtrate from the 4.4 g. of precipitate above was washed three times with water, dried, and acidified with hydrogen chloride gas to give 1.5 g. of hydrochloride, m. p. 198–202°, after recrystallization from absolute ethanol–ether. A small sample was treated with aqueous alcoholic picric acid. The resulting picrate crystallized from 95% ethanol in yellow prisms, m. p. 127–129°.

Anal. Calcd. for $C_{26}H_{26}N_4O_8$: C, 59.8; H, 5.0. Found: C, 60.2; H, 5.2.

9-(2-Diethylamino-1-hydroxyethyl)-9,10-dihydroanthracene (III, R = C_2H_5) **Hydrochloride** (NIH 2874).—A mixture of 1.5 g. of the hydrochloride of II (R = C_2H_5), 0.05 g. of platinum oxide and 10 cc. of methanol absorbed one mole of hydrogen in three-fourths of an hour. The filtered solution was concentrated to about 3 cc. and diluted with ether to give 1.3 g. of the amino alcohol hydrochloride; prisms from methanol–ether, m. p. 200–202°.

Anal. Calcd. for $C_{20}H_{26}ClNO$: C, 72.4; H, 7.9. Found: C, 72.1; H, 7.8.

Synthesis of V (R = C_2H_5) **by the Arndt–Eistert Reaction.**—A solution of 1.7 g. of 9,10-dihydro-9-anthroyl chloride in 25 cc. of dry ether was added dropwise to 25 cc. of an ice-cooled, stirred ether solution of diazomethane (from 2.5 g. of nitrosomethylurea). After stirring for fifteen minutes in ice and for two hours at room temperature, the mixture was concentrated and diluted with ligroin to give 1.2 g. of IV, m. p. 104–106.5° (frothing). This diazo ketone (0.4 g.) in 4 cc. of dioxane was treated at 50–60° with a mixture of 0.5 cc. of diethylamine, 0.7 cc. of 10% silver nitrate, and 0.5 cc. of water. After refluxing for fifteen minutes the solution was filtered, diluted with a little water and cooled to give 0.3 g. (66%) of V (R = C_2H_5) of m. p. 132–134°. Recrystallized from methanol, it melted at 134–135°; the m. p. was not depressed by amide prepared as described above.

Hydrolysis of V (R = C_2H_5) **to 9,10-Dihydro-9-anthrylacetic Acid (VI).**—A mixture of 1 g. of the amide, 8 cc. of concentrated hydrochloric acid, and 2 cc. of acetic acid was refluxed vigorously for one week. During this time 4 cc. of concentrated hydrochloric acid and 1 cc. of acetic acid were added. The mixture was diluted with water, cooled, filtered, and the precipitate digested with boiling, dilute sodium carbonate. Filtration gave 0.15 g. of starting material. Acidification of the filtrate gave 0.6 g. (90% based on used amide) of VI, m. p. 165–168°. It crystallized from methanol–water in oblong plates of m. p. 168–169.5°. It appears to be oxidized slowly in air.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.7; H, 5.9. Found: C, 80.5; H, 6.2.

The acid VI was converted to the oily acid chloride with thionyl chloride. This acid chloride, in ether, was treated with diethylamine to give V (R = C_2H_5) in a yield of 90%.

9-(ω-Chloroacetyl)-9,10-dihydroanthracene.—To 0.3 g. of IV in ether was added dropwise 15% alcoholic hydrogen chloride until gas evolution had ceased. Dilution of the mixture with ligroin (b. p. 30–60°) gave 0.3 g. of needles. The analytical sample, from methanol, melted at 113–114°.

Anal. Calcd. for $C_{16}H_{13}ClO$: C, 74.9; H, 5.1. Found: C, 75.2; H, 5.2.

When this chloro ketone, in ether, was allowed to react with diethylamine, V (R = C_2H_5) was obtained in a yield of 45%.

9-(2-Dipropylamino-1-hydroxyethyl)-9,10-dihydroanthracene Hydrochloride (III, R = C_3H_7).—A mixture of 2 g. of I, 1.4 g. of dipropylamine and 15 cc. of dry ether was shaken for one-half hour, cooled in ice and filtered. The filtrate was shaken with three portions of dilute hydrochloric acid, dried, and the ether evaporated to give 1.2 g. of oily amide (V, R = C_3H_7) which was hydrolyzed to VI as described above. The combined aqueous fractions were basified with aqueous ammonia and the resulting oil dried in ether. The ethereal solution was acidified with 15% alcoholic hydrogen chloride to give, after recrystallization from acetone–ether, 0.6 g. of hydrochloride. This in 15 cc. of methanol with 0.01 g. of platinum oxide absorbed one mole of hydrogen during one hour. The filtered solution was evaporated to dryness *in vacuo*. The residue crystallized from acetone–ether in a yield of 0.5 g., m. p. 160–167°. The analytical sample melted at 171–172.5° after drying in a vacuum desiccator.

Anal. Calcd. for $C_{22}H_{30}ClNO$: C, 73.4; H, 8.4. Found: C, 73.6; H, 8.7.

The picrate crystallized from ethanol in yellow hexagons, m. p. 182–184°.

Anal. Calcd. for $C_{28}H_{32}N_4O_8$: C, 60.9; H, 5.8. Found: C, 61.0; H, 5.9.

9-(2-Diamylamino-1-hydroxyethyl)-9,10-dihydroanthracene (III, R = C_5H_{11}) **Hydrochloride** (NIH 2885).—A mixture of 3 g. of I, 3.3 g. of diamylamine and 25 cc. of dry ether was shaken for one-half hour, cooled in ice and filtered. The filtrate was acidified to congo red with hydrogen chloride gas, diluted with ligroin (b. p. 30–60°) and filtered. The 2 g. of solid was recrystallized from acetone–ether to give 1.6 g. of a mixture of II (R = C_5H_{11}) and diamylamine hydrochloride. This in 15 cc. of methanol with 0.05 g. of platinum oxide absorbed 0.85 mole of hydrogen in three-fourths hour. The filtered solution was evaporated to dryness *in vacuo*. The residue was triturated with ether–ethyl acetate to give 0.3 g. of diamylamine hydrochloride. Slight dilution of the filtrate with ligroin gave 1.0 g. of III (R = C_5H_{11}) hydrochloride. It crystallized from acetone–ether in triangles, m. p. 113–115.5°.

Anal. Calcd. for $C_{26}H_{38}ClNO \cdot {}^1/_2CH_3OH$: C, 73.7; H, 9.3; CH_3OH, 3.7. Found: C, 73.8; H, 9.2; loss in wt. (97° at 1 mm.), 4.5.

After the loss-in-weight determination, the sample was analyzed for carbon and hydrogen.

Anal. Calcd. for $C_{26}H_{38}ClNO$: C, 75.0; H, 9.2. Found: C, 74.6; H, 9.0.

The picrate crystallized from ethanol in yellow crusts of m. p. 143–145°.

Anal. Calcd. for $C_{32}H_{40}N_4O_8$: C, 63.1; H, 6.6. Found: C, 63.1; H, 6.5.

The ether–ligroin filtrate from the 2 g. of II (R = C_5H_{11}) above was washed with water, dried and evaporated to dryness. The residual oily amide (V, R = C_5H_{11}), hydrolyzed as described above, gave VI in a yield of 37%.

9,10-Dihydro-9-anthrylacetpiperidide (V, NR_2 = piperidino).—A mixture of 1.0 g. of I and 15 cc. of dry ether was swirled while adding 1 cc. of piperidine. The mixture was shaken vigorously for fifteen minutes and extracted three times with water. The dried ether solution was acidified with dry hydrogen chloride. The resulting semisolid was recrystallized from methanol–ether to give 0.9 g. of a precipitate which was digested with water and filtered. The crystals (0.15 g., m. p. 109–110.5°) were recrystallized from methanol–water to give the amide in long prisms, m. p. 108–110°.

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.6; H, 7.6. Found: C, 82.4; H, 7.6.

This compound was also prepared from VI as described above for V ($R = C_2H_5$).

9-(2-Piperidino-1-oxoethyl)-9,10-dihydroanthracene Hydrochloride.—The aqueous filtrate from the 0.15 g. of amide above was basified with aqueous ammonia and the liberated base dried in ether. The ethereal solution was acidified with 1.7 cc. of 15% alcoholic hydrogen chloride. Enough acetone and absolute ethanol were added to dissolve the precipitated oil. The amino ketone salt crystallized in a yield of 0.5 g., m. p. 221–223°; flakes from methanol–ether, m. p. 222–224° (d.).

Anal. Calcd. for $C_{21}H_{24}ClNO$: C, 73.8; H, 7.1. Found: C, 74.0; H, 7.1.

Summary

In the reaction of 9-ω-bromoacetyl-9,10-dihydroanthracene with secondary aliphatic amines, the 9-(2-dialkylamino-1-oxoethyl)-9,10-dihydroanthracenes and the corresponding amides of 9-(9,10-dihydroanthryl)-acetic acid were obtained in nearly equal amounts.

Two convenient methods for the preparation of 9,10-dihydro-9-anthroic acid are described.

BETHESDA 14, MD. RECEIVED OCTOBER 23, 1947

[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

Studies in the Anthracene Series. VI. Derivatives of 1,2,3,4-Tetrahydroanthracene

BY H. GEORGE LATHAM, JR., EVERETTE L. MAY AND ERICH MOSETTIG

As a key substance for further synthetic work, 9-bromo-1,2,3,4-tetrahydroanthracene was needed in quantity. Bachmann and Cronyn[1] have shown that the bromination of tetrahydrophenanthrene gives exclusively and in good yield, the 9-bromo derivative. When tetrahydroanthracene was similarly treated,[2] 9-bromo-1,2,3,4-tetrahydroanthracene (VIII) was formed in a yield of *ca.* 30%. In addition, varying amounts of a dibromo-1,2,3,4-tetrahydroanthracene (IX) could be isolated.

The position of the bromine atom in VIII was established in the following way: VIII was converted, with cuprous cyanide, to the nitrile VI, which was also synthesized from 9-anthroic acid (I) *via* II and III as shown in Fig. 1. Furthermore, we hydrolyzed VI to amide V which, again, was obtained in the catalytic hydrogenation of IV. The dibromo derivative IX appears to be identical with the compound cursorily described by Schroeter[3] as the only bromination product of tetrahydroanthracene. Since it can also be prepared from VIII, one of its bromine atoms must be located in position 9.

The conversion of VI into ketone X constitutes additional evidence for the structure of the latter[4] and supports the formula assigned to the oily acetyltetrahydroanthracene, obtained together with the 6 isomer in the Friedel–Crafts reaction on tetrahydroanthracene.[5]

9-Anthroic acid was conveniently prepared in a yield of 60–70% by heating under reflux, anthracene and oxalyl chloride in nitrobenzene.[6] When 9-bromoanthracene was treated under the same conditions, carboxylation took place to the extent of only 12%. The acid is obviously identical with the 9-bromo-10-anthroic acid of Beyer and Fritsch,[7] since it can be readily oxidized to 9,10-anthraquinone.

Acknowledgment.—We are indebted to Edward A. Garlock, Jr., for much of the preliminary work on the bromination of tetrahydroanthracene and the hydrogenation of 9-anthroic acid.

Experimental[8,9]

9-Anthroic Acid (I).—A mixture of 50 g. of anthracene,[10] 30 cc. of oxalyl chloride, and 150 cc. of dry nitrobenzene in a one-liter flask was heated in a metal-bath. A gentle reflux was maintained by raising the temperature of the bath from 120 to 240° during five to six hours. After steam-distillation of the nitrobenzene, 100 cc. of 10 *N* sodium hydroxide and enough water to make the total volume 700 cc. were added, and the mixture was refluxed for one-half hour. Insoluble material (11 g. of anthracene after purification)[11] was collected. The filtrate was washed with ligroin (b. p. 30–60°), treated with decolorizing carbon (Norit), filtered hot, and the Norit washed with 2 *N* sodium carbonate. Acidification of the combined filtrate and washings gave 41.6 g. (67%) of I, m. p. 208–212°.

9-Bromo-10-anthroic Acid.[7]—This acid was prepared from VIII, as described for I (reaction time twenty-five hours), in a yield of 12%, m. p. 263–266° (dec.). The

---

[1] Bachmann and Cronyn, *J. Org. Chem.*, **8**, 456 (1943).

[2] The preliminary experiments of the bromination were carried out by E. A. Garlock, Jr.

[3] Schroeter, *Ber.*, **57**, 2014 (1924).

[4] See Paper III of this series, May and Mosettig, THIS JOURNAL, **70**, 686 (1948).

[5] Garlock and Mosettig, THIS JOURNAL, **67**, 2255 (1945).

[6] We were unable to duplicate the experiments of Liebermann and Zsuffa [*Ber.*, **44**, 208 (1911)] who obtained 9-anthroic acid in yields of 70–80% by heating anthracene and oxalyl chloride in a sealed tube at 160–170°. In our hands the experiment yielded only 15–20% of 9-anthroic acid. Furthermore, Nenitzescu, *et al.* [*Ann.*, **491**, 210 (1931)] prepared 9-benzoylanthracene in nearly quantitative yields by refluxing a solution of anthracene and benzoyl chloride in nitrobenzene. In repeated attempts to reproduce the results of these authors, anthracene was hardly attacked and was recovered nearly quantitatively.

[7] Beyer and Fritsch, *Ber.*, **74**, 494 (1941).

[8] All melting points given are uncorrected.

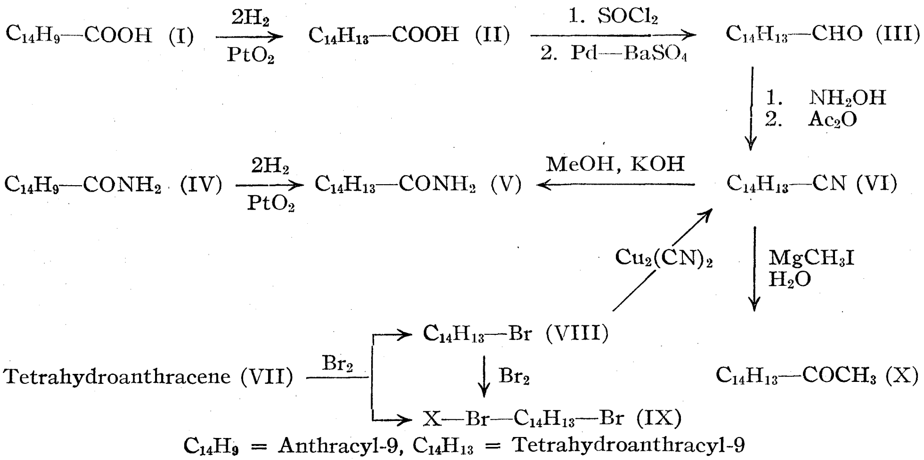
[9] The microanalyses were carried out by the microanalytical Laboratory of this Institute under the direction of C. A. Kinser.

[10] See Garlock and Mosettig[5] for the grade of anthracene used.

[11] During some preliminary work on this reaction, appreciable amounts of a yellow solid, m. p. 260–262°, were encountered.

Anal. Calcd. for $C_{29}H_{18}O$: C, 91.1; H, 4.7. Found: C, 90.8; H, 5.0.

This analysis indicates that the compound might be 9,9′-dianthryl ketone.



$C_{14}H_9$ = Anthracyl-9, $C_{14}H_{13}$ = Tetrahydroanthracyl-9

Fig. 1.

methyl ester melted at 112–114°. Oxidation of the acid with chromic acid gave 9,10-anthraquinone in a yield of 70%, m. p. 277–278°. The m. p. of the quinone was not depressed by authentic material.

1,2,3,4-Tetrahydro-9-anthroic Acid (II).[12]—A mixture of 10 g. of I (recrystallized from aqueous acetic acid), 0.3 g. of platinum oxide and 200 cc. of absolute ethanol absorbed 2000 cc. of hydrogen during two to three hours. The reaction was interrupted, catalyst was filtered, and the filtrate concentrated to one-fourth its volume. Ice-cooling gave 6.4 g. of II, m. p. 198–201°. This material was pure enough for use in the next reaction.

1,2,3,4-Tetrahydro-9-anthracenecarboxaldehyde (III).—A mixture of 5 g. of II and 10 cc. of thionyl chloride was refluxed for two hours, and excess reagent was distilled *in vacuo*. The resulting acid chloride was dissolved in 20 cc. of dry decalin, 0.6 g. of 5% palladium–barium sulfate was added, and a rapid stream of dry hydrogen bubbled through the mixture, heated to 175–180°. After one and one-half to two hours, hydrogen chloride evolution had almost ceased. The catalyst was filtered, and the solvent was distilled *in vacuo*. The residue was distilled at 0.05 mm. (bath temperature 175°) and the distillate crystallized from ether–ligroin (b. p. 30–60°) to give 2.0 g. (49%) of III, m. p. 53.5–55°. The analytical sample melted at 54.5–56°; light yellow prisms.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.7; H, 6.7. Found: C, 85.9; H, 6.8.

The oxime, prepared from hydroxylamine hydrochloride, sodium carbonate, and aqueous ethanol, crystallized from methanol in long prisms of m. p. 158.5–160°.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 80.0; H, 6.7. Found: C, 79.8; H, 6.7.

1,2,3,4-Tetrahydro-9-anthronitrile (VI).—The above oxime (0.5 g.) and 5 cc. of acetic anhydride were refluxed for fifteen minutes. Addition of water and cooling gave a solid which, after recrystallization from ethanol (Norit), weighed 0.3 g. (65%), m. p. 84.5–86°. The analytical sample melted at 85–86.5°, plates.

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.9; H, 6.3. Found: C, 87.0; H, 6.4.

9-Bromo-1,2,3,4-tetrahydroanthracene (VIII).—To a mixture of 100 g. of VII,[5] 10 g. of reduced iron powder, and 800 cc. of benzene was added (stirring at 3° to 6°) during three-fourths hour, 90 g. of bromine in 200 cc. of benzene. After stirring at 0 to 5° for four hours, the mixture was filtered. The filtrate was washed three times with 5 *N* sodium carbonate and dried over sodium sulfate. Evaporation of solvent and distillation of the residue at 3 mm. gave (1) 10–15 g. of mainly VII, b. p. 160–170°, (2) 85 g., b. p. 180–190° and (3) about 10 g., b. p. 190–201°. Fraction (2) was dissolved in about 60 cc. of ligroin (b. p. 85–100°) and the solution cooled in ice for fifteen minutes. The supernatant liquid was decanted from a mass of prisms which were washed with a little cold ligroin. The prisms were dissolved in 300 cc. of absolute ethanol to give, after cooling at room temperature for three to four hours, 27 g. of VIII, m. p. 59–61°. It crystallized from ethanol in prisms of m. p. 60.5–61.5°.

Anal. Calcd. for $C_{14}H_{13}Br$: C, 64.4; H, 5.0. Found: C, 64.7; H, 4.8.

The ligroin filtrate and washings above gave an additional 19 g. of VIII (total yield 32%) after tedious fractional crystallizations from ethanol and from ligroin.

9,x-Dibromo-1,2,3,4-tetrahydroanthracene (IX).—Fraction (3) was recrystallized three times from ligroin (b. p. 85–100°) to give 3.2 g. of IX, m. p. 165–166°[7]. In addition 5 g. of IX was obtained in the course of the isolation of the 19 g. of VIII; needles.

Anal. Calcd. for $C_{14}H_{12}Br_2$: C, 49.4; H, 3.6. Found: C, 49.4; H, 3.6.

Compound IX was also obtained in a yield of 20% by brominating VIII according to the above procedure. It melted at 164–166° and the m. p. was not depressed by the IX isolated as described above.

Conversion of VIII to VI.—A mixture of 5 g. of VIII and 2.5 g. of cuprous cyanide was heated for two to three hours at 245–255°. Distillation at 0.1 mm. (bath temperature 180–200°) followed by recrystallization of the distillate from 95% ethanol gave 3.0 g. (75%) of plates, m. p. 85–87.5°. Mixed with VI prepared from I *via* II and III, it melted at 85.5–87°.

1,2,3,4-Tetrahydro-9-anthramide (V). (a) By Hydrolysis of VI.—A mixture of 0.5 g. of VI, 5 g. of potassium hydroxide, 25 cc. of methanol and 1 cc. of water was refluxed for twenty hours and diluted with water to give 0.4 g. of V, m. p. 203–207°. It crystallized from methanol–water in prisms, m. p. 210–211.5°.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 80.0; H, 6.7. Found: C, 80.3; H, 6.7.

(b) **By Hydrogenation of 9-Anthramide.**—A mixture of 0.5 g. of 9-anthramide,[13] 0.05 g. of platinum oxide, and 10 cc. of methanol absorbed two moles of hydrogen in seventeen hours. The filtered solution was concentrated to about 5 cc. and diluted with a little water to give 0.4 g. of prisms, m. p. 209–211°. When mixed with the V prepared as described under (a), the melting point was unchanged.

9-Acetyl-1,2,3,4-tetrahydroanthracene (X).—Two grams of VI in 10 cc. of dry benzene was added dropwise to a

---

[12] Meerwein and Migge, *Ber.*, **62**, 1046 (1929).

[13] See Paper V of this series, May and Mosettig, This Journal, **70**, 1077 (1948).

stirred mixture of 12 cc. of 1 *M* methylmagnesium iodide in 25 cc. of dry benzene. The mixture was stirred and refluxed for 3.5 hours and poured into 75 cc. of saturated ammonium chloride. The benzene layer was extracted with two 50-cc. portions of *N* hydrochloric acid. To the combined extracts was added 10 cc. of concentrated hydrochloric acid and the solution refluxed for fifty hours. The resulting dark oil was dried in ether and evaporatively distilled at 150–170° (0.5 mm.). Recrystallization of the distillate from methanol gave 0.15 g. of prisms, m. p. 71–73°. The m. p. was not depressed by mixture with X previously prepared.

Summary

In the bromination of tetrahydroanthracene, 9-bromo-1,2,3,4-tetrahydroanthracene is formed in a yield of *ca.* 30%.

Its structure has been established by linking it with 9-anthroic acid.

A simple and efficient preparative method for 9-anthroic acid is described.

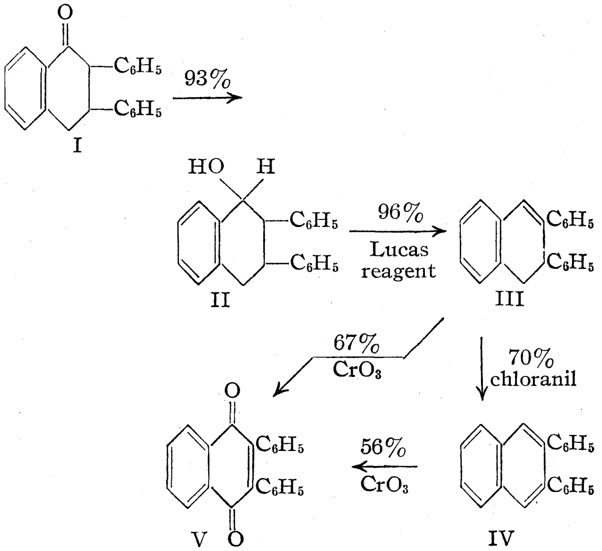
BETHESDA 14, MD. RECEIVED OCTOBER 23, 1947

[CONTRIBUTION FROM THE SANDERS LABORATORY OF CHEMISTRY, VASSAR COLLEGE]

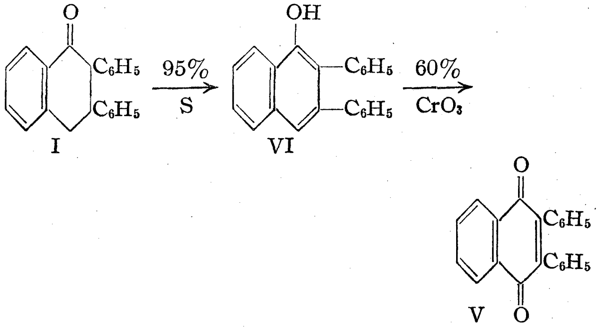
The Preparation of 2,3-Diphenyl-1,4-naphthoquinone and its Reaction with Phenylmagnesium Bromide and Phenyllithium

BY H. MARJORIE CRAWFORD

2,3-Diphenyl-1,4-naphthoquinone has been prepared by Crawford and Nelson[1] by the series of reactions



and by Bergmann and Szmuszkovic[2] as follows:



In preparing this quinone in larger quantities for the study reported here, variations in these procedures were carried out in attempts to improve the yield. Direct oxidation of 2,3-diphenyl-1,2-dihydronaphthalene (III) with chromium trioxide in glacial acetic acid gave 67% of the quinone (V). This makes the over-all yield of the quinone from the tetralone about 60% as compared to 35% when the dehydrogenation step is included. This is a more satisfactory method of preparing the quinone than that described by Bergmann[2] for, although three steps are involved instead of two, the yield is about the same and the products are much more easily purified.

Dehydrogenation of the tetralone (I) by sulfur gave the naphthol (VI) in 85–90% yields but there were red products formed which made the purification of the naphthol by recrystallization very difficult. In variations of the dehydrogenation reaction, selenium and chloranil gave poorer yields than sulfur. In the oxidation of the naphthol (VI) with chromium trioxide, the quinone (V) was obtained in 30–60% yields, accompanied by a high molecular weight white compound melting at 265–267°, and considerable quantities of yellowish oils.

As it has already been shown,[3,4,5] the reactions of phenylmagnesium bromide with methyl substituted naphthoquinones give complex mixtures of products. The solid compounds isolated from these mixtures resulted from both 1,2-additions to the carbonyl group and 1,4-additions to the conjugated systems, as well as reduction of the quinones to the hydroquinones and the accompanying formation of biphenyl. When phenyllithium reacted with these methyl substituted naphthoquinones the only products isolated were those resulting from the 1,2-addition of two molecules of the reagent to the carbonyl groups.

The behavior of 2,3-diphenyl-1,4-naphthoquinone has now been studied, hoping that the phenyl groups would be large enough to prevent the 1,4-

---

(1) Crawford and Nelson, THIS JOURNAL, **68**, 134 (1946).

(2) [illegible] *ibid.*, **68**, 1662 (1946).

(3) Crawford, *ibid.*, **57**, 2000 (1935).

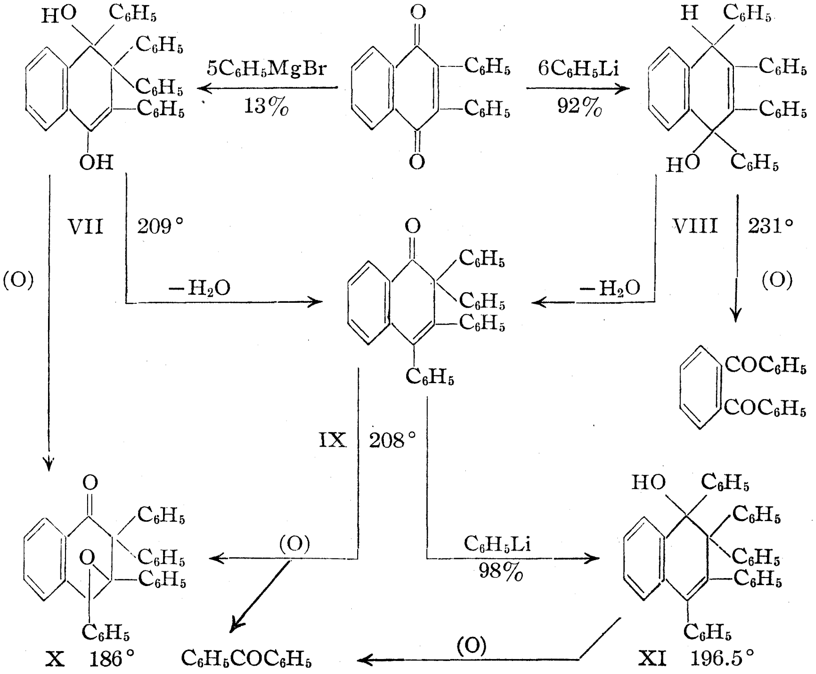
(4) Crawford, *ibid.*, **61**, 3310 (1939).

(5) Crawford, *ibid.*, **63**, 1070 (1941).

addition of the phenylmagnesium bromide to the conjugated system. This hope has not been realized, for the only addition product isolated was that resulting from the 1,2- and 1,4-addition of two molecules of phenylmagnesium bromide to one molecule of the quinone. Biphenyl and the hydroquinone were formed as in the other cases. Phenyllithium, on the other hand, gave excellent yields (92%) of the 1,2-1,2-diaddition product.

The two diols resulting from these reactions were dehydrated with great ease to give practically quantitative yields of a single rearrangement product.

The relationships of these compounds are summarized below.



The structure of VIII was established by oxidation to benzoic acid and *o*-dibenzoylbenzene (38%). It was impossible to obtain direct evidence for the structure of VII since attempts to oxidize it with potassium permanganate gave only unchanged starting material, and oxidation with chromium trioxide in glacial acetic acid gave the same product (X) which was formed by the oxidation of IX. Later it was shown that simply boiling VII in glacial acetic acid for one hour caused dehydration and rearrangement to give IX. In other cases of the addition of phenylmagnesium bromide to naphthoquinones[3,5,6] the principal product has always been the compound resulting from 1,2- and 1,4-additions of two molecules of phenylmagnesium bromide to one molecule of the quinone. Analytical data show that VII is a diaddition product, and it is different from VIII which is the 1,2-1,2-diaddition compound. The structure proposed for VII would represent the first product of the reaction but it may well exist in the keto form.

Compound IX is quite inert, having been recovered unchanged from boiling for one hour with potassium permanganate or potassium dichromate, from attempts to make a 2,4-dinitrophenylhydrazone, from treatment with perbenzoic acid, and from treatment with alkaline hydrogen peroxide. Oxidation of IX with chromium trioxide in glacial acetic acid gave benzoic acid, benzophenone (identified as the 2,4-dinitrophenylhydrazone) and compound X. This type of rearrangement accompanying dehydration has been encountered before[4] in compounds similar in structure to VII and VIII and the formation of benzophenone locates two of the phenyl groups on the same carbon atom. Compound IX reacted readily with phenyllithium to give a 98% yield of a product for which structure XI is proposed. Phenylmagnesium bromide also reacted readily and gave a mixture of products which have not been identified. Compound X corresponds to the addition of one atom of oxygen to IX, and the epoxide structure is suggested as the most probable one although it is inert toward every reagent tried with the exception of phenyllithium. It was recovered unchanged from attempts to make the 2,4-dinitrophenylhydrazone, from heating for forty hours with acetic acid and potassium iodide or for eight hours with dilute sulfuric acid. Its inertness to oxidation is indicated by its mode of formation.

Experimental

Preparation of 2,3-Diphenyl-1,4-naphthoquinone, V.—This quinone was prepared by the oxidation of various compounds by chromium trioxide in glacial acetic acid. The oxidation of 2,3-diphenylnaphthalene[1] (IV) gave 56% of the quinone. The oxidation of 2,3-diphenyl-1-naphthol[2] (VI) gave 30–60% of the quinone. The oxidation of 2,3-diphenyl-1,2-dihydronaphthalene (III) is described here for the first time.

Oxidation of 2,3-Diphenyl-1,2-dihydronaphthalene, III.—2,3-Diphenyl-1,2-dihydronaphthalene (16 g.) was refluxed for fifteen minutes with 32 g. of chromium trioxide, 25 ml. of water and 200 ml. of glacial acetic acid. After pouring onto ice and diluting with water, the solid was filtered off and crystallized from ethyl alcohol. The resulting 2,3-diphenyl-1,4-naphthoquinone (11.9 g., 67%) melted at 133–140°. Another crystallization from ethyl alcohol or glacial acetic acid raised the melting point to 138–140°.

Dehydrogenation of 2,3-Diphenyl-1-keto-1,2,3,4-tetrahydronaphthalene (I) by Selenium and by Chloranil.—Heating 4.5 g. of the tetralone (I) and 1.3 g. of selenium at 290° for twelve hours, dissolving the cooled mass in ether,

---

(6) Smith and Hoehn, This Journal, **61**, 2619 (1939).

boiling with Norite and filtering from Norite and selenium gave 0.9 g. (20%) of the naphthol (VI) and much black tar.

The tetralone (4.5 g., 0.015 mole) was refluxed for five hours with 4.5 g. (0.018 mole) of chloranil and 20 ml. of xylene. The mixture was cooled, diluted with petroleum ether and allowed to stand overnight, after which most of the tetrachlorohydroquinone could be removed by filtration. The last traces could be removed by extraction with 4% potassium hydroxide solution, as the 2,3-diphenyl-1-naphthol was not dissolved under these conditions. Evaporation of the solvent gave 1.03 g. of unchanged tetralone and black tar. This result is in marked contrast to the good yield (70%) of 2,3-diphenylnaphthalene (IV) obtained from 2,3-diphenyl-1,2-dihydronaphthalene (III) by means of chloranil.[1]

The Reaction between 2,3-Diphenyl-1,4-naphthoquinone and Phenylmagnesium Bromide.—As in other studies of this type[3,5,7] the quantities of reactants and the method of procedure were varied. In some cases the phenylmagnesium bromide (0.1 mole) was added to a solution of 6.2 g. (0.02 mole) of the quinone in ether. In other cases the quinone (0.02 mole) in ether was added to the phenylmagnesium bromide (0.1 mole) in ether. In still other cases the quinone (0.025 mole) was extracted from a soxhlet by a boiling solution of phenylmagnesium bromide (0.15 mole) in ether. After standing overnight, the reaction mixtures, usually containing a brown solid, were decomposed with ice and either dilute hydrochloric acid or ammonium chloride solution. The dried ether extracts of these mixtures were allowed to stand and various crops of solids were filtered off and recrystallized.

These variations made little difference in the amounts of the products obtained from this quinone. The only solid addition product which could be isolated was the white compound VII which was obtained in about 13% yield. The quinone or the hydroquinone could always be isolated and steam distillation of the residue gave biphenyl. The final residue was a dark oil. Even when the hydroquinone was detected among the products, recrystallization in the presence of air caused its oxidation to the quinone and there was always the problem of separating the quinone from VII. This could be best accomplished by using a mixture of benzene and petroleum ether as the solvent for recrystallization.

1,2,2,3-Tetraphenyl-1,4-dihydroxy-1,2-dihydronaphthalene, VII, m. p. 208–210°.—This white solid was the only addition product isolated (13%) from the reaction between 2,3-diphenyl-1,4-naphthoquinone and phenylmagnesium bromide. It is soluble in the usual solvents such as ether, ethyl alcohol, ethyl acetate and benzene, but is only slightly soluble in petroleum ether. The best solvent for separating it from quinone (after first filtering the mixture of solids from the oily reaction mixture) was a mixture of benzene and petroleum ether. VII was recovered unchanged after three hours of refluxing with alkaline potassium permanganate. When 1 g. of VII was refluxed for six hours with 3 g. of potassium dichromate, 25 ml. of glacial acetic acid, 1 ml. of water and 10 drops of concd. sulfuric acid, the only product isolated was benzoic acid. When 1 g. of VII was boiled for five minutes with 1 g. of chromium trioxide and 10 ml. of glacial acetic acid the only product obtained was X, which was the same compound obtained by the oxidation of IX. When 0.75 g. of VII was refluxed for one hour with 0.4 g. of iodine in 10 ml. of glacial acetic acid it lost a molecule of water and was converted quantitatively into IX. After the oxidation of VII was found to give the same product as the oxidation of IX, experiments were carried out to show that the iodine was not necessary in the dehydration. Boiling VII with acetic anhydride or with glacial acetic acid for one hour converted it into IX. Since this was the case, no conclusion could be drawn as to the structure of VII from the oxidation experiments.

Anal. Calcd. for $C_{34}H_{26}O_2$ (466.6): C, 87.5; H, 5.6. Found: C, 87.6, 87.1; H, 5.8, 5.8; mol. wt., 456.

1,2,3,4-Tetraphenyl-1,4-dihydroxy-1,4-dihydronaphthalene, VIII, m. p. 231–233°.—This white solid was the only product of the reaction between 2,3-diphenyl-1,4-naphthoquinone and phenyllithium. The phenyllithium (0.15 mole) in ether was refluxed and the quinone (0.025 mole) was extracted from a soxhlet. The extraction required about one hour. The mixture was then decomposed with ice and dilute hydrochloric acid. The clear ether and water layers were separated from the white solid and the water layer was discarded. Evaporation of the ether layer gave more solid identical with that separated earlier. Crystallization from ethyl alcohol and ethyl acetate gave a pure compound melting 231–233° (yield 92%). Refluxing VIII (3 g.) for one hour in 50 ml. of glacial acetic acid with 0.5 g. of iodine gave IX (yield, 90%). Refluxing VIII (0.5 g.) with 10 ml. of acetic anhydride gave a quantitative yield of IX. Oxidation of VIII (2 g.) by refluxing for five minutes with 2 g. of chromium trioxide and 10 ml. of glacial acetic acid gave *o*-dibenzoylbenzene (38%) and benzoic acid, identified by comparison with known samples. Oxidation of VIII (2 g.) by boiling for four hours with 6 g. of potassium dichromate in 50 ml. of glacial acetic acid gave 1.75 g. of solid, which was a mixture of IX and a small amount of an unidentified white solid, m. p. 168–170°, which may have been impure X.

Anal. Calcd. for $C_{34}H_{26}O_2$ (466.6): C, 87.5; H, 5.6. Found: C, 85.9, 86.3; H, 6.2, 6.0; mol. wt., 468.

2,2,3,4-Tetraphenyl-1-keto-1,2-dihydronaphthalene, IX, m. p. 208–210°.—This pale yellow compound was formed very readily and in excellent yields (90–100%) from either VII or VIII by the loss of a molecule of water, accompanied by the migration of a phenyl group. The dehydration could be brought about by boiling either of the diaddition products with acetic anhydride, with glacial acetic acid and a trace of iodine, or with glacial acetic acid alone if a longer time were allowed. The solution was diluted with water, the solid filtered off and recrystallized from ethyl alcohol and ethyl acetate. IX was quite soluble in the latter and only slightly soluble in the former. The only reagents which had any effect on IX were phenylmagnesium bromide, phenyllithium and chromium trioxide. Treatment of IX (2.24 g.) with a large excess of phenyllithium caused the ether to boil vigorously. After refluxing for five minutes, the mixture was poured onto ice and made acid with dilute hydrochloric acid. The ether layer gave 2.58 g. (98%) of XI. IX does not react in such a clean cut fashion with phenylmagnesium bromide but gave a mixture of yellow products. IX does not react with cold chromium trioxide but is oxidized on heating. Two grams of IX, 2 g. of chromium trioxide and 10 ml. of glacial acetic acid were refluxed for five minutes, then poured onto ice. After the ether extract was treated with potassium hydroxide solution, benzoic acid was isolated from the alkaline layer and benzophenone and X (46%) were recovered from the ether layer. The benzophenone was identified as the 2,4-dinitrophenylhydrazone. IX was recovered unchanged after boiling for two hours with potassium dichromate in glacial acetic acid, after boiling with neutral or acid potassium permanganate, after treatment with perbenzoic acid or alkaline hydrogen peroxide, and after attempts to make a 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_{34}H_{24}O$ (448.5): C, 91.0; H, 5.4. Found: C, 91.1, 91.0; H, 5.7, 5.7; mol. wt., 453.

2,2,3,4-Tetraphenyl-1-keto-3,4-epoxy-1,2,3,4-tetrahydronaphthalene, X, m. p. 186–187°.—This white compound was formed by the chromium trioxide oxidation of IX or VII (probably following its rearrangement to IX). It is very inert, having been recovered unchanged after attempts to make a 2,4-dinitrophenylhydrazone, after eighteen hours heating on the steam-bath with 10 ml. of glacial acetic acid, 8 ml. of water and 2 ml. of concd. sulfuric acid, and after refluxing for six days with sodium hydroxide in alcohol, or forty hours with potassium iodide and acetic acid. It turns yellow when exposed to light. With phenyllithium it reacts to give a white compound, melting about 260°, which was not identified.

---

(7) Smith and Crawford, THIS JOURNAL, **50**, 869 (1928).

Anal. Calcd. for $C_{34}H_{24}O_2$ (464.5): C, 87.9; H, 5.2. Found: C, 87.4, 87.4; H, 5.4, 5.2; mol. wt., 467.

1,2,2,3,4-Pentaphenyl-1-hydroxy-1,2-dihydronaphthalene, XI, m. p. 196.5–197.5°.—This white compound was formed in 98% yield from the reaction of phenyllithium on IX. Oxidation of 1.5 g. of XI by boiling for five minutes with 1.5 g. of chromium trioxide in 10 ml. of glacial acetic acid gave only a pinkish oil from which a small amount of benzophenone could be isolated as the 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_{40}H_{30}O$ (526.6): C, 91.2; H, 5.7. Found: C, 90.4, 89.9; H, 5.9, 6.2; mol. wt., 520.

Summary

The reactions of 2,3-diphenyl-1,4-naphthoquinone with phenylmagnesium bromide and phenyllithium have been studied.

Structures have been proposed for the main products of these reactions and for the compound which results from the dehydration of both of them.

Five new compounds are described.

An improved method is described for the preparation of 2,3-diphenyl-1,4-naphthoquinone in three steps from 2,3-diphenyl-1-keto-1,2,3,4-tetrahydronaphthalene in 60% over-all yield.

POUGHKEEPSIE, NEW YORK RECEIVED AUGUST 4, 1947

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Amines Related to 2,5-Dimethoxyphenethylamine. IV. 2,5-Diethoxy, 2-Hydroxy-5-methoxy and 2-Hydroxy-5-ethoxyphenylalkanolamines[1]

BY WALTER S. IDE AND RICHARD BALTZLY

In continuation of our studies on this interesting family of pressors, we report the preparation of the primary and secondary β-hydroxy-β-(2,5-diethoxyphenyl)-ethylamines and isopropylamines, and their analogs having hydroxyl groups in the 2-position with methoxyl or ethoxyl groups in the 5-position.

The 2,5-diethoxy family (I–IV) was prepared by a line of synthesis shown in the upper part of Chart I. In the main, this approach resembles that used in Paper II[2] of this series to prepare the corresponding dimethoxy compounds. The 2,5-diethoxyphenylalkanolamines and their precursors tend to be more soluble and less readily crystallized than their methoxy analogs and were usually isolated in lower yield.

The preparations of the 2-hydroxy-5-alkoxyphenylalkanolamines (V–XII) largely followed the scheme used in Paper III of this series[3] for the 2-hydroxy-5-methylphenylalkanolamines. These syntheses are outlined in the lower part of Chart I. A few comments are in order.

In the first preparation of the aminoalcohol VII, the isonitrosoketone VIIb was reduced directly with platinum in ethanolic hydrogen chloride solution. Compound VII was obtained without difficulty although it later became apparent that other substances were present in the mother liquors. In a later preparation, palladized charcoal was used for the first stage of the reduction and the 2-benzyloxyaminoketone hydrochloride, VIIa, was isolated as the major product. It is rather surprising that the 2-benzyl group was retained in the presence of this catalyst; the only rational explanation is that the sample of palladized charcoal had been partially inactivated. Successive hydrogenations of VIIa with fresh palladized charcoal and with platinum yielded VII.

In the preparation of Compound IX, the usually reliable hexamethylenetetramine method broke down, only traces of chloroform-insoluble material being obtained from the reaction of hexamethylene tetramine and IXc.[4] The bromoketone was then treated with benzhydrylamine[5] but apparently considerable tertiary as well as secondary amine was formed and the desired product was not readily separated. The synthesis of IX was finally accomplished by treating IXc with dibenzylamine. The reaction was slow and far from quantitative (in contrast to similar reactions with benzylmethylamine) but the tertiary amine IXb was isolated easily. On hydrogenation with palladized charcoal, IXb absorbed two mols of hydrogen rapidly at room temperature and a third more slowly at 65°.[6]

At the time this work was started, attempts were made to prepare amino alcohols having the

---

[1] This work is part of a joint research being carried out in collaboration with a pharmacological group in the same laboratories.

[2] Baltzly and Buck, THIS JOURNAL, **62**, 164 (1940).

[3] Ardis, Baltzly and Schoen, *ibid.*, **68**, 591 (1946).

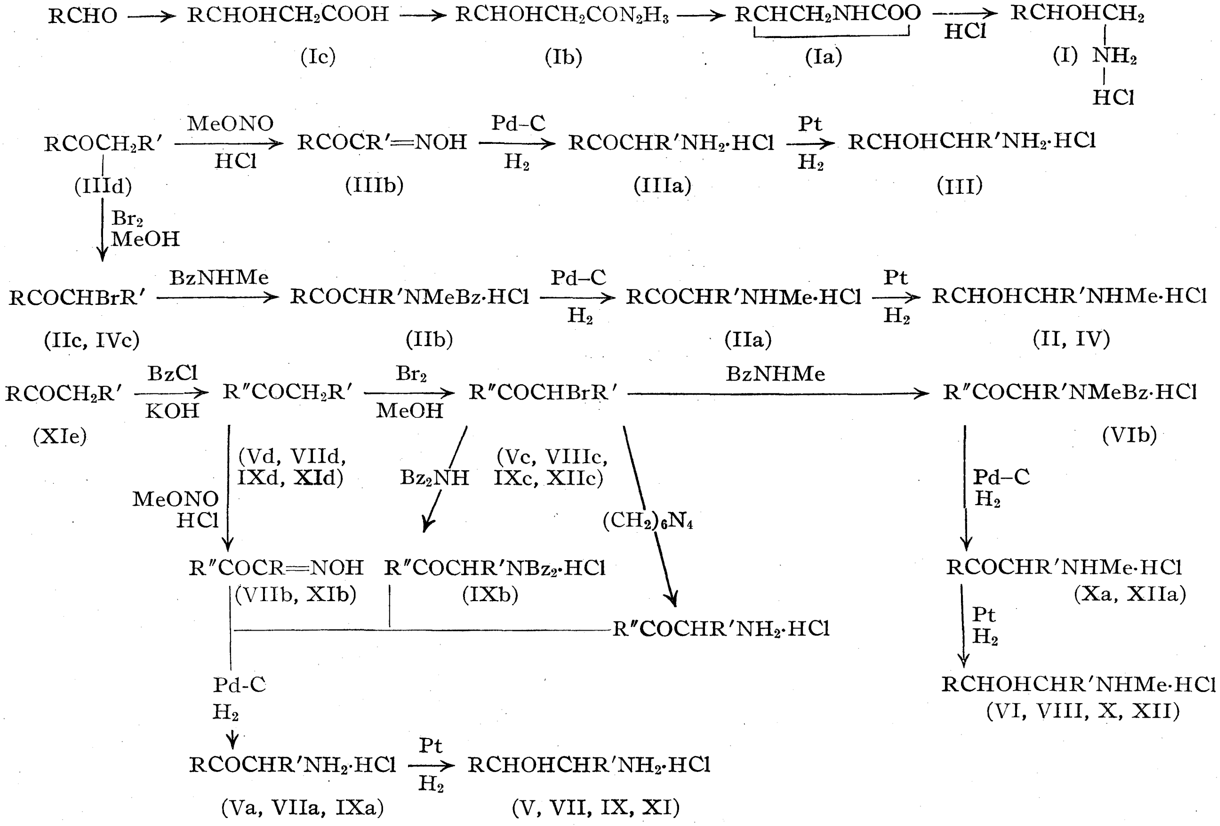
[4] Although this bromoketone is not especially active the failure of the preparation cannot be attributed to sluggishness since IXc reacts with reasonable speed with benzylmethylamine, benzhydrylamine and dibenzylamine. We are inclined to suspect that the initial reaction product was relatively soluble in chloroform and was accordingly exposed to the further reactions with bromoketone that should be possible from the conventional formula for hexamethylenetetramine but which are usually avoided by the precipitation of the first reaction-product. In the work reported in Paper III of this series it was found that if the temperature in a hexamethylenetetramine reaction was above 30–40°, the usual reaction product sometimes failed to precipitate. The original paper on this method as applied to phenacyl halides (Mannich and Hahn, *Ber.*, **44**, 1542 (1911) states that the reactions were carried out at room temperature but gives no indication that this condition is essential.

[5] *Cf.* Suter and Ruddy, THIS JOURNAL, **66**, 747 (1944).

[6] *Cf.* Simonoff and Hartung, *J. Amer. Pharmaceutical Assoc.*, **35**, 306 (1946). Obviously, this method involves a cleavage of benzylphenacylamine. It has gradually become apparent that although the benzyl group is usually removed preferentially from benzylphenacyl, benzyl β-hydroxyphenethyl and benzyl phenethylamines, these other groups have considerable labilizing effect, cleavage being achieved under conditions comparable with those required for cleavage of dibenzylamines.

CHART I

The numbers are those of new substances isolated in pure form: Bz = benzyl; R = 2,5-diethoxyphenyl for I, II, III, IV; R = 2-hydroxy-5-methoxyphenyl for V, VI, VII, VIII; R = 2-hydroxy-5-ethoxyphenyl for IX, X, XI, XII; R = 2-benzyloxy-5-methoxyphenyl for VIIa; R″ = benzyl ether of corresponding hydroxyphenyl compound; R′ = H for II, V, VI, IX, X; R′ = Me for III, IV, VII, VIII XI, XII.



2-hydroxyl group protected in form of an ester. The acetylation of 2-hydroxy-5-methoxypropiophenone yielded 2-acetoxy-5-methoxypropiophenone (XIIId) which was brominated in methanol (with de-esterification) to 2-hydroxy-5-methoxy-α-bromopropiophenone (XIIIc). Carbethoxylation of 2-hydroxy-5-methoxypropiophenone followed by nitrosation gave 2-ethylcarbonato-5-methoxy-α-isonitrosopropiophenone (XIVb). On hydrogenation it was found that the carbethoxyl was lost and this line of synthesis was abandoned.[3]

Since Compounds III, IV, VII, VIII, XI and XII were prepared by hydrogenation of ketones in weakly acidic solution, it is reasonable to assume that they possess the ephedrine rather than the pseudo ephedrine configuration.

Physiological Properties.—An extended report on the pharmacology of these substances will be published elsewhere. Briefly, the 2-hydroxy-5-methoxyphenylalkanolamines resemble rather closely their 2,5-dimethoxy analogs which are powerful, long-acting pressors, but are somewhat less potent and less toxic. Potency falls off in the other two classes, the 2,5-diethoxyphenylalkanolamines being the least active, and also the most toxic. Of the Compounds I–IV, only Compound III is at all comparable to the 2,5-dimethoxy series in length of action.

Experimental

Physical and analytical data on the substances isolated in pure form are presented in Table I. All melting points are corrected.

2-Hydroxy-5-alkoxyketones and 2,5-Diethoxyketones.—These compounds were prepared by Friedel–Crafts reactions between hydroquinone dialkyl ethers and the appropriate acyl chlorides or anhydrides. Since in these Friedel–Crafts reactions there is little tendency to form tarry or polymeric material, anhydrides were not superior to acyl chlorides for our purposes. In our hands some *o*-hydroxy ketone was always formed even under conditions designed to minimize dealkylation (addition of aluminum chloride to the other reactants below 5° and short reflux times). The amount of dealkylation could, however, be held below 20% under mild conditions. When more drastic conditions were employed (addition of acyl chloride last without temperature control and with longer reflux times) up to about 40% of 2-hydroxy-5-alkoxyketone could be obtained. With hydroquinone dimethyl ether the 2,5-dimethoxyketones were still isolated in 45–60% yield together with small amounts of starting material. With hydroquinone diethyl ether, dealkylation seemed to be easier and the more drastic conditions resulted in extensive formation of 2,5-dihydroxyketones which were not conveniently separated at this point. Mixtures of the 2-hydroxy-5-ethoxy and of 2,5-dihydroxyketones were usually benzylated, giving products easily separable by distillation.

TABLE I

Compound	M. p., °C.	Appearance[a]	Crystallizing solvent	Empirical formula	Analyses, % Carbon		Hydrogen	
					Calcd.	Found	Calcd.	Found
			Intermediates in Synthesis of I					
Ic	94		Benzene–hexane	$C_{13}H_{18}O_5$	61.38	61.42	7.14	7.26
Ib	167		Absolute ethanol	$C_{13}H_{20}N_2O_4$	58.17	58.26	7.52	7.62
Ia	86.5	Small needles	Benzene–hexane	$C_{13}H_{17}NO_4$	62.12	62.42	6.82	6.79
			Ketones					
IIId	28[b]			$C_{13}H_{18}O_3$	70.23	70.18	8.17	7.77
Vd	50[c]	Stout prisms	Hexane	$C_{16}H_{16}O_3$	74.96	74.62	6.30	6.32
VIId	47[d]	Rhombs		$C_{17}H_{18}O_3$	75.52	75.36	6.72	7.04
XIIId	54	Rhombs	Hexane	$C_{12}H_{14}O_4$	64.83	64.67	6.35	6.40
IXd	42[e]	Needle-prisms	Hexane	$C_{17}H_{18}O_3$	75.51	75.79	6.72	6.80
XIe	82	Yellow needles	Hexane	$C_{11}H_{14}O_3$	68.00	68.31	7.27	7.40
XId	43[f]	Fine silky needles	Hexane	$C_{18}H_{20}O_3$	76.01	75.78	7.09	7.19
			α-Isonitrosoketones					
IIIb	84	Yellow powder	Ethyl acetate–hexane	$C_{13}H_{17}NO_4$	62.12	62.12	6.82	6.70
VIIb	98.5	Bright yel. need. prisms	Ethyl acetate–hexane	$C_{17}H_{17}NO_4$	68.20	68.25	5.73	6.01
XIVb	89–89.5	Golden yel. need. prisms	Ethyl acetate–hexane	$C_{13}H_{15}NO_6$	55.49	55.33	5.38	5.24
XIb	86	Yellow powder	Ethyl acetate–hexane	$C_{18}H_{19}NO_4$	68.97	68.82	6.11	6.49
			α-Bromoketones					
IIc	77	Leaflets	Methanol–hexane	$C_{12}H_{15}BrO_3$	50.17	50.49	5.27	5.41
IVc	42	Flat needles	Methanol–hexane	$C_{13}H_{17}BrO_3$	51.82	51.81	5.69	5.47
Vc	87–87.5	Needles	Ethyl acetate–hexane	$C_{16}H_{15}BrO_3$	57.31	57.22	4.51	5.01
XIIIc	60	Yellow powder	Hexane	$C_{10}H_{11}BrO_3$	46.33	46.15	4.28	4.35
VIIIc	60	Prisms	Hexane	$C_{17}H_{17}BrO_3$	58.44	58.69	4.99	4.93
IXc	73	Platelets	Hexane	$C_{17}H_{17}BrO_3$	58.44	58.72	4.99	4.76
XIIc	78		Hexane	$C_{18}H_{19}BrO_3$	59.49	59.26	5.28	5.55
			α-Aminoketone hydrochlorides					
IIIa	161		Abs. ethanol–ether	$C_{13}H_{26}ClNO_3$	57.01	56.81	7.37	7.29
Va	192–193	Yellow rhombs	Aqueous alcohol	$C_9H_{12}ClNO_3$	49.64	49.52	5.56	5.79
VIIa	179.5	Felted needles	Absolute ethanol	$C_{17}H_{19}ClNO_3$	63.43	63.58	6.27	6.31
IXa	182–185 (dec.)	Pale yellow needles	Abs. ethanol–ether	$C_{10}H_{14}ClNO_3$	51.82	51.64	6.10	6.00
			α-Methylaminoketone hydrochlorides					
IIa	163	Fine felted needles	Absolute ethanol	$C_{13}H_{20}ClNO_3$	57.01	57.05	7.37	7.63
Xa	186	Small stout prisms	Absolute ethanol	$C_{11}H_{16}ClNO_3$	53.75	53.94	6.57	6.62
XIIa	164.5	Yellow leaflets	Absolute ethanol	$C_{12}H_{18}ClNO_3$	55.47	55.60	6.99	6.86
			Tertiary aminoketone hydrochlorides					
IIb	145		Abs. ethanol–ether	$C_{20}H_{26}ClNO_3$	65.99	65.74	6.93	6.93
VIb	156.5–158	Hexagonal prisms	Abs. ethanol–ether	$C_{24}H_{26}ClNO_3$	69.96	69.82	6.37	6.55
IXb	185–187 (dec.)	Silky needles	Abs. ethanol–ether	$C_{31}H_{32}ClNO_3$	74.15	73.99	6.43	6.43
			Aminoalcohol hydrochlorides					
I	178		Abs. ethanol–ether	$C_{12}H_{20}ClNO_3$	55.04	55.12	7.71	7.68
II	150		Abs. ethanol	$C_{13}H_{22}ClNO_3$	56.59	56.60	8.04	7.88
III	216	Fine needles	Abs. ethanol	$C_{13}H_{22}ClNO_3$	56.59	56.28	8.04	7.91
IV	146		Abs. ethanol–ether	$C_{14}H_{24}ClNO_3$	58.00	57.69	8.35	8.10
V	160	Leaflets	Abs. ethanol–ether	$C_9H_{14}ClNO_3$	49.19	49.43	6.43	6.53
VI	130	Rhombs	Abs. ethanol–ether	$C_{10}H_{16}ClNO_3$	51.37	51.57	6.91	7.11
VII	228 (dec.)	Prisms	Abs. ethanol	$C_{10}H_{16}ClNO_3$	51.37	51.67	6.91	7.06
VIII	202		Abs. ethanol	$C_{11}H_{18}ClNO_3$	53.31	53.21	7.33	7.59
IX	152.5–153	Platelets	Abs. ethanol–ether	$C_{10}H_{16}ClNO_3$	51.37	51.43	6.91	6.66
X	133		Abs. ethanol–ether	$C_{11}H_{18}ClNO_3$	53.31	53.13	7.33	7.51
XI	217 (dec.)		Abs. ethanol	$C_{11}H_{18}ClNO_3$	53.31	53.09	7.33	7.38
XII	182.5	Fine felted needles	Abs. ethanol–ether	$C_{12}H_{20}ClNO_3$	55.04	54.93	7.71	7.52

[a] Appearance noted only when characteristic. [b] B. p. (18 mm.) 178–180°. [c] B. p. (1 mm.) 187–192°. [d] B. p. (1 mm.) 194–196°. [e] B. p. (1 mm.) 198–202°. [f] B. p. (1 mm.) 198–202°.

2-Benzyloxy-5-alkoxyketones.—The crude alkali-soluble fractions from Friedel–Crafts reactions were benzylated in methanol with potassium hydroxide and benzyl chloride, slightly less than one equivalent of each being added initially with two later additions of half equivalents at two-hour intervals. Stirring was found to be desirable in order to minimize bumping. The products were washed with alkali, dried over potassium carbonate and distilled *in vacuo*. Yields varied from 60–90% dependent largely on the amount of dihydroxyketone present.

α-Bromoketones.—Bromination was carried out in methanol solution as described in Paper III of this series.[3] Yields of pure product varied between 55 and 90%, the lower yields corresponding to the lower-melting and more soluble compounds.

α-Isonitrosopropiophenones.—The propiophenones were nitrosated by the methyl nitrite method of Hartung and Crossley.[7] Yields were from 50–75% of pure isonitrosoketone.

Tertiary Aminoketones.—The technique used in the reaction of benzylmethylamine with the α-bromoketones was that of Ardis, Baltzly and Schoen.[3] It became apparent during the course of this work that the acetic anhydride treatment was not adequate to remove traces of secondary amine from the tertiary aminoketones and, due largely to this defect, only two of the six α-benzylmethylamines were obtained analytically pure. One of these, IIb, was isolated in an 89% yield, the other (VIb) in only 20%. The quantities of benzylmethylamine hydrobromide precipitated from the reaction mixture were in all cases approximately the calculated amount and it is believed that the reaction itself is effectively quantitative. Of the four tertiary aminoketones that had to be reduced as crude preparations, two afforded pure α-methylaminoketones (Xa and XIIa) after debenzylation. The yields of Xa and XIIa were 90 and 55%, respectively, reckoned on the crude tertiary aminoketones employed. In the other two lines of synthesis, only the final aminoalcohols (IV and VIII) were completely pure—the intermediates were crystalline but apparently contaminated with tenacious impurities.

Compound IXb (2-benzyloxy-5-ethoxy-α-dibenzylaminoacetophenone) was prepared by treating 0.05 mole of the corresponding bromoketone (IXc) with 0.1 mole of dibenzylamine in 500 cc. of absolute ether at room temperature. After standing 40 hours, 7 g. (0.025 mole) of dibenzylamine hydrobromide was obtained. Only 3 g. more separated after standing three days longer. The filtrate from the salt was extracted with water, allowed to stand three hours with 5 cc. of acetic anhydride and then shaken with 1 *N* hydrochloric acid solution. At this point, a copious precipitate formed and was filtered off. After recrystallization of this solid, analysis showed it to be the desired product (IXb). The yield was 60%. The technique of Simonoff and Hartung[6] might have given better results but seemed inadvisable at the time.

α-Methylaminoketones.—The palladized charcoal reduction of the α-benzylmethylaminoketone hydrochlorides removed the N-benzyl groups smoothly and the 2-benzyl group when present. Compounds IIa, Xa and XIIa were isolated in good yield. The product of the reduction of VIb was hydrogenated directly with platinum without attempting the isolation of the intermediate. The precursors of IV and VIII, although crystalline, could not be purified so as to give satisfactory analyses. When debenzylation can be applied to a pure substance the reaction is usually quantitative. The reduction of IIb, for example, gave the calculated quantity of IIa, and after two recrystallizations the yield was 75%.

α-Aminoketones.—Compound Va was prepared by the hexamethylenetetramine method. The initial product of the hydrolysis with alcoholic hydrogen chloride of the addition compound from hexamethylenetetramine and Vc was not readily separated from ammonium chloride. The crude product, contaminated with ammonium chloride, was debenzylated with palladized charcoal yielding Va which was purified easily. The yield was 55% from the bromoketone Vc. A similar situation had been found with the 5-methyl analog.[3] The debenzylation of IXb afforded IXa in quantitative yield.

The aminopropiophenones IIIa and VIIa were prepared by reduction of the corresponding isonitroso ketones with palladized charcoal in alcoholic hydrogen chloride solution. Yields were 60–70% of pure material. The reduction of XIb to XI was performed in two stages with no attempt to isolate the intermediate aminoketone.

Aminoalcohols.—With the exception of Compound I, all the aminoalcohols were prepared by hydrogenation of the corresponding aminoketone hydrochlorides with platinum catalyst. Yields of pure compounds were 40 to 90% dependent largely on losses in crystallization.

Compound I was prepared by the line of synthesis indicated in Chart I and followed by Baltzly and Buck,[2] in the preparation of the 2,5-dimethoxy analog. The substances shown in Chart I are those actually isolated. The 2,5-diethoxybenzaldehyde was prepared in 57% yield by the Gattermann reaction. The product from the Reformatzky reaction of this aldehyde and ethyl bromoacetate was saponified in the cold and the β-hydroxy acid Ic (yield 72%) was purified by recrystallization. Reesterification was accomplished by the use of diazomethane (to avoid dehydration) and the ester was refluxed directly with alcoholic hydrazine hydrate forming Ib, in effect quantitatively. The azide obtained from Ib by the action of cold nitrous acid was taken up in benzene and dried briefly. Cautious warming of the benzene solution of the azide produced the oxazolidone Ia in 67% yield from the hydrazide. Cleavage with cold concentrated hydrochloric acid[8] afforded I, yield 50% after two crystallizations.

Acknowledgment.—The authors wish to express their gratitude to Mr. Samuel W. Blackman for the microanalyses here reported.

Summary

The primary and secondary aminoalcohols of the 2,5-diethoxy, 2-hydroxy-5-methoxy and 2-hydroxy-5-ethoxyphenethyl and phenylisopropylamine series have been prepared.

TUCKAHOE 7, NEW YORK RECEIVED APRIL 10, 1947

---

[7] Hartung and Crossley, "Organic Syntheses," **16**, 45 (1936).

[8] *Cf.* Schroeter, German Patent, 220,852.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Pyrimidine. III. Study of the Bromination of 5-Acetyl-4-methyl-2-phenylpyrimidine[1]

BY RAY A. CLARKE, BRUCE GRAHAM AND BERT E. CHRISTENSEN

An amino alcohol substituent in the 5-position of the pyrimidine nucleus has recently been reported in the literature.[2] A series of these compounds were prepared by coupling various secondary amines with 5-acetyl-4-methyl-2-phenylpyrimidine by means of the Mannich reaction. Since this procedure gives one type of amino alcohol, the preparation of amino alcohols by reaction of amines with bromomethyl ketones was investigated.

The bromomethyl ketones are usually prepared either by direct bromination of the acetyl derivative or by the diazomethane synthesis. Whenever possible this latter method is preferable since it utilizes the acid rather than the less common acetyl derivatives of the desired nucleus.

4-Methyl-2-phenyl-5-pyrimidinecarboxylic acid was prepared according to the directions of Mitter and Bardham.[3] Preliminary attempts to convert the acid to the bromomethyl ketone by means of the diazomethane synthesis were unsuccessful.

For this reason, the direct bromination of the easily prepared 5-acetyl-4-methyl-2-phenylpyrimidine (Fig. 1, I) was studied. Bromination in chloroform solution at room temperature gave over a 90% yield of crude bromination product. Analysis and solubility characteristics indicated the crude product to be the hydrobromide salt of the bromo derivative.

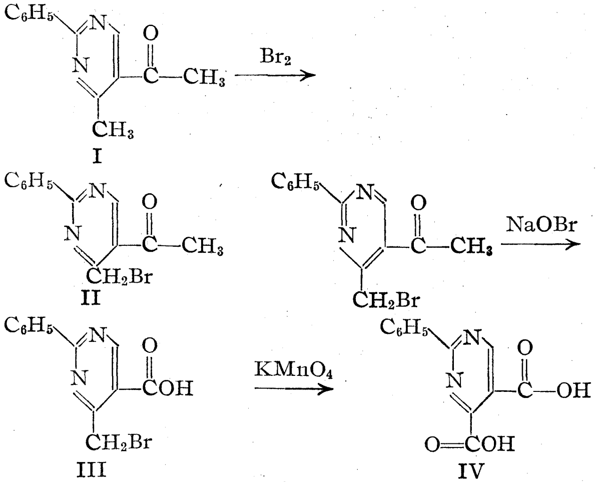


Fig. 1.

It was very evident from initial tests that this brominated derivative was probably an isomeric mixture. The crude product loses the ionizable bromine atom very readily. Shaking the material with chloroform containing a small amount of water converted it to the free base.

The principal product of the bromination was a petroleum ether insoluble compound. The structure of this compound was established to be 5-acetyl-4-bromomethyl-2-phenylpyrimidine (II) on the basis of oxidation studies. Sodium hypobromite oxidized the compound to an acid (III) which still retained one bromine atom. The same procedure using 5-acetyl-4-methyl-2-phenylpyrimidine gave a product which was identical with 4-methyl-2-phenyl-5-pyrimidinecarboxylic acid. Potassium permanganate oxidation of the bromo acid gave a dicarboxylic acid which analysis indicated to be the 2-phenyl-4,5-dicarboxylic acid (IV).

The 5-acetyl-4-bromomethyl-2-phenylpyrimidine reacted readily with amines in a benzene–ether solution. The 5-acetyl-4-morpholinomethyl-2-phenylpyrimidine hydrochloride was oxidized with sodium hypobromite to the 5-carboxyl-4-morpholinomethyl-2-phenylpyrimidine hydrochloride which confirmed the position of the amino substituent.

Experimental

Bromination of 5-Acetyl-4-methyl-2-phenylpyrimidine.—Eleven and one-half grams (0.054 mole) of 5-acetyl-4-methyl-2-phenylpyrimidine was dissolved in 75 ml. of chloroform. Two and eight-tenths milliliters (0.054 mole) of bromine in 15 ml. of chloroform was added to the solution of the acetylpyrimidine. The solution was then placed in a quartz beaker, fitted with a cover and exposed to ultraviolet light. After one and one-fourth hours the bromine color had disappeared and the solution was diluted with an equal volume of dry ether to precipitate a white to light yellow solid, 18.5 g. (92% yield).

Anal. of crude mixture. Calcd. for $C_{13}H_{12}Br_2N_2O$: Br total, 43.0; ionizable, 21.5. Found: Br total, 44.5; ionizable, 21.3.

Separation and Purification of 5-Acetyl-4-bromomethyl-2-phenylpyrimidine.—Hydrogen bromide was removed from the crude bromine-containing mixture (10 g.) by shaking it in a separatory funnel with 35 ml. of chloroform and 5 ml. of water. The chloroform was removed from the extract by distillation under reduced pressure leaving 7.5 g. of a white solid.

This solid was placed in a soxhlet thimble and extracted in a soxhlet apparatus with petroleum ether (boiling range, 36–65°). The insoluble material (4.10 g.) left in the thimble was the crude 5-acetyl-4-bromomethyl-2-phenylpyrimidine. As an alternate purification procedure 0.50 g. of the crude bromination product was dissolved in 15 ml. of hot isopropyl alcohol. Upon cooling, crystals (0.23 g.) deposited which were identical with petroleum ether insoluble fractions. The pure material (m. p. 168–170°) was obtained as white needles by several recrystallizations from ligroin (boiling range 97–140°).

---

(1) The work described in this paper was made possible by a grant in aid from the Research Corporation. Published with the approval of the Monograph Publications Committee, Oregon State College, as Research Paper No. 116, School of Science, Department of Chemistry.

(2) Bruce Graham, A. M. Griffith, C. S. Pease and B. E. Christensen, THIS JOURNAL, **67**, 1294 (1945).

(3) P. G. Mitter and J. C. Bardham, *J. Chem. Soc.*, **123**, 2179 (1923).

Anal. Calcd. for $C_{13}H_{11}BrN_2O$: Br, 27.5; C, 53.61; H, 3.81. Found: Br, 27.4; C, 53.23; H, 4.16.

4-Bromomethyl-2-phenylpyrimidine-5-carboxylic Acid.—5-Acetyl-4-bromo-methyl-2-phenylpyrimidine (1.00 g., 0.00344 mole) was dissolved in 20 ml. of warm dioxane. A sodium hypobromite solution was prepared by adding a solution of 1.30 g. (0.0275 mole, assuming 85% purity) of sodium hydroxide in 10 ml. water to 0.71 ml. (0.0138 mole) of bromine. The sodium hypobromite was then added to the dioxane solution. The temperature immediately rose to 60° and the solution became reddish brown in color. After about two minutes, the solution was cooled and diluted with 50 ml. of cold water. A small amount (0.25 g.) of starting material precipitated and was removed by filtration. The aqueous solution was extracted with ether to remove bromoform and was then treated with an aqueous sodium bisulfite solution, until a negative starch-potassium iodide test was obtained, to reduce excess sodium hypobromite. Acidification with nitric acid precipitated a solid. This was filtered by suction and washed with water. The yield of the crude acid was 0.48 g. (62%).

Anal. Calcd. for $C_{12}H_9BrN_2O_2$: Br, 27.3; neutral equivalent, 293. Found: Br, 25.6; neutral equivalent, 290.

2-Phenylpyrimidine-4,5-dicarboxylic Acid.—The crude 4-bromomethyl-2-phenyl-5-pyrimidinecarboxylic acid (0.66 g. 0.00225 mole) was dissolved in an equivalent molar amount of dilute sodium hydroxide solution. A solution of 1.19 g. (0.075 mole) of potassium permanganate in 60 ml. of water was added and the resulting solution was refluxed for one and one-half hours. After cooling to room temperature, the excess permanganate was reduced with sulfur dioxide and the manganese dioxide was removed by centrifuging. The supernatant liquid was evaporated to a volume of 25 ml. and the hot solution was acidified with nitric acid. The dicarboxylic acid gradually crystallized on cooling and was removed by filtration and washed with water. The weight of product was 0.32 g. This acid was purified for analysis by one recrystallization from hot water. It melted (capillary tube) at 279–281° with decomposition.

Anal. Calcd. for $C_{12}H_8N_2O_4$: N, 11.47; neutral equivalent, 122. Found: N, 11.36; neutral equivalent, 123.

Directions for Reaction of Amines with 5-Acetyl-4-bromomethyl-2-phenylpyrimidine.—Three-tenths gram (0.00103 mole) of 5-acetyl-4-bromomethyl-2-phenyl-pyrimidine was dissolved in 5 ml. of warm benzene. To this solution was added 0.00206 mole of the free base. Usually after a few minutes the hydrobromide of the free base (*i. e.*, morpholine hydrobromide) formed. Dry ether was then added to the mixture and the solid removed by filtration and washed with dry ether. Dry hydrogen chloride was passed into the filtrate to precipitate the product as a white solid. This was removed by filtration and washed with dry ether.

5-Acetyl-4-dimethylaminomethyl-2-phenylpyrimidine Hydrochloride.—The product was purified by recrystallization from absolute ethanol to obtain a white crystalline product, 63% yield, m. p. 236° with decomposition:

Anal. Calcd. for $C_{15}H_{18}ClN_3O$: C, 61.75; H, 6.18; N, 14.40; Cl, 12.17. Found: C, 61.97; H, 6.50; N, 14.30; Cl, 12.05.

5-Acetyl-4-morpholinomethyl-2-phenylpyrimidine Hydrochloride.—The product was purified by recrystallization from 3 *N* hydrochloric acid. The yield was 84% of fine white needles which started to decompose at 213° and finally melted with decomposition at 220°.

Anal. Calcd. for $C_{17}H_{20}ClN_3O_2$: N, 12.60; Cl, 10.63. Found: N, 12.51; Cl, 10.40.

5-Acetyl-4-diethylaminomethyl-2-phenylpyrimidine Hydrochloride.—The yield of crude product was 95%. This was purified by recrystallization (twice) with absolute ethanol resulting in white crystals, m. p. 215–220° with decomposition.

Anal. Calcd. for $C_{17}H_{22}ClN_3O$: N, 13.15; Cl, 11.10. Found: N, 13.10; Cl, 11.02.

Directions for the Reduction of the Amino Ketones.—Two to two and one-half grams of the amino ketone hydrochloride was dissolved in 100 ml. methanol and reduced with hydrogen at 30 pounds pressure using platinum oxide catalyst (50 mg.). After shaking for a few hours, the catalyst was removed by filtration and the filtrate evaporated to dryness.

4-Dimethylaminomethyl-5-(1-hydroxyethyl)-2-phenylpyrimidine Hydrochloride.—The residue from the reduction was dissolved in 75 ml. of hot absolute ethanol, and diluted with equal volume of dry ether. The crystalline product which formed on standing was removed by filtration. This product melted at 236–237°; yield was 75%.

Anal. Calcd. for $C_{15}H_{20}ClN_3O$: C, 61.33; H, 6.81; N, 14.31; Cl, 12.08. Found: C, 61.36; H, 7.11; N, 14.36; Cl, 12.0.

A mixed melting point determination of the reduced and unreduced dimethylamine derivative indicated that they were not identical compounds, m. p. 220–225° with decomposition.

5-(1-Hydroxyethyl)-4-morpholinomethyl-2-phenylpyrimidine Hydrochloride.—Since the acetylmorpholinomethylphenylpyrimidine was only slightly soluble in ethanol or methanol it was first converted to the free base. Two and one-half grams of 5-acetyl-4-morpholinomethyl-2-phenylpyrimidine hydrochloride was converted to the free base with 5% sodium bicarbonate, extracted with ether and the ether evaporated. The residue was reduced in the usual manner. The reduction product (a sirupy residue) was dissolved in dry ether and dry hydrogen chloride was added to precipitate the product as the hydrochloride. The solid was removed by filtration and dissolved in 50 ml. of hot absolute ethanol. The alcohol solution was diluted with an equal volume of dry ether and the solution allowed to stand. The crystals which gradually formed were removed. This solid was recrystallized again in a similar manner to give 42% yield of white crystals, m. p. 230–232°, softening and darkening at about 220°.

Anal. Calcd. for $C_{17}H_{22}ClN_3O_2$: C, 60.80; H, 6.56; N, 12.52; Cl, 10.57; Found: C, 60.87; H, 6.76; N, 12.22; Cl, 10.50.

4-Diethylaminomethyl-5-(1-hydroxyethyl)-2-phenylpyrimidine Hydrochloride.—The residue from the reduction was dissolved in 20 ml. of hot absolute ethanol and diluted with 40 ml. of dry ether. The crystalline solid which formed on standing was removed and recrystallized again in a similar manner to give 71% yield of a crystalline product, m. p. 185–187°.

Anal. Calcd. for $C_{17}H_{24}ClN_3O$: C, 63.45; H, 7.47; N, 13.07; Cl, 11.03. Found: C, 63.75; H, 7.69; N, 13.19; Cl, 10.95.

5-Carboxy-4-morpholinomethyl-2-phenylpyrimidine Hydrochloride.—5-Acetyl-4-morpholinomethyl-2-phenylpyrimidine hydrochloride (0.50 g., 0.0015 mole) was suspended in 5 ml. of dioxane. A sodium hypobromite solution was prepared by adding a solution of 0.636 g. of sodium hydroxide in 10 ml. of water to 0.31 ml. (0.006 mole) of bromine. The sodium hypobromite solution was added to the dioxane suspension. The reaction was exothermic, and the solution became dark red in color. After standing for fifteen minutes the solution was diluted with 40 ml. of water and extracted with ether. The excess sodium hypobromite was reduced by adding a few drops of a saturated sodium bisulfite solution and the solution was then acidified with concentrated hydrochloric acid. A fine crystalline solid gradually formed on standing. This was removed by filtration yielding 0.24 g. of a tan-colored solid. Two-tenths gram of this material was recrystallized from isopropyl alcohol containing dry hydrogen chloride to yield 0.13 g. of product.

Anal. Calcd. for $C_{16}H_{18}ClN_3O_3$: N, 12.52; Cl, 10.58; neutral equivalent, 168. Found: N, 12.92; Cl, 10.34; neutral equivalent, 173.

Summary

Bromination of 5-acetyl-4-methyl-2-phenyl-

pyrimidine gave 5-acetyl-4-bromomethyl-2-phenylpyrimidine as one of the bromination products. Its structure was established by oxidation to 4-bromomethyl-2-phenyl-5-pyrimidine-carboxylic acid and 2-phenyl-4-,5-pyrimidinedicarboxylic acid.

By the coupling of 5-acetyl-4-bromomethyl-2-phenylpyrimidine with various secondary amines (dimethylamine, diethylamine, morpholine) followed by catalytic reduction, compounds of the type 4-dialkylaminomethyl-5-(1-hydroxyethyl)-2-phenylpyrimidine have been prepared.

RECEIVED AUGUST 26, 1947

[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

Condensation of Some Tertiary Octyl Alcohols with Benzene

BY RALPH C. HUSTON, GORDON L. GOERNER, E. ROBERT BREINING,[1a] CHARLES O. BOSTWICK,[1b] KENNETH D. CLINE[1c] AND LOUIS J. SNYDER[1d]

Previous communications[2] from this Laboratory have reported the condensation of eight of the seventeen possible tertiary octyl alcohols with benzene in the presence of aluminum chloride. The purpose of this investigation was to condense the remaining tertiary octyl alcohols with benzene and to determine the boiling points, refractive indices and surface tensions of the resulting octylbenzenes. To this end, the alcohols shown in Table I were prepared.[3] Of these, 3,4-dimethyl-3-hexanol has not been reported previously. This alcohol was synthesized successfully from 3-methyl-2-pentanone and ethyl Grignard reagent and from 3-methyl-4-hexanone and methyl Grignard reagent. Attempts to prepare it from butanone and secondary butyl Grignard reagent failed, the product being contaminated with large amounts of homomesityl oxide, which boils at approximately the same temperature as the desired alcohol.[4]

TABLE I

TERTIARY OCTYL ALCOHOLS

	Carbonyl cpd.	Grignard	B. p., °C. (mm.)	$n^{20}\mathrm{D}$
3-Methyl-3-heptanol	MeCOEt	BuMgBr[a]	158 (742) 63–64 (13)	1.4270 (22°)
4-Methyl-4-heptanol	MeCO$_2$Et	PrMgBr[b]	62–63 (12)	1.4258
3-Ethyl-3-hexanol	PrCO$_2$H PrCOCl	EtMgBr[c] EtMgBr[d]	153–155 (748) 64–65 (14)	1.4326
2,3-Dimethyl-3-hexanol	*i*-PrCOMe	PrMgBr[e]	155.5–157.5 (748) 54–56 (13)	1.4332
2,4-Dimethyl-4-hexanol	MeCOEt *i*-BuCOMe	*i*-BuMgBr[f] EtMgBr[g]	54.5 (13) 60–62 (16)	1.4278
3,4-Dimethyl-3-hexanol	See Experimental		150–152 (740) 58 (11)	1.4350
2-Methyl-3-ethyl-3-pentanol	*i*-PrCO$_2$H *i*-PrCOCl	EtMgBr[c] EtMgBr[d]	156–157 (748) 53 (10)	1.4372
2,3,4-Trimethyl-3-pentanol	(*i*-Pr)$_2$CO	MeMgBr[h]	146–147 (740) 53–54 (13)	1.4342

[a] Whitmore and Badertscher, THIS JOURNAL, **55**, 1559 (1933). [b] Halse, *J. prakt. Chem.*, **89**, 453 (1914). [c] Ref. 14. [d] E. R. Breining, Master's Thesis, Michigan State College, 1938. [e] Clarke, THIS JOURNAL, **33**, 528 (1911). [f] Meyer and Tuot, *Compt. rend.*, **196**, 1232 (1933). [g] Clarke, THIS JOURNAL, **30**, 1147 (1908). [h] Whitmore and Laughlin, *ibid.*, **54**, 4392 (1932).

In general the condensations of the alcohols with benzene were carried out as described previously.[2c,5] The products were distilled under diminished pressure, traces of octyl chloride were removed from the octylbenzene fraction by refluxing with alcoholic potassium hydroxide or alcoholic silver nitrate, and the octylbenzene fraction was carefully distilled through a Fenske-type column.

Our results agree with previous observations from this Laboratory[2b,5] that branching on the β-carbon atom of the alcohol results in a decreased yield of the octylbenzene (see Table II). The alcohols without branching on the β-carbon atom, namely, 3-methyl-3-heptanol, 4-methyl-4-heptanol, 3-ethyl-3-hexanol and 2,4-dimethyl-4-hexanol gave their respective octylbenzenes in yields of 19 to 31%. These hydrocarbons possess closely related physical properties and the determined molecular refractions are within 0.1 unit of the theoretical value. Because of the large yields of pure hydrocarbons with practically constant boiling points and indices of refraction, the accuracy with which the physical constants of these compounds were determined is greater than for the other four octylbenzenes.

Those alcohols with branching on one β-carbon atom, 2,3-dimethyl-3-hexanol, 3,4-dimethyl-3-hexanol, and 2-methyl-3-ethyl-3-pentanol fall into a second group. The crude octylbenzene fraction obtained from these is more complex than that obtained from the alcohols in the first group. Fractionation gave only a few grams (5 to 9%) of ma-

---

(1) Present location: (a) Flint Junior College, Flint, Michigan; (b) Pigments Division, du Pont Company, Newport, Del.; (c) Wyeth, Inc., Mason, Mich.; (d) Ethyl Corporation, Baton Rouge, La.

(2) (a) Huston and Guile, THIS JOURNAL, **61**, 69 (1939); (b) Huston, Guile, Sculati and Watson, *J. Org. Chem.*, **6**, 252 (1941); (c) Huston and Krantz, *ibid.*, **13**, 63 (1948).

(3) The condensation of 2,3,3-trimethyl-2-pentanol is now being reinvestigated along with the condensation of 2,2,3-trimethyl-3-pentanol.

(4) Grignard and Fluchaire, *Ann. chim.*, **9**, 27 (1927), have shown that butanone yields homomesityl oxide when treated with bromo- or iodo-magnesium butoxides. Since appreciable quantities of 2-butanol were recovered in our work, the bromo-magnesium alkoxide of this alcohol was probably responsible for the condensation.

(5) Huston, Fox and Binder, *J. Org. Chem.*, **3**, 251 (1938).

TABLE II[a]

TERTIARY OCTYLBENZENES

	Yield, %	B. p., °C. Macro (mm.)	B. p., °C. Micro (mm.)[b]	$n^{20}D$	d^{20}_4	γ_{20}	$M^{20}D$	Analyses, %[d] C	Analyses, %[d] H
3-Methyl-3-phenylheptane	19.2	105.2–106.5 (8.5–9)	241.4–241.6 (732)	1.4928	0.8729	29.51	63.35[c]		6.74[e]
4-Methyl-4-phenylheptane[f]	30.6	110 (11)	239.4–239.6 (732)	1.4930	.8736	29.37	63.31	88.34	11.64
3-Ethyl-3-phenylhexane[f]	25.3	106.5–107.5 (10)	240.8 (732)	1.4938	.8752	29.61	63.29	88.17	11.65
2,3-Dimethyl-3-phenylhexane	9.5	109.2–110 (15)	234.6 (754)	1.4860	.8543	28.03	63.96	88.43	11.68
2,4-Dimethyl-4-phenylhexane	23.2	107–107.5 (12)	236.6–236.8 (732)	1.4924	.8722	28.87	63.35		6.67[e]
3,4-Dimethyl-3-phenylhexane	5.5	105–105.6 (12)	232–232.2 (732)	1.4860	.8590	27.8	63.61	81.41[g]	10.57[g]
2-Methyl-3-ethyl-3-phenylpentane	8.2	103.2–105 (10.5)	231.6–231.8 (732)	1.4850	.8573	27.82	63.63	88.13	11.64
2,3,4-Trimethyl-3-phenylpentane	4.3–7.6	104–106 (13)[h]	234–236 (743)[i]	1.4968	.8808	31.76[j]	63.20	88.55	11.51

[a] The provisional values for the physical constants for these hydrocarbons were included in Egloff, "Physical Constants of Hydrocarbons," Vol. III, Reinhold Publishing Corporation, New York, N. Y., 1946. [b] Micro boiling points are corrected (using Anschütz thermometers). [c] Calcd. 63.25. [d] Calcd. for $C_{14}H_{22}$: C, 88.35; H, 11.65. [e] N for *p*-amino-octylbenzenes. Calcd. for $C_{14}H_{23}N$: N, 6.82. [f] Previously reported, ref. *b*, Table I. [g] For 3,4-dimethyl-3-(*p*-hydroxyphenyl)-hexane. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. [h] Huston and Awuapara, *J. Org. Chem.*, **9**, 405 (1944), report 104–105 (11 mm.). [i] Macro b. p. [j] Determined by du Noüy method.

terial with nearly constant boiling point and index of refraction. Figure 1 shows the weight of hydrocarbon plotted against index of refraction for 3,4-dimethyl-3-phenylhexane and 2-methyl-3-ethyl-3-phenylpentane. The portions with constant index of refraction at 1.4850 and 1.4860 are considered to be hydrocarbons of maximum obtainable purity under the experimental conditions used. Although the 2,3-dimethyl-3-phenylhexane was passed through a spinning band column[6] 80 cm. in length rather than through the Fenske-type column, its constants are almost identical with those of the two hydrocarbons just described. The observed molecular refractions for these three compounds varied from the theoretical by 0.35 to 0.61 unit.

The alcohol with branching on two β-carbon atoms, 2,3,4-trimethyl-3-pentanol, gave a low yield of the corresponding octylbenzene. Although the 2,3,4-trimethyl-3-phenylpentane has a high refractive index, the value corresponds quite closely to the 1.4958 reported for 2,3,4-trimethyl-2-phenylpentane.[2c] The observed molecular refraction checks the theoretical very closely.

Each of these eight octylbenzenes was nitrated, reduced, diazotized and hydrolyzed to the corresponding para-tertiary octylphenol.[7] The phenols were identified by the melting points of their derivatives. Nitration was shown to be *para* to the alkyl group by oxidizing the nitro derivatives to *p*-nitrobenzoic acid.

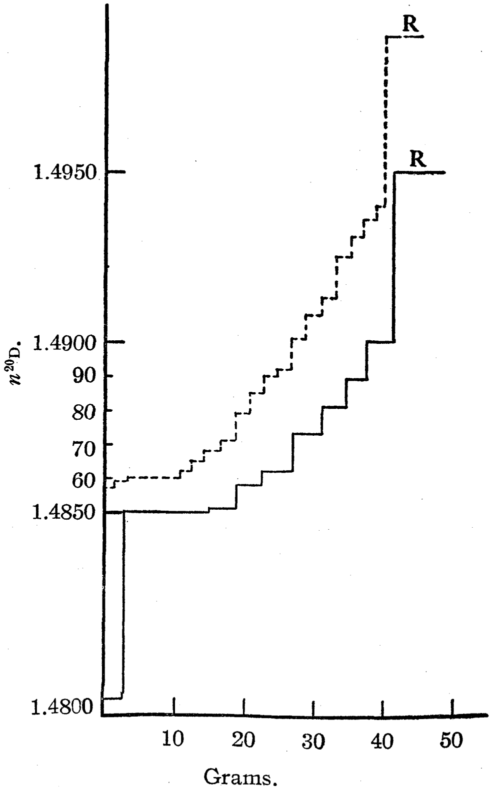


Fig. 1.—Refractive index *vs.* weight for distillation of crude octylbenzene fraction of 2-methyl-3-ethyl-3-phenylpentane — (from 1.25 moles of alcohol) and 3,4-dimethyl-3-phenylhexane - - - - (from 1 mole of alcohol). R is the residue in each distillation.

---

[6] Baker, Barkenbus and Roswell, *Ind. Eng. Chem., Anal. Ed.*, **12**, 468 (1940). The head was of the type described by Whitmore and Lux, THIS JOURNAL, **54**, 3451 (1932).

[7] Huston and Meloy, *ibid.*, **64**, 2655 (1942); Huston, Langdon and Snyder, *ibid.*, in press.

Experimental

Boiling points are uncorrected unless otherwise noted.

Preparation of Alcohols.—The alcohols were prepared by the reaction of the appropriate carbonyl compound and Grignard reagent as shown in Table I.

3,4-Dimethyl-3-hexanol. (a) From 3-Methyl-2-pentanone and Ethylmagnesium Bromide.—One mole of *s*-butylmagnesium bromide was added dropwise to one mole of acetyl chloride. After standing overnight, the reaction mixture was hydrolyzed, acidified, washed with dilute sodium carbonate solution and dried over anhydrous sodium sulfate. Removal of the ether followed by fractionation gave the ketone distilling at[8] 118°. The ketone was added dropwise to an equimolecular solution of ethylmagnesium bromide. The reaction mixture was worked up as usual and the alcohol fractionated under diminished pressure; b. p. 59–61° (14 mm.); 150–152° (740 mm.); yield, 61% based on the ketone, d^{25} 0.8345. *Anal.* Calcd. for $C_8H_{18}O$: C, 73.78; H, 13.93. Found: C, 73.72; H, 13.67.

(b) From 3-Methyl-4-hexanone and Methylmagnesium Bromide.—The ketone was prepared as follows: to 53 g. (2.3 moles) of powdered sodium,[9] suspended in 200 ml. of anhydrous ether in a two-liter, three-neck flask equipped with strrer, condenser and dropping funnel, was added 63 ml. (1.1 moles) of absolute ethyl alcohol. The condenser was replaced by a 60-cm. Fenske-type column packed with 3/32 inch glass helices. Eight hundred fifty grams of ethyl propionate was added portionwise and the reactants maintained at reflux temperature. The ether slowly distilled and was followed by a mixture of ethyl alcohol and ethyl propionate. After four hours, the condensation of the ethyl propionate and the sodium enolate of ethyl α-propionylpropionate[10] was considered to be complete as judged by the boiling point (95°+) and the refractive index (1.3840). To this solution was added 150 ml. of toluene (dried over sodium). In a period of three to four hours, the sodium enolate was alkylated[11] to ethyl α-methyl-α-propionylbutyrate by slowly adding 316 g. of ethyl bromide (65 g. excess). During this addition and for one additional hour, the reaction mixture was maintained at the reflux temperature.

The solid sodium bromide was removed by suction and the liquid layer A saved for fractionation. The sodium bromide was dissolved in water, the solution acidified with acetic acid, the oil separated and the water layer extracted with ether. The liquids were washed with 10% sodium carbonate and, after drying over anhydrous potassium carbonate, were combined with the liquid layer A. Distillation through the Fenske-type column gave 239 g. (1.285 moles) of ethyl α-methyl-α-propionylbutyrate, b. p. 94–95° (11 mm.); n^{20}D 1.4288; reported,[12] b. p. 98–100° (15 mm.); yield, 55.8% based on sodium.

Ketone hydrolysis of the ester[13] required fourteen hours. The reaction mixture was poured onto ice and made alkaline with sodium hydroxide. The oil was separated and the water layer extracted with ether. The combined oil and ether extracts were dried and distilled. The average yield for the hydrolysis of two 250-g. batches of the keto ester was 84%. The 3-methyl-4-hexanone boiled at 76–76.4° (107 mm.); micro b. p. 135.2 (743 mm.) (cor.); n^{20}D 1.4069; d^{20}_4 0.8162; reported,[13] (b. p. 135–136 (760 mm.).

To the methylmagnesium bromide prepared from 3.3 moles of magnesium and methyl bromide (Dow Chemical) in 900 ml. of anhydrous ether was added dropwise 262 g. (2.3 moles) of 3-methyl-4-hexanone. After standing overnight, large colorless crystals settled around the sides of the flask and on the stirrer. These were identified by analysis (Mg, 11.1%) as the complex $C_{16}H_{46}O_5Mg_4Br_6$ observed in this Laboratory in the preparation of tertiary alcohols from acids and the Grignard reagent.[14] Five hundred milliliters of ether was distilled from the reaction mixture, 200 ml. of dry benzene was added and the whole refluxed four or five hours at a temperature of 60°. After hydrolysis, and after washing and drying the ethereal solution, distillation gave 261 g. of 3,4-dimethyl-3-hexanol (87% yield based on the ketone).

Condensation of the Alcohols with Benzene.—All but three of the alcohols were condensed according to the method described by Huston, *et al.*,[5] using 0.5 mole of aluminum chloride per mole of alcohol. The technique described by Huston and Krantz[2c] was used for the condensation of 2,3-dimethyl-3-hexanol, 3,4-dimethyl-3-hexanol and 2-methyl-3-ethyl-3-pentanol, using, respectively, 0.33, 0.41 and 0.25 mole of aluminum chloride per mole of alcohol. No gaseous organic compounds were obtained in these reactions. The condensation of 2,3-dimethyl-3-hexanol was varied further in that dry hydrogen chloride gas was bubbled into the reaction flask during the addition of the last 0.7 mole of alcohol.

After standing for two to twelve hours, the reaction mixture was hydrolyzed by adding water. If the aqueous layer did not become clear, a small volume of C. P. hydrochloric acid was added. The benzene layer was removed and the aqueous layer extracted with benzene. The combined benzene extracts were washed with 10% sodium carbonate solution and dried over anhydrous potassium carbonate.

Fractionation of Crude Product.—Distillations were through the Fenske-type column described above except for the products obtained from the condensation of 2,3-dimethyl-3-hexanol (spinning band column[6]) and of 2,3,4-trimethyl-3-pentanol (Vigreux). After removal of the benzene, the following fractions were obtained in each case:

1. **Alkane–Alkene Fraction.**—B. p. 50–60° at 90 to 100 mm.: from alcohols with branching on the β-carbon atom, unsaturated (bromine in carbon tetrachloride), chloride-free liquids were obtained, probably alkenes formed by dehydration of the alcohols. From alcohols without branching on the β-carbon atom, saturated, chloride-free liquids with physical constants approximating alkanes were obtained. Product from 4-methyl-4-heptanol: yield, 24.2%; b. p. 56° (93 mm.); micro b. p. 117.2° (744 mm.) (cor.); n^{20}D 1.3980; d^{20}_4 0.7036. These values agree fairly well with the physical constants of 4-methylheptane.[15] These liquids are under further investigation.
2. **Chloride Fraction.**—B. p. 50–55° at 10–12 mm.: these liquids were not identified but were probably the chlorides derived from the respective alcohols since they gave heavy precipitates with alcoholic silver nitrate.
3. **Crude Octylbenzene Fraction.**—B. p. 102–110° at 10–15 mm.: these fractions usually contained an appreciable quantity of chlorides.
4. **Residue.**—B. p. above 110° (11 mm.) and refractive index greater than 1.5000.

Purification and Isolation of Pure Octylbenzenes.—In each case fraction 3 was refluxed for three to six hours with an equal volume of alcoholic potassium hydroxide solution (1 g. potassium hydroxide to 10 ml. 95% ethyl alcohol). (2,3-Dimethyl-3-phenylhexane required additional treatment with alcoholic silver nitrate.) To this solution was added 200 ml. of water, the oil was separated and the aqueous layer extracted with benzene. The combined oil–benzene solution was washed with 10% acetic acid, 10% sodium carbonate and water and dried over anhydrous potassium carbonate.

The dry liquids were fractionated at reduced pressure through the columns described above. The head was maintained at total reflux until equilibrium was reached. A small volume of liquid was then removed and the head

---

[8] Ginnings, Plonk and Carter, This Journal, **62**, 1923 (1940).

[9] "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 272.

[10] McElvain, This Journal, **51**, 3124 (1929).

[11] Dieckmann and Kron, *Ber.*, **41**, 1269 (1908).

[12] Hudson and Hauser, This Journal, **63**, 3159 (1941).

[13] Hudson and Hauser, *ibid.*, **63**, 3163 (1941).

[14] Huston and Bailey, *ibid.*, **68**, 1382 (1946).

[15] Egloff, "Physical Constants of Hydrocarbons," Vol. I, Reinhold Publishing Corporation, New York, N. Y., 1939, p. 51.

returned to total reflux. When equilibrium was again attained, the process was repeated. Individual samples of one to three grams of liquid were taken and the refractive index determined. Samples of nearly constant boiling point and equal refractive index were combined. The yields of the octylbenzenes recorded in Table II are based on the weight of the liquid where the refractive index varies by no more than 0.001 unit (the 2,3,4-trimethyl-3-phenylpentane was repeatedly distilled through a Vigreux column until pure). The physical constants were determined on the largest combined sample of constant refractive index. In Fig. 1, the fractions of constant refractive index were obtained by combining a number of samples of the same refractive index.

Surface tensions were determined by the drop-weight method. The correction factor was calculated according to the "International Critical Tables."[16]

Summary

Eight tertiary octyl alcohols have been condensed with benzene to produce the corresponding tertiary octylbenzenes. The physical constants of the latter have been determined.

3,4-Dimethyl-3-hexanol has been synthesized by two methods.

[16] "I. C. T.," 1928, Vol. IV, p. 435.

EAST LANSING, MICHIGAN RECEIVED AUGUST 25, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Allylic Chlorides. IV. Relative Reactivities with Potassium Iodide in Acetone[1]

BY LEWIS F. HATCH, LEON B. GORDON AND JOHN J. RUSS[2]

A number of different reactions has been used to demonstrate marked differences in relative reactivity between various types of organic halides. Of these methods, the most satisfactory bimolecular ($S_{\mathrm{N}}2$) reaction for alkyl chlorides is the metathetical reaction between the chloride and potassium iodide in dry acetone.[3] This reaction usually proceeds at an easily measured rate for most chlorides, at readily obtainable temperatures, and without side reactions.

Although this reaction has been used to compare the relative reactivities of a large number of alkyl chlorides, it was not until 1941 that the reaction was utilized in a study of the relative reactivities of several allylic chlorides.[4] The reaction proved to be entirely satisfactory for this type of chloride.

Recent work[5] on the cuprous chloride catalyzed acid hydrolysis of the isomeric 1,3-dichloropropenes has shown that geometrical configuration has a marked influence on the rate of reaction. The present investigation was undertaken to reinvestigate the reaction between allylic chlorides and potassium iodide and to determine if the previously noted effect of geometrical configuration on the hydrolysis reaction also applied to a bimolecular metathetical reaction.

Materials

Potassium Iodide.—C. P. potassium iodide was recrystallized from water and dried three hours at 120°. It failed to give a positive test for iodate ion.

Acetone.—The actone used boiled at 56.6° and did not color anhydrous copper sulfate in one hour. It retained a faint pink color of potassium permanganate for thirty minutes and liberated neither iodine nor hydriodic acid from 0.04 molar potassium iodide when kept in the dark.

1-Chloro-1-propene.—A mixture of *cis*- and *trans*-1-chloro-1-propene[6] was distilled to obtain a fraction with a boiling range of 33–34°. This fraction, being intermediate in boiling range between the two isomers (*cis* 32.0–32.2°; *trans* 36.7°), contained both isomers.

Allyl Chloride.—Allyl chloride boiling at 44.9° was obtained by distillation from crude allyl chloride[7] with a boiling range of 44.5–45.1°. It was used without further purification.

2-Bromo-3-chloro-1-propene.—2-Bromo-3-chloro-1-propene, obtained from Halogen Chemicals of Columbia, S. C., was distilled at 150 mm. pressure. The fraction used had the following constants: b. p. 61.6° (150 mm.); $n^{25}\mathrm{D}$ 1.4968; $d^{25}{}_4$ 1.6290; *MR* (calcd.) 28.22, (obsd.) 27.61.

2,3-Dichloro-1-propene.—2,3-Dichloro-1-propene[6] with a boiling range of 93–94° was distilled at 150 mm. pressure and a fraction boiling at 48.0° was used.

Methallyl Chloride.—Methallyl chloride[7] was redistilled and a fraction boiling at 72.1° was used.

1,3-Dichloropropene.—In the still bottoms remaining from the distillation of crude allyl chloride, prepared by the high temperature substitutive chlorination of propylene, there remains an appreciable quantity of higher boiling material containing a dichloride fraction consisting of approximately 63% 1,3-dichloropropene (*cis* and *trans*), 35% 1,2-dichloropropane and 2% 2,3-dichloro-1-propene. This material[7,8] was separated by distillation into fractions containing the low and high boiling isomers of 1,3-dichloropropene. These fractions were redistilled at 150 mm. pressure and the following data were obtained: low boiling 1,3-dichloropropene, b. p. 57.0°, $n^{20}\mathrm{D}$ 1.4673; high boiling 1,3-dichloropropene, b. p. 64.7°, $n^{20}\mathrm{D}$ 1.4745.

1,3-Dichloro-2-methyl-1-propene.—The isomeric 1,3-dichloro-2-methyl-1-propenes were prepared from methallyl chloride.[9] The methallyl chloride was chlorinated to 1,2,3-trichloro-2-methylpropane using sulfuryl chloride. The trichloride was dehydrochlorinated and hydrolyzed to a mixture of the 3-chloro-2-methyl-2-propen-1-ols which were separated using a Podbielniak Hypercal distillation column. The chloroalcohols were converted to the corresponding dichlorides using concentrated hydrochloric acid.

---

[1] Presented in part at the Texas Regional Meeting of the American Chemical Society, Dallas, Texas, December 13, 1946.

[2] Present address: Magnolia Petroleum Company, Dallas, Texas.

[3] (a) Conant and Kirner, THIS JOURNAL, **46**, 232 (1924); (b) Conant and Hussey, *ibid.*, **47**, 476 (1925); (c) Conant, Kirner and Hussey, *ibid.*, **47**, 488 (1925).

[4] Tamele, Ott, Marple and Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).

[5] Hatch and Roberts, THIS JOURNAL, **68**, 1196 (1946).

[6] Obtained from Research Chemicals, San José, California.

[7] Furnished us for this investigation by Shell Development Co., Emeryville, California.

[8] These isomers are now available from Shell Chemical Co., San Francisco, California.

[9] Hatch, Russ and Gordon, THIS JOURNAL, **69**, 2614 (1947).

TABLE I

RELATIVE REACTIVITIES OF ALLYLIC CHLORIDES: REACTION WITH POTASSIUM IODIDE IN ACETONE AT 20°

1-Chloro-1-propene[a]	Time, hr.	6.00	8.00				
	% reacted	0.0	0.0				
	k	0.00	0.00				
				Av. *k*	0.000		
Allyl chloride	Time, hr.	3.00	4.50	5.00	6.00	7.00	7.50
	% reacted	22.4	34.6	41.5	44.1	50.0	50.7
	k	0.187	0.212	0.243	0.221	0.230	0.217
				Av. *k*	0.218[b]		
2-Bromo-3-chloro-1-propene	Time, hr.	3.00	3.50	4.00	4.50	5.00	
	% reacted	24.4	25.9	27.8	30.9	33.2	
	k	0.208	0.191	0.183	0.186	0.181	
				Av. *k*	0.190		
2,3-Dichloro-1-propene	Time, hr.	2.00	3.00	4.00	5.00	6.00	7.00
	% reacted	13.1	18.9	24.3	30.1	35.7	38.5
	k	0.155	0.154	0.155	0.161	0.166	0.156
				Av. *k*	0.158		
Methallyl chloride	Time, hr.	3.00	4.00	5.00			
	% reacted	38.0	43.8	52.4			
	k	0.362	0.328	0.343			
				Av. *k*	0.344[c]		
1,3-Dichloropropene (High boiling)	Time, hr.	3.00	4.50	4.75	5.00	6.00	7.00
	% reacted	55.6	69.4	71.8	74.5	78.3	84.6
	k	0.607	0.625	0.635	0.654	0.614	0.654
				Av *k*.	0.632		
1,3-Dichloropropene (Low boiling)	Time, hr.	1.00	1.50	2.00	2.50	3.25	3.50
	% reacted	55.3	72.3	79.3	85.9	91.0	91.9
	k	1.87	2.04	1.84	1.92	1.76	1.81
				Av. *k*	1.87		
1,3-Dichloro-2-methyl-1-propene (High boiling)	Time, hr.	0.50	1.00	1.50	2.00	2.25	2.50
	% reacted	37.7	56.6	70.0	77.2	78.3	80.8
	k	2.14	1.94	1.91	1.78	1.64	1.60
				Av. *k*	1.84		
1,3-Dichloro-2-methyl-1-propene (Low boiling)	Time, hr.	0.25	0.50	0.75	1.00	1.25	
	% reacted	62.0	80.4	88.5	92.4	92.8	
	k	9.06	7.91	7.10	6.45	5.27	
				Av. *k*	7.16		
1,1,3-Trichloro-2-methyl-1-propene	Time, hr.	0.50	1.00	1.50			
	% reacted	83.6[d]	95.4	97.5			
	k	Not calculated					

[a] A mixture of the *cis* and *trans* isomers. [b] Tamele, Ott, Marple and Hearne (*Ind. Eng. Chem.*, **33**, 119 (1941)) give $k = 0.226$. [c] Tamele, Ott, Marple and Hearne give $k = 0.354$. [d] Probably low.

The following physical data were obtained: low boiling 1,3-dichloro-2-methyl-1-propene: b. p. 130° (741 mm.); n^{25}_{D} 1.4698; d^{25}_{4} 1.1629; *MR* (calcd.) 29.94, (obsd.) 29.97. High boiling 1,3-dichloro-2-methyl-1-propene: b. p. 132.0° (754 mm); n^{25}_{D} 1.4740; d^{25}_{4} 1.1667; *MR* (calcd.) 29.94, (obsd.) 30.08.

1,1,3-Trichloro-2-methyl-1-propene.—1,1,3-Trichloro-2-methyl-1-propene was obtained from Halogen and Perfume Chemicals, Columbia, S. C., and was distilled at 150 mm pressure. A center fraction gave the following constants: b. p. 101.0° (150 mm); n^{25}_{D} 1.4933; d^{25}_{4} 1.3211; *MR* (calcd.) 34.81, (obsd.) 35.08.

Experimental

The rate studies were carried out in 16 × 150 mm. Pyrex tubes maintained at 20.00 ± 0.01° in a constant temperature bath. The procedure used was the same as that described by Tamele, *et al.*[4], and the same equation was used to calculate the specific reaction rate constant, *k*. The data obtained are given in Table I.

Discussion

Table II lists the allylic chlorides for which rate constants were obtained. These compounds are listed in the increasing order of their relative reactivity with the rate constant of allyl chloride taken as unity. Allyl chloride was taken as unity because all the other allylic chlorides may be considered as derived from it by replacing one or more hydrogen atoms.

TABLE II

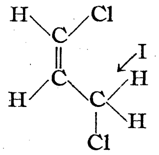
RELATIVE REACTIVITIES OF ALLYCLIC CHLORIDES WITH KI IN ACETONE

Compound		Relative reactivities
$\mathrm{Cl{-}\underset{\underset{H}{\vert}}{C}{=}\underset{\underset{H}{\vert}}{C}{-}CH_3}$	*cis* and *trans*	0.00
$\mathrm{H{-}\underset{\underset{H}{\vert}}{C}{=}\underset{\underset{Cl}{\vert}}{C}{-}CH_2Cl}$		0.72
$\mathrm{H{-}\underset{\underset{H}{\vert}}{C}{=}\underset{\underset{Br}{\vert}}{C}{-}CH_2Cl}$		0.87
$\mathrm{H{-}\underset{\underset{H}{\vert}}{C}{=}\underset{\underset{H}{\vert}}{C}{-}CH_2Cl}$		1.00
$\mathrm{H{-}\underset{\underset{H}{\vert}}{C}{=}\underset{\underset{CH_3}{\vert}}{C}{-}CH_2Cl}$		1.58
$\mathrm{Cl{-}\underset{\underset{H}{\vert}}{C}{=}\underset{\underset{H}{\vert}}{C}{-}CH_2Cl}$	High boiling	2.90
$\mathrm{Cl{-}\underset{\underset{H}{\vert}}{C}{=}\underset{\underset{H}{\vert}}{C}{-}CH_2Cl}$	Low boiling	8.58
$\mathrm{Cl{-}\underset{\underset{H}{\vert}}{C}{=}\underset{\underset{CH_3}{\vert}}{C}{-}CH_2Cl}$	High boiling	8.45
$\mathrm{Cl{-}\underset{\underset{H}{\vert}}{C}{=}\underset{\underset{CH_3}{\vert}}{C}{-}CH_2Cl}$	Low boiling	32.8
$\mathrm{Cl{-}\underset{\underset{Cl}{\vert}}{C}{=}\underset{\underset{CH_3}{\vert}}{C}{-}CH_2Cl}$		>33

Because several of the compounds contain a vinyl halogen as well as an allylic chlorine, it was necessary to determine if a vinyl chlorine reacts with potassium iodide in acetone at 20°. 1-Chloro-1-propene was used as the test compound, for it was available as a mixture of the *cis* and *trans* isomers. It was desirable to use a mixture of geometrical isomers because geometrical configuration might cause some difference in reactivity. A mixture of these two isomers did not give a measurable reaction in eight hours, and it has been assumed that only the allylic chlorine reacts in those compounds containing both types of halogen.

The influence of the relative electronegativity of the atom or group on the number 2 carbon ($\overset{1}{C}{=}\overset{2}{C}{-}\overset{3}{C}$) is not great, but nevertheless definite. The rate of reaction increases with a decrease in the relative electronegativity of the group or atom in the order: $CH_3 > H > Br > Cl$. This effect would be expected if the reaction takes place through an attack of the iodide ion on the carbon atom opposite the point of attachment of the allylic chlorine. The influence of a negative group on the number 2 carbon in this position is to cause the allylic carbon to become relatively less positive and consequently to exert less attraction for the negative iodide ion.

The nature of the effect of a substituent on the number 1 carbon is more involved than for substituents on the number 2 carbon because of the role played by geometrical configuration. This effect may be through steric hindrance or electrostatic interference or both. A group with a large negative field in the *cis* position would offer electrostatic impedance to the approach of the negative iodide ion. In *cis*-1,3-dichloropropene, for example, it is assumed that the allylic chlorine is oriented in a position away from the vinyl chlorine. If this were true, the iodide ion must approach the carbon through the negative field of the vinyl chlorine.



A scale model of this molecule also indicates that there would be considerable steric hinderance to the approach of the iodide ion. The *trans* isomer should have a greater reactivity than the *cis* isomer, provided the other group (H in this case) is relatively less negative than chlorine and smaller in size. With 1,1,3-trichloro-2-methyl-1-propene the activating influence of another vinyl chlorine apparently is somewhat greater than the deactivating effect of a chlorine in the *cis* position. This compound is somewhat more reactive than *trans*-1,3-dichloro-2-methyl-1-propene.

The two isomers of both 1,3-dichloropropene and 1,3-dichloro-2-methyl-1-propene have distinctly different rates of reaction with the *low* boiling isomer in each case being the *more* reactive. If the foregoing reaction mechanism applies, it would seem that the *low* boiling isomer of 1,3-dichloropropene and of 1,3-dichloro-2-methyl-1-propene is the *trans* isomer and the high boiling isomer the *cis* form.

This conclusion is the same as that drawn by Hatch and Roberts[5] from the fact that the *low* boiling isomer of 1,3-dichloropropene reacts more *slowly* in its cuprous chloride catalyzed acid hydrolysis. Andrews and Kepner,[10] however, have pointed out that the data presented to substantiate this conclusion are amenable to other interpretations.

The only previously reported investigation of the relative reactivities of allylic chlorides with potassium iodide is that of Tamele and co-workers[4] on allyl and methallyl chlorides, crotyl chloride and 1-chloro-2-methyl-2-butene. With neither of the latter two compounds is it possible to determine from the data given if the compound used was the *cis* or the *trans* isomer or a mixture of the two. A confirmation of their conclusions as to the influence of the position of the methyl group must await the establishment of configuration and the determination of the reaction rate of both isomers of each compound. This investigation is now in progress.

[10] Andrews and Kepner, THIS JOURNAL, **69**, 2230 (1947).

Acknowledgment.—The authors wish to thank both the University of Texas Research Institute and the Research Corporation for their support of these and related researches on allylic chlorides.

Summary

The reaction of allylic chlorides with potassium iodide in acetone has been used to elucidate the influence of substitutents on both the number 1 and number 2 carbons and also of geometrical isomerism on the relative reactivity of the allylic chlorine.

The greater the relative electronegativity of the group on the number 2 carbon, the less is the activity of the allylic chlorine toward iodide ion. The differences in reactivity, however, are small.

Because the reaction of potassium iodide with allylic chlorides is an S_N2 type reaction, either a relatively negative group or a relatively large group, or both, in the *cis* position on the number 1 carbon would inhibit the reaction.

Since the low boiling geometrical isomers of both 1,3-dichloropropene and 1,3-dichloro-2-methyl-1-propene react more readily than the high boiling isomers, the low boiling isomers have tentatively been assigned the *trans* structure.

RECEIVED JUNE 16, 1947

[CONTRIBUTION FROM LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Pteroic Acid Derivatives. I. Pteroyl-α-glutamylglutamic Acid and Pteroyl-α,γ-glutamyldiglutamic Acid

BY J. H. MOWAT, B. L. HUTCHINGS, R. B. ANGIER, E. L. R. STOKSTAD, J. H. BOOTHE, C. W. WALLER
J. SEMB AND Y. SUBBAROW

In the course of the degradation of the fermentation *L. casei* factor[1] this compound was found to contain three molecules of glutamic acid in contrast to the liver *L. casei* factor (pteroylglutamic acid) which contained only one molecule of glutamic acid.

The synthesis of the fermentation *L. casei* factor became of particular interest when Lewisohn and his associates[2] reported that the substance caused regression of spontaneous breast tumors in mice.

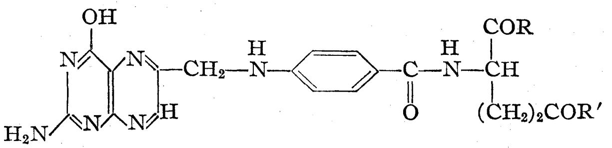
This communication describes the synthesis of one of the two possible isomers of pteroyldiglutamic acid and one of the five possible isomers of pteroyltriglutamic acid. These compounds were prepared during the course of our work on the structure and synthesis of the fermentation *L. casei* factor.

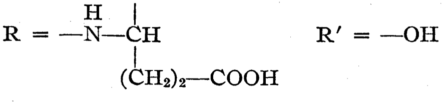
In the preparation of pteroyl-α-glutamylglutamic acid (I) the dipeptide α-glutamylglutamic acid[3] was treated with *p*-nitrobenzoyl chloride and after reduction of the nitro group the resulting *p*-aminobenzoyl-α-glutamylglutamic acid was condensed with 2,4,5-triamino-6-hydroxypyrimidine and 2,3-dibromopropionaldehyde by the procedure of Waller, *et al.*[4]

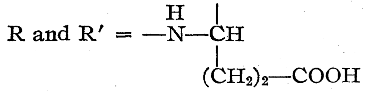
The purified product was only slightly active when assayed with *Lactobacillus casei* or *Streptococcus faecalis R.* The low activity with *Lactobacillus casei* indicated that the fermentation *L. casei* factor probably contained at least one gamma-linkage in the peptide side chain. It therefore seemed desirable to prepare pteroyl-α,γ-glutamyldiglutamic acid (II).

This substance was prepared by condensing diethyl glutamate[5] with the γ-acid chloride of carbobenzoxy-α-glutamyldiethylglutamate[3] to give carbobenzoxy-α,γ-glutamyldiglutamic acid tetraethyl ester. The carbobenzoxy group was removed in the usual manner with hydrogen and palladium charcoal catalyst in the presence of acetic acid, giving the acetate of α,γ-glutamyldiglutamic acid tetraethyl ester which was then converted to the *p*-nitrobenzoyl derivative. After reduction of the nitro group, the resulting *p*-aminobenzoyl-α,γ-glutamyldiglutamic acid was condensed with 2,4,5-triamino-6-hydroxypyrimidine and 2,3-dibromopropionaldehyde by the procedure of Waller, *et al.*[4]

The crude product, pteroyl-α,γ-glutamyldiglutamic acid, was not available in quantities sufficient for a satisfactory purification but the biological assay of both the crude and the partially purified material did not differ appreciably from that of pteroyl-α-glutamylglutamic acid and it



I 
$$R = -\overset{H}{N}-\underset{(CH_2)_2-COOH}{\overset{COOH}{CH}} \qquad R' = -OH$$

II 
$$R \text{ and } R' = -\overset{H}{N}-\underset{(CH_2)_2-COOH}{\overset{COOH}{CH}}$$

---

[1] Hutchings, *et al.*, THIS JOURNAL, **70**, 10 (1948).

[2] Lewisohn, C. Leuchtenberger, R. Leuchtenberger and Keresztesy, *Science*, **104**, 436 (1946).

[3] Bergmann and Zervas, *Ber.*, **65**, 1192 (1932).

[4] Waller, *et al.*, THIS JOURNAL, **70**, 19 (1948).

[5] Chiles and Noyes, *ibid.*, **44**, 1798 (1922).

was evident that this α,γ-isomer was not identical with the fermentation *L. casei* factor.

Since the above procedure was not entirely satisfactory for the preparation of useful quantities of the pure α,γ-compound, other methods of synthesis have been investigated and will be described in a later communication.

Experimental

***p*-Nitrobenzoyl-α-glutamylglutamic Acid.**—A mixture of α-glutamylglutamic acid[3,6] (17.0 g.), 43 cc. of water, and 111 cc. of 2 *N* sodium hydroxide solution was treated with 22.88 g. of *p*-nitrobenzoyl chloride and 104.8 cc. of 2 *N* sodium hydroxide solution. These reagents were added in several portions during about twenty minutes with vigorous stirring. After about forty-five minutes the mixture was acidified by the addition of 51 cc. of 6 *N* hydrochloric acid, cooled and filtered. The filter-cake was then extracted several times with a total volume of 200 cc. of hot water. The combined aqueous extracts were filtered while hot and then allowed to cool. The crystalline precipitate was collected, washed with cold water and dried; yield, 17.8 g. (68%). A sample of the material was recrystallized from hot water and dried at 60° *in vacuo* for analysis; m. p. 146–148°, cor.; $[\alpha]^{29}_{D}$ +8.12° (*C* 4, acetone).

Anal. Calcd. for $C_{17}H_{19}O_{10}N_3$: C, 48.00; H, 4.50; N, 9.88. Found: C, 47.71; H, 4.86; N, 9.77.

***p*-Aminobenzoyl-α-glutamylglutamic Acid Triethyl Ester Hydrochloride.**—A mixture of *p*-nitrobenzoyl-α-glutamylglutamic acid (35.0 g.) glacial acetic acid (32 cc.), water (750 cc.), and platinum oxide catalyst (0.6 g.) was shaken with hydrogen at room temperature and atmospheric pressure until 6.57 l. of hydrogen had been absorbed. After filtering off the catalyst, the solution was adjusted to *p*H 3.0 and extracted several times with ether to remove any traces of *p*-aminobenzoic acid which might be present. The aqueous solution contained 28.8 g. of *p*-aminobenzoyl-α-glutamylglutamic acid as determined by the method of Bratton and Marshall.[7] After evaporation to dryness *in vacuo* 21.6 g. of the non-crystalline residue was esterified at room temperature for eight hours with absolute ethanol containing 0.1 g. of hydrogen chloride per cc. of solution. After cooling overnight the crystalline precipitate was collected, washed with ethanol and dried; wt. 16.9 g., m. p. 164–167°. This was recrystallized from 140 cc. of ethanol for analysis; wt. 12.6 g., m. p. 166–168°, cor.

Anal. Calcd. for $C_{23}H_{33}O_8N_3 \cdot HCl$: C, 53.54; H, 6.64; N, 8.14. Found: C, 53.34; H, 6.63; N, 8.19.

***p*-Aminobenzoyl-α-glutamylglutamic Acid Triethyl Ester.**—A suspension of the above hydrochloride (12 g.) in 120 cc. of water at 60° was treated with 8 cc. of pyridine. The oily precipitate crystallized upon cooling; wt. 10.7 g., m. p. 113–115°. This material was recrystallized from 75 cc. of ethanol; wt. 6.8 g., m. p. 114–115°, cor.; $[\alpha]^{28}_{D}$ −8.75° (*C* 2, ethanol).

Anal. Calcd. for $C_{23}H_{33}O_8N_3$: C, 57.61; H, 6.94; N, 8.76. Found: C, 57.99; H, 7.32; N, 8.69.

Pteroyl-α-glutamylglutamic Acid.—*p*-Nitrobenzoyl-α-glutamylglutamic acid (35 g.) was reduced as previously described, and the solution, containing about 29 g. of *p*-aminobenzoyl-α-glutamylglutamic acid, was diluted to a volume of 2 liters. To this solution was added 2,4,5-triamino-6-hydroxypyrimidine dihydrochloride (31.2 g.) and sufficient sodium hydroxide to bring the mixture to *p*H 4.0. Then with vigorous stirring, a solution of 2,3-dibromopropionaldehyde (31.5 g.) in 750 cc. of ethanol was added during about thirty minutes, together with sufficient sodium hydroxide solution to maintain the reaction mixture at *p*H 4.0. After adding all of the reagents, the mixture was stirred for about thirty minutes. The precipitate was collected on the filter, washed with water, ethanol, acetone and ether and dried. The crude product weighed 36.8 g. Chemical assay[8] indicated that the crude material contained 22.2% by weight of pteroyl-α-glutamylglutamic acid.

Purification.—The above crude product, containing 8.17 g. of activity, was dissolved in 22.8 l. of 0.2 *N* sodium hydroxide solution and treated with 557 g. of barium chloride dihydrate. Alcohol was then added to 2.5% by volume and the mixture was filtered. The filtrate, containing 6.45 g. of activity, was diluted with water to a volume of 75 liters and the barium was removed as barium sulfate. The filtrate was treated with 18.75 liters of alcohol and diluted with water to a volume of 125 liters. After adjusting the solution to *p*H 6.0, 225 g. of zinc acetate was added and the mixture was then adjusted to *p*H 6.9, heated to 70° and filtered. The filter cake, containing the active material, was suspended in about 125 liters of water, treated with sodium hydroxide to 0.05 *N* and the active material was then precipitated with zinc at *p*H 6.9 as described above. After again precipitating with zinc, the zinc salt precipitate was extracted with 7 liters of 0.1 *N* sodium hydroxide solution. The alkaline extract, containing 4.46 g. of activity, was decolorized with 5 g. of Norite A, filtered and made up to 0.2 *N* with sodium hydroxide. The solution was treated with barium chloride to 0.2 *N* and then alcohol was added to 2% by volume. After filtering off the precipitate, the filtrate was acidified to *p*H 2.8, cooled and filtered. The filter-cake was dissolved in hot water (8 liters) and on cooling, the active material precipitated. After repeating this precipitation from hot water, 2.11 g. of material was obtained; chemical assay,[8] 93.9%. Extinction coefficient: calcd. 164. Found: 151–152; 151/164 = 92.2% which compares favorably with the above chemical assay. After further purification from hot water a sample was obtained for analysis.

Anal. Calcd. for $C_{24}H_{26}O_9N_8$: C, 50.52; H, 4.59; N, 19.64. Found (corrected for 1.1% ash): C, 50.40; H, 5.11; N, 19.86. Biological assay: *S. faecalis R.* 0.5%; *L. casei* 0.8%; (pteroylglutamic acid, 100%). The compound was fully active (on a molar basis) in the chick assay.[9]

Carbobenzoxy-α,γ-glutamyldiglutamic Acid Tetraethyl Ester.—To a cold (−10°) well-stirred solution of diethyl carbobenzoxy-α-glutamylglutamate[3] (43 g.) in 140 cc. of dry, alcohol-free chloroform was added 29.5 g. of phosphorous pentachloride in several portions during thirty minutes. The mixture was stirred at −10° for an additional forty-five minutes and the solution was then decanted from a small amount of residual solid matter and evaporated *in vacuo* (below 0°) to remove most of the chloroform. The residue was quickly washed several times by decantation with 400 cc. of cold, dry heptane and then dissolved in 90 cc. of cold, dry chloroform. This solution was added immediately to a solution of 47 g. of diethyl glutamate in 66 cc. of cold (−30°) dry chloroform. After about ten minutes, the reaction mixture was removed from the cooling bath and allowed to stand at room temperature for about three hours.

The reaction mixture was then extracted several times with each of the following, 0.2 *N* hydrochloric acid, water, 10% sodium bicarbonate solution, water, 0.1 *N* hydrochloric acid, and water. The chloroform solution was then dried over magnesium sulfate, clarified with charcoal, filtered and evaporated to dryness *in vacuo*. The waxy residue was triturated with ether and the crystalline product was collected, washed with ether and petroleum ether and dried; wt. 27.5 g. This material was recrystallized from 28 cc. of warm, dry chloroform by the addition of ether; wt. 22 g. A sample of the material was recrystallized several times from chloroform and ether for analysis; m. p. 140.5–142.0°, cor. (sintering 105–107°).

---

(6) The melting point of this peptide was found to be 184–185°, cor. instead of 205°, cor. All other properties of this material and of its precursors agreed with the values reported by Bergmann and Zervas.[3]

(7) Bratton and Marshall, *J. Biol. Chem.*, **128**, 537 (1939).

(8) Hutchings, *et al.*, *ibid.*, **168**, 705 (1947).

(9) L. J. Oleson, unpublished data.

Anal. Calcd. for $C_{31}H_{45}O_{12}N_3$: C, 57.13; H, 6.96; N, 6.45. Found: C, 57.13; H, 7.56; N, 6.52.

The Acetate of α,γ-Glutamyldiglutamic Acid Tetraethyl Ester.—Carbon dioxide-free hydrogen was passed into a well-stirred mixture of carbobenzoxy-α,γ-glutamyldiglutamic acid tetraethyl ester (10 g.), ethanol (150 cc.), water (50 cc.), glacial acetic acid (3.0 cc.), and 10% palladium–charcoal catalyst (0.7 g.) for two hours. An additional 0.6 g. of catalyst was added and the reduction was continued until carbon dioxide was no longer evolved. The carbon dioxide liberated in the reaction was absorbed in potassium hydroxide solution, and then precipitated as barium carbonate which was collected and weighed. Nearly the theoretical amount of barium carbonate was obtained. The reduction mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was shaken with dry ether, giving a white, crystalline precipitate which was collected, washed with dry ether and petroleum ether and dried; wt. 7.05 g. This material was satisfactory for the subsequent *p*-nitrobenzoylation. Some difficulty was experienced in recrystallizing the material directly, and finally an analytical sample was prepared as follows: The above crude product (0.222 g.) was suspended in about 5 cc. of dry ether and a small excess of diethylamine was added. The mixture was filtered to remove diethylamine acetate and the filtrate was evaporated to dryness *in vacuo* several times with small portions of ether to remove excess diethylamine. The final residue was taken up in a little dry ether, filtered and treated with a few drops of acetic acid. The crystalline acetate precipitated, and after washing with ether and petroleum ether it was dried *in vacuo*.

Anal. Calcd. for $C_{25}H_{43}O_{12}N_3$: C, 51.98; H, 7.50; N, 7.28. Found: C, 52.30; H, 7.40; N, 7.20.

No sharp melting point was obtained. The sample softened between 71.5 and 78.0° and melted at 78.0–81.0°, cor.

***p*-Nitrobenzoyl-α,γ-glutamyldiglutamic Acid Tetraethyl Ester.**—A stirred solution of the acetate of α,γ-glutamyldiglutamic acid tetraethyl ester (3.0 g.) in 50 cc. of dry ether was treated with 1 cc. of diethylamine. The ether solution was decanted and the gummy residue was washed twice with dry ether. The combined ether solution was filtered and treated with a solution of *p*-nitrobenzoyl chloride (1.0 g.) in 10 cc. of dry ether. After thirty minutes the precipitate was collected and washed with ether and then with water. The residue was dried *in vacuo*; wt. 1.72 g. For analysis a sample (0.070 g.) was twice recrystallized from 2 cc. of alcohol and 3 volumes of water; m. p. 144.0–145.0° cor. (sintering about 130°).

Anal. Calcd. for $C_{30}H_{42}O_{13}N_4$: C, 54.04; H, 6.35; N, 8.40. Found: C, 53.88; H, 6.75; N, 8.15.

***p*-Aminobenzoyl-α,γ-glutamyldiglutamic Acid Tetraethyl Ester.**—A well-stirred mixture of *p*-nitrobenzoyl-α,γ-glutamyldiglutamic acid tetraethyl ester (0.666 g.), ethanol (20 cc.), water (10 cc.), concentrated hydrochloric acid (0.25 cc.), and iron dust (0.333 g.) was warmed to 50° for about thirty minutes and then allowed to react at room temperature for an additional four hours. The reduction of the nitro group was then 95% complete as determined by the method of Bratton and Marshall.[7] The mixture was filtered and the filtrate was adjusted to *p*H 8.2. The precipitate was removed and washed with a little ethanol and the combined filtrates were acidified to *p*H 6.5. After evaporation to dryness *in vacuo*, the residue was suspended in a little water, collected on the filter, washed with water and dried; wt. 0.435 g. The material was recrystallized from aqueous alcohol and dried *in vacuo*; wt. 0.344 g.; m. p. melted to a semi-solid at 146.5–147.5° and became completely liquid at 149.0–150.0°, cor.

Anal. Calcd. for $C_{30}H_{44}O_{11}N_4$: C, 56.59; H, 6.97; N, 8.81. Found: C, 56.76; H, 7.19; N, 9.00.

Pteroyl-α,γ-glutamyldiglutamic Acid.—A mixture of *p*-aminobenzoyl-α,γ-glutamyldiglutamic acid tetraethyl ester (0.158 g.), ethanol (1.0 cc.), and 0.1 *N* sodium hydroxide solution (10 cc.) was warmed to about 60° for a few minutes and then allowed to stand at room temperature for about ninety minutes. The solution was filtered to remove a trace of insoluble material. The filtrate was acidified with 1 cc. of acetic acid and treated with 0.107 g. of 2,4,5-triamino-6-hydroxypyrimidine dihydrochloride. The mixture was then adjusted to *p*H 4.0 and reacted at *p*H 4.0 with 1.5 cc. of an acetic acid solution containing 0.108 g. of 2,3-dibromopropionaldehyde during twenty minutes. The precipitated crude product was collected, washed with ethanol, acetone, and ether and air dried; wt. 0.064 g.; chemical assay,[8] 26.8%. Microbiological assay: *S. faecalis R.* 0.14%; *L. casei* 0.17% (pteroylglutamic acid, 100%).

Acknowledgment.—The authors wish to acknowledge the assistance of Messrs. Willard McEwen, William Kinley and Albert Gazzola in preparing various intermediates, Mr. Louis Brancone and associates for the microanalyses, Miss Eleanora Boggiano for the biological assays, and Mrs. Anna deGrunigen for the chemical assays.

Summary

Pteroyl-α-glutamylglutamic acid and pteroyl-α,γ-glutamyldiglutamic acid have been prepared. The latter compound was not identical with the fermentation *L. casei* factor.

Pearl River, New York Received October 14, 1947

[CONTRIBUTION FROM LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Pteroic Acid Derivatives. II. Pteroyl-γ-glutamylglutamic Acid and Pteroyl-γ-glutamyl-γ-glutamylglutamic Acid

BY J. H. BOOTHE, J. H. MOWAT, B. L. HUTCHINGS, R. B. ANGIER, C. W. WALLER, E. L. R. STOKSTAD
J. SEMB, A. L. GAZZOLA AND Y. SUBBAROW

In the course of its degradation the fermentation *L. casei* factor was shown to contain three molecules of glutamic acid in contrast to the liver *L. casei* factor which contained only one molecule of glutamic acid.[1] Because pteroyl-α-glutamylglutamic acid and pteroyl-α,γ-glutamyldiglutamic acid which are described in the preceding communication showed[2] very low activities when assayed biologically against *S. faecalis R* or *L. casei*, it was decided to prepare some glutamic acid peptides in which only the γ-carboxyl groups were involved in the peptide linkages. This communication deals with the preparation of the dipeptide and the tripeptide of this type, and the subsequent preparation of their pteroyl derivatives. The general method used in this synthesis was to start with α-ethyl carbobenzoxyglutamate[3] which could not be satisfactorily crystallized from ether as described by Neuberger. Therefore, the crude mono ester was converted to the acid chloride[4,5] and treated with diethyl glutamate to form the carbobenzoxy dipeptide which was then reduced to triethyl γ-glutamylglutamate and crystallized as the hydrochloride.

For the preparation of pteroyl-γ-glutamylglutamic acid this dipeptide was *p*-nitrobenzoylated by the Schotten–Baumann method which at the same time hydrolyzed the esters to form *p*-nitrobenzoyl-γ-glutamylglutamic acid. The nitro group was reduced and without isolation of the intermediate *p*-aminobenzoyl dipeptide, the product was condensed with α,β-dibromopropionaldehyde and 2,4,5-triamino-6-hydroxypyrimidine as described for pteroylglutamic acid.[6] The pteroyl-γ-glutamylglutamic acid was isolated from the crude reaction product and was found to be in the range of 60 to 70% as active as pteroylglutamic acid when assayed against *S. faecalis R*, or *L. casei*.

For the preparation of the pteroyl tripeptide, triethyl γ-glutamylglutamate was condensed with the acid chloride of α-ethyl carbobenzoxyglutamate to form tetraethyl carbobenzoxy-γ-glutamyl-γ-glutamylglutamate. This carbobenzoxy tripeptide was reduced to tetraethyl γ-glutamyl-γ-glutamylglutamate hydrochloride which was *p*-nitrobenzoylated in benzene in the presence of diethyl amine. The *p*-nitrobenzoyl tripeptide was reduced to the corresponding *p*-aminobenzoyl derivative and condensed with α,β-dibromopropionaldehyde and 2,4,5-triamino-6-hydroxypyrimidine to form the pteroyl derivative.

The amount of pteroyl-γ-glutamyl-γ-glutamylglutamic acid prepared by this method was too small to isolate and completely characterize. It was biologically assayed, however, and showed the same ratio of activity for the two test organisms as does the fermentation *L. casei* factor, *i. e.* a low activity for *S. faecalis R* and a high activity for *L. casei*.

This method of synthesis served to indicate the probable structure of the fermentation *L. casei* factor but was not a desirable method from a preparative standpoint. Therefore, relatively little further work was done on this procedure, and efforts were directed toward finding a method more feasible for large scale preparations. This work will be the subject of future communications.

Experimental[7]

Triethyl Carbobenzoxy-γ-glutamylglutamate.—Seventy-eight grams of crude α-ethyl carbobenzoxyglutamate was dissolved in 250 cc. of anhydrous ether and cooled to −10°. With stirring and exclusion of moisture, 67.8 g. of phosphorus pentachloride was added in portions over a twenty minute period, not allowing the temperature to rise over −5°. The mixture was stirred thirty-five minutes more at −5 to 0°, filtered quickly and concentrated *in vacuo* to a residual sirup keeping the temperature below 0°. This residue was washed four times by decantation with cold, dry heptane, and then dissolved in 250 cc. of cold, dry chloroform and put in a Dry Ice-bath. It was then mixed with 114 g. of diethyl glutamate in 250 cc. of cold, dry chloroform and allowed to stand at room temperature two and one-half hours. The chloroform solution was then extracted several times with 0.2 *N* hydrochloric acid until the excess diethyl glutamate had been removed. It was then extracted twice with 0.2 *N* sodium bicarbonate solution and washed with water. This solution was dried over magnesium sulfate and the chloroform distilled off *in vacuo*. The oily residue changed to a hard wax-like material which was used directly for the next step; wt. 90.3 g. A small amount was purified by dissolving in hot ether and cooling. It tended to gel but by alternate warming and cooling it changed over to a white solid which was filtered off and dried; m. p. 91–92°.

Anal. Calcd. for $C_{24}H_{34}O_9N_2$: C, 58.2; H, 6.9; N, 5.66. Found: C, 59.0; H, 6.89; N, 5.54.

Triethyl γ-Glutamylglutamate Hydrochloride.—Sixty-five grams of crude triethyl carbobenzoxy-γ-glutamylglutamate was dissolved in 435 cc. of alcohol, treated with Norite and filtered. Two hundred seventeen cc. of water, 17 cc. of acetic acid and 2.6 g. of 10% palladium–charcoal catalyst were added. A stream of hydrogen was passed through with good stirring and carbon dioxide was evolved. After two hours the carbon dioxide evolution had almost ceased. Another 2.6 g. of catalyst was

---

(1) Hutchings, *et al.*, THIS JOURNAL, **70**, 10 (1948).

(2) Mowat, *et al.*, *ibid.*, **70**, 1096 (1948).

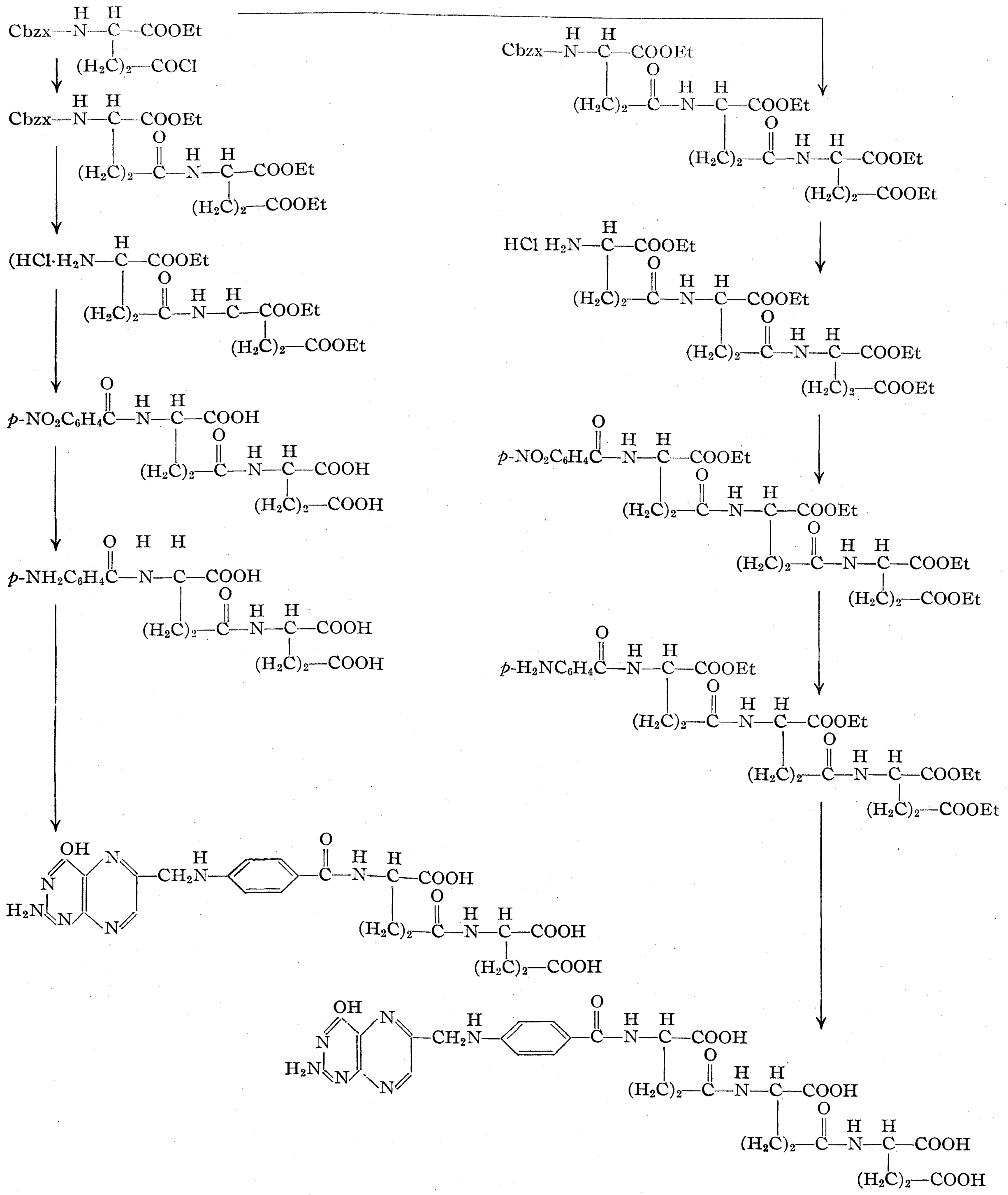
(3) Neuberger, *Biochem. J.*, **30**, 2085 (1936).

(4) du Vigneaud and Miller, *J. Biol. Chem.*, **116**, 469 (1936).

(5) Harrington and Mead, *Biochem. J.*, **29**, 1602 (1935).

(6) Waller, *et al.*, THIS JOURNAL, **70**, 19 (1948).

(7) All melting points are corrected and were taken by U. S. P. prescribed conditions.



added and the reduction was complete in another hour. Some runs of this reaction took much longer to reduce and required more catalyst, apparently due to catalyst poisons. The catalyst was filtered off and the filtrate was concentrated to complete dryness *in vacuo*. The residue was dissolved in 100 cc. of dry chloroform, hydrogen chloride was bubbled through for twenty minutes, and 650 cc. of anhydrous ether was added which precipitated an oil. This oil slowly crystallized and was filtered off and dried; wt. 36.5 g. Upon repeated crystallization from ethyl acetate or from chloroform and ether, a constant m. p. was reached at 132–133°, $[\alpha]^{26}_{D}$ −5.6° (*c* 4 in water).

Anal. Calcd. for $C_{16}H_{28}O_7N_2 \cdot HCl$: C, 48.4; H, 7.31; N, 7.08; α-amino N, 3.54. Found: C, 48.7; H, 7.62; N, 7.26; α-amino N, 4.18.

***p*-Nitrobenzoyl-γ-glutamylglutamic Acid.**—Four hundred twenty milligrams of triethyl γ-glutamylglutamate hydrochloride was dissolved in 0.7 cc. of water and 1.8 cc. of 2 *N* sodium hydroxide. Three hundred sixty-two milligrams of *p*-nitrobenzoyl chloride and 1.7 cc. of 2 *N* sodium hydroxide was added concurrently over a ten to fifteen minute period. The solution was stirred twenty minutes more and 0.425 cc. of concentrated hydrochloric acid was added. The precipitated *p*-nitrobenzoic acid was quickly filtered off and on cooling the filtrate, the product crystallized out rather slowly. After filtering and drying the product weighed 0.370 g. After repeated crystallization from water the m. p. was 194–195°.

Anal. Calcd. for $C_{17}H_{19}O_{10}N_3$: C, 48.0; H, 4.51; N, 9.88. Found: C, 48.28; H, 5.01; N, 9.97.

This reaction was also run in the same way on crude triethyl γ-glutamylglutamate before forming the hydrochloride. The same product was obtained in lower yield and the aqueous solution had to be concentrated after filtering off the *p*-nitrobenzoic acid.

Pteroyl-γ-glutamylglutamic Acid.—Eighteen grams of *p*-nitrobenzoyl-γ-glutamylglutamic acid was mixed with 720 cc. of water, 72 cc. of acetic acid, and 0.9 g. of platinum oxide. This mixture was shaken with hydrogen until 3.28 liters was absorbed, which required about two and one-half hours. The catalyst was removed by filtration and the filtrate was diluted to 1170 cc. A Bratton–Marshall amine test showed that the solution contained 14.0 g. (83.5% yield) of *p*-aminobenzoyl-γ-glutamylglutamic acid. Eighteen grams of 2,4,5-triamino-6-hydroxypyrimidine dihydrochloride was dissolved in the solution and while the *p*H was maintained at 4.0 by the addition of sodium hydroxide, 8.35 cc. of α,β-dibromopropionaldehyde in 600 cc. of alcohol was added slowly. After stirring one hour the precipitated product was filtered off and dried; yield 12.5 g. This crude material contained 2.4 g. of pteroyl-γ-glutamylglutamic acid by chemical assay.[8] The 12.5 g. of crude material was dissolved in 10 liters of 0.2 *N* sodium hydroxide, barium chloride was added to make 0.2 *N* and ethanol was added to the extent of 3%. The precipitate was discarded, the filtrate was diluted to 40 liters, and the barium ions were removed with sulfate ions. Zinc chloride was then added to *p*H 6.8 and the precipitate containing the desired material was filtered off and stirred with 65 liters of dilute sodium hydroxide containing 15% ethanol.

The *p*H was brought to 6.8 with zinc chloride, then heated to 90° and filtered, the active material remaining in the precipitate. This hot zinc salt precipitation was repeated twice and then the material was dissolved in 10 l. of 0.2 *N* sodium hydroxide and treated with barium chloride and alcohol as previously described. After removal of the barium ions the *p*H of the solution was brought to 3 and the precipitate was collected. It was then reprecipitated four times from 2 liters of hot water, by cooling and after filtering and drying weighed 0.522 g.

Anal. Calcd. for $C_{24}H_{26}O_9N_8$: C, 50.5; H, 4.56; N, 19.65. Found (corrected for 1.46% ash): C, 49.55; H, 4.96; N, 19.53. Microbiological assays: *S. faecalis R.*, 70.9%; *L. casei*, 62.9%. Both assays used pteroylglutamic acid as a standard.

Tetraethyl Carbobenzoxy-γ-glutamyl-γ-glutamylglutamate.—Twenty-five g. of triethyl γ-glutamylglutamate hydrochloride was dissolved in 100 cc. of chloroform. A solution of 1.448 g. of sodium in 50 cc. of ethanol was added to the chloroform solution which formed a colloidal precipitate of sodium chloride. The solution was evaporated to complete dryness *in vacuo*, taken up in 30 cc. of chloroform, and treated with a chloroform solution of the acid chloride of α-ethyl carbobenzoxyglutamate as already described for the dipeptide. The reaction mixture was worked up the same way and on concentrating the chloroform solution to dryness *in vacuo* a solid residue was obtained which was shaken with ether and filtered off; yield 9.5 g. A small portion was crystallized from chloroform and ether; m. p. 109–110°.

Anal. Calcd. for $C_{31}H_{45}O_{12}N_3$: C, 57.2; H, 6.91; N, 6.45. Found: C, 56.4; H, 6.57; N, 6.52.

Tetraethyl γ-Glutamyl-γ-glutamylglutamate Hydrochloride.—Tetraethyl carbobenzoxy-γ-glutamyl-γ-glutamylglutamate (11.32 g.) was reduced in 125 cc. of alcohol, 40 cc. of water, 4 cc. of acetic acid, and 0.4 g. of 10% palladium–charcoal catalyst as described above. It was necessary to add 0.4 g. more of catalyst after two hours and the total reduction time was five hours. The catalyst was filtered off and the filtrate was concentrated to 40 cc. and diluted with 75 cc. of water which precipitated a small amount of white flocculent material. This was removed by filtration and the filtrate was concentrated to dryness *in vacuo* and dried under vacuum over phosphoric anhydride. The residue was dissolved in 30 cc. of chloroform, hydrogen chloride was bubbled through, and the product was precipitated by adding 150 cc. of ether. The dried product weighed 7.5 g. A portion was precipitated twice from hot ethyl acetate by cooling but was apparently amorphous; m. p. 147–150°.

Anal. Calcd. for $C_{23}H_{39}O_{10}N_3$: C, 49.8; H, 7.07; N, 7.59. Found: C, 49.45; H, 7.8; N, 7.45.

Tetraethyl *p*-Nitrobenzoyl-γ-glutamyl-γ-glutamylglutamate.—A mixture of 5.32 g. of tetraethyl γ-glutamyl-γ-glutamylglutamate hydrochloride, 50 cc. of dry benzene, and 1.94 cc. of diethylamine were mixed well and the diethylamine hydrochloride was filtered off. To the filtrate was added a solution of 3.56 g. of *p*-nitrobenzoyl chloride in 15 cc. of ether and 50 cc. of benzene. The solution changed to a jelly-like solid in a few minutes and was then shaken well for thirty minutes. The mixture was then diluted with ether and the solid was removed by filtration and washed well with ether. After drying, the product was powdered, washed well with water, and again dried; yield 4.2 g. A small portion was crystallized twice from hot alcohol by cooling very slowly to prevent gelling: m. p. 173–174°,[9] $[\alpha]^{28}_{D}$ −4.0° (*c* 2 in acetic acid).

Anal. Calcd. for $C_{30}H_{42}O_{13}N_4$: C, 54.0; H, 6.34; N, 8.40. Found: C, 54.0; H, 6.95; N, 8.60.

Tetraethyl *p*-Aminobenzoyl-γ-glutamyl-γ-glutamylglutamate.—A mixture of 3.0 g. of tetraethyl *p*-nitrobenzoyl-γ-glutamyl-γ-glutamylglutamate, 25 cc. of water, 50 cc. of ethanol, 1.5 g. of iron powder, and 1 cc. of concentrated hydrochloric acid was warmed to 35–40° and stirred vigorously for two and one-half hours during which time the solid all dissolved. Two cc. of 28% ammonium hydroxide was added and hydrogen sulfide was bubbled in for twenty minutes. The mixture was filtered and the precipitate was washed with ethanol. A Bratton–Marshall amine test on the filtrate indicated that it contained an 87% yield of the product. Eighty per cent. of the solution was adjusted to *p*H 7.5 and evaporated to a small volume *in vacuo*. Ethanol and several drops of ammonium hydroxide were added and the solution was evaporated to complete dryness. The residue was taken up in 35 cc. of ethanol, filtered to remove the ammonium chloride and evaporated to dryness. The product was taken up in 12 cc. of ethanol and 30–40 cc. of water was added which caused an oil to separate. This oil crystallized on standing overnight; yield 1.6 g. One gram of this material was dissolved in 10 cc. of ethanol, 60 cc. of water, and 0.3 cc. of concentrated hydrochloric acid and was filtered to remove traces of unreduced nitro compound. To the filtrate was added 0.6 cc. of pyridine which caused the product to oil out and later crystallize. A portion of this was recrystallized twice from alcohol and ether; m. p. 147–148°.

Anal. Calcd. for $C_{30}H_{44}O_{11}N_4$: C, 56.6; H, 6.90; N, 8.80. Found: C, 56.57; H, 6.56; N, 8.71.

Pteroyl-γ-glutamyl-γ-glutamylglutamic Acid.—One hundred milligrams of tetraethyl *p*-nitrobenzoyl-γ-glutamyl-γ-glutamylglutamate was reduced as described

---

[8] Hutchings *et al.*, *J. Biol. Chem.*, **168**, 705 (1947).

[9] In some other preparations of this compound by the same method, it was obtained in a form melting at 158–159°. One form could not be changed to the other at will by seeding although this occasionally happened during recrystallization. *Anal.* C, 54.08; H, 5.48; N, 8.34. This compound was later prepared by other methods and the same m. p. behavior was noted.

above. After one and one-half hours the excess iron was filtered out and washed with 0.5 cc. of acetic acid and 3 cc. of water. The filtrate was diluted to 8 cc. and a Bratton–Marshall amine test showed that 97% of the theoretical amine was present. Sixty-five milligrams of 2,4,5-triamino-6-hydroxypyrimidine dihydrochloride was added to the reduced solution and the *p*H was adjusted to 3.8. Sixty-six milligrams of dibromopropionaldehyde in 1 cc. of acetic acid was added slowly with stirring and maintaining the *p*H at 3.5 to 4. The precipitate was rather sticky so the water was poured off and precipitate was washed with alcohol and ether; yield, 25 mg. Chemical assay: 23.4%. Microbiological assays after hydrolysis of the esters for twelve hours in 0.1 *N* sodium hydroxide: *S. faecalis R.*, 0.6%; *L. casei*, 16.5%. If these assay figures are corrected for the inert material present in the crude reaction mixture the values are then: *S. faecalis R.*, 2.57%; *L. casei*, 70.6%. These figures are very similar to those obtained for the fermentation of *L. casei* factor.

Acknowledgments.—The authors wish to acknowledge the able assistance of Miss Eleanora Boggiano in doing microbiological assays and Mrs. Anna deGrunigen in doing chemical assays. The chemical analyses were performed by Mr. Louis Brancone and co-workers. We are also indebted to Mr. Willard McEwen and Mr. William Kinley for the preparation of intermediates used in this synthesis.

Summary

Pteroyl-γ-glutamyl-glutamic acid has been synthesized and found to stimulate the growth of the two test organisms, *S. faecalis R.* and *L. casei*, to the extent of 60–70% as well as does pteroylglutamic acid.

Pteroyl-γ-glutamyl-γ-glutamylglutamic acid has been synthesized and found to show the same ratio of activity for the two test organisms as does the fermentation *L. casei* factor. This synthetic compound was not isolated from the reaction mixture and was only characterized to the extent of its microbiological activity.

PEARL RIVER, NEW YORK RECEIVED OCTOBER 14, 1947

[CONTRIBUTION NO. 657 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Configuration of Vaccenic Acid[1]

BY P. C. RAO AND B. F. DAUBERT

Recent interest in the purported growth-promotional activity for the rat of vaccenic acid, a fatty acid reportedly isolated from several animal fats by Bertram[2] in 1928, has prompted a reinvestigation of the presence of the fatty acid in animal fat and a confirmation of its configuration.

Several investigators,[3,4] including Bertram,[2] had observed that the iodine value of the solid fatty acids separated from the mixed fatty acids of an animal fat (tallow) by the Twitchell lead salt procedure invariably showed a higher iodine value than the solid acids separated from vegetable fat. This seemed to indicate the presence of a solid unsaturated fatty acid. It therefore seemed desirable to Bertram[2] to prove the presence of the fatty acid in beef tallow and, if present, to accomplish its isolation. As a result of his investigation, Bertram[2] reported the isolation of a solid unsaturated acid from beef tallow and furthermore, on the basis of a study of the fatty acid, concluded that it was an 11,12-octadecenoic acid of *trans* configuration (11,12-elaidic acid). He also reported its isolation from sheep fat and butterfat.

Subsequently other investigators[5,6,7] have confirmed the presence of vaccenic acid in animal fat but, to the authors' knowledge, the *trans* configuration of vaccenic acid as postulated by Bertram[2] has not been confirmed. However, the preparation of an 11,12-elaidic acid (vaccenic) has been reported by Böeseken and Hoagland[8] on partial hydrogenation of α-eleostearic acid.

In view of the alleged nutritional significance of vaccenic acid, the purpose of the current communication is to present further evidence concerning its configuration.

Experimental

Preparation of Vaccenic Acid.—The vaccenic acid was isolated from beef tallow essentially by the procedure described by Bertram.[2] However, a final lead salt separation of the acids from the liquid mercury salts was made in order to free the vaccenic acid of liquid unsaturated fatty acids. The vaccenic acid (10 g.) so obtained was esterified to the methyl ester, and fractionated in an efficient fractionating column. A highly purified methyl ester fraction (2.2 g.) was obtained of iodine value 84.0 (calcd. 85.6), and b. p. 172–173° at 3 mm. The vaccenic acid obtained after saponification of the methyl ester was crystallized several times from cold acetone, and had the constants as listed in Table I.

TABLE I

	This study	Bertram[2]
Iodine value, Wijs	87.6 (calcd. 89.9)	86.5
Saponification equivalent	282.1 (calcd. 282.4)	281.5
Melting point, °C.	42.5	39.0
Saturated acids	Trace	0.9%
Refractive index	1.4439[a] at 60°	1.44071 at 70°

[a] Assuming d*n*/d*t* to be 0.00037, the calculated value at 70° is 1.4402.

---

(1) The generous financial assistance of the Buhl Foundation in support of this investigation is gratefully acknowledged.

(2) Bertram, *Biochem. Z.*, **196**, 433 (1928).

(3) Twitchell, *J. Ind. Eng. Chem.*, **13**, 806 (1921).

(4) Hilditch, "Chemical Constitution of Fats," John Wiley and Sons, New York, N. Y., 1941.

(5) Boer, Jansen and Kentie, *J. Nutrition*, **33**, 339 (1947).

(6) Elvehjem, *et al.*, *J. Biol. Chem.*, **169**, 229 (1947).

(7) Grossfeld and Simmer, *Z. Untersuch Lebens.*, **59**, 237 (1930.)

(8) Böeseken and Hoagland, *Rec. trav. chim.*, **46**, 632 (1927).

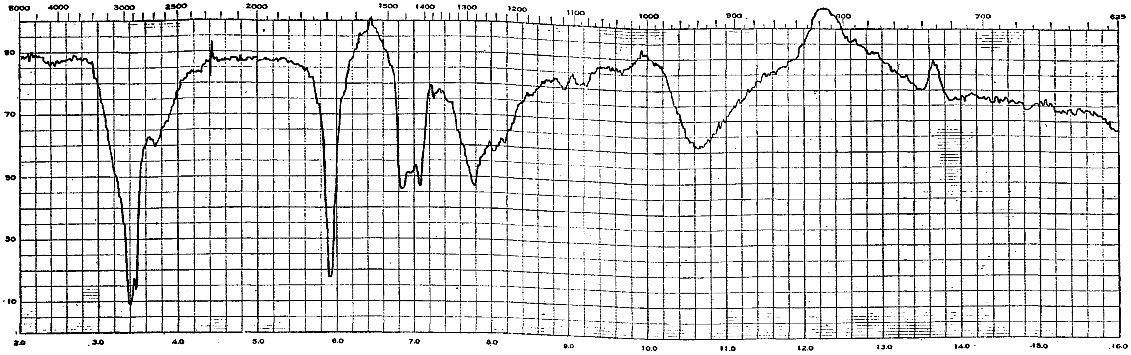


Fig. 1.—Infrared absorption curve for oleic acid.

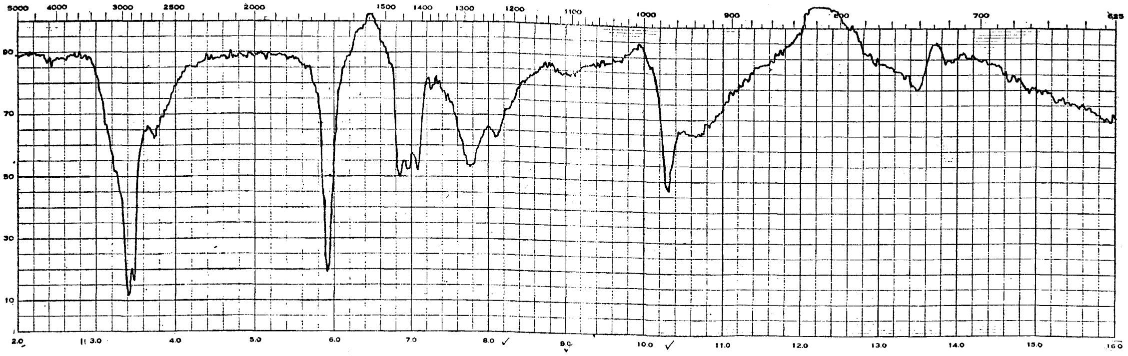


Fig. 2.—Infrared absorption curve for vaccenic acid.

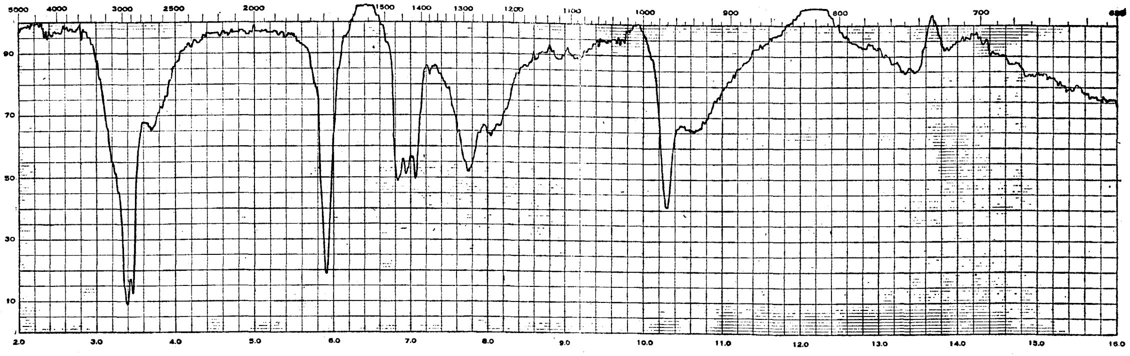


Fig. 3.—Infrared absorption curve for elaidic acid.

Preparation of Oleic and Elaidic Acids.—The oleic acid was prepared by fractional distillation and low-temperature crystallization of the methyl esters of the fatty acids of olive oil. Subsequent saponification of the highly purified methyl oleate and fractional distillation of the oleic acid gave a product of iodine value 89.8 (calcd. 89.9) containing a trace of dienoic acid. The purity of the oleic acid was comparable to the oleic acid prepared for use in the synthesis of glycerides as previously reported.[9]

Elaidic acid, m. p. 44.5°, I. V. 89.7, was prepared from the oleic acid by elaidinization according to the method of Lyutenberg.[10]

Infrared Spectra.—Infrared absorption curves for the vaccenic, oleic and elaidic acids were obtained using a Baird infrared spectrophotometer.[11] Solution of the respective fatty acids (10%) in carbon tetrachloride using 0.01-cm. cells was found satisfactory for measurement of the infrared absorption.

Discussion of Results

Essentially all of the evidence presented by Bertram in support of his conclusion that vaccenic acid is of *trans* configuration was based on a comparison of its freezing point and the constant *K* of van der Steur with those of oleic and elaidic acids, and the fact that on elaidinization the original vaccenic acid was recovered unchanged. Al-

---

[9] Daubert, Fricke and Longenecker, THIS JOURNAL, **65**, 2142 (1943).

[10] Lyutenberg, *Fettchem. Umschau*, **42**, 89 (1935).

[11] The coöperation of Dr. Harold Klug and Dr. A. L. Marston of the Mellon Institute for their assistance in obtaining the infrared absorption curves is gratefully acknowledged.

though all of the above evidence certainly seemed to support the conclusions of Bertram,[2] it was felt that additional proof of the configuration of vaccenic acid could be obtained by infrared absorption measurements in comparison with oleic and elaidic acids. The infrared absorption curves for oleic, elaidic and vaccenic acids, respectively, are given in Figs. 1, 2, and 3. On the assumption that oleic acid is *cis* and elaidic acid *trans*, it may be seen from the general similarity of the infrared patterns of elaidic and vaccenic acids that the latter is probably of *trans* configuration. Comparison of the curves for the three fatty acids in the region of wave length 3 to 7.5 μ shows a striking similarity. The minimum at 10.25 μ in the pattern for elaidic acid is also present in the vaccenic acid pattern, but absent for oleic acid. However, the doublets in the region of 8.8 to 9.2 μ present in the oleic acid curves are absent in the infrared pattern for vaccenic acid. Perhaps this may be attributed to the difference in the position of the double bond. Because of light scattering, no particular significance is attributed to small differences in the region 13 to 16 μ.

Although the vaccenic acid is probably of greater purity than the acid isolated by Bertram, the magnitude of the melting point in comparison with that reported by Bertram is somewhat surprising.

X-Ray diffraction analysis of the vaccenic acid is in progress and the results of this study will be reported in a separate communication.

In view of the pronounced similarity in infrared absorption of elaidic and vaccenic acids, additional evidence is therefore presented to confirm the *trans* configuration of vaccenic acid.

Infrared absorption measurements of highly purified vaccenic acid are reported in comparison with values for oleic and elaidic acids.

Acknowledgment.—The technical assistance of Miss Leatrice Klein in the preparation of the vaccenic acid is gratefully acknowledged.

Summary

Comparison of the infrared patterns of the three fatty acids seems to confirm the *trans* configuration of vaccenic acid.

PITTSBURGH, PENNSYLVANIA

RECEIVED NOVEMBER 6, 1947

[CONTRIBUTION NO. 637 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Kinetics of the Fumarase System[1]

BY E. M. SCOTT AND RUTH POWELL

Dakin[2] in 1922 showed that an enzyme, fumarase, catalyzed the equilibrium reaction

$$\text{fumarate} + H_2O \rightleftarrows l\text{-malate}$$

Clutterbuck[2a] found that phosphate affected both the solubility of the enzyme and the rate of the reaction. Borsook and Schott[3] studied the equilibrium and calculated the heat of formation of *l*-malic acid. It was reported by Ionescu, *et al.*,[4] that the *p*H of optimum activity of the enzyme with *l*-malate as substrate was more alkaline than that with fumarate. Jacobsohn[5] found that while the reaction with both substrates appeared to follow the first-order course, the well-known relation of the first-order reaction constants to the equilibrium constant

$$K_1/K_2 = K_{\text{eq.}} \qquad (1)$$

did not apply.

The present investigation was designed to test Jacobsohn's observations and to determine why equation (1) did not hold. In contrast to the experiments cited above, highly purified enzyme prepared according to the crystallization procedure of Laki and Laki[6] was used in our investigations.

A titrimetric determination of fumarate similar to the method of Straub[6a] was found to be much more convenient and somewhat more accurate than the polarimetric methods used in earlier kinetic studies.[2a,4,5]

Experimental

Eastman Kodak Co. fumaric acid was recrystallized from water, dissolved and neutralized as one substrate; Eastman *l*-malic acid was dissolved and neutralized to provide the other. Purity of the substrates for present purposes was established by the following evidence: (1) Both acids gave correct neutral equivalents; (2) *l*-malic acid gave no reaction with permanganate under the conditions stated below; (3) both substrates gave the same equilibrium concentration of fumarate; and (4) no evidence of inhibition by either substrate was found (*vide infra*, "Effect of Substrates on Stability").

The enzyme used was an amorphous fraction, obtained after crystallization of the protein described by Laki and Laki. This preparation had about three times as much activity per unit protein N as did the crystals. The initial rate of hydration of fumarate at *p*H 7.29 and 30° by this enzyme was 0.015 mole/sec. g. of protein N.

Unless otherwise indicated, the enzyme tests were run in 10 ml. of a solution containing phosphate buffer (*p*H 7.29, ionic strength 0.2), 0.1 *M* sodium fumarate or *l*-malate, and enzyme to give a protein N concentration of 4.2 p. p. m. One ml. samples were removed, added to 10 ml. of water containing 0.5 ml. of concentrated

---

(1) Aided by grants of the National Institute of Health and the Buhl Foundation. Presented at the 111th Meeting of the American Chemical Society, April 14–18, 1947.

(2) Dakin, *J. Biol. Chem.*, **52**, 183 (1922).

(2a) Clutterbuck, *Biochem. J.*, **22**, 1193 (1928).

(3) Borsook and Schott, *J. Biol. Chem.*, **92**, 559 (1931).

(4) Ionescu, Stanciu and Radalescu, *Ber.*, **72B**, 1949 (1939).

(5) Jacobsohn, *Biochem. Z.*, **254**, 112 (1932); **274**, 167 (1934).

(6) Laki and Laki, *Enzymologia*, **9**, 139 (1941).

(6a) Straub, *Z. physiol. Chem.*, **236**, 43 (1935).

hydrochloric acid, and titrated with 0.02 *M* potassium permanganate. The end-point of the titration was taken when one drop (0.03 ml.) of potassium permanganate solution gave a pink color which persisted for sixty seconds. Analyses by this method of mixtures of known amounts of fumarate and *l*-malate without enzyme were accurate within 0.5% total substrate content. Acetic acid–acetate buffers were used below *p*H 5.8, phosphate buffers between 5.8 and 8.0, and ammonia–ammonium chloride buffers above *p*H 8.0. All buffers had an ionic strength of 0.2. Temperatures were maintained by immersion in a water-bath, controlled to within 0.05°.

Since the reaction did not follow a path predictable from an equation for a reaction of integral order, rates were expressed in terms of the initial value as determined graphically. This appeared to be justified by the data in Fig. 1, from which it was concluded that initial rate was directly proportional to enzyme concentration.

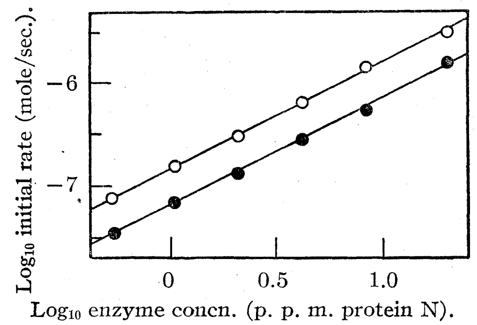


Fig. 1.—Effect of enzyme concentration on initial rate of reaction: –○–○–, fumarate as substrate; –●–●–, *l*-malate as substrate.

Results

Equilibrium Constant.—The equilibrium constant was found to be independent of substrate or enzyme concentration. It was independent of *p*H, except that below *p*H 6.0, *l*-malate was favored. Since *l*-malic is a somewhat weaker acid than fumaric, this was expected. The variation of equilibrium constant with temperature is shown in Fig. 2. From this figure, the heat change of hydration of fumarate ion was calculated as −3560 cal./mole and the free energy change at 25° was −826 cal./mole. These values agree satisfactorily with those of previous investigators.[3,5]

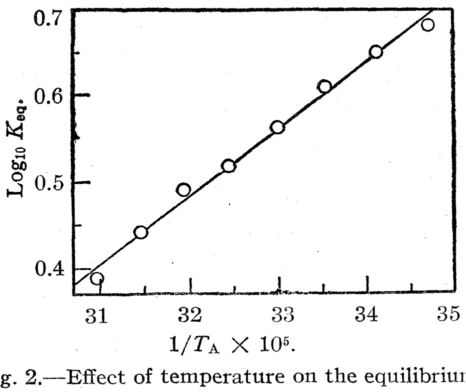


Fig. 2.—Effect of temperature on the equilibrium.

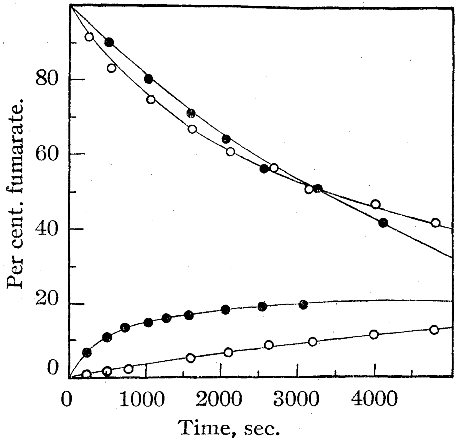


Fig. 3.—Path of the reaction: –○–○–, *p*H 8.46; –●–●–, *p*H 5.97.

Course of Reaction.—Typical curves of the course of the reaction are shown in Fig. 3. When these were plotted according to the first-order equilibrium reaction equation

$$K_{\mathrm{F}} + K_{\mathrm{M}} = 1/t \ln\left(\frac{x_0 - x_e}{x - x_e}\right) \qquad (2)$$

(where x_0 is original concentration x_e the equilibrium concentration, x the concentration of fumarate at time t, and K_{F} and K_{M} the first-order reaction constants with fumarate and *l*-malate, respectively), the curves shown in Fig. 4 were obtained. As is apparent, the slopes of the curves do not agree when the reaction starting with 100% *l*-malate is compared with that starting with 100% fumarate. This confirms the work of Jacobsohn.

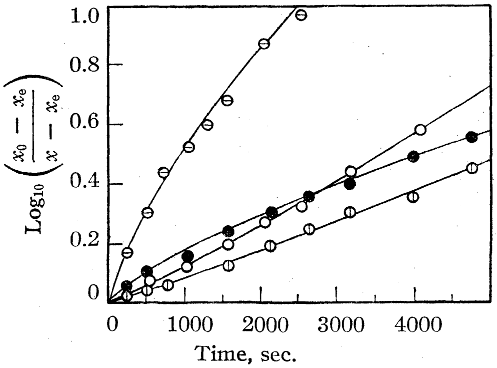


Fig. 4.—The reaction as fitted to the first order equation: –●–●–, fumarate, *p*H 5.97; –⦶–⦶–, *l*-malate, *p*H 5.97; –○–○–, fumarate, *p*H 8.46; –⊖–⊖–, *l*-malate, *p*H 8.46.

Effect of *p*H.—The relative rates of the reaction starting with either *l*-malate or fumarate varied greatly with *p*H as shown in Fig. 5. Thus, at *p*H 6.0 equilibrium was reached with fumarate in about one-half the time required for the reaction with *l*-malate, but at *p*H 9.0, over six times as long was required with fumarate as with *l*-malate.

Effect of Temperature.—Variation of initial rate of reaction with temperature at *p*H 7.29 is shown in Fig. 6. The apparent activation

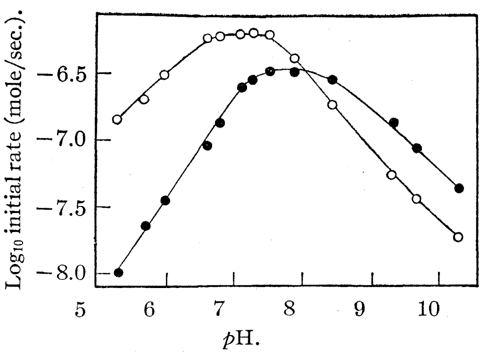


Fig. 5.—Effect of pH on reaction rate: –○–○–, fumarate; –●–●–, l-malate.

energies starting with the two substrates were: fumarate, 8,100 cal./mole; l-malate, 12,200 cal./mole.

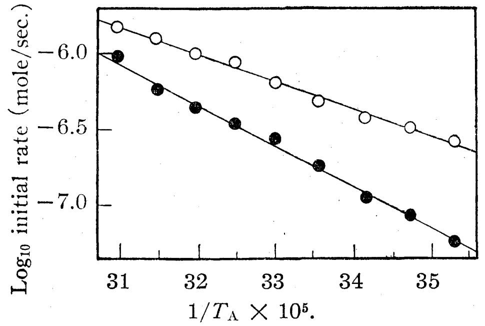


Fig. 6.—Effect of temperature on reaction rate: –○–○–, fumarate; –●–●–, l-malate.

Effect of Substrates on Stability.—In one experiment l-malate was added, the system brought to equilibrium, and then fumarate was added. The rate of hydration of fumarate was found to be the same as when fumarate was added, the system brought to equilibrium, and more fumarate added. This indicated that no inhibitors were being added with either substrate, and that the substrates had no differential effect on stability of the enzyme. Independent tests showed that under the usual conditions of our experiments, enzyme destruction was very slow or negligible.

Effect of Substrate Concentration.—Over the range shown in Table I, the initial rate of reaction at pH 7.29 appeared to be independent of substrate concentration. This could have been true only if the rate-controlling step of the reaction was not of the first order but was, at least at the start, of the zero order.

TABLE I

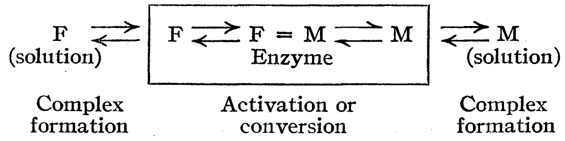
EFFECT OF SUBSTRATE CONCENTRATION ON INITIAL RATE

Substrate concentration, M	Initial rate, mole/sec. $\times 10^7$ Fumarate	l-Malate
0.4	5.0	2.8
.2	6.0	3.2
.1	5.9	3.2
.05	5.6	4.0
.025	5.4	2.5
.0125	6.0	3.0

Discussion

It is evident from the results that the reason equation (1) does not apply to the case of fumarase is that the reaction is not of the first order. Superficially it appears to follow the course predicted by the first-order equation because, in an equilibrium system, the reverse reaction is so important in determining rate that different orders of reaction are not clearly distinguishable. Equation (1) will apply ordinarily only to those reactions in which there is a single step conversion of one reactant to the other. Accordingly, these results can be interpreted as indicating that the fumarate–l-malate interconversion proceeds through a series of steps, any one of which may limit the rate. Consequently, the rate with one substrate may bear no obvious relationship to the rate with the other.

The only steps in enzyme-catalyzed reactions of which we have some conception at present are those of activation and complex formation. By complex formation is meant the fact that the substrate must combine with, or be adsorbed on, or at least come in contact with, the enzyme for the reaction to proceed. The reaction might then be pictured as



in which water is assumed to be present in great excess. The processes within the rectangle take place on the surface of the enzyme.

A priori, one cannot decide whether the process of complex formation involves a change in free energy, nor can one predict whether complex formation has an appreciable activation energy of its own. Three possibilities exist: (1) one can assume that the energy of activation of complex formation is small (*i. e.*, complex formation is much more rapid than conversion; this was the assumption of Michaelis and Menten[7]); (2) it can be assumed that the energy of activation of complex formation is appreciably greater than the energy of activation of the conversion process (*i. e.*, complex formation limits the rate); or (3) one can assume that the rates of complex formation and conversion are approximately the same, as did Briggs and Haldane.[8] In all three cases, one arrives at the following equation for the kinetic process

$$\alpha(x_0 - x) + \beta \ln \left(\frac{x_0 - x_e}{x - x_e}\right) = t \qquad (3)$$

α and β are constants which differ in meaning depending on the assumptions made.

---

[7] Michaelis and Menten, *Biochem. Z.*, **49**, 1333 (1913).

[8] Briggs and Haldane, *Biochem. J.*, **19**, 338 (1925).

Equation (3) fits much of the data in a quite satisfactory manner. Its essential applicability was indicated by the fact that, unlike several other possible equations, the same values of the constants were found whether starting with fumarate or with *l*-malate as substrate. In Fig. 3, the lines were drawn from this equation with values of α and β as follows: *p*H 5.97, $\alpha = -27{,}800$, $\beta = 2040$; *p*H 8.46, $\alpha = 35{,}700$, $\beta = 570$. Considering the great uncertainties in the processes involved in the fumarase reaction, however, the exact meaning of α and β is questionable, and equation (3) can be regarded as little more than an empirical expression that fits observed data. Thus, there is no indication in these data as to which of the three assumptions above may be correct, nor whether the real mechanism may not be in fact much more complicated than any of those here visualized.

Summary

The initial rate of the forward reaction in the system

$$\text{fumarate} + H_2O \underset{}{\overset{\text{fumarase}}{\rightleftharpoons}} l\text{-malate}$$

bears no obvious relation to the initial rate of the reverse reaction. This was shown to be due to the reaction being composed of a series of steps of which the rate-controlling step was of the zero order. The effect on the system of temperature, *p*H, and enzyme and substrate concentrations was studied, and an equation derived which described the data obtained.

PITTSBURGH, PENNSYLVANIA RECEIVED JUNE 11, 1947

[CONTRIBUTION FROM INSTITUTE OF POLYMER RESEARCH POLYTECHNIC INSTITUTE OF BROOKLYN]

Rate of Exchange of Cellulose with Heavy Water

BY V. J. FRILETTE,[1a] J. HANLE AND H. MARK

Introduction

The interchain structure of cellulose has aroused considerable interest in recent years. As with other polymers, there is reason to believe that the physical and chemical properties of cellulose are strongly influenced by the supermolecular texture that exists in a given sample. A generally accepted hypothesis concerning the texture of cellulose is[1b] that individual chain molecules having average extended lengths of several thousand Ångströms pass successively through regions of lower and higher lateral order. These ordered and disordered domains are not sharply distinguished and separated from each other but may be connected by areas of intermediate order. They are usually as a matter of convenience referred to as amorphous and crystalline constituents. One could expect different portions of a chain in such a structure to have different degrees of reactivity with small reagent molecules, for the behavior of an individual chain segment would depend upon how tightly it is bound laterally to its nearest neighbors. The reacting groups in the most disordered regions of a sample would be expected to be most easily accessible, while they would be inaccessible in the areas of high lateral order. Consequently, one would expect hydroxyl groups or glucoside bonds in amorphous regions to be most susceptible to reactions so that if the rate or extent of a particular reaction is followed quantitatively, it may be interpreted in terms of structural accessibility.

Until now, three chemical reactions have been used to characterize the reactivity of cellulose samples. Goldfinger, Siggia and Mark[2] measured the rate of periodate oxidation of various cellulose samples and established the existence of a rapid and a slow reaction. Assaf, Haas and Purves[3] treated cellulose with thallous ethylate in different solvents and found that only a fraction of the existing hydroxyl groups were converted to the thallium salt. Finally, Nickerson[4] and Conrad and Scroggie[5] studied the oxidative hydrolysis of cellulose to carbon dioxide and water. The rate of carbon dioxide evolution, which at first is rapid, gradually decreases to an almost constant value. It is claimed that by an analysis of the rate curves an estimate can be made of the amount of easily accessible (amorphous) cellulose originally present in the sample.

In this paper we shall describe a fourth reaction suitable for characterizing cellulose. It was first observed by Bonhoeffer[6] that the hydroxyl groups of cellulose react with heavy water. Champetier and Viallard,[7] who made a more systematic study of this effect, reported that a moderately slow reaction occurred and that practically all of the hydroxyl groups exchanged. The curves reported by these investigators showed little promise of yielding any information on accessibility, but a careful reading of the paper revealed that the cell in which the reaction was conducted had been

---

(1a) The material for this paper was abstracted in part from the thesis of V. J. Frilette, submitted to the Faculty of the Graduate School of the Polytechnic Institute in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1947.

(1b) O. Kratky, *Z. angew. Chem.*, **53**, 153 (1940).

(2) Goldfinger, Siggia and Mark, *Ind. Eng. Chem.*, **35**, 1083 (1943).

(3) Assaf, Haas and Purves, THIS JOURNAL, **66**, 59 (1934).

(4) Nickerson, *Ind. Eng. Chem.*, **34**, 85 (1942).

(5) Conrad and Scroggie, *ibid.*, **37**, 592 (1945).

(6) Bonhoeffer, *Z. Elektrochem.*, **40**, 469 (1934).

(7) Champetier and Viallard, *Bull. soc. chim.*, [5] **33**, 1042 (1938).

opened for each density measurement made on the water, thus introducing the possibility that exchange with moisture vapor from the air may have occurred. While the errors thus introduced would not affect the over-all shape of the exchange curve, the calculated extent of the reaction would be too high. We felt, therefore, that a few more experiments along these lines would be of interest and observed, in fact, that the exchange is not of moderate speed, but very fast; to properly follow it, one must introduce some device for agitating the cellulose.

The mild conditions under which the cellulose–heavy water reaction can be carried out is a very advantageous feature from the point of view of characterization, for there is hardly a question but that the investigated sample remains chemically and physically unchanged during the course of the reaction.

Experimental

Treatment of Samples.—Through the courtesy of Drs. Conrad and Scroggie of the Rayon Department, E. I. du Pont de Nemours and Company, a variety of cellulose samples were obtained which had already been characterized for accessibility by the Nickerson method as modified by Conrad and Scroggie.[6] In addition to these samples, two native cottons which exhibited the normal X-ray fiber patterns were analyzed.

All of the samples were air-dried and contained considerable amounts of moisture (6–13%). It was not considered desirable to dry at elevated temperatures the samples which were actually to be used for the exchange reaction, since such a procedure might change the accessibility. As an alternative, about 100–200 g. of each cellulose was kept in a screw-cap jar for one week in order to ensure that all parts of the gross sample had achieved moisture equilibrium. Small portions of the conditioned gross sample were then used for the exchange reaction, while another portion was used to determine the moisture content. The latter analysis was made in duplicate by drying in an air oven at 110° in accordance with standard practice. To the experimentally determined values was added in all cases an arbitrary correction of 0.5%, since it is well known that cellulose dried under the conditions described tends to retain about this amount of water.[8]

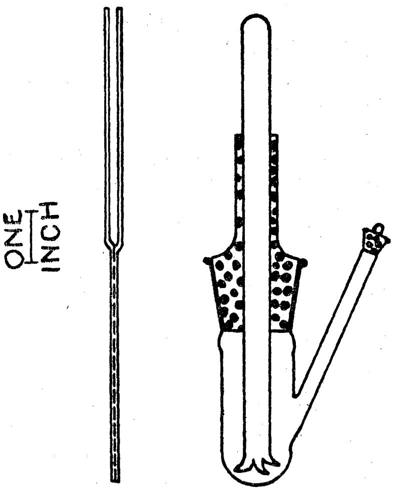


Fig. 1.—Reaction cell and micropipet.

Apparatus and Techniques.—The reaction cell is shown in Fig. 1. It was designed to permit intermittent agitation and the removal of microsamples of water without exposing the contents to air.

Approximately 2 g. of the conditioned sample was quickly weighed into the tared reaction cell, and 8 to 10 g. of heavy water of known specific gravity added. During transfer and weighing, the obvious precautions were taken to minimize changes in the moisture content of the cellulose as well as changes in the specific gravity of the heavy water.

When the weighings were completed, the glass stopper (not shown) was removed from the reaction cell and the ground-glass stirring assembly inserted in its place, where it remained until the run was completed. The cellulose was alternately loosened and compressed for about twenty minutes by manually manipulating the glass rod. After this initial period it was found sufficient to loosen and compress the wet cellulose only two or three times every half hour. The efficiency of the recommended agitation may be judged by the fact that if no agitation at all is used, one obtains what is apparently a very slow reaction which requires twenty-four to thirty-six hours to achieve maximum exchange,[7] but with the cell described above, if one breaks up and compresses the cellulose just once, a process requiring about three minutes, is found that exchange has proceeded to within a few per cent. of the value found after one or two hours. In other words, the reaction is diffusion-controlled, and is such a fast reaction that with a slight amount of agitation it goes practically to completion within a matter of minutes.

In order to follow the reaction, samples of water were removed and purified at intervals, and specific gravity measurements then were made. Purification was necessary in order to remove the buffer salts, suspended cellulose particles, and also any traces of impurities that might have been extracted from the cellulose. Before taking a sample of the free water, the reaction cell was tilted and the stirring rod pressed into the cellulose in such a way that a drop of water would run into the narrow side-arm to form an air-lock. To obtain the sample, the capillary pipet shown in Fig. 1, fitted with a medicinal dropper bulb (not shown), was inserted through the side-arm of the reaction cell and a sample drawn up from the cellulosic mass. The capillary was then removed and wiped dry with hard filter paper.

The pipets were calibrated to contain 0.1 cc. of water. Manipulation of the sample was facilitated by a small hole at the top of the rubber bulb which was closed and opened at will by the index finger.

The water sample in the pipet was then transferred to a microdistillation flask. In Fig. 2 the construction and use of the flasks are illustrated. The flask at stage (3) is ready to receive the sample. The pipet was inserted until it touched the back wall of the flask, and the sample was run into the bulb. The tip of the pipet was then rotated against the portion of the horizontal tube adjoining the bulb in order to remove any large excess of water, after which it was carefully withdrawn so as to avoid contaminating the "receiver" portion of the flask. The flask containing the sample was then evacuated to *ca.* 20 mm. and the neck quickly sealed off with a hand torch. By simply hanging the flask with the "receiver" portion in ice water, distillation to dryness is attained in about one-half hour.

Several precautions should be observed in using the described distillation technique. It is advisable, for example, to store the retorts (stage 3) in a desiccator to provide a dry atmosphere for the sample; otherwise, large errors may be incurred. Also, in the evacuation step, one must be careful not to distil off any appreciable quantity of water before the seal is made.

After complete distillation, the flask was removed from ice-bath. The tube, maintained in a vertical position, was dried and then cut; the "receiver" portion of the flask thus became a convenient microbeaker containing the purified water. The specific gravity was immediately determined by the falling-drop method. This analysis

---

[8] Hermans, "Physics of Cellulose Fibers," Elsevier, 1946, p. 200.

required 9 cu. mm. of the sample, and provided an accuracy of 1 × 10^{-6} specific gravity units. The method is in principle the same as that described previously by D. Rittenberg, *et al.*,[9] with some modifications by the present authors.[10]

Calculation of Extent of Exchange.—To derive a simple expression for calculating the extent of the exchange reaction, it is desirable to make two assumptions. It is assumed that the moisture present in the cellulose sample very rapidly dilutes the heavy water. It is further assumed that all three cellulose hydroxyls are indistinguishable so far as rate of exchange is concerned.

Now, the following definitions are adopted

x = grams of cellulose used;
m = percentage moisture content of x (wet basis);
Σ = moles of water ($D_2O + H_2O$) added to cellulose;
ξ_0 = initial mole fraction of D_2O in heavy water;
ξ_t = mole fraction of D_2O in heavy water at time t;
F = extent of reaction; *i. e.*, number of cellulose hydroxyls which have exchanged D for H divided by the number of such groups which would exchange if all of them were in equilibrium with the water.

If we write the exchange equilibrium as

$$2/3R(OH)_3 + D_2O \rightleftharpoons 2/3R(OD)_3 + H_2O$$

then, for complete reaction, the number of moles of D_2O consumed from an infinite excess of 100% D_2O is given by

$$\frac{(1 - 0.01m)x}{108.1} \tag{1}$$

For a *finite* amount of *dilute* heavy water, the number of moles consumed at time t is given by

$$\xi_t F\left[\frac{(1 - 0.01m)x}{108.1}\right] \tag{2}$$

By definition

$$\xi_t = \frac{\text{Moles } D_2O \text{ initially present} - \text{moles } D_2O \text{ consumed}}{\text{Total moles } (D_2O + H_2O)} \tag{3}$$

The assumption made at the beginning of this derivation regarding the moisture in the cellulose permits us to write

$$\xi_t = \frac{\xi_0\Sigma - \xi_t F\left[\frac{(1 - 0.01m)x}{108.1}\right]}{\Sigma + \frac{0.01mx}{18.02}} \tag{4}$$

Now, if W is the original weight of the heavy water added to the cellulose, it is evident that

$$W = 20.0\ \xi_0\Sigma + 18.0(1 - \xi_0)\Sigma \tag{5}$$

and this equation may be used to eliminate Σ from equation (4).

To eliminate the mole fractions ξ_0 and ξ_t, let the corresponding specific gravities be S_0 and S_t. The relationship between ξ and the corresponding S may be written

$$\xi = (S - 1.00000)/0.1080 \tag{6}$$

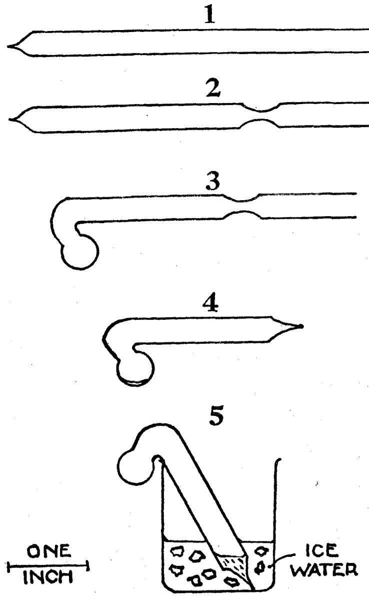


Fig. 2.—Preparation and use of microdistillation flasks.

Consideration of equations (4, 5, 6) with appropriate transpositions leads to the final relationship for F in terms of the weights of materials used and the observed specific gravities

$$F = A\left[\frac{S_0 - S_t}{S_t - 1}\right] - B \tag{7}$$

where A and B are constants in any given reaction, and their equivalents are

$$\left.\begin{aligned} A &= \frac{108.1W}{(18.02 + 2\xi_0)(1 - 0.01m)x} \\ B &= \frac{1.081m}{18.02(1 - 0.01m)} \end{aligned}\right\} \tag{8}$$

From a consideration of the quantities of cellulose and heavy water used, together with the precision attainable in the heavy water analysis,[10] it can be estimated that the value of F should be precise to within about (1 to 2) × 10^{-2}; in terms of percentage of the hydroxyls exchanged, the precision should be about 1% over the entire range.

Results

Effect of *p*H and Temperature.—In order to choose the most advantageous reaction conditions rather than to adopt them arbitrarily, a set of experiments were run at different acidities and different temperatures.

For this study, sheeted, high-grade commercial cotton linters was used. The reaction was run at room temperature and 70°, both at *p*H 6. To adjust the *p*H, sufficient potassium dihydrogen phosphate was added to the water to give a 0.05*M* concentration; then, sufficient sodium hydroxide as a concentrated solution in water was added to achieve the desired *p*H. A Beckmann *p*H meter was used to determine acidity. For the 70° run, the cell was immersed in a thermostated bath and the water brought to temperature before adding the cellulose. The cell was not removed from the

---

[9] Keston, Rittenberg and Schoenheimer, *J. Biol. Chem.*, **122**, 227 (1937).

[10] Frilette and Hanle, *Anal. Chem.*, **19**, 984 (1947).

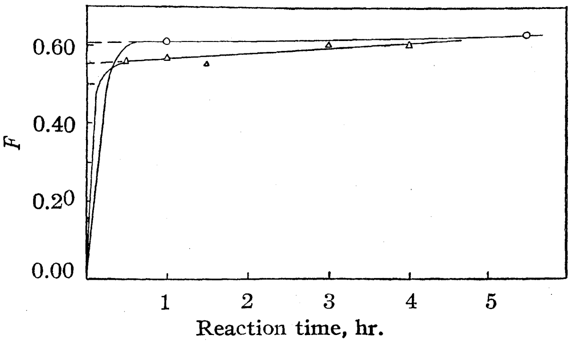


Fig. 3.—Effect of temperature on rate of exchange: O, cotton linters, *p*H 6, 70°; Δ, cotton linters, *p*H 6,25°.

bath until the run was completed. In this experiment, two triplicate samples were taken, the first set after one hour and the second after five and one-half hours. For the room temperature experiment, samples were taken singly but at more frequent intervals, and in addition a sample was taken after ten days of standing at room temperature. The results for both of these runs are plotted in Fig. 3; it can be seen that the influence of temperature is negligible over the range studied. The nature of the data obtained empirically in these two runs and its conversion into extent of exchange is illustrated by Tables I and II. In order to conserve space all other runs are summarized by the "characterization values" defined in the next section.

TABLE I

EXCHANGE OF COTTON LINTERS AT 70°

Weight of cellulose, x = 2.060 g.; moisture content on wet basis, m = 5.7%; weight of heavy water used, W = 9.653 g.; initial mole fraction of D_2O in heavy water, ξ_0 = 0.22; calculated values, A = 29.13 and B = 0.363.

Reaction time, t, hr.	Specific gravity, S	$\frac{S_0 - S_t}{S_t - 1}$	$A\left[\frac{S_0 - S_t}{S_t - 1}\right]$	Extent of exchange, F
	1.024220			
0	1.024216	0	0	0
	1.024218			
	1.023440			
1.0	1.023440	0.0333	0.969	0.61
	1.023433			
	1.023420			
5.5	1.023422	0.0341	0.992	0.63
	1.023417			

TABLE II

EXCHANGE OF COTTON LINTERS AT 25°

Weight of cellulose, x = 2.200 g.; moisture content on wet basis, m = 5.7%; weight of heavy water used, W = 11.13 g.; initial mole fraction of D_2O in heavy water, ξ_0 = 0.23; calculated values, A = 31.37 and B = 0.363.

Reaction time, t, hr.	Specific gravity, S	$\frac{S_0 - S_t}{S_t - 1}$	$A\left[\frac{S_0 - S_t}{S_t - 1}\right]$	Extent of exchange, F
0	1.024533[a]	0	0	0
0.5	1.023818	0.0300	0.942	0.58
1.0	1.023818	.0300	.942	.58
1.5	1.023822	.0298	.935	.57
3.0	1.023788	.0313	.980	.62
4.0	1.023795	.0310	.974	.61
168	1.023770[b]	.0321	1.005	.64

[a] Average for three samples. [b] Average for two samples.

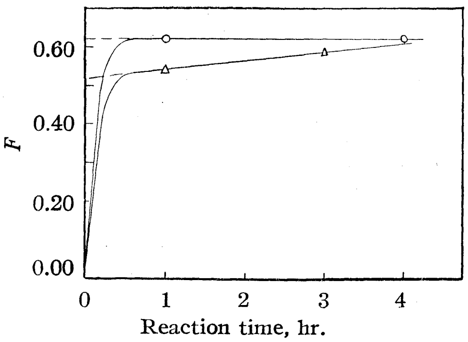


Fig. 4.—Effect of *p*H on rate of exchange: O, cotton linters, *p*H 3.9, 25°; Δ, cotton linters, *p*H 10.5, 25°.

Two additional runs were made at room temperature, one at *p*H 3.9, the other at *p*H 10.5. The results of these two experiments were plotted in Fig. 4; these curves together with the room temperature run of Fig. 3 indicate that the influence of *p*H also is negligible.

General Character of the Exchange Curve.—The shape of the exchange *vs.* time curve is simple and essentially similar for all the cellulose samples which were studied. Its characteristics are: (1) a very steep rise which is substantially terminated after a fraction of an hour, and (2) a horizontal part with such a small slope that the exchange value even after one week differs only slightly from the value observed at one hour.

Since the curves for different cellulose samples are so consistent in shape, a generalized notation to represent the data may be adopted which is more concise and lends itself to comparison better than the original curves. Specifically, let the intercept of the horizontal portion of the curve extrapolated to zero time be called the *a* value; the magnitude of *F* at four hours, the *b* value; and

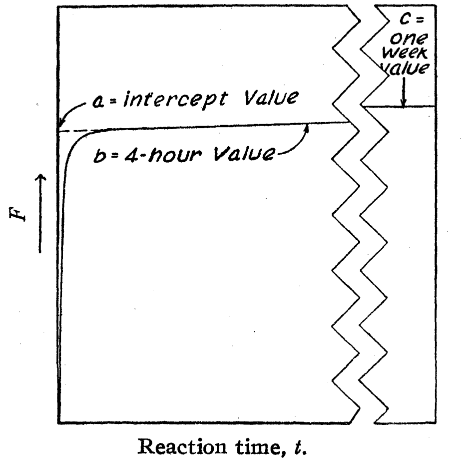


Fig. 5.—Generalized reaction curve and characterization values.

the magnitude of F at one week, the c value, all as indicated in Fig. 5. For convenience, these values collectively will be called the "characterization values" for the various samples.

Returning once again to the effect of temperature and *p*H on the exchange rate of a cotton linters sample, we may summarize the results by the characterization values as presented in Table III. It may be noted at this point that the four runs indicate an experimental precision that is about as good as that estimated in a previous section, especially if one considers the b value as the correct measure of accessibility. The average deviation of the a value is ±0.025, which is poorer than expected; but the average deviation of the b value is ±0.005, which agrees with the predicted value corrected for the multiplicity of the determinations.

TABLE III

EFFECT OF *p*H AND TEMPERATURE: COTTON LINETRS

Run	Reaction conditions *p*H	°C.	Characterization values *a*	*b*	*c*
1	6	70	0.61	0.62	..
2	6	25	.57	.61	0.64
3	3.9	25	.62	.62	..
4	10.5	25	.54	.61	..

It can be seen from the tables that many of the samples produce perfectly flat curves in the interval from the first to the fourth hour. Some of the samples, however, show a significant difference between the a and the b value. All samples appear to continue to exchange a small, but always a significant amount, in the interval from four hours to one week, and the extent of this exchange does not seem to be related to the magnitude of the difference between a and b. The reasons for the differences in magnitude of a, b, and c are under investigation at the present time; the results so far indicate that where b differs significantly from a, it may be attributed to a residual diffusion error. Accordingly, we shall tentatively assume the b value, *i. e.*, the value of F after four hours, to be the measure of accessibility.

Wood Pulp Samples.—Since the rate of exchange was not noticeably influenced by the variables studied, all of the experiments which follow were made at room temperature and *p*H 6.

Wood pulp samples previously studied by Drs. Conrad and Scroggie were used after the described one-week conditioning. The practice in this instance was to take frequent single samples rather than triplicate samples at widely spaced intervals. The data are summarized in Table IV.

TABLE IV

CHARACTERIZATION VALUES FOR WOOD PULPS

Run	Sample description	Characterization values *a*	*b*	*c*
5	Wood pulp from beech	0.53	0.54	0.68
6	Same, from southern pine	.48	.55	.57
7	Same, from western hemlock	.54	.55	.67
8	High alpha wood pulp from southern pine	.68	.68	.73
9	Wood pulp treated with caustic of approx. 10% concn.	.68	.74	.81

Regenerated Cellulose Samples.—Four different regenerated cellulose fibers were studied by the same methods as described above. The results are shown in Table V. In addition to these samples, two native cotton fibers were run; for one of these a b value of 0.41 was found, and for the other 0.46. These values are the lowest found for any of the samples studied and indicate that native cotton has a relatively small fraction of accessible chain segments.

TABLE V

CHARACTERIZATION VALUES FOR VISCOSE RAYON FIBERS

Run	Sample description	Characterization values *a*	*b*	*c*
10	"Cordura" high tenacity viscose rayon	0.86	0.86	0.89
11	Fiber G, high tenacity viscose rayon	.67	.67	.74
12	Textile viscose rayon	.66	.68	.75
13	Special viscose rayon spun without appreciable tension	.78	.81	.90

Discussion

If it is assumed that cellulose is composed of easily accessible (amorphous) and more difficultly accessible (crystalline) domains, it is probable that the rapid, limited exchange with D_2O involves all of the hydroxyls in the amorphous regions together with those in the surface of the crystalline arrays. One cannot ignore the contribution of the surface hydroxyls to the extent of the exchange reaction in estimations of crystallinity, for experimental evidence indicates that the areas of high lateral order are very small and, as a consequence, a large fraction of their hydroxyl groups are arranged in the surface. If this factor is taken into account, the relationship between the amount of crystalline material in a cellulose sample and the extent of the exchange reaction may be written

$$F' = \sigma\alpha + (100 - \alpha),$$

where

F' = $100F$, *i. e.*, the percentage of all of the hydroxyls which react rapidly with D_2O
σ = the fraction of the hydroxyls of the crystalline domains which are in the surface and accessible to D_2O
α = the per cent. of crystalline material in the sample

Solving for α

$$\alpha = \frac{100 - F'}{1 - \sigma}$$

In order to arrive at estimates of α for the samples which were studied, it is first necessary to assign a value to σ. To arrive at this value, it may be assumed that the effective surface development of the crystalline regions is represented by an infinitely long, square prism with a base of between

50 and 100 ångströms on edge.[11,12] A cross-section of such a prism would contain approximately twenty rows of cellulose chains, each row in turn consisting of ten chains. Now, if one takes a volume element of the idealized prism by passing through it two parallel planes which are perpendicular to the long edges of the prism, the surface development may be computed readily. In particular, if the transecting planes are spaced so that the element contains 200 anhydroglucose units, it is evident that 20 of these units will lie in the hydroxyl-rich surfaces, and 36 (edgewise) in the other two faces. Thus, for every 100 anhydroglucose residues in a crystalline domain, 28 lie in the surface. Assuming now that all hydroxyls attached to the latter are reactive, we arrive at $\sigma = 0.28$. This value was used to calculate the values for α shown in Table VI; values derived from a different method are shown for comparison.

TABLE VI

CRYSTALLINITY AS ESTIMATED FROM D_2O EXCHANGE AND NICKERSON DEGRADATION

		Accessibility		Crystallinity	
Run	Sample description	From D_2O exchange, F' (%)	Nickerson method[b] (%)	From D_2O exchange,[a] α (%)	Nickerson method,[c] %
..	Cotton	41	..	82	..
..	Cotton	46	..	75	..
1 to 4	Cotton linters	61	5	54	95
5	Wood pulp, beech	54	12	64	88
6	Wood pulp, pine	55	10	63	90
7	Wood pulp, hemlock	55	9	63	91
8	Wood pulp, pine	68	8	44	92
9	Wood pulp, pine	74	15	36	85
10	"Cordura" rayon	86	30	19	70
11	Fiber "G"	67	15	46	85
12	Textile rayon	68	27	44	73
13	Special rayon	81	..	26	..

[a] Crystallinity estimated from D_2O exchange, $\alpha = (100 - F')/(1 - \sigma)$. [b] Values in this column determined by Nickerson method as modified by Drs. Conrad and Scroggie; these data were supplied through the courtesy of these investigators. [c] Crystallinity estimated from the Nickerson degradation by subtracting from 100 the per cent. accessibility to $FeCl_3$:HCl.

It might be well to mention at this point that while the accessibility, F, is an exact empirical value, the crystallinity, α, is only an approximation. How close α approaches the true value for crystallinity depends in part on the validity of σ and in part on the magnitude of the accessibility. For a sample in which all but 10% of the hydroxyls are accessible the magnitude of α would vary only from 14 to 23% if the value of σ were doubled; on the other hand, if one were to consider a much more crystalline sample, *e. g.*, cotton with 41% of the hydroxyls accessible, then the value for α would vary from 82% for $\sigma = 0.28$ to 100% for $\sigma = 0.41$, a much larger change in α for a much smaller change in σ. Since the computation of σ is based on two methods for estimating crystallite size,[11,12] it is not likely that it is in error by the magnitudes just discussed. In fact, if one compares the averaged values of Table VI with the estimates of crystallinity arrived at by Hermans[13] through a study of the density of various types of cellulose, it is noted that a fairly good agreement exists. The average values for crystalline content reported by Hermans are 60% for ramie and cotton, 50% for wood pulp and 25% for regenerated cellulose.

In contrast to the density method of Hermans, it is interesting to point out that the accessibility of cellulose to heavy water is in all cases distinctly greater than that observed with the Nickerson method, as is shown in Table VI. A possible explanation is that additional crystallization occurs in the early stages of the reaction. During hydrolysis, cellulose chains in the easily accessible areas are broken and new, free, chain ends are produced; this process removes constraints on these chains and makes their segments more easily mobile. They will now be able to arrange themselves in a higher degree of lateral order under the influence of the strong intermolecular forces between the chains, and part of the material which was disordered before will undergo crystallization. It has been pointed out previously by several observers[14] that, for the same polymer, low molecular weight fractions have a greater tendency to crystallize than those of higher molecular weight; also, Ingersol[15] has recently reported that treating cellulose fibers with hydrochloric acid sharpens their X-ray patterns. The increased density[16] and decreased moisture regain[17] of cellulose fibers upon prolonged treatment with the Nickerson reagent also points to the fact that additional crystallization occurs while glucosidic bonds are hydrolyzed in the easily accessible areas. It is therefore understandable that the D_2O exchange method indicates larger amounts of disordered material than the Nickerson method. Similar reasoning will also hold for the oxidation method[2] mentioned in the introduction, for it was carried out at a low *p*H and partial hydrolysis with subsequent crystallization was bound to occur in the easily accessible arrays.

The thallation method of Assaf, Haas and Purves[3] leads to lower accessibilities than any of the other procedures; this is probably due to the fact that it is carried out in an anhydrous system. It tests the texture of the sample in the bone-dry state and indicates only those domains as accessible that can be approached by an organic (hydrophobic) solvent. The ingenious extrapolation to zero molecular volume eliminates the volume re-

---

(11) Hengstenberg and Mark, *Z. Krist.*, **69**, 271 (1928).

(12) Kratky and Mark, *Z. physik. Chem.*, **B36**, 129 (1937).

(13) Hermans, "Physics of Cellulose Fibers," Elsevier, 1946, p. 71.

(14) Baker, Fuller and Pape, THIS JOURNAL, **64**, 776 (1942).

(15) Ingersol, *J. Applied Phys.*, **17**, 924 (1946).

(16) Tessler, Woodberry and Mark, *J. Polymer Sci.*, **1**, 437 (1946).

(17) Nickerson, *Ind. Eng. Chem.*, **34**, 1480 (1942).

quirements of the solvent and probably leads to a true value of accessible hydroxyl groups for a non-swelling reagent. In an aqueous medium, swelling takes place and a number of weak (van der Waals) bonds between hydroxyl groups of adjacent chains are opened and hitherto inaccessible areas are made penetrable by the reagent. One should, therefore, expect that all methods using aqueous systems should indicate higher degrees of accessibility, which is in fact the case. The highest proportions of disordered areas should be given by X-rays, by density considerations,[13] and by the heavy water exchange method; the figures deduced from these three methods should also agree numerically. Table VII contains the accessibilities as reported by all methods and shows, indeed, that the thallation method gives the lowest values whereas the two "destructive methods" in aqueous media, involving hydrolysis and oxidation, give higher figures for the disordered areas and agree with each other to a first approximation. Finally, the non-destructive methods of X-ray diffraction, density evaluation and heavy water exchange lead to the highest figures for the accessible domains; these methods, too, agree with one another reasonably well.

TABLE VII

ORDER OF ACCESSIBILITY FOUND BY DIFFERENT METHODS

	% Accessible or amorphous			
Method	Cotton	Cotton linters	Wood pulp	Rayon
Thallation[3]	..	0.4[c]	..	...
Nickerson oxidation[5a]	..	5.3	10	24
Periodate oxidation[2]	1–2	6.0	..	7–19
Density[11]	40	...	50	75
Heavy water exchange[b]	21	46	46	66
X-Ray densitometry[5]	..	...	..	81

[a] Data supplied through courtesy of Drs. Conrad and Scroggie. [b] Values averaged from Table IV. [c] Unswollen samples.

Summary

It has been found that cellulose reacts very rapidly with heavy water, provided sufficient agitation is used; the rapid reaction is of limited extent, and is succeeded by a much slower reaction which persists for days. In none of the cases studied were all of the hydroxyls exchanged, even at the end of one week. The techniques used and the calculations involved are outlined.

The extent of the rapid reaction is a measure of the accessibility of the cellulose sample, and from the accessibility an estimate is made of the amount of amorphous material present in each of the samples studied. The average amounts found for different types of cellulose were as follows: 21% for cotton, 46% for wood pulp and 66% for rayon.

The different accessibility values found for the same cellulose sample when different methods are used are discussed and compared. These methods fall into three classes. In the first class is the thallation method, where a non-swelling solvent is used, and with which the lowest values are found. In the second class are the two hydrolytic, aqueous methods, which give intermediate values for accessibility. In the last class are the physical, non-destructive methods which give the highest values.

BROOKLYN, NEW YORK RECEIVED JULY 8, 1947

[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE]

n-Alkyl Diselenides

BY GEORGE G. STONER AND ROGER W. WILLIAMS

In connection with a program[1] of research on selenium and its compounds, it was of interest to examine a number of *n*-alkyl diselenides. Of this particular homologous series, methyl,[2,3] ethyl,[2,4] propyl,[2,3,5] butyl[3] and dodecyl[6] diselenides are known, having been prepared by a variety of methods.

A convenient method of synthesis, based on the following three reactions,[7] and not previously applied to this series, was used to prepare butyl, amyl, hexyl, heptyl, octyl, and nonyl diselenides.

$$\mathrm{Se} + \mathrm{K_2SO_3} = \mathrm{K_2SeSO_3}$$

$$\mathrm{RX} + \mathrm{K_2SeSO_3} = \mathrm{RSeSO_3K} + \mathrm{KX}$$

$$2\mathrm{RSeSO_3K} + \mathrm{I_2} + 2\mathrm{H_2O} = \mathrm{RSeSeR} + 2\mathrm{KHSO_4} + 2\mathrm{HI}$$

This sequence of reactions yields *n*-alkyl diselenides which are less likely to be contaminated than those prepared by the other methods,[2–6] and the yields are good (Table I). The offensive odors of the *n*-alkyl diselenides decrease considerably in intensity above hexyl in the homologous series.

---

(1) Sponsored by the Selenium Development Committee.

(2) Beilstein, "Handbuch der organischen Chemie," 4th ed., Vol. I, pp. 291, 349 and 360; and 2d supplement, pp. 278 and 357. Also, M. L. Bird and F. Challenger, *J. Chem. Soc.*, 570–574 (1942).

(3) H. J. Backer and W. van Dam, *Rec. trav. chim.*, **54**, 531–538 (1935).

(4) A. Baroni, *Atti accad. Lincei*, **14**, 28–32 (1931); *C. A.*, **26**, 1896 (1932).

(5) E. P. Painter, K. W. Franke and R. A. Gortner, *J. Org. Chem.*, **5**, 579–589 (1940).

(6) G. H. Denison, Jr., and P. C. Condit, U. S. Patents 2,398,414, 2,398,415, and 2,398,416 (April 16, 1946).

(7) This method was discovered by T. S. Price and L. M. Jones, *Proc. Chem. Soc.*, **24**, 134 (1908), and *J. Chem. Soc.*, **95**, 1729–1738 (1909), who used it in preparing benzyl and nitrobenzyl diselenides; *cf.* T. S. Price and D. F. Twiss, *J. Chem. Soc.*, **95**, 1489 (1909). Recently, H. P. Ward and I. L. O'Donnell, THIS JOURNAL, **67**, 883 (1945), used the same method to prepare two bis-(2-alkoxyethyl) diselenides, hydrogen peroxide having been used in place of iodine.

TABLE I

n-ALKYL DISELENIDES

Diselenide	Distn. range, °C.[a]	Mm.	Distd. yield, %	M. p., °C.[a]	d^{20}_4	n^{20}_D	Exptl. MR_D	r_D[b]	Formula	Selenium, % Calcd.	Found[c]	
Butyl	113–119[d]	6–8	67	<−78	1.390	1.5399	61.41	11.14	$C_8H_{18}Se_2$	58.03	57.2	
Amyl	134–137	3	63	<−78	1.324	1.5343	70.51	11.06	$C_{10}H_{22}Se_2$	52.60	52.6	
Hexyl	150–152	3	83	−44	1.258	1.5246	79.91	11.14	$C_{12}H_{26}Se_2$	48.11	48.1	47.8
Heptyl	178–179	3	83	−11	1.211	1.5184	89.21	11.17	$C_{14}H_{30}Se_2$	44.32	45.3	45.5
Octyl	197–205	3	74	− 8	1.175	1.5142	98.53	11.22	$C_{16}H_{34}Se_2$	41.09	41.6	41.6
Nonyl	178–184	0.12	67	10	1.142	1.5092	107.89	11.28	$C_{18}H_{38}Se_2$	38.29	39.5	39.3

[a] Temperature readings were not corrected for emergent stem. [b] The atomic refraction of each Se in the diselenide calculated from the experimental molecular refraction (formula of Lorenz and Lorentz), assuming the atomic refraction for C and H to be 2.418 and 1.100 ml., respectively (sodium D light). [c] Selenium was determined by a method developed by Justin S. McNulty (to be published). Samples were decomposed and selenium was determined gravimetrically as elemental selenium. [d] Backer and van Dam (ref. 3) reported that butyl diselenide distilled in the range of 129–130° at 13 mm.

At room temperature these liquid diselenides are orange, but this coloration becomes weaker as the temperature is lowered. This is suggestive of a certain degree of dissociation into RSe radicals, increasing with temperature.[8]

From values obtained for d^{20}_4 and n^{20}_D, the atomic refraction of each selenium atom in these diselenides was 11.17 ± 0.11 ml. (sodium D light).[9]

Experimental

Materials.—The 1-bromoalkanes, each of which distilled within a two-degree range, were purchased from Columbia Organic Chemicals Co., Inc., Columbia, South Carolina. Powdered gray-black selenium, 99.5% pure, was obtained from Canadian Copper Refiners, Ltd., Montreal East, Quebec. The other compounds were chemically pure.

General Procedure.—In an atmosphere of nitrogen, 40 g. (0.50 g.-atom) of selenium was allowed to react for two hours with a mechanically stirred, hot solution of 119 g. (0.75 mole) of anhydrous potassium sulfite in 1200 ml. of 50% aqueous ethanol. Some undissolved matter was filtered from the hot mixture, and the filtrate was transferred immediately into a 5-liter, 3-neck flask. Without delay, 0.40 mole of the appropriate 1-bromoalkane was added portionwise during a period of one-half hour, while the mixture was kept refluxing in an atmosphere of nitrogen and mechanically stirred. An additional period of two hours under these conditions was allowed for the reaction. The solution of potassium alkylselenosulfate was cooled to room temperature and oxidized to the *n*-alkyl diselenide by iodine added portionwise until the color of the iodine persisted. The small excess of iodine was reduced by bubbling sulfur dioxide into the solution. The diselenide separated out as an orange oil.

In each case, the oil was washed with water and distilled at reduced pressure. Experimental data are given in Table I. Practically no unreacted 1-bromoalkanes were recovered in the purification of butyl, amyl, hexyl and heptyl diselenides. However, in the cases of octyl and nonyl diselenides, 10% of the original 1-bromoöctane and 27% of the original 1-bromononane were recovered. Hence, a period of reaction longer than two hours is indicated in the case of these higher 1-bromoalkanes.

All the diselenides had offensive odors, but those of heptyl, octyl, and nonyl diselenides were much less pronounced. All six of these compounds were orange at room temperature. Butyl and amyl diselenides remained liquid at −78°, at which temperature they were straw-colored. The higher diselenides formed yellow crystals below their melting points (Table I).

For the purpose of comparison, amyl diselenide also was prepared from 1-chloropentane (Sharples Chemicals, Inc., Philadelphia, Pa.). The period allowed for reaction was extended to twelve hours. In other respects the conditions were the same as those described above. After distillation, the yield of amyl diselenide was 65%, which is practically identical with the yield of 63% resulting from the use of 1-bromopentane (Table I).

Acknowledgment.—The authors are grateful to Phyllis K. Distelhorst and Justin S. McNulty, who performed the determinations of selenium.

Summary

Potassium alkylselenosulfates were used as intermediate compounds in conveniently preparing five new *n*-alkyl diselenides (amyl through nonyl). Several properties characterizing these homologs were determined. The value of the atomic refraction for each atom of selenium in such diselenides was found to be 11.17 ± 0.11 ml. (sodium D light).

COLUMBUS 1, OHIO RECEIVED OCTOBER 23, 1947

---

(8) Analogous to radicals containing univalent sulfur, discussed by W. E. Bachmann in H. Gilman's "Organic Chemistry, an Advanced Treatise," Vol. I, 1st ed., John Wiley & Sons, Inc., New York, N. Y., p. 528.

(9) G. R. Levi and A. Baroni, *Atti accad. Lincei*, [6] **9**, 1022 (1929), according to Beilstein, *op. cit.*, Vol. I, p. 357, reported that d^{13} and $n^{12.8}_D$ for ethyl diselenide were, respectively, 1.6962 g. per ml. and 1.5885, from which the experimental molecular refraction is 42.89 ml. and the atomic refraction for each selenium atom is 11.11 ml. L. Chugaev, *Ber.*, **42B**, 53 (1909), reported that $d^{22.2}$, $n^{22.2}_D$, MR_D, and r_D (Se) were, respectively, 1.4991 grams per ml., 1.55535, 52.20 ml., and 11.33 ml. for propyl diselenide. A recalculation gave 52.29 and 11.19, respectively, for MR_D and r_D (Se), when 1.008, 12.010, and 78.96 were used as the atomic weights for H, C, and Se, and 1.100 and 2.418 were used as the respective atomic refractions (sodium D light) for H and C.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC COMPANY]

Methylphenylpolysiloxanes

BY RICHARD N. LEWIS

Many compounds in the series of methylpolysiloxanes and phenylpolysiloxanes have been reported in the literature[1]; polymers containing both methyl and phenyl groups on the same silicon atom[2] and copolymers of methyl and phenylpolysiloxanes[3] have also been reported. However, few pure compounds containing both methyl and phenyl groups have been described. Kipping[4] has prepared dimethyltetraphenyldisiloxane, a solid melting at 51–52°. Daudt[5] has disclosed tetramethyldiphenyldisiloxane without describing its properties and has prepared pentamethylphenyldisiloxane, b. p. 206°.[6] Hexamethyldiphenyltrisiloxane was studied by Hurd[7] but has not been fully characterized.

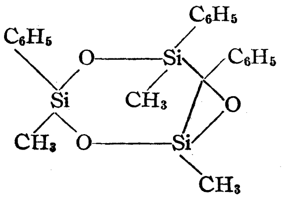
The shorthand notation used in this paper is based on that of Wilcock,[8] in which M and D represent mono- and difunctional units; primes are used to indicate phenyl groups, thus:

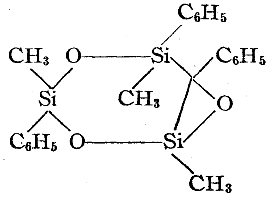
Unit	Formula	Unit	Formula
M	$(CH_3)_3SiO_{1/2}$	D	$(CH_3)_2SiO$
M′	$(CH_3)_2C_6H_5SiO_{1/2}$	D′	$CH_3C_6H_5SiO$
M″	$CH_3(C_6H_5)_2SiO_{1/2}$	D″	$(C_6H_5)_2SiO$

According to this system, the compounds mentioned above may be written, M''_2, M'_2, MM′, M_2D'', respectively.

A series of cyclic compounds was made by hydrolyzing methylphenyldichlorosilane[2] and distilling the resultant oil at a pressure of 2 mm. During the distillation the liquid was heated to 460°, at which temperature there is a strong possibility of thermal rearrangement of silicon–oxygen bonds.[9,10] The fact that there was no appreciable residue, therefore, does not mean that the original hydrolyzate was composed entirely of low molecular weight products. There was no indication, however, of rearrangement of the carbon–silicon bonds or of any other type of decomposition.

On fractional distillation of this oil there were obtained two forms of the cyclic trimer, D'_3, both solid at room temperature, and a cyclic tetramer, D'_4, as well as a non-volatile residue consisting of higher polymers of unusual thermal stability. Since the two forms of the trimer can be separated by distillation, they are apparently two distinct compounds. A type of *cis–trans* isomerism, in which the phenyl groups may or may not all lie on the same side of the ring, appears to be a reasonable explanation. The *cis*-configuration, which has a threefold axis of symmetry, is assigned to the higher melting isomer. This type of isomerism probably occurs with the tetramer as well. However, it was not possible to obtain any crystalline material from it, although four stereoisomers are theoretically present.


cis-Trimer, m. p. 99.5°


trans-Trimer, m. p. 39.5°

It is to be expected that these cyclic polysiloxanes can be converted to linear ones by equilibration with monofunctional units or "chain-stoppers." In the methyl series, M_2 and D_4, for instance, when shaken with sulfuric acid, produce compounds of the general formula M_2D_x.[9] Since the phenyl–silicon bond is known to be somewhat unstable toward acidic reagents,[11] it was considered desirable to use an alkaline catalyst in the present work. (Methods involving alkaline equilibration have recently been patented.[6,12])

It was found that compounds of the type D'_x, could be equilibrated with M'_2 and with M_2 by means of potassium hydroxide in isopropyl alcohol containing a small amount of water. In the first case, no other solvent was required, but when M_2 was used, it was necessary to add toluene because of the limited miscibility of D'_x with M_2 and isopropyl alcohol. This lack of solubility must be due to the presence of higher polymers as the tetramer is miscible with M_2. The phenyl–silicon bond is apparently quite inert toward this treatment as no appreciable quantity of benzene was produced.

In the reaction of D'_x with M_2 small amounts of dimethylphenylsilanol and dimethylphenylisopropoxysilane were formed; this means that the condensation of silanols and the hydrolysis of silyl ethers are reversible. Because of the acidic nature of silanols[13] some of the potassium salt must also have been formed. The following types of bonds are therefore present at equilibrium:

---

(1) C. A. Burkhard, E. G. Rochow, H. S. Booth and J. Hartt, *Chem. Rev.*, **41**, 97 (1947).

(2) J. F. Hyde and R. C. DeLong, THIS JOURNAL, **63**, 1194 (1941).

(3) E. G. Rochow, "Introduction to the Chemistry of the Silicones," John Wiley and Sons, Inc., New York, N. Y., 1946.

(4) F. S. Kipping, *J. Chem. Soc.*, 104 (1927).

(5) W. H. Daudt, U. S. Patent 2,397,727; *C. A.*, **40**, 3938 (1946).

(6) W. H. Daudt and J. F. Hyde, British Patent 583,878; *C. A.*, **41**, 3115 (1947).

(7) C. B. Hurd, THIS JOURNAL, **68**, 364 (1946).

(8) D. F. Wilcock, *ibid.*, **69**, 477 (1947).

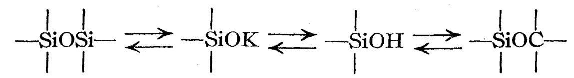
(9) W. Patnode and D. F. Wilcock, *ibid.*, **68**, 358 (1946).

(10) D. W. Scott, *ibid.*, **68**, 356 (1946).

(11) F. S. Kipping and L. L. Lloyd, *J. Chem. Soc.*, **79**, 449 (1901).

(12) J. F. Hyde, British Patent 583,875; *C. A.*, **41**, 3115 (1947).

(13) L. H. Sommer, E. W. Pietrusza and F. C. Whitmore, THIS JOURNAL, **68**, 2282 (1946).



$$\text{—SiOSi—} \rightleftarrows \text{—SiOK} \rightleftarrows \text{—SiOH} \rightleftarrows \text{—SiOC—}$$

Alkoxysilane formation, which might have been predicted, has not been observed before. The formation of silanols from siloxanes was reported by Kipping and Robison.[14]

Experimental[15]

Hydrolysis of Methylphenyldichlorosilane.—Eleven and six-tenths moles (2210 g.) of redistilled methylphenyldichlorosilane (*Anal.* Calcd.: Cl, 37.10. Found: Cl, 36.69) was hydrolyzed in six portions by running it into ice water with vigorous stirring. The oil which was produced was distilled rapidly at 2 mm. from a Claisen flask, which was completely surrounded by an electric heater. The temperature outside the flask reached 460° while the vapor (probably superheated) reached 295°. No appreciable residue was left. The distillate (1318 g., 9.7 moles of D′) was redistilled at 1.5 mm. through a 1.5 inch by 18-inch column packed with stainless steel helices, and the resulting fractions were grouped as follows: I, forerun, 3%; II, 12% boiling at 165–185°; III, another 12% boiling chiefly at 190°; IV, 48% boiling chiefly at 237°; and V, 24% of residue.

Fraction II crystallized on cooling and was recrystallized from alcohol; flat plates, m. p. 99.5°; yield, 60 g.

Anal. Calcd. for $C_{21}H_{24}Si_3O_3$ (D'_3): C, 61.73; H, 5.92; mol. wt., 408. Found: C, 61.7, 61.7; H, 6.0, 5.9; mol. wt., 390.

Several fractions of the material boiling at 190° (1.5 mm.) were left at 0°. The first of these, apparently contaminated with the previous material, developed crystals in a few hours. After one week, however, the entire mass crystallized, and a portion of it was used successfully to seed the other fractions. Upon recrystallization from alcohol there were obtained small needles, m. p. 39.5°; yield, 137 g. There were also some intermediate fractions containing considerable amounts of both II and III. The following properties of III were determined on an unrecrystallized sample: n^{20}_D 1.5397, d^{20}_4 1.1062, R_D 0.2835, R_D (calcd.) 0.2826.

Anal. Calcd. for $C_{21}H_{24}Si_3O_3$ (D'_3): C, 61.73; H, 5.92; mol. wt., 408. Found: C, 61.6, 61.2; H, 6.2, 5.9; mol. wt., 437.

IV remained a viscous liquid well below 0° and could not be made to crystallize. It was miscible with *n*-heptane, acetone, M_2 and D_4, but not with alcohol. A middle fraction had the following properties: n^{20}_D 1.5461, d^{20}_4 1.1183, R_D 0.2832, R_D (calcd.) 0.2826. The yield of pure material was 453 g.

Anal. Calcd. for $C_{28}H_{32}Si_4O_4$ (D'_4): C, 61.73; H, 5.92; mol. wt., 544. Found: C, 61.8, 61.5; H, 6.0, 6.1; mol. wt., 545.

V was not characterized; it was assumed to consist of higher polymers of D′. It is a viscous liquid of high thermal stability as the following experiment shows: A 3-cc. portion was heated in a 6-cc. beaker in contact with zinc metal. There was no change, except for some fuming above 240°, until the melting point of zinc (419.4) was reached. After two hours in contact with molten zinc (average temperature about 450°) some thickening occurred; the material was then cooled to room temperature, at which point it was rubbery.

Dimethylphenylchlorosilane and Dimethylphenylbromosilane.—These two compounds were obtained together from the reaction of phenylmagnesium bromide with dimethyldichlorosilane.[16] From 3.0 moles of bromobenzene and 3.0 moles of dimethyldichlorosilane there were obtained 1.44 moles of the chloride, b. p. 197° at 766 mm., and 0.53 mole of the bromide, b. p. 215° at 766 mm. The combined yield of both halides was 65%. The chloride had a pleasant odor like that of the silanol described below, while the bromide was almost odorless.

Anal. Calcd. for $C_8H_{11}SiCl$: Cl, 20.77. Found: Cl, 20.5.

Anal. Calcd. for $C_8H_{11}SiBr$: Br, 37.15. Found: Br, 36.8.

Tetramethyl-1,3-diphenyldisiloxane (M'_2).—The above halides (1.93 moles) were hydrolyzed in ice water with vigorous stirring, and the product was diluted with ether, washed well, dried and distilled. The major portion of it distilled at 140–144° (5.7 mm.); yield, 250.5 g. (91%). A sample was redistilled at 110–111° (1.0 mm.); n^{20}_D 1.5122, d^{20}_4 0.9763, R_D 0.30745, R_D (calcd.) 0.3096.

Anal. Calcd. for $C_{16}H_{22}Si_2O$: C, 67.08; H, 7.74. Found: C, 66.2, 66.0; H, 7.6, 7.8.

Pentamethyl-1,3,5-triphenyltrisiloxane (M'_2D').—M'_2 (245 g., 0.857 mole) was mixed with 75 cc. of isopropyl alcohol and 38.8 g. (0.275 mole of D′) of cyclic polymers, D'_x, from which most of the tetramer had been distilled. A homogeneous solution resulted, although the cyclic compounds alone were immiscible with isopropyl alcohol. A solution of 10 g. of potassium hydroxide in 8 cc. of water was added and all but 5.3 cc. dissolved. The mixture was heated thirty-nine hours at 71°. After cooling it was washed, first with 10% sodium chloride (to help break the emulsion), then with 10% ammonium chloride and dried. On distillation the following fractions were obtained: 15.1 g., 60–119° at 1.8 mm.; 166.5 g., 120–138° at 2.0 mm. (recovered M'_2); 59.3 g., 130–173° at 0.5 mm. (0.140 mole, 51%, of M'_2D'); and a 25.3 g. residue of much lower viscosity than the original D'_x, presumably polymeric material of the general formula $M'_2D'_x$. The third fraction was redistilled at 169° and 0.7 mm.; n^{20}_D 1.5280, d^{20}_4 1.0227, R_D 0.3011, R_D (calcd.) 0.3009.

Anal. Calcd. for $C_{23}H_{30}Si_3O_2$ (M'_2D'): C, 65.36; H, 7.15. Found: C, 64.5, 64.9; H, 7.1, 7.2.

Dimethylphenylsilanol and Dimethylphenylisopropoxysilane.—The low-boiling fraction from the preceding preparation had a strong, pleasant odor similar to that of dimethylphenylchlorosilane and was therefore believed to contain the corresponding silanol. On redistillation 2.8 g. of material was obtained; b. p. 65–66° (3.5 mm.), n^{20}_D 1.4714, d^{20}_4 0.9074, R_D 0.3082, R_D (calcd. for silanol) 0.3034. The only other compound which seemed at all likely to be present was the isopropyl derivative; its calculated specific refraction, 0.3091, is closer to the observed value. A test-tube portion treated with sodium liberated hydrogen. Another portion treated with potassium hydroxide and potassium triiodide (the iodoform test) gave a precipitate, slowly on standing, more rapidly on warming to 70°, as would be expected from the slow formation of isopropyl alcohol. Similar tests with M'_2 and D_4 gave no precipitate. It was therefore concluded that the material was a difficultly separable mixture of dimethylphenylsilanol and dimethylphenylisopropoxysilane.

Heptamethyl-3-phenyltrisiloxane (M_2D').—A mixture of unfractionated cyclic methylphenylpolysiloxanes (13.6 g., 0.1 mole of D′) was dissolved in 48 g. (0.3 mole) of M_2 by adding 50 cc. of toluene and 25 cc. of isopropyl alcohol. To this was added 6.6 g. of 50% aqueous potassium hydroxide solution of which all but 1.5 cc. dissolved. The mixture was heated twenty-four hours at 60°. It was washed with water to remove alkali and alcohol, then dried and distilled through a 9-inch packed column. One cc. distilled from 76.4 to 89.5°. Of this only the first few drops had any odor of benzene; the rest appeared to be a mixture of water and M_2. The amount of benzene produced in the reaction was therefore considered to be negligible. A large fraction with an odor of toluene

---

[14] R. Robison and F. S. Kipping, *J. Chem. Soc.*, **105**, 40 (1913); F. S. Kipping and R. Robison, *ibid.*, **105**, 484 (1913).

[15] Melting points and boiling points are corrected. Molecular weights were determined cryoscopically in cyclohexane. Specific refractions were calculated according to R. O. Sauer, THIS JOURNAL, **68**, 954 (1946).

[16] For a similar reaction see R. N. Lewis, *ibid.*, **69**, 717 (1947).

distilled at 99.6° (750 mm.); n^{20}_D 1.3910. It was assumed to be an azeotrope between M_2 (b. p. 100.4°) and toluene (b. p. 110.8°). After the excess toluene was removed, the next fraction (10 g., 0.036 mole) was distilled at about 250°, leaving as a residue a low viscosity oil, which was assumed to consist of linear compounds of the type $M_2D'_x$. The 250° fraction was redistilled; b. p. 95° (5.0 mm.), n^{20}_D 1.4468, d^{20}_4 0.9080, R_D 0.2941, R_D (calcd.) 0.2929.

Anal. Calcd. for $C_{13}H_{26}Si_3O_2$ (M_2D'): C, 52.30; H, 8.78. Found: C, 52.8, 52.6; H, 8.9, 8.7.

Acknowledgment.—The author is indebted to Miss Mary L. Caldwell, who carried out the microanalyses for carbon and hydrogen.

Summary

1. Two stereoisomeric cyclic trimers and a cyclic tetramer have been obtained by the hydrolysis of methylphenyldichlorosilane.

2. Linear methylphenylpolysiloxanes have been prepared from the cyclic ones by means of hexamethyldisiloxane or tetramethyl-1,3-diphenyldisiloxane and an alkaline catalyst.

3. Evidence for an equilibrium between siloxanes, silanols and silyl ethers has been found.

SCHENECTADY, NEW YORK RECEIVED OCTOBER 3, 1947

[CONTRIBUTION FROM MELLON INSTITUTE AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Preparation and Properties of Trimethylsilylmethanol

BY JOHN L. SPEIER, B. F. DAUBERT AND R. R. MCGREGOR

Organo-silicon compounds containing organic functional groups such as the carbinol group are not readily prepared by the usual methods of synthesis of organo-silicon compounds. The literature records the preparation of only two compounds in which this group is contained. The first is triethylsilylethanol of uncertain structure[1] obtained by the chlorination of tetraethylsilane, conversion of the chloride to the acetate and hydrolysis of the acetate. The second is 1-trimethylsilyl-2-propanol prepared from trimethylsilylmethylmagnesium chloride and acetaldehyde.[2]

Since it was desired to investigate the properties of an α-hydroxyalkylsilane, trimethylsilylmethanol was synthesized in good yield through the sequence of reactions:

Me_3SiCH_2Cl[3] $\xrightarrow[\text{190°C.}]{\text{KOAc, HOAc}}$

$$Me_3SiCH_2OAc \xrightarrow[H_2SO_4]{\text{MeOH}} Me_3SiCH_2OH$$

The trimethylsilylmethanol so prepared was found to be approximately six times as reactive in forming a phenylurethan as its carbon analog, neopentyl alcohol, and approximately three times as reactive as methanol in the same reaction.

Experimental

Preparation of Trimethylsilylmethyl Acetate.—Chloromethyltrimethylsilane[4] (3.1 moles), potassium acetate (3.8 moles), and glacial acetic acid (420 ml.) were charged into a stainless steel high-pressure reactor and shaken at 190–192° for eighteen hours. The contents of the reactor were then washed thoroughly with distilled water. The water-insoluble liquid, after drying over anhydrous sodium carbonate, was slightly amber in color and weighed 416.5 g. (92%). The mixture was distilled through a three-foot Stedman column and was found to boil entirely between the temperatures of 136.2–136.8° at 748 mm., all but 5 ml. distilling at the higher temperature. The ester has the following constants: b. p. 136.8° at 748 mm., $[n]^{25}_D$ 1.4060, $[d]^{25}_4$ 0.8667. Molar refraction: Calcd.[5] for Me_3SiCH_2OAc, 41.31. Found: 41.37. Sapn. equiv.: Calcd., 146.2. Found: 146.5, 146.6. *Anal.* Calcd. for $C_6H_{14}O_2Si$: Si, 19.2. Found: Si, 19.3, 19.1.

Preparation of Trimethylsilylmethanol.—Trimethylsilylmethyl acetate (420 ml., 2.5 moles) was dissolved in absolute methanol (9 moles) and acidified with 10 drops of concentrated sulfuric acid. After standing at room temperature for two days, 165 ml. of the azeotropic mixture of methanol and methyl acetate was removed by distillation. The charge was then diluted with methanol (4 moles) and permitted to stand four days at room temperature before fractionation to yield 268 ml. (80%) of constant boiling trimethylsilylmethanol, b. p. 121.6° at 729 mm. The alcohol redistilled from lime had the following properties: b. p. 121.7–121.9° at 751 mm., $[n]^{25}_D$ 1.4169, $[d]^{25}_4$ 0.8261. Molar refraction: Calcd.[5] for Me_3SiCH_2OH, 31.83. Found, 31.71. The alcohol has a strong odor resembling that of menthol.

Preparation of Trimethylsilylmethyl 3,5-Dinitrobenzoate.—Trimethylsilylmethanol (1.1 g.) was added dropwise to 3,5-dinitrobenzoyl chloride (2.5 g.) and heated to 90° until no more hydrogen chloride was evolved. The mixture was cooled, and ground into a fine powder in the presence of two portions of warm 5–6% sodium carbonate solution. It was heated with a third portion of sodium carbonate solution until it fused. On stirring vigorously as it cooled, solidification occurred. The solids were washed with water in a suction filter, dissolved in boiling 95% ethanol, and filtered while hot. On cooling to room temperature, 2.3 g. of crystalline product was obtained which melted at 69.5–70°. The mother liquor was heated to boiling and diluted with water to the point of incipient turbidity. Again on cooling, 0.9 g. of crystalline product formed, m. p. 68.5–70°. The two crops of crystals were combined and recrystallized once from 95% ethanol. The recrystallized product melted at 70–70.5°. Further recrystallizations did not change this melting point.

Anal. Calcd. for $C_{11}H_{14}O_6N_2Si$: C, 44.26; H, 4.73; N, 9.33; Si, 9.41. Found: C, 44.04; H, 4.41; N, 9.33; Si, 9.47, 9.45.

Preparation of (Trimethylsilylmethoxy)-trimethylsilane.—Trimethylsilylmethanol (19.7 g.) dissolved in dry

---

[1] Friedel and Crafts, *Compt. rend.*, **61**, 792 (1865).

[2] Whitmore, Sommer, Gold and Van Strien, THIS JOURNAL, **69**, 1551 (1947).

[3] Whitmore and Sommer, *ibid.*, **68**, 481 (1946), first prepared chloromethyltrimethylsilane and showed that it reacted with potassium acetate in glacial acetic acid.

[4] Chloromethyltrimethylsilane was prepared for use in this work by the method of Whitmore, Sommer and Gold, *ibid.*, **69**, 1976 (1947).

[5] Warrick, *ibid.*, **68**, 2455 (1946).

chloroform–quinoline solution was treated with an equivalent amount of trimethylchlorosilane. The mixture, which was kept cool during the addition of the trimethylchlorosilane, separated into two layers. After the addition was complete, the mixture was shaken vigorously for fifteen minutes and then diluted with absolute ether (250 ml.). The quinoline hydrochloride was removed by filtration. The filtrate was distilled to yield a fraction (36 ml., 84%) boiling at 129.8° at 738 mm. which was found to be (trimethylsilylmethoxy)-trimethylsilane of the following properties: b. p. 129.8° at 738 mm., $[n]^{25}_D$ 1.3971, $[d]^{25}_4$ 0.7781. Molar refraction: Calcd.[5] for $Me_3SiCH_2OSiMe_3$, 54.00. Found, 53.91. *Anal.* Calcd. for $C_7H_{20}OSi_2$: Si, 31.81; C, 47.71; H, 11.42. Found: Si, 31.4, 31.4; C, 47.86; H, 11.61.

Reactivity of Trimethylsilylmethanol with Phenyl Isocyanate Relative to Other Alcohols.—The method of Davis and Farnum[6] for comparing the relative reaction rate constants of alcohols by means of the competitive reaction of one equivalent of each of two alcohols for one equivalent of phenyl isocyanate in benzene solution was adapted for use in studying the reactivity of trimethylsilylmethanol. These authors showed that the reaction of alcohols with phenyl isocyanate to form the phenylurethans is rapid, essentially irreversible, complete, and free from side reactions. Also, the products can be isolated quantitatively free from solvent and excess alcohol.

The methyl, ethyl, neopentyl and trimethylsilylmethyl alcohols used in this study were all carefully dried and purified. Commercial absolute methanol was refluxed over magnesium shavings and distilled. Commercial absolute ethanol was refluxed two days over amalgamated aluminum foil and distilled. The neopentyl alcohol[7] was prepared from *t*-butylmagnesium chloride and formaldehyde. Only the portion of the product distilled from lime boiling at 111.1° at 737 mm., m. p. 50–53° was used. The phenyl isocyanate was freshly distilled *in vacuo* immediately before use to ensure its being free of carbanilide.

An equivalent of phenyl isocyanate (*ca.* 1 g.) reacted with two equivalents of trimethylsilylmethanol in dry benzene (10 ml.) in a vial closed with a well-fitted ground-glass stopper. The vial was permitted to stand twenty-four hours at approximately 25°. The benzene and excess alcohol were then evaporated in a stream of filtered air with final drying under high vacuum for twenty-four hours. The product so obtained had a melting point of 80–80.5°. Repeated recrystallization from several solvents caused no change in this melting point. *Anal.* Calcd. for $C_{11}H_{17}O_2NSi$: Si, 12.57; C, 59.23; H, 7.68; N, 6.28. Found: Si, 12.59, 12.61; C, 58.89, 59.10; H, 7.37, 7.46; N, 6.15, 6.07.

The same technique was applied to a sample of neopentyl alcohol to produce a derivative melting sharply at 113°. Recrystallization from several solvents did not change this melting point. The phenylurethan of neopentyl alcohol is reported as melting at 114°.[8,9]

Trimethylsilylmethanol was made to compete with the alcohols mentioned essentially by the method of Davis and Farnum.[6] A dry benzene solution containing exactly equimolar amounts of trimethylsilylmethanol and neopentyl alcohol was prepared. From a buret there was added an amount of this solution calculated to contain exactly enough of each alcohol to react with 1.096 g. of phenyl isocyanate delivered from a carefully calibrated pipet into a glass-stoppered vial. The solution was quickly and thoroughly mixed and permitted to stand at least twenty-four hours at approximately 25°. In the same fashion solutions of trimethylsilylmethanol and methanol, trimethylsilylmethanol, and ethanol were prepared and reacted. The amounts of silicon in the nonvolatile products of the reaction were determined and the mole fraction of the silicon derivative present was calculated (Table I).

TABLE I

Competing alcohol	Trial	% Si in products of reaction				K_{Si}/K_{ROH}
Neopentyl	1	10.13	10.04	10.09	10.04	6.56
	2	10.12	10.10			
	3	10.07				
Methyl	1	9.53	9.56			2.92
	2	9.53	9.54			
	3	9.55				
	4	9.53				
Ethyl	1	9.68				3.57
	2	9.62				

The relative reaction rate constants were calculated according to the formula given by Davis and Farnum,[6] where K_{Si}/K_{ROH} is the ratio of the reaction rate constants of the silicon-containing alcohol and the other alcohol concerned.

Method of Analysis for Organo-silicon Compounds.—All determinations of silicon content in the compounds in this communication were carried out by the following procedure: A "Vycor" brand Kjeldahl flask (30-ml. capacity) was brought to constant weight at about 800° in a furnace. The flask was cooled in a desiccator, stoppered tightly to keep moisture from the interior, and permitted to stand in the balance case for from twenty to thirty minutes so that the exterior surfaces reached equilibrium with atmospheric moisture. The weight of the flask and stopper was determined accurately. A sample yielding between 500 and 1500 mg. of silica on oxidation was added to the flask and weighed carefully. About one and one-half ml. of 30% fuming sulfuric acid was added to the flask to dissolve the sample. Fuming nitric acid was cautiously added dropwise with gentle heating between additions until the oxidized material in the flask turned white. The flask was slowly brought to a high temperature to drive off all volatile material, and the flask and contents brought to constant weight at about 800°. The weighing procedure described above was employed again, the gain in weight of the flask being taken as due to silica formed by oxidation. The silica was quite hygroscopic. Therefore, the flask during weighing was stoppered to exclude moisture. All organo-silicon compounds may be analyzed in this manner except those that are volatile or not readily soluble in fuming sulfuric acid.

Discussion

The unusual reactivity of trimethylsilylmethanol in forming the phenylurethan indicates a pronounced activating influence by the silicon atom upon the O–H bond. Primary alcohols branched in the β position are generally less reactive than their normal homologs. The results of several different methods of determining the relative reactivities of alcohols agree quite well in that they usually place the alcohols in the same relative order. Table II shows some of the results of various workers, and the results of this study.

From the data in Table II it can be seen that the effect of branching in the β position is most apparent in neopentyl alcohol. The same effects of branching either are not present in the silicon analog of neopentyl alcohol or they are completely masked by a pronounced activating influence of the silicon atom upon the O–H bond. The large covalent radius 1.17 Å. for the silicon atom compared to 0.77 Å. for carbon causes less packing and thus less interaction between the methyl groups on

---

[6] Davis and Farnum, THIS JOURNAL, **56**, 883 (1934).

[7] Rice, Jenkins and Hardin, *J. Am. Pharm. Assoc.*, **27**, 303 (1938).

[8] Whitmore and Rothrock, THIS JOURNAL, **54**, 3431 (1932).

[9] Richard, *Ann. Chemie*, [6] **21**, 337 (1910).

TABLE II

RELATIVE REACTION RATES OF ALIPHATIC ALCOHOLS

Alcohol	K^6	K (this work)	K^{10}	K^{11}	% reacted[12]
$(CH_3)_3SiCH_2OH$	.....	2.92	...	..	..
CH_3OH	1.000	1.00	1.00	1.00	55.6
C_2H_5H	0.961	0.82	0.46	0.81	46.9
n-C_3H_7OH	.782	..	.36	.79	46.9
n-C_4H_9OH	.972	..	.40	.80	46.8
n-$C_5H_{11}OH$	.908	..	.43	.98	..
i-C_4H_9OH	.693	..	.17	.66	..
$(C_2H_5)(CH_3)CHCH_2OH$	.....	..	.19	..	..
$(CH_3)_3CCH_2OH$	.....	.45	...	..	..
$(CH_3)_2CHOH$	.305	..	.054	.55	26.5
$(CH_3)_3(C_2H_5)CHOH$	.321	..	.04	.53	22.6
$(CH_3)_3COH$	.00318	..	.015	..	1.4
$(CH_3)_2(C_2H_5)COH$	.00728	..	.014	..	.8

the silicon atom than would be the case for similar groups on a carbon atom, as has been pointed out by Whitmore and Sommer.[3] The interaction of the closely packed groups on a carbon atom probably is partly responsible for the inactivity of neopentyl alcohol. The lack of this effect, however, can scarcely explain the enhanced activity of its silicon analog which appears to be more active than any other alcohol. The explanation for the enhanced activity of this compound might be related to the highly electronegative nature of the Me_3SiCH_2-radical as found by Whitmore, Sommer and Bernstein,[3,13] who found that order of certain radicals was as follows: phenyl > Me_3SiCH_2- > Me- > Et- > n-Pr- > (n-Bu-, n-Hex-) > Benzyl > (Me_3CCH_2-, t-Bu-) as determined by the method of Kharasch and Marker.[14] This relationship of reactivity of alcohol to electronegativity of the radical seems to hold true for the normal alcohols but glaring exceptions are noticeable where branching in the alcohol occurs. Thus benzyl, neopentyl and t-butyl radicals are about equal in electronegativity, but the corresponding alcohols are quite different in relative reactivities. The reactivity of an alcohol probably is dependent upon the electronegativity of the radical as well as upon the steric effects of structure and the separation of the two effects is not possible.

Trimethylsilylmethanol dissolves sodium slowly at room temperature with the evolution of hydrogen. A sample (22 g.) containing a small amount of dissolved sodium was found to be unchanged by heating at 175° in a sealed tube for four days. The same sample diluted with a mixture of methanol (4 ml.) and water (0.5 ml.) was heated at 180° for sixteen hours followed by heating at 210° for two hours. No appreciable change was observed.

The alcohol dissolved slowly in boiling 75% potassium hydroxide solution over a period of several hours to form a clear solution from which an infusible combustible gel was precipitated by the addition of acid. Apparently cleavage of silicon–carbon bonds occurred resulting in the production of a polymeric siloxane material upon acidification of the solution.

Trimethylsilylmethanol dissolved clean amalgamated aluminum foil very quickly with the evolution of much heat when a trace of carbon tetrachloride was added to catalyze the reaction.

Summary

The synthesis of trimethylsilylmethanol and a study of its chemical reactivity is reported.

PITTSBURGH, PENNSYLVANIA
RECEIVED SEPTEMBER 2, 1947

---

[10] Norris, Ashdown and Cortese, THIS JOURNAL, **47**, 837 (1925); **49**, 2640 (1927); found these rate constants for esterification of alcohols with p-nitrobenzoyl chloride recalculated on basis of the rate for methanol equal to unity.

[11] Fehlandt and Adkins, *ibid.*, **57**, 193 (1935); Hatch and Adkins, *ibid.*, **59**, 1694 (1937), found relative reactivities from methanolysis studies.

[12] Menschutkin, *Ann. chim. phys.*, [5] **30**, 81 (1883), reacted alcohols with acetic acid one hour at 155°.

[13] Whitmore and Bernstein, THIS JOURNAL, **60**, 2626 (1938).

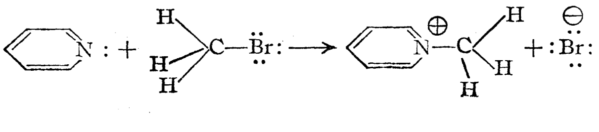
[14] Kharasch and Marker, *ibid.*, **48**, 3140 (1926).

[CONTRIBUTION NO. 1145 FROM THE GATES AND CRELLIN LABORATORIES OF CALIFORNIA INSTITUTE OF TECHNOLOGY AND FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Kinetic Evidence for a Termolecular Mechanism in Displacement Reactions of Triphenylmethyl Halides in Benzene Solution

BY C. GARDNER SWAIN[1]

According to current theory there are only two commonly occurring mechanisms for nucleophilic displacement reactions. One is the bimolecular, kinetically second order (S_N2) substitution or "Walden Inversion."[2] In this mechanism the driving force is exclusively a "push" or *nucleophilic* attack by the entering atom or group, which has an unshared pair of electrons that it is eager to donate in bond formation. The attack is entirely from the back side. An example is the reaction of *primary* halides, such as methyl bromide, with pyridine in benzene solution.

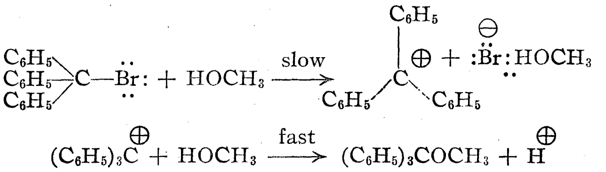


---

[1] National Research Fellow 1945–1946; American Chemical Society Fellow 1946–1947. Paper presented at the New York meeting of the American Chemical Society, September 17, 1947.

[2] (a) Walden, *Ber.*, **28**, 1287 (1895); (b) Lewis, "Valence and the Structure of Atoms and Molecules," 1923, p. 113; (c) Hughes, Juliusberger, Masterman, Topley and Weiss, *J. Chem. Soc.*, 1525 (1935); (d) A. G. Evans, "Reactions of Organic Halides in Solution," Manchester University Press (1946); *Trans. Faraday Soc.*, **42**, 719 (1946).

The other is the ionization (S_N1) mechanism,[3] which dominates for reactions of *tertiary* halides. It is with this second mechanism that the present paper is concerned. According to the most widely accepted interpretation,[3e] the driving force in this case is exclusively a "pull" or front side attack by the solvent or some *electrophilic* solute, which hydrogen bonds with or otherwise solvates the leaving atom or group due to simple electrostatic attraction or to formation of a coördinate bond with the unshared electron pair on the leaving group. This weakens the old bond, allowing it to ionize in the rate-determining step. The reaction is kinetically first order when it is with a solvent which is in large excess. An example is the solvolysis of trityl bromide in methanol solution.



$$(C_6H_5)_3\overset{\oplus}{C} + HOCH_3 \xrightarrow{\text{fast}} (C_6H_5)_3COCH_3 + \overset{\oplus}{H}$$

Previous workers have quite generally used a hydroxylic solvent as the reagent in studying the ionization (S_N1) mechanism, and hence have been unable to determine the kinetic order with respect to the reagent, since it was in large excess and did not change in concentration appreciably during the reaction.

There is a qualitative impression, arising from studies in mixed solvents, however, that more than one molecule of the hydroxylic solvent is involved in the rate determining reaction. Hammett considers that from one to three molecules may hydrogen bond with the halogen atom simultaneously, in a "polymolecular" solvolysis, still involving only attack on halogen. Others have proposed that dimers and trimers of the hydroxylic reagent may be involved. Nearly all are unanimous in declaring that there is no experimental evidence for any attack on carbon by the reagent in the rate-determining step.

By using reactants in low, approximately equivalent concentrations in an inert solvent, benzene, we have been able to determine the kinetic order with respect to all nucleophilic and electrophilic species present. As a model tertiary group we selected triphenylmethyl (trityl) rather than *t*-butyl, to avoid the possibility of elimination of hydrogen halide. The various nucleophilic and electrophilic reagents included tertiary amines, methanol and phenol, separately and in mixtures, with the concentration of each species being independently varied.

Our results indicate that the rate determining ionization step occurs by a termolecular mechanism. The ionization is a result of concomitant or "concerted" solvating attacks on carbon and halogen. Simultaneous attack on both atoms is required to effect any reaction. In the rate-determining step one and only one molecule forms a solvation bond (chiefly ionic) to carbon; similarly one and only one hydroxylic molecule becomes bound by a hydrogen bond (ionic bond) to halogen. The result is always a push–pull termolecular mechanism with exactly third order kinetics.

Data.—Triphenylmethyl (trityl) chloride or bromide (0.1 *M*) reacts with methanol (0.05–0.1 *M*) in dry benzene solution containing a tertiary amine (0.1–0.2 *M*) at 25° to give trityl methyl ether. The tertiary amine is used simply to take up the hydrogen halide formed and render the reaction irreversible. The reaction between trityl halides and tertiary amines is negligibly slow under these conditions, and the rate of the reaction with methanol is unaffected by changing the concentration of tertiary amine used. Triethylamine, a stronger base than pyridine by five powers of ten, gives approximately the same rate as pyridine.

Within experimental error the reaction with methanol is exactly third order (first order in trityl halide, second order in methanol). Rate "constants" calculated assuming that the reaction is second order (first order in each) decrease twofold within a kinetic run, while third order constants show less than 15% scatter and no trend. Comparing two runs having a two-fold ratio of initial concentration of methanol, the calculated average second order "constants" differ by twofold; while the average third order constants are the same within 5%. The fact that the order is so precisely third, rather than intermediate between second and third or between third and fourth, suggests that we are dealing with a pure mechanism which accounts for all of the reaction observed.

If phenol is used instead of methanol, the phenyl ether is obtained but at less than one-fiftieth the rate. The reaction appears to be still third order (second order in phenol), although an inverse, roughly first order dependence on pyridine concentration indicates that about half of the phenol is complexed by the pyridine. If the reaction proceeded by an ionization (S_N1) mechanism, one would have expected phenol to bring about a faster reaction than methanol, since it is known to form stronger hydrogen bonds with halogens.[4] The slower reaction of phenol can best be explained by assuming that a solvation of the carbon is required, in which phenol, due to its larger size, would be much less effective than methanol.

---

[3] (a) Ward, *J. Chem. Soc.*, 2285 (1927). (b) Hughes and Ingold, *Nature*, **132**, 933 (1933). (c) Steigman and Hammett, THIS JOURNAL, **59**, 2536 (1937); Farinacci and Hammett, *ibid.*, **59**, 2542 (1937); **60**, 3097 (1938). (d) Hughes, *Trans. Faraday Soc.*, **37**, 604, 612 (1941). (e) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 54, 172. Solvation of the carbon has generally been considered a negligible contribution to the driving force. However, theoretical arguments for it have been occasionally advanced (*cf.* Winstein and Buckles, THIS JOURNAL, **64**, 2780 (1942), and Evans, ref. 2d).

[4] Bartlett and Dauben, THIS JOURNAL, **62**, 1339 (1940) Hantzsch, *Ber.*, **58**, 627 (1925).

When both methanol and phenol are present, only methanol is consumed as long as the methanol lasts. However the rate of reaction is many times faster than in the absence of phenol. The rapid phase of the reaction ends when trityl chloride or bromide equivalent to the methanol present has been consumed. Beyond this point reaction proceeds further at the very slow rate characteristic of runs with phenol alone, until additional trityl halide equivalent to the phenol present has been consumed. An average third order rate constant calculated for the rapid phase of the reaction with trityl chloride in the same way as in the absence of phenol was twenty times larger in the presence of phenol equivalent to the methanol. However this constant increased three-fold within the run, indicating that this kinetic order was incorrect. The reaction was found to be exactly second order within a run (first order in trityl chloride, first order in methanol). However, when runs of different initial concentration of phenol were compared, it was found that the reaction was also first order in phenol, hence again exactly third order over-all. The lack of a kinetic dependence on phenol within a run was evidently due to the fact that phenol was not consumed until all methanol was exhausted. A new third order rate constant, calculated for $dx/dt = k_3'$ (RX) (CH_3OH)(C_6H_5OH), was seven times as large as the old third order constant for runs in the absence of phenol.

This seven-fold acceleration of the rate of reaction of trityl halides with methanol, caused by adding phenol, a substance which reacts only very slowly with trityl halides by itself, is best explained by assuming that a solvation of halogen is also required in these reactions. Phenol is an excellent reagent for solvating halogen, but a very poor one for solvating carbon. Since solvation of both halogen and carbon is required, it reacts very slowly. Methanol is moderate as a halogen reagent, excellent as a carbon reagent, hence reacts moderately rapidly by itself. However, when both are present, each performs independently the function to which it is best adapted and a very high rate results.

The data from typical runs is presented in Tables I and II. Figure 1 shows the course of the reaction of trityl chloride with methanol, phenol, and a mixture of the two. Tables III and IV give detailed data for the more important runs. It is by such tables that all the rate constants of Tables I and II were obtained. The constants are defined as follows. Let

τ = initial moles/liter of trityl halide
μ = initial moles/liter of methanol
ϕ = initial moles/liter of phenol
x = moles/liter of reaction
t = minutes
$Q = \tau/\mu$; $z = x/\mu$

For methanol

$$k_3 = \frac{dx/dt}{(\mu - x)^2(\tau - x)} = \frac{1}{\mu(Q-1)t}\left(\frac{z}{\mu(1-z)} - \frac{2.303}{\mu(Q-1)}\log\left[\frac{Q-z}{Q(1-z)}\right]\right)$$

For phenol the expression is the same except that μ is replaced by ϕ. For methanol and phenol

$$k_3' = \frac{dx/dt}{\phi(\mu - x)(\tau - x)} = \frac{2.303}{\phi\mu(Q-1)t}\log\left[\frac{Q-z}{Q(1-z)}\right]$$

These equations were applied to the data in their integrated rather than in their differential forms to obtain the maximum accuracy.

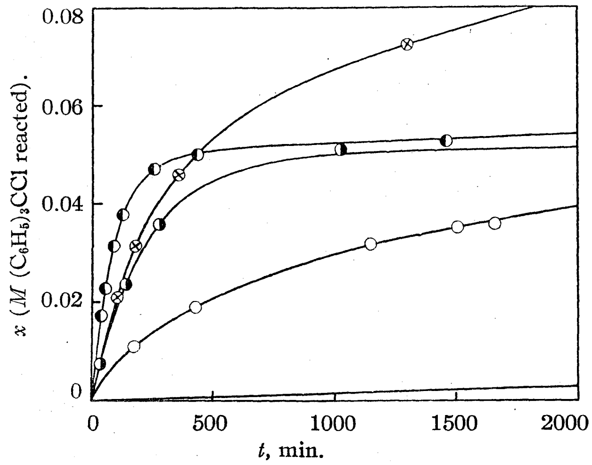


Fig. 1.—Reactions of 0.106 M trityl chloride in dry benzene solution in the presence of 0.108 M pyridine at 25°: lowest line for reaction with 0.056 M phenol; ⊙, 0.054 M methanol; ⊗, 0.109 M methanol; ◑, 0.054 M methanol plus 0.023 M phenol; ◐, 0.054 M methanol plus 0.056 M phenol.

The Salt Effect.—The concentration of dissolved pyridine hydrochloride is five times greater in the presence of phenol than with just methanol (see experimental section on procedure). However, the increased salt concentration caused by the presence of the phenol is not the cause of the greatly increased rate of reaction with methanol. It is true that there is a positive salt effect in this reaction, but it is of small magnitude. It was measured by substituting other tertiary amines having successively more soluble hydrochlorides for the pyridine, and observing the effect on the reaction with methanol in the absence of phenol. Quinaldine is less soluble by a factor of two and gave $k_3 = 0.21$ instead of 0.26. Quinoline is more soluble by a factor of three and gave $k_3 = 0.35$. With diethylaniline the salt dissolved indefinitely, giving $k_3 = 0.25$. A further check on this point was made by substituting quinaldine for pyridine in a reaction with methanol and phenol. In spite of the lower salt solubility, the same seven-fold acceleration was observed.

TABLE I

REACTIONS OF TRITYL CHLORIDE IN DRY BENZENE SOLUTION AT 25°

Run	M $(C_6H_5)_3CCl$	M R_3N	M CH_3OH	M C_6H_5OH	k_2 (l./mole min.)	k_3 (l.²/mole² min.)	k_3' (l.²/mole² min.)
32, 55	0.106	0.108^{a}	...	...	<0.000001	....	....
46	.106	.064^{a}	0.054	...	.0096^{e}	0.275 ± 0.04	....
50	.106	.108^{a}	.054	...	.0083^{e}	.263 ± .04	....
47	.106	.215^{a}	.054	...	.0088^{e}	.252 ± .04	....
40	.106	.108^{a}	.109	...	.0199^{e}	.252 ± .04	....
48	.106	.103^{b}	.054	...	....	.21 ± .04	....
51	.106	.108^{c}	.054	...	....	.35 ± .06	....
49	.106	.107^{d}	.054	...	....	.25 ± .04	....
54	.064	.108^{a}	.054	...	....	.21 ± .06^{f}	....
34, 56	.106	.108^{a}	...	0.056	....	.004 ± .002	....
43	.106	.108^{a}	.054	.023	....	1.3^{g}	1.98 ± 0.3
35	.106	.108^{a}	.054	.056	....	5.0^{g}	1.89 ± .3
52	.106	.103^{b}	.054	.056	....	3.5^{g}	2.03 ± .4
58	.106	.215^{a}	.054	.056	....	2.5^{g}	1.18 ± .2
53	.106	.108^{a}	.054	.030^{h}	....	...	4.9 ± .8
60	.106	.108^{a}	.054	...	....	0.75 ± .12^{j}	....
59	.075^{k}	.093^{a}	.054	...	....	8.0 ± 1.2^{k}	....

[a] R_3N = pyridine. [b] R_3N = quinaldine. [c] R_3N = quinoline. [d] R_3N = diethylaniline. [e] Not constant. Compare runs 40 and 50, which would have same k_2 if the kinetics were second order. Also note two-fold decrease in k_2 during a run in Table III. [f] Less accurate than constants from other runs due to smaller titers. [g] Not constant. Note three-fold increase in this k_3 during a run in Table IV. [h] Used p-$O_2NC_6H_4OH$ instead of C_6H_5OH. [j] At 56.5° rather than 25°. [k] $(p\text{-}t\text{-}C_4H_9C_6H_4)_3CCl$ rather than $(C_6H_5)_3CCl$.

TABLE II

REACTIONS OF TRITYL BROMIDE IN DRY BENZENE SOLUTION IN THE PRESENCE OF PYRIDINE AT 25°

Run	M $(C_6H_5)_3CBr$	M C_5H_5N	M Addend	Addend	k_2 (l./mole min.)	k_3 (l.²/mole² min.)	k_3' (l.²/mole² min.)
19	0.103	0.110	...	....	≤0.000002	....	......
10	.098	.108	0.106	$(C_6H_5)_3COH$	....	0.0014^{a}	......
45	.098	.108	.054	$C_6H_5NHCH_3$	....	.03 ± 0.01	......
21	.103	.220	.032	C_6H_5OH	.00072	.038 ± .006	......
17	.098	.108	.032	C_6H_5OH	.0015	.066 ± .010	......
24	.103	.074	.032	C_6H_5OH	.0018	.081 ± .013	......
20	.103	.110	.190	C_6H_5OH	.027	.178 ± .03	......
22	.103	.110	.037	p-$O_2NC_6H_4OH$	....	.17 ± .03	......
28	.103	.055	.037	p-$O_2NC_6H_4OH$	....	.79 ± .12	......
23	.103	.110	.055	p-$H_3CC_6H_4SH$	....	12 ± 2	......
31	.103	.111^{b}	.055	CH_3OH	....	18 ± 6^{c}	......
39	.098	.108	.033	CH_3OH	....	21.9 ± 4	......
26	.103	.220	.055	CH_3OH	....	21.3 ± 4	......
25	.103	.110	.055	CH_3OH	....	23.6 ± 4	......
30	.103	.110	.055 .032	CH_3OH C_6H_5OH	....	200. ± 70^{d}	90 ± 30^{d}
27	.103	.110	.054	p-$H_3CC_6H_4NH_2$		Too fast to measure	
18	.103	.110	.011	H_2O			

[a] At 60° rather than 25°. [b] Triethylamine used instead of pyridine. [c] Chloride ion titration necessitated only in this run was not as accurate as hydrogen ion titration used elsewhere. [d] Based on first (nine minute) point. Other points were too close to infinite titer to give accurate results.

One might argue that in the mixed methanol–phenol runs we might have an increased concentration of salt arising not only from the increased solubility of pyridine hydrochloride but also from the association of pyridine and phenol. However the latter type of complex, if it were a salt, should be even less effective electrically than the hydrochloride, because the charges would be buried in the middle of much organic material. To check this, the concentration of pyridine in a mixed methanol–phenol run was doubled, and it was observed, as expected, that the rate constant decreased to 64% of its previous value as a result of the decreased concentration of free phenol, in spite of an increased concentration of the dissolved pyridine–phenol complex.

The Mass Effect.—There is no indication of a mass effect, *i. e.*, of reversal of carbonium ion formation caused by chloride ion accumulating as a reaction product. In the experiments on the salt effect the rate at first showed a steady, though small, increase rather than decrease as the con-

TABLE III

REACTION OF 0.106 *M* TRITYL CHLORIDE WITH 0.054 *M* METHANOL IN DRY BENZENE SOLUTION IN THE PRESENCE OF PYRIDINE AT 25°

Run 46, 0.064 *M* pyridine; run 50, 0.108 *M* pyridine; run 47, 0.215 *M* pyridine. Q = 1.963.

Run	t, min.	x, moles/l.	$x_{\text{cor.}}$	z	k_2	k_3
50	20	0.0010	....	...	....	...
47	22	.0003	....	...	....	...
46	22	.0010	....	...	....	...
47	168	.0067	0.0091	0.169	0.0107	0.224
46	174	.0086	.0110	.204	.0127	.278
47	418	.0157	.0181	.335	.0101	.234
50	426	.0165	.0189	.350	.0105	.248
46	444	.0183	.0207	.384	.0115	.278
50	1150	.0294	.0318	.589	.0089	.272
47	1440	.0310	.0334	.618	.0077	.252
46	1510	.0321	.0345	.639	.0080	.264
50	1660	.0330	.0354	.656	.0077	.263
47	2890	.0394	.0418	.774	.0066	.296
46	2900	.0390	.0414	.767	.0064	.281
50	3120	.0392	.0416	.771	.0060	.269
47	193000	.0490	.0514	.952	....	...
				Av.	0.0089	0.263

TABLE IV

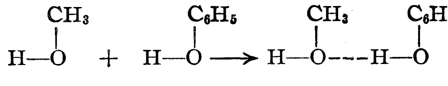
REACTION OF 0.106 *M* TRITYL CHLORIDE WITH 0.054 *M* METHANOL IN DRY BENZENE SOLUTION WITH 0.056 *M* PHENOL AT 25°

Run 35, 0.108 *M* pyridine; run 52, 0.103 *M* quinaldine. Q = 1.963.

Run	t	x	$x_{\text{cor.}}$	z	k_3	k_3'
52	21	0.0003	....	...	..	..
35	27	.0003	....	...	..	..
35	39	.0017	0.0172	0.318	2.30	1.82
52	53	.0157	.0227	.420	2.74	1.98
35	55	.0055	.0210	.389	2.30	1.69
35	91	.0159	.0314	.582	3.32	1.97
52	127	.0309	.0379	.702	4.35	2.08
35	203	.0295	.0450	.834	6.55	2.10
35	258	.0315	.0470	.870	7.14	1.93
35	434	.0344	.0499	.924	8.31	1.54
35	1460	.0372	.0527	...	..	..
35	40,500	.0550	.0705	...	..	..
35	57,800	.0577	.0732	...	..	..
52	111,000	.0762	.0832	...	..	..
						Av. 1.89

centration of dissolved tertiary amine hydrochloride was increased by varying the amine used.

Evidence Against a Methanol–Phenol Complex.—Another alternative interpretation of the increased rate of reaction with methanol caused by adding phenol must be ruled out before the picture of simultaneous solvation of carbon by methanol and solvation of halogen by phenol will be on a firm footing. One might interpret the increase by saying that only halogen solvation is involved, but that the solvating agent is a hydrogen bonded complex between methanol and phenol.

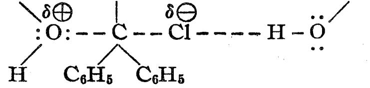


$$H-\overset{\overset{CH_3}{|}}{O} + H-\overset{\overset{C_6H_5}{|}}{O} \longrightarrow H-\overset{\overset{CH_3}{|}}{O}---H-\overset{\overset{C_6H_5}{|}}{O}$$

However, if this view were correct, this complex would have to form an even stronger hydrogen bond to halogen than phenol, to account for the much faster rate than in the case of solvolysis by phenol alone. That no complex having such hydrogen bonding ability exists in appreciable concentration can be shown by measurement of the enhancement of the acidity of hydrogen chloride dissolved in ether caused by methanol, phenol and a mixture of the two.[4] This enhancement depends on and is a measure of the extent of hydrogen bonding of the hydroxylic species with the chlorine of $(C_2H_5)_2O \cdot HCl$. This hydrogen bonding weakens the H–Cl bond and increases the extent of ionization. Evidently the system used for measuring the effect is very similar to our kinetic system where the C–Cl bond of $(C_6H_5)_3CCl$ is being weakened in the same way. Yet the results showed that phenol is much better at hydrogen bonding than methanol, rather than poorer, and that the mixture of the two is no better than the sum of phenol and methanol solutions taken separately. The above experiment argues against the existence of hydrogen bonding between methanol and phenol. The fact that the rate of reaction with methanol is completely independent of pyridine concentration shows that there is less than 15% hydrogen bonding between pyridine and methanol. However, the effect of pyridine concentration on the rate with phenol is probably due to hydrogen bonding.

Other Reagents.—*p*-Nitrophenol is almost entirely associated, probably in a hydrogen bonded complex, by excess pyridine in benzene solution at 25°, as shown by the inverse second order dependence of rate on pyridine concentration in reactions with trityl bromide. However, the small portion which is free, by reason of its great hydrogen bonding ability, is able to increase the overall rate to a higher value than phenol, in spite of the fact that a smaller concentration is acting. The constant k_3', calculated as if all the *p*-nitrophenol were uncombined and effective, is twenty times, rather than seven times, as large as k_3 with just methanol present.

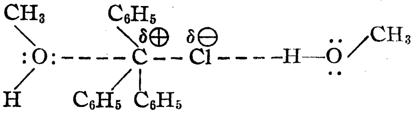
tris-(*p*-*t*-Butyl)-trityl chloride reacts with methanol in dry benzene solution thirty times as rapidly as does trityl chloride. According to Hammett's treatment[5] of the reactions of *m*- and *p*-substituted benzene derivatives, the *p*-*t*-butyl group has a substituent constant of −0.20. This gives a reaction constant of −7.5, or −2.5 per *t*-butyl group, representing a rather high sensitivity of the reaction to substituents. The direction of the change in rate is opposite to what one would expect if stabilization of the transition state



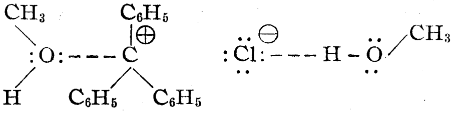
---

(5) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., N. Y., 1940, pp. 118–124, 184–228.

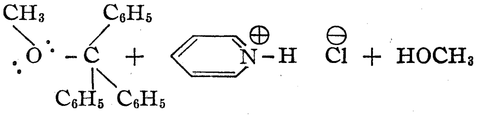
or formation of the covalent bond to oxygen were the most important factors determining the rate. However, it is what one would expect if the transition state were



and if the product formed by the rate-determining step is

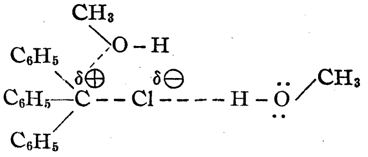


i. e., a solvated ion pair. The bonds with three dashes represent ion-dipole solvation bonds. The solvated ion pair may then react to form the products



in a fast follow-up step or succession of such steps. The methanol molecule which finally reacts, *i. e.*, becomes covalently bonded to carbon in the product determining step is not necessarily the same molecule that solvates the carbon in the rate determining step. The two steps are *independent*, and our study sheds light on only the rate-determining step. However, in this particular case it is possible that the same methanol molecule is involved in both steps.

We have pictured the solvation of halogen as a *front side* attack and the solvation of carbon as a *back side* attack. This stereo-relationship seems most likely but is not uniquely consistent with our experimental results. It is conceivable that the molecule solvating carbon may approach from the front side.



We are conducting experiments on displacement reactions of optically active halides in benzene solution which may shed light on the stereochemistry. However, pending further results we favor the picture of back side solvation of carbon.

Table II shows the relative reactivity of a number of different types of compounds toward trityl bromide. This series shows at least two forces at work.

(1) Steric Hindrance.—While methanol reacts very rapidly, triphenylcarbinol does not react detectably. Also pyridine does not react even when there is phenol in the system. Stuart molecular models, which have approximate interference radii, confirm the impossibility of back side collision of the oxygen or nitrogen with the trityl bromide carbon in these cases. On the other hand, phenol has less hindrance, and in the models its oxygen can just be caused to touch the carbon by proper orientation of groups. With methanol this is considerably easier and contact can be achieved with a large variety of orientations. The water molecule has the least steric hindrance of all. The relative rates for these compounds are the ones expected on the basis of these steric considerations.

(2) Basicity of the Atom Solvating Carbon.—On steric grounds *p*-toluidine and *p*-thiocreosol would be expected to react about as slowly as phenol. They are certainly much less hindered than pyridine but no less hindered than phenol. Actually *p*-toluidine reacts immeasurably fast (like water), and thiocresol almost as fast as methanol. We consider that solvation bonds are chiefly ionic in type. However the solvation bonds to carbon might have 25% covalent character, so that differences in nucleophilic tendency of the solvating atom could effect some difference in the rate of reaction. The high "reaction basicity" or nucleophilic character of S is a striking thing, since S is not a basic atom in the usual sense, *i.e.*, when an equilibrium measurement is made involving addition of a proton.

Examination of molecular models indicates that *t*-butyl halides would have the same high degree of back side hindrance as trityl halides, but no experiments were run on *t*-butyl halides.

Termolecular Reactions in Liquid Phase.—The evidence presented indicates that simultaneous solvating attacks on the carbon and halogen are necessary to effect reaction of the trityl halides in benzene solution. The reaction of trityl chloride with methanol has the surprisingly low activation energy of 6.6 ± 1.0 kcal. This means a frequency factor of only 300 $1.^2$ $/\text{mole}^2$ sec., or the large negative entropy of activation[6] of -49 ± 4 cal./mole, referred to a standard state of one mole/l., as compared with an activation entropy of about -15 ± 5 cal./mole, referred to the same standard state, calculated for a hypothetical termolecular reaction in the gas phase having a steric factor of unity and hence a frequency factor equal to the termolecular collision rate of 10^{10} $1.^2/\text{mole}^2$ sec. This indicates a very precise orientation requirement for reaction, but an energetically very easy reaction path once the proper steric relationships are satisfied.

Third order kinetics have been observed previously in the bromination of olefins,[7] the cleavage of ethers with hydrogen bromide,[8] and the hydrogen chloride catalyzed addition of hydrogen bromide to olefins.[9] These reactions very probably

---

(6) Glasstone, Laidler and Eyring, "Theory of Rate Processes," McGraw-Hill Book Co., Inc., N. Y., 1941, p. 199, eqn. 178.

(7) Nozaki and Ogg, This Journal, **64**, 706 (1942).

(8) Mayo, Hardy and Schultz, *ibid.*, **63**, 433 (1941).

(9) Maass and Sivertz, *ibid.*, **47**, 2888 (1925).

also involve termolecular mechanisms. They too have abnormally low activation energies.

It is impossible kinetically to distinguish a termolecular reaction from a rapid bimolecular association of two of the reactants to give a low equilibrium concentration of a complex, followed by slow bimolecular reaction of the complex with the third reactant. Thus the rate determining step in our experiments might be a back side attack by methanol on a solvated trityl halide complex, $(C_6H_5)_3CCl---- HOR$. In the opinion of the author the distinction between this and a simultaneous back and front side attack, or termolecular reaction, lacks physical significance because the two pictures are so nearly identical. The complex, pictured above, would have a very short lifetime. The making and breaking of bonds between hydrogen and halogen, oxygen, sulfur or nitrogen is never activation controlled, and so cannot be postulated as a slow step in any organic reaction unless the reactants are in exceptionally minute concentration. If the back side attack must follow so quickly after the front side solvation, one might as well call the process a termolecular reaction.

Let us consider a trityl halide molecule and a methanol or phenol molecule which have just diffused together and collided for the first time. They are surrounded by a "cage" of benzene molecules which makes it difficult for them to separate again. Even if there were no attractive force between them, they might undergo a great many repeated collisions, perhaps a thousand or more, with the solvent molecules forming the wall of the cage, and with each other, before one of them would break out of the cage. The existence of a hydrogen bond of 3.0 to 6.0 kcal. strength between the halide molecule and the methanol or phenol will further significantly prolong (by a factor of 150 to 25,000) the period that a pair is associated together in one "encounter."[10] If at any time within this period another methanol or phenol molecule happens to break into the same cage, there is a minute but nevertheless finite probability of reaction, since a sizeable number of termolecular collisions may occur before one of the three molecules breaks out of the cage.

Bringing a new methanol dipole (1.7 Debye units, 1 Å. long) up to the interference distance (2.8 Å.) between oxygen and carbon would contribute 5.5 kcal./mole to the driving force of the reaction if one assumes an internal dielectric constant of 2.0. This added driving force is equivalent to a ten thousand-fold increase in rate, which must evidently outweigh the steric unlikelihood of a termolecular route as compared to a simple bimolecular reaction not involving solvation of carbon.

This double attack (or termolecular mechanism) is closely similar to the effects which were observed by Lowry in the mutarotation of tetramethylglucose.[11] Both an acid and a base appeared to be necessary in that reaction. The rate in a mixture of pyridine and cresol was far greater than that in either solvent alone.

Range of Applicability of this Mechanism.—Thus far the interpretation has been backed by experimental evidence. What follows is an extrapolation of the findings in the one particular system studied to other systems. The generalizations and predictions which follow seem probable now and should be helpful in planning future work, but must be recognized as speculative.

At most we have established this mechanism only for benzene solution, and it is hard to see how we could even go about determining the order with respect to methanol or water in methanol or aqueous solution with certainty. However, it seems inevitable that, as the concentration of hydroxylic reagent is increased, the higher order mechanism involving solvation of both carbon and halogen should still further outstrip a lower order mechanism involving only solvation of halogen. The ease of production of a solvated ion pair should reflect the internal dielectric constant of the halide ($\sim$2?), the polarizability of its electrons, and the specific nature and concentration of the solvating species. It does not seem reasonable to expect a large dependence on the dielectric constant of the medium, since internal dielectric constant should be much more important, and this is a function of only the halide and its two nearest neighbors, *e.g.*, two methanol molecules involved in back and front side solvation. On this view, methanol is not a much different medium than benzene containing 0.1 M methanol, for carrying out halide solvolyses. The large difference in rate is chiefly due to the difference in concentration of methanol in the two cases, although self-association of methanol in the pure solvent may have some small effect on the comparison.

Except for a generally higher reactivity, the situation with water should be similar to the situation with methanol.

Trityl halides are more strongly hindered with respect to attack on carbon than most other halides, yet these experiments indicate that such attack in the form of solvation is still required as part of the driving force which effects reaction. This suggests that attack on carbon is involved in the rate determining step of all displacements on carbon. According to this idea, attack on carbon is always necessary. Attack on the grouping to be displaced is optional; it occurs with tertiary halides; but there are certainly cases where it is not involved among the reactions of primary halides, *e.g.*, the reaction of methyl bromide with pyridine in benzene solution.[12]

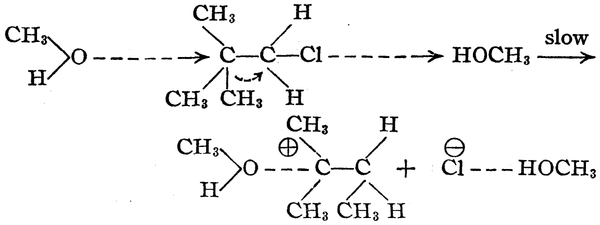
---

(10) Rabinowitz, *Trans. Faraday Soc.*, **33**, 1227, 1229 (1937).

(11) Lowry and Faulkner, *J. Chem. Soc.*, **127**, 2883 (1925).

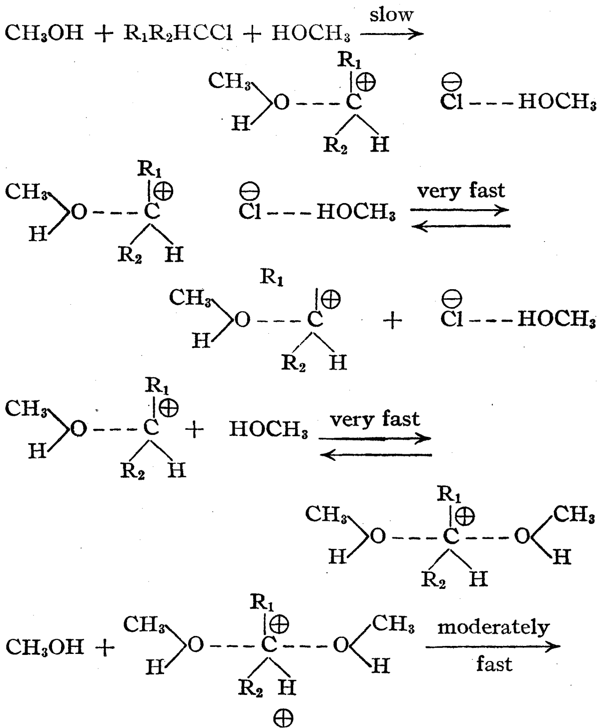
(12) We are neglecting solvation by benzene through van der Waals attractive forces, which, estimated by the heat of vaporization of benzene or methanol, may amount to 8 kcal./mole. This would be important in any comparison with the corresponding reaction run in gas phase. However, halide solvolyses have never been accomplished in homogeneous gas phase, and all real experiments compared in this paper were in liquid phase, for which these van der Waals forces are approximately constant.

The type of attack on carbon involved in the rate determining step may vary. With primary halides it gives a covalent bond; with tertiary halides it is a solvation giving a chiefly ionic or ion-dipolar bond. In other cases the attack on carbon may even be on a different carbon than that from which the leaving group is displaced, as in neopentyl chloride.



Here the whole process including the Wagner–Meerwein shift can be pictured as occurring in one step. Elimination (E_1) and displacement (S_N1) would both involve the same solvated carbonium ion intermediate. If this view is correct, it should be possible to substantiate the requirement of attack on carbon by demonstrating termolecular kinetics as we have done with trityl chloride.

First order racemizations in alcoholic or aqueous solution may be due to rapid formation of a disolvated carbonium ion, facilitated by dissociation of the ion pair in these polar solvents and by the high concentration of hydroxylic reagent present. These two factors would permit the existence of two very fast steps in alcoholic or aqueous solution which would not be probable steps in an inert solvent of low dielectric constant such as benzene.



Failure of hydroxide ion to accelerate the hydrolysis of tertiary halides in an aqueous solution is probably due to the ion's large solvation shell of water, which prevents it sterically from approaching very close to the central carbon.

Experimental

Reagents:—Trityl chloride was prepared from bromobenzene by the procedures of "Organic Syntheses."[13] The acetyl chloride was C. P. reagent grade. The white product was recrystallized from a benzene–pentane solution. All operations were designed to exclude atmospheric moisture. The product was washed with pentane and dried in a vacuum desiccator. The crystals (160 g., m. p. 109–111°) were as coarse as granulated sugar and had a very pale yellow tint. A 0.425 *M* solution in dry benzene was made up by weight, and this was used for kinetic experiments.

Trityl bromide was prepared from tritanol and dry hydrogen bromide gas. It was crystallized several times from benzene, m. p. 153–155°, with a yellow tint. The stock solution in benzene (0.392 or 0.412 *M*) was kept in a desiccator in the cold room at 4° whenever it was not in use.

Pyridine and methanol were reagent grade, dried over Drierite.

Phenol was reagent grade, dried over Drierite and recrystallized from petroleum ether, yielding snow white needles which were dried in a vacuum desiccator and kept protected from atmospheric moisture.

Benzene was thiophene-free reagent grade, dried over sodium wire.

The tris-(*p*-*t*-butyl)-trityl chloride was prepared by Dr. Marvel and his co-workers,[14] was white, and melted with decomposition at 263–266°.

Other reagents were repurified Eastman Kodak Co. chemicals.

Procedure.—Stock solutions of the reagents in dry benzene were kept in Pyrex glass-stoppered bottles in desiccators over potassium hydroxide to protect them from atmospheric moisture. All bottles, pipets and other glassware were dried in an oven at 130°, then packed while hot into a vacuum desiccator and evacuated to 2 mm. to remove surface moisture.

Run 35 is typical of the procedure used. Twenty cc. of benzene, 20 cc. of 0.430 *M* pyridine, 10 cc. of 0.435 *M* methanol and 10 cc. of 0.448 *M* phenol were pipetted into a dry glass-stoppered Erlenmeyer flask. At zero time 20 cc. of 0.425 *M* trityl chloride was added, and the flask thoroughly swirled to give a clear, homogenous solution. Five cubic centimeter aliquot samples were pipetted into each of ten 125 × 16 mm. soft-glass test-tubes which had been drawn out to give a neck 80 × 3 mm., 20 mm. below the lip, for easy sealing. The tubes were sealed off with a microburner and placed in a 25.0 ± 0.02° thermostat within five minutes. Turbidity first appeared after forty minutes. Eight tubes were saved for regular kinetic points, one tube was opened and analyzed after twenty-seven minutes, before any precipitation, to check the initial concentration, and one at 58,000 minutes to measure the total reaction.

The reaction was followed by taking advantage of the fact that pyridine hydrohalides are only very slightly soluble in benzene and precipitate out as the reaction proceeds. A separate sealed tube was used for each point. After filtering out the hydrohalide, the filtrate was shaken with water to hydrolyze the unreacted trityl halide, and the resulting hydrohalic acid titrated with standard sodium hydroxide. The filtration was performed in a special apparatus in an atmosphere of air which had been dried over potassium hydroxide and finally Drierite, and the sealed tube, filtered crystals and filter paper were washed with three 5-cc. portions of dry benzene and the washings

---

(13) Bachmann and Hetzner, "Organic Syntheses," **23**, 98, 100, John Wiley and Sons, Inc., New York, N. Y., 1943.

(14) Marvel, Kaplan and Himel, This Journal, **63**, 1894 (1941).

TABLE V

SOLUBILITIES OF TERTIARY AMINE HYDROCHLORIDES IN DRY BENZENE SOLUTIONS AT 25°

M R_3N	R_3N	*M* CH_3OH	*M* Addend	Addend	*M* $R_3N{\cdot}HCl$	Run
0.108	Pyridine	...	...	....	0.0006	32, 55
.108	Pyridine	0.054	...	....	.0024	46, 47, 50, 59, 60
.108	Pyridine	.109	...	....	.0045	40
.108	Pyridine	.054	1.5	$(C_2H_5)_2O$	.0017	.....
.103	Quinaldine	.054	...	....	.0015	48
.108	Quinoline	.054	...	....	.0071	51
.107	Diethylaniline[a]	.054	...	....	.0033[a]	49
.108	Pyridine	...	0.056	C_6H_5OH	.0121	34, 56
.108	Pyridine	.054	.023	C_6H_5OH	.0060	43
.108	Pyridine	.054	.056	C_6H_5OH	.0155	35, 58
.103	Quinaldine	.054	.056	C_6H_5OH	.0070	52
.108	Pyridine	.054	.030	*p*-$O_2NC_6H_4OH$	.0100	53
.108	Pyridine	.054	.056	C_6H_5OH	.0016[b]	.....

[a] The solubility of diethylaniline hydrochloride in this medium is 0.041. Consequently no salt precipitation occurred during run 49. The figure given refers to quinaldine, which was added as a precipitating agent just before analyses.
[b] Pyridine hydrobromide used instead of pyridine hydrochloride.

added to the filtrate. The filtrate was shaken with 20 cc. of ethanol and 20 cc. of water for five minutes, then with two successive 20-cc. portions of water. The combined lower layers were titrated with 0.0483 *M* carbonate-free sodium hydroxide using three drops of 0.2% brom thymol blue as indicator.

The data on trityl chloride tend to be more accurate because the reaction with methanol could be followed for two days, as compared to the reaction of trityl bromide with methanol which was half over in about ten minutes. On the other hand, pyridine hydrochloride is about ten times as soluble in the media used as pyridine hydrobromide. This is no longer a negligible solubility in some cases, and must be corrected for in the analysis by adding to the molarity calculated from the sodium hydroxide titer a figure equal to the solubility of pyridine hydrochloride in the particular medium used. Fortunately, these solubilities can be directly measured independently, and do not have to be derived from the kinetic data, although the latter derivation is possible and does give agreement with the direct solubility measurements. Only trityl chloride and the ethers which are reaction products were omitted in the solubility measurement, being replaced by benzene. These have much less effect on the solubility than do methanol or phenol in the solution. Replacement of 13% by volume of the benzene by diethyl ether, for example, had almost no effect on the solubility, whereas 0.1 *M* phenol increased it five-fold. The solubility determinations are given in Table V. All the analytical data for the experiments with trityl chloride have been corrected by these directly measured solubility figures, before plotting or obtaining rate constants such as those in Table I. No corrections for solubility were necessary in the trityl bromide runs.

Reaction Products.—No detectable reaction of trityl bromide occurred in fifty minutes in a solution of 0.103 *M* trityl bromide and 0.055 *M* methanol in dry benzene in run 29. The analytical method used here involved adding 15 cc. of benzene and excess pyridine (2 cc. of 0.440 *M* pyridine) to each 5-cc. aliquot at the end of the measured time interval, immediately filtering out any precipitated pyridine hydrobromide, shaking the filtrate with water to hydrolyze trityl bromide, and titrating with sodium hydroxide. Precipitation was uniformly negligible even when six minutes waiting time was allowed before filtering. Evidently in the absence of tertiary amines accumulating hydrogen bromide can cleave the trityl methyl ether formed, and an equilibrium is reached which is very far on the side of the reactants. Although the reaction may be moderately fast, no net reaction is observed because it is reversible.

A very slow irreversible reaction with a half life of about one year was subsequently observed to take place in these same tubes, however, which converted the bromine to a non-ionic, not readily hydrolyzable form, presumably methyl bromide

$$(C_6H_5)_3CBr + MeOH \underset{\text{fast}}{\rightleftharpoons} (C_6H_5)_3COMe + HBr$$

$$(C_6H_5)_3COMe + HBr \overset{\text{slow}}{\rightleftharpoons} (C_6H_5)_3COH + MeBr$$

The reaction with tertiary amines alone is probably irreversible but very slow. Only 4% reaction occurred between 0.103 *M* trityl bromide and 0.110 *M* pyridine in run 19 in 250,000 minutes (six months). The triethylamine used instead of pyridine in run 31 gave 24% reaction beyond the endpoint with methanol, which was obtained in a day, on waiting a further 250,000 min. The rates of these reactions with tertiary amines are negligible compared to the rates of the other reactions measured in Tables I and II.

This does not mean that the trityl halides cannot be caused to react with tertiary amines under different conditions than those which we have used in our kinetic study. Tritylpyridinium bromide monophenolate, $(C_6H_5)_3\overset{\oplus}{C}NC_5H_5\ \overset{\ominus}{Br}HOC_6H_5$, was actually obtained by mixing and immediately refrigerating 50 cc. of a homogeneous benzene solution of 0.078 *M* trityl bromide, 0.86 *M* pyridine and 0.038 *M* phenol in a Dry Ice-bath for five minutes. Apparently the solvent froze and gave a high local concentration of the three reactants. On warming to 10° a heavy white precipitate was found to be present. This was filtered out and dried in a vacuum desiccator. It was a white, odorless powder, not particularly hygroscopic. The yield was 0.90 g. (theoretical, 0.93 g.), dec. p., 80°. Molecular weight by sodium hydroxide titer using brom thymol blue, 492 (theoretical, 496). Pyridine concentration by hydrochloric acid titration of resulting neutral solution using methyl orange, 16.1% (theoretical, 15.9%) ionic bromide, 16.2% (theoretical, 16.1%). The phenol was shown to be present in quantity equivalent to the bromide by a comparison of bromine uptake by this material and by phenol itself in 1:1 benzene–ethanol solutions. Under these conditions pyridine, trityl bromide, and tritanol did not absorb bromine. The compound was unstable and spontaneously decomposed to a brown material with a strong odor of phenol when allowed to stand at room temperature overnight in a desiccator.

The above compound is interesting in that it probably contains a hydrogen bond between phenol and bromide ion. However, tritylation of pyridine occurs only when the concentrations of reactants are each several molar, never significantly under our kinetic conditions.

Occasionally kinetic points in the runs with methanol, phenol or both were titrated for bromide as well as for hydrogen ion. Agreement within the limits of experimental error was always obtained, demonstrating that the reaction was entirely a solvolysis by the hydroxylic component and not at all the formation of a quaternary ammonium salt.

Pyridine hydrobromide or hydrochloride precipitates out in the usual procedure as the reaction progresses. In the analysis of one of the tubes in run 37 between 0.106 *M* trityl chloride, 0.112 *M* phenol and 0.108 *M* pyridine, the benzene layer, after extraction with alcohol and water and separation of the water layers for titration with sodium hydroxide, was further extracted with dilute sodium hydroxide, then water, and dried over sodium sulfate. The benzene was evaporated and the flask evacuated at 2 mm. for several hours. There was obtained 0.148 g. (83%) of white crystalline *trityl phenyl ether*, m. p. 93–98°. The recorded m. p. is 103°, as contrasted to 282° for the *p*-tritylphenol. The same treatment applied to a tube from run 40 between 0.106 *M* trityl chloride 0.109 *M* methanol and 0.108 *M* pyridine yielded 0.101 g. (70%) of white crystalline *trityl methyl ether*, m. p. 77–79°. The recorded m. p. is 82°.

Enhancement of Acidity of Hydrogen Chloride in Ether by Methanol, Phenol and a Mixture.—The solutions were prepared by adding a total of 2 cc. of various dry benzene solutions to each of a number of 10-cc. samples of a dry ether solution containing 0.001 *M* butter yellow plus enough dry hydrogen chloride gas to turn the indicator from yellow to a very pale yellow orange. The color was measured with a Cenco "Photelometer" (photoelectric colorimeter) using a Corning No. 401 primary green filter, which gave the largest difference between red and yellow solutions of a number of filters tested. The results are presented in Table VI.

TABLE VI

No.	*M* CH_3OH	*M* C_6H_5OH	Color	% transmission
1	...	...	Yellow-orange	100.0
2	0.036	...	Yellow-orange	89
3	.073	...	Yellow-orange	82
4	...	0.037	Orange	57
5	.036	.037	Orange	53.5
6	...	.075	Red	34.5

Acknowledgment.—The author wishes to thank Professors Linus Pauling, Paul D. Bartlett, Saul Winstein and Alwyn G. Evans for criticisms and suggestions which made a major contribution to this work.

Summary

Methanol reacts rapidly with triphenylmethyl chloride or bromide in benzene solution containing excess pyridine at 25° to give the methyl ether. When phenol is used instead of methanol, the phenyl ether is obtained at a slower rate. However, when both are present, the methyl ether is formed at a rate which is seven times as fast as the *sum* of the rates of reaction with methanol or phenol separately. Evidence is obtained to show that this cannot be a salt effect nor due to a complex between methanol and phenol. The kinetics are third order. In the mixed case this means that the rate is proportional to the product of concentrations of methanol, phenol and halide, although the phenol is not consumed in the rapid phase of the reaction.

This indicates that one molecule of alcohol or phenol hydrogen bonds with the halogen atom, weakening its bond to carbon, while another molecule simultaneously solvates the carbon which is becoming a carbonium ion. Phenol solvates halogen better than carbon; the converse is true for methanol. Therefore the concerted, termolecular attack proceeds at a high rate when both phenol and methanol are present and each can play the part to which it is best adapted.

The relative reactivity of a number of types of compounds toward triphenylmethyl bromide in benzene solution has been measured.

CAMBRIDGE, MASS. RECEIVED AUGUST 11, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA]

The Chemical Properties of Elements 94 and 93

BY GLENN T. SEABORG AND ARTHUR C. WAHL[1a,b]

This report describes the chemical experiments which we have performed on elements 94 and 93 and the chemical properties which we have deduced from these experiments.

Although these chemical experiments have been under way for 94 since December, 1940, when element 94 was discovered,[2] and for 93 since somewhat earlier than this, the investigation has not been a very systematic one. In the case of element 93, we have repeated most of the experiments reported by McMillan and Abelson[3] in their original publication and have confirmed their results. It has been of paramount importance to develop as quickly as possible methods of isolating in very thin precipitates elements 94 and 93 from large amounts of uranium in order to study the properties of 94^{239},[4] and, therefore, the experiments have been of a very practical and explora-

---

(1a) Now at Department of Chemistry, Washington University, St. Louis, Missouri.

(1b) This article was mailed as a secret report from Berkeley, California, to the "Uranium Committee" in Washington, D. C., on March 21, 1942. The experimental work was done throughout all of 1941 and the early part of 1942. Part of the original material is omitted in order to shorten the article to Journal length; otherwise it is unchanged from its original report form except for slight editing to make it conform to JOURNAL standards.

(2) G. T. Seaborg, E. M. McMillan, J. W. Kennedy, and A. C. Wahl, *Phys. Rev.*, **69**, 366 (1946) (submitted January 28, 1941); G. T. Seaborg, A. C. Wahl and J. W. Kennedy, *ibid.*, **69**, 367 (1946) (submitted March 7, 1941).

(3) E. M. McMillan and P. H. Abelson, *Phys. Rev.*, **57**, 1185 (1940).

(4) J. W. Kennedy, G. T. Seaborg, E. Segrè and A. C. Wahl, *Phys. Rev.*, **70**, 555 (1946) (submitted May 29, 1941).

tory nature. It is only recently that we have begun a systematic investigation of the chemical properties; the description of these experiments is included also.

As the tracer for element 94 we have used the alpha-emitting, 50-year 94, whose production and properties are described elsewhere,[2] and for which the best isotopic assignment seems to be 94^{235} or 94^{238}.[5] As the tracer for element 93, we have used the beta-emitting 2.3-day 93^{239}.

The alpha-particles from 94^{238}, which have a range in air of about 4.1 cm., are detected with an ionization chamber connected to a linear amplifier and recording system. Only thin samples are prepared (< 1 mg. carrier material per sq. cm.). The weak samples are counted by placing them on one electrode of the ionization chamber, the "inside" chamber, for which the counting efficiency, as determined with a weighed sample of uranium, is about 45%. The strong samples are counted with poor geometry sometimes with screens interposed, depending upon the strength of the samples, by placing them near an ionization chamber with a screen window.

Although the beta-particles from 93^{239} have an upper energy limit of 0.78 Mev. (aluminum absorption end-point 260 mg.), the major portion of the radiation being rather soft,[6] with a half thickness of 9 mg. of aluminum and therefore demanding thin samples, a correction for self-absorption of the beta-particles is made. Correction for the back-scattering of the beta-particles from the backing material upon which the samples are mounted is always made in the quantitative experiments. The beta radiation is detected with (1) a Geiger–Müller counter connected to an amplifier, scaling and recording system, (2) an ionization chamber connected to an FP-54 electrometer tube or (3) a Lauritsen electroscope, depending on the strength of the sample and the type of experiment.

Naming the Elements.—Since formulas are confusing when the symbols "93" and "94" are used, we have decided to use symbols of the conventional chemical type to designate these elements. Following McMillan, who has suggested the name neptunium (after Neptune, the first planet beyond Uranus) for element 93, we suggest plutonium (after Pluto, the second planet beyond Uranus) for element 94. The corresponding chemical symbols would be Np and Pu. (The names ekarhenium and ekaosmium seem inappropriate in view of the marked dissimilarity of the chemical properties of elements 93 and 94 from those of rhenium and osmium.)

Experimental

General Remarks on Radiochemistry.—All of the experiments which we have performed have, of course, used exceedingly small amounts, in the macroscopic sense, of radioactive 94^{238} and 93^{239} as tracers, and great care must be exercised in deducing from these experiments the true chemical properties of macroscopic quantities of 94 and 93. Our experiments have employed amounts of 94^{238} and 93^{239} varying from about 10^{-7} microgram to about 1 microgram and concentrations of about 10^{-15} to 10^{-6} molal. The relationship of the chemical behavior of such small amounts to the behavior of macroscopic amounts of materials has been studied, using the natural radioactive isotopes as indicators, in the classical work of Fajans and Paneth and Hahn. The work of the numerous investigators in artificial radioactivity, which involves a great number of other elements, seems to lend confirmation to the rules of Hahn and Paneth and Fajans.

Precipitation reactions are among the most important reactions in studying the chemistry of an element by the use of microscopic amounts of a radioactive isotope of the element. It is well known that compounds of radioelements, though present in such dilution that their solubility is not exceeded, may be "carried down," even quantitatively, by a macroscopic precipitate of a non-isotopic element. Rules for this phenomenon have been formulated by Fajans and Paneth and Hahn. For example, Hahn[7] summarized Fajans' and Paneth's rule in a joint rule which he states as follows: "A radioelement, as cation, is more strongly adsorbed by a separating or a preformed precipitate, the less soluble is the compound it forms with the anion of the precipitate." From a study of these rules and the detailed discussion Hahn[7] gives them, it seems reasonably safe to assume that if a radioelement as cation is "carried down" by a precipitate formed in the presence of excess anion the compound between the radioelement and the anion is relatively insoluble, and if the radioelement is not "carried down" it is assumed that the compound is relatively soluble. That this is true has been confirmed in many instances since the discovery of artificial radioactivity in that many "pure" radioelements, that is, elements free from their stable isotopes, have been prepared and subjected to precipitation reactions of this sort. We believe that our conclusions as to the solubility and insolubility of the compounds of 94 and 93 are valid for macroscopic amounts, but it must be emphasized that in all the work there exists the possibility of drawing incorrect conclusions from such precipitation reactions.

It is remarkable, and it should be emphasized, that it has been found in many cases, when the radioelement is not "carried down" by the precipitate upon the addition of the precipitating

---

(5) Note added at time of publication: This alpha radioactivity was later shown to be due to the isotope 94^{238} with a slight admixture of alpha radioactivity due to the isotope 94^{236}; the isotopic assignment, of course, makes no difference from the standpoint of this paper. In order to avoid confusion this paper has been edited so that it always refers to this radioactivity as due to the isotope 94^{238}.

(6) Our work has shown that there are roughly as many conversion electrons as there are disintegration beta-particles in the 93^{239} radiation.

(7) O. Hahn, "Applied Radiochemistry," Cornell University Press, Ithaca, N. Y., 1936.

agent, it is not necessary that there be present some carrier material in the solution to "stabilize" the radioelement in order to prevent its precipitation. Thus, we have found in the case of elements 94 and 93 that we can make precipitations from solutions containing these elements leaving them behind in the solution with no carrier material in the solution with them.

It is well established that in the distribution between solvents, in the cases where there is no chemical combination with the solvents, these extremely small amounts (concentrations as low as 10^{-15} M) obey the same distribution coefficient as do macroscopic amounts of material; therefore it is quite possible to make deductions as to true thermodynamic distribution coefficients from experiments with solutions of pure radioelements. Similarly, it has been found that the properties of volatility can be correctly deduced from experiments performed with such microscopic amounts of radioelements. In addition, it has been found that a great deal of information about the oxidation and reduction properties of an element, and of the ions of this element, can be deduced from experiments performed with these small amounts (concentrations as low as 10^{-15} M) of radioelement material, when proper account is taken of the concentration of the ions and of the possibility of slow reactions.

Precipitation Reactions.—Since one of the most common precipitating agents which we use is hydrofluoric acid, it is often necessary to use platinum ware where heat is necessary and waxed glassware for room temperature reactions and precipitations. Coating the glassware with a mixture of paraffin and beeswax has given very satisfactory results. However, it is possible to use ordinary Pyrex glassware, instead of waxed glassware, if, instead of hydrofluoric acid, potassium fluoride is used in solutions of low acidity and the solutions do not stand in the glass for more than an hour or two. We have used waxed glassware and bakelite almost always because we wanted to be absolutely sure that no silica appeared in our very thin samples.

We found it to be very advantageous to use a centrifuge[8] rather than to filter precipitates, and a great number of our precipitation reactions were carried out right in the centrifuge tube in order to avoid loss by transfer. Where hydrofluoric acid is employed, waxed centrifuge tubes or "lusteroid" tubes should be used. In some experiments, particularly in the final precipitation in which the sample is isolated, it has been found convenient to centrifuge onto a platinum or cellophane plate in a clear bakelite centrifuge tube with a removable bottom. Similarly, some electrolysis reactions have been performed with the metallic cathodes in bakelite tubes with removable bottoms.

A number of qualitative precipitation reactions were carried out using various carriers and always having an excess of the anion present. As stated above, the radioactive isotopes used to follow the behavior of elements 94 and 93 were the alpha-emitting 50-year 94^{238} and the beta-emitting 2.3-day 93^{239}.

We have found that, similarly to element 93, element 94 has two oxidation states; in its lower oxidation state 94 forms an insoluble fluoride, but the fluoride of its higher oxidation state is soluble. Peroxydisulfate ion ($S_2O_8^{--}$), in the presence of silver ion (Ag^+) as catalyst, has sufficient oxidizing power to oxidize 94 to its higher oxidation state. This reaction takes place in about fifteen minutes in an acid solution (few normal) at a temperature just below boiling when the concentration of peroxydisulfate ion is of the order of 0.2–1.0 g. and the silver ion of the order of 50 mg. per 100 cc. A number of precipitation experiments on the oxidized and reduced states of 94 and 93 are summarized in Table I, where (i) indicates that the activity was "carried down" with the precipitate and therefore the transuranium compound is considered to be insoluble, (s) that the activity was not "carried" and therefore that the compound is considered to be soluble. The experiments on the oxidized state of 93 took place in an acid solution (few normal) of bromate ion (BrO_3^-), with about 0.5 g. of BrO_3^- per 100 cc.

TABLE I

SOLUBILITY OF 93 AND 94 COMPOUNDS

	93		94	
	Reduced	Oxidized	Reduced	Oxidized
Fluoride	i	s	i	s
Sulfide (0.3 N H^+)	s	...	s	...
Sulfide (10^{-3} N H^+)	s	...	...	...
Iodate	i	s	i	...
Phosphate	s	...	...	...
Peroxyhydrate	...	...	i	...
Chloride	s	...	...	...
Hydroxide (NaOH)	i	i	...	...
Hydroxide (NH_4OH)	i	i	i	...
Hydroxide (NH_4OH and CO_3^{--})	...	s	...	...
Carbonate	i	...	...	...

Elements 94 and 93 are precipitated quantitatively, in their reduced states, with lanthanum or cerous fluoride even from rather strong acid (6 N) solutions. This is in rather sharp contrast to the behavior of thorium, where we have found, using UX_1 as tracer, that the precipitation is not quantitative from solutions in which the acidity is as high as 6 N.

An experiment was performed in which 0.5 mg. of lanthanum was added last to a hydrofluoric acid solution containing 94 and 93 in their reduced states, in order to determine whether 94 and 93 would be carried down into the lanthanum fluoride precipitate under these conditions. After the precipitate was digested in the hot solution

---

[8] A convenient centrifuge, which handles 15 cc., 50 cc., 100 cc. and 250 cc. centrifuge tubes, is the Size 1 centrifuge of the International Centrifuge Company. This company also sells the "lusteroid," hydrofluoric-acid-proof, centrifuge tubes.

for about 20 min., the lanthanum fluoride precipitate was centrifuged out. It was found that this precipitate contained only about 50% of the 94 and about 90% of the 93. This would indicate that 94 and 93 are not precipitated quantitatively on "preformed" precipitates, and it is quite probable that the amount of 94 and 93 which is "adsorbed" would vary markedly with the conditions under which the precipitation was performed.

Oxidation and Reduction Reactions.—McMillan and Abelson[3] found that element 93 is not reduced to the metal by zinc. We have found the same to be true for element 94. To check the conditions of the experiment (stirring the acid solution over zinc amalgam for two hours at room temperature), very dilute solutions ($\sim 10^{-12}$ *M*) of polonium and 158-day $Cd^{107,109}$ were plated on zinc, proving (1) that if 94 had been plated out its alpha-particles could have been detected and (2) since no 94 was plated out it must be more difficult than cadmium to reduce to the metallic state.

The potential required to oxidize elements 94 and 93 from their "fluoride-insoluble" state to their "fluoride-soluble" state (see Table I) was studied in the following way: (1) 1 *M* sulfuric acid solutions of elements 94 and 93 were treated with various oxidizing agents (and with their reduction products) under varying conditions of time and temperature; (2) lanthanum fluoride, LaF_3, was precipitated from the solutions; and (3) the activity of the precipitate was measured on a Lauritsen electroscope to detect 93^{239} and ionization chamber plus linear amplifier to detect 94^{238}. The activity indicated whether the element had been in its lower, "fluoride-insoluble," state or its higher, "fluoride-soluble," state.

The results of these experiments are summarized in Table II. In this table "oxidized" indicates that less than 5% of the activity was carried with lanthanum fluoride; "not oxidized," that more than 85% was carried; "partially oxidized," that between 5 and 85% was carried.

TABLE II

OXIDATION OF 94 AND 93 SOLUTIONS

0.1 *M* Oxidizing agent in 1 *M* H_2SO_4	Approx. temp., °C.	Approx. time, min.	Effect on	
			93	94
$S_2O_8^{--}$, SO_4^{--} (Ag^+ catalyst)	20	10	Oxidized	Partially ox.
$S_2O_8^{--}$, SO_4^{--} (Ag^+ catalyst)	80	15	Oxidized	Oxidized
H_5IO_6, IO_3^-	80	60	Oxidized	Oxidized
MnO_4^-, MnO_2	20	10	Oxidized	Not oxid.
MnO_4^-, MnO_2	80	30	Oxidized	Oxidized
BrO_3^-, Br_2	20	10	Oxidized	Not oxid.
BrO_3^-, Br_2	80	20	Oxidized	Not oxid.
Ce^{+4}, Ce^{+3}	80	30	Oxidized	Partially ox.
$Cr_2O_7^{--}$, Cr^{+3}	20	25	Oxidized	Not oxid.
$Cr_2O_7^{--}$, Cr^{+3}	80	11 hr.	Oxidized	Oxidized
Br_3^-, Br^-	20	2 hr.	Not oxid.	Not oxid.
Br_3^-, Br^-	80	15	Not oxid.	Not oxid.
HNO_3 (concd.)	80	15	Not oxid.	Not oxid.

In the few reduction experiments that were tried, it was found that 93 is reduced to the "fluoride-insoluble" oxidation state at room temperature by sulfur dioxide, SO_2, bromide ion, Br^-, manganous ion, Mn^{++}, and partially by thallous chloride, TlCl, while 94 is reduced by sulfur dioxide, partially by bromide ion and not by manganous ion or thallous chloride. The oxidized form of 93 in these experiments was obtained by the use of a small amount of permanganate ion, MnO_4^-, or bromate ion, BrO_3^- (in 1 *M* sulfuric acid). To these oxidized solutions, there was added an excess of the reducing agent and after separating out any manganese dioxide that formed (which did not carry the 94 and 93), lanthanum fluoride was precipitated and the activity measured.

Although there occurs no oxidation of 94 by bromate ion in 20 min. at 80° in the absence of cerium, some rough experiments indicate that partial oxidation of 94 by bromate ion occurs when cerium is present. This would suggest that bromate ion is capable of oxidizing 94 from its lower to its higher oxidation state and that it is a very slow reaction and is catalyzed by the $Ce^{+3} \rightarrow Ce^{+4}$ couple. In the separation of 94 and 93, bromate ion is used under conditions where it oxidizes 93 and not 94, advantage being taken of the apparently slow rate of reaction between 94 and bromate ion; therefore, this separation is carried out in the absence of cerium.

A reaction of the oxidized form of 94 which should be emphasized is the following. If a sulfuric acid solution of the oxidized form of 94 containing peroxydisulfate ion is heated until fumes of sulfur trioxide appear, so as to decompose all of the peroxydisulfate ion, the 94 is reduced to its lower, "fluoride-insoluble," form. Evidently in a solution of this acidity the 94 is reduced by water. This reaction is important in that, when an oxidizing agent is present which can be completely reduced by heating the solution, such as is true in the case of peroxydisulfate ion, the 94 can be reduced by heating the sulfuric acid solution until fumes of sulfur trioxide appear and the addition of a reducing agent is not necessary. Element 93 is likewise reduced from its higher to its lower oxidation state when a sulfuric acid solution of 93 containing peroxydisulfate ion is heated until fumes of sulfur trioxide appear. However, it is not entirely certain how quantitative these reductions are under varying conditions of evaporation and time of heating, and therefore in most of our experiments we add some reducing agent such as sulfur dioxide, even when the oxidizing agent which is present is completely decomposed during the evaporation procedure, in order to ensure the complete reduction of the 94 and 93.

Electrolysis Experiments.—The primary purpose of the experiments on the electrolysis of elements 94 and 93 was to develop a method of preparing very thin adherent layers, containing these elements, suitable for the performance of physical measurements upon them. The aim was not to use electrolysis as a method of isolating these elements free from all of the fission products in this manner, but experiments in the future may show that electrolysis can be helpful in such a separation. Haissinsky[9] has shown that actinium, thorium and uranium can be deposited electrolytically from absolute ethyl alcohol solution of their nitrates. It seems quite certain that it is the oxides of these elements, and not the elements themselves, that are deposited in these experiments. We have found that elements 94 and 93, with 0.2 mg. of lanthanum carrier, can be electrolyzed out of absolute alcohol solution quantitatively under conditions similar to the experiments of Haissinsky in which no acid may be present. This procedure, however, has not yet solved for us the problem of the preparation of very thin adherent layers of material containing 94 or 93 because, (1) in order to transfer 94 or 93 at all quantitatively from the water solution, where it is present just before the final stage of its isolation into a thin layer, it is necessary to use an amount as large as a few milligrams of rare earth carrier material and (2) the rare earths are deposited electrolytically along with the 94 and 93. When 0.2 mg. of rare earth, which is the maximum amount wanted on the final plate, has been used, the transfer to absolute alcohol, which involves an evaporation to dryness in order to eliminate all the water and acid, has not been quantitative due to the difficulty of redissolving all the material in the absolute alcohol. However, as stated above, all of the 94 or 93 that is put into the alcohol is deposited quantitatively in this electrolysis procedure, and the problem of transferring the 94 or 93 from a water to an anhydrous alcohol solution is a separate problem with which we happen to be concerned only because we want to transfer these elements, with practically 100% yield, to extremely thin layers.

Experiments were also undertaken to electrolyze 94 and 93 out of water solution, where the rare earths can be completely removed by making a rare earth fluoride precipitation from an oxidizing solution, and procedures for the electrolytic deposition of 94 and 93 were developed. It has previously been found in work in this laboratory that thorium, protactinium and uranium could be deposited from an acetic acid solution in which the acidity was kept very low by the addition of sodium acetate. We found that elements 94 and 93 could be deposited from such solutions when they were originally present in their oxidized form, but the conditions for quantitative deposition have not yet been perfected. Element 94 was put into its oxidized form by use of periodate ion and element 93 by the use of bromate ion in these experiments. Again it seems quite likely that it is the oxides of these elements and not the elements themselves that are deposited. In these experiments the electrolytically deposited layer is extremely thin, consisting only of a very small amount of what is probably platinum black and which is present also in the blank experiments. In experiments similar to these, elements 94 and 93 are not deposited when they are originally present in such an acetic acid–acetate solution in their reduced form.

Other Experiments.—Since ruthenium and osmium form volatile tetroxides and since element 94 is directly below these elements in the same column of the periodic table, it seemed important to establish whether 94 also forms a volatile tetroxide, even though it was not expected that it should do so in view of the dissimilarity between the chemical properties of 94 and osmium. Experiments were performed with both 94 and 93 to see whether they could be distilled, presumably in the form of their tetroxides, from a nitric acid solution containing peroxydisulfate ion and silver ion, in which these elements probably exist in their highest oxidation states. The delivery tube from the distillation flask was immersed in an alkaline solution in which the distillate of osmium tetroxide, which was used as a carrier material in this experiment, was absorbed. Upon acidification, reduction with sulfur dioxide, and precipitation of rare earth fluoride from the distillate solution, it was found that none of the 94 or 93 had distilled over.

Experiments have been performed to measure the distribution of 94 and 93 in the lower oxidation state as their nitrates between diethyl ether and neutral water. These experiments were performed in the presence of high concentrations of uranyl nitrate. Less than 1% of the 94 and 93 were found to be present in the ether in experiments of this type.

Chemical Properties of 94 and 93

Because of the similarity, in their reduced states, of 94 and 93, in their precipitation reactions, to the trivalent rare earths and actinium and to quadrivalent cerium, thorium and uranium, it is extremely probable that the reduced state of these elements has an oxidation number of +3 or +4, and the formulas NpF_3 and PuF_3 or NpF_4 and PuF_4 for the fluorides. Whether the oxidation number is +3 or +4 cannot be decided on the basis of the experiments which have been performed to date. Comparison with the neighboring elements thorium and uranium suggests +4, but 94 and 93 resemble the +3 rare earths in that they are carried quantitatively with lanthanum fluoride from quite acid solution whereas quadripositive UX_1 is not carried quantitatively with lanthanum fluoride from acid solution.

Although it is again not possible to assign with

---

[9] S. Cotelle and H. M. Haissinsky, *Compt. rend.*, **206**, 1644 (1938).

certainty oxidation numbers to the oxidized states of 94 and 93 which exist in our experiments, it seems certain that the oxidation numbers will not exceed +7 and +8 for 93 and 94, respectively, and there may be intermediate oxidation states, such as, for example, +5 and +6 for 93 and +5, +6 and +7 for 94. It seems quite certain that the ions of the oxidized states of these elements will contain oxygen, similar to uranyl ion, UO_2^{++}, and because of their electropositive nature, the formulas may be of the type NpO_3^+ and PuO_3^{++}.

It should be possible, on the basis of our oxidation and reduction experiments, to assign some sort of values for the oxidation potentials of 94 and 93. We will attempt to assign values for these potentials in the system of standard oxidation potentials which is referred to the hydrogen–hydrogen ion couple as zero.[10] There are for each element the two oxidation potentials to be considered: (1) the potential for the oxidation of the element from its metallic to its reduced ionic (+3 or +4) state and (2) the potential for the oxidation of the element from its reduced ionic state (+3 or +4) to its oxidized ionic state (+5, +6, +7 or +8).

If the failure of zinc to reduce 94 and 93 to the metal is actually due to thermodynamic equilibria and not to slow rates, more than 0.75 volt must be needed to reduce the very dilute solutions ($\sim 10^{-12}$ *M*) of 94 or 93 to the metallic state. Assuming, for example, a three-electron change, more than 0.5 volt is required to reduce solutions at unit activities to the metals.

The experiments show quite strikingly that the reduced ionic state of 94 is oxidized very slowly and that the oxidized ionic state of 94 is reduced very slowly, while the corresponding reactions for 93 are quite rapid. Because 94 reacts so slowly with oxidizing and reducing agents, it is impossible from the existing data to assign an accurate potential to the change from the lower to the higher oxidation state of this element. However, since dichromate ion does oxidize 94 and bromide ion at last partially reduces it, some 1.0–1.4 volts must be needed to oxidize 94 from its "fluoride-insoluble" oxidation state to its "fluoride-soluble" state. These are not necessarily the "standard" oxidation potentials for these couples because we purposely neglected concentration effects which would be important if (1) the couple involves ions or molecules containing more than one 93 or 94 atom or (2) if the oxidation–reduction equilibrium is rapid enough so that it may be shifted by the adsorption of the reduced form (Np^{+4} or Pu^{+4}) by the rare earth fluoride. However, these are practical oxidation potentials in that they aid the experimenter in choosing a proper oxidizing agent when working with tracer amounts of these elements. The following couples summarize the oxidation–reduction data:

Couple	Volts
$Ac \longrightarrow Ac^{+3}$	+2.4 (?)
$Th \longrightarrow Th^{+4}$	$\sim +2.0$
$U \longrightarrow U^{+4}$	+1.4
$Np \longrightarrow Np^{+4}$	$> +0.5$
$Pu \longrightarrow Pu^{+4}$	$> +0.5$
$U^{+4} \longrightarrow UO_2^{++}$	−0.4
$Np^{+4} \longrightarrow NpO_3^{+}$ [11]	−1.35
$Pu^{+4} \longrightarrow PuO_3^{++}$ [11]	−1.0 to −1.4

In this table we have arbitrarily assigned an oxidation number of +4 to the "fluoride-insoluble" states and +7 and +8 to the "fluoride-soluble" states of 93 and 94, merely for the convenience of writing definite formulas.[11] The oxidation potentials for similar oxidations in actinium, thorium and uranium have been included for purposes of comparison.

The soluble and insoluble compounds of 94 and 93 in the reduced (+3 and +4) state are very similar to those of actinium, thorium and +4 uranium. For example, the fluorides and iodates and hydroxides of all five of these elements are insoluble in water and their sulfides are all soluble in acid. Likewise all five of these elements show quite a similarity in that their metals are all of an electropositive nature. On the other hand, there is little, if any, similarity between 94 and 93 and their homologs, osmium and rhenium. This supports McMillan and Abelson's suggestion and Mayer's calculations[12] that a new "rare earth" group may be starting at the upper end of the periodic table, *though from the present data we could just as well consider the group to be starting with actinium or thorium as with uranium.* In addition, it should be noted that uranium and 94 and 93 do differ in the values of their potentials for oxidation from the "fluoride-insoluble" to the "fluoride-soluble" state. It may be that in the chemistry that involves the higher oxidation states there will be marked differences between these three elements.

In the case of the electrolytic deposition of 94 and 93, it is probable that oxides of the formulas PuO_2 and NpO_2 are formed.

Yields

In this section we will discuss the yields of radioactive 94 and 93 which are obtained with the Berkeley 60-inch cyclotron. We have attempted no specific experiments to determine accurate yields, but, since it seems desirable to include in this report some yield data, we will summarize the rough yield data, obtained as incidental information, from our experiments. The isotope of 94 which can be formed most easily with the

---

(10) See, for example, W. M. Latimer, "The Oxidation States of the Elements and their Potentials in Aqueous Solution," Prentice-Hall, New York, N. Y., 1938, or the Table of W. M. Latimer and J. H. Hildebrand in the "Handbook of Chemistry and Physics," The Chemical Rubber Publishing Co., Cleveland, Ohio.

(11) Note added at time of publication: It is now known that the "fluoride-soluble" oxidation states studied here correspond to the formulas NpO_2^{++} and PuO_2^{++}.

(12) M. Goeppert Mayer, *Phys. Rev.*, **60**, 184 (1941).

most intensity is the 50-year 94. This alpha-emitting isotope is the decay product of the beta-emitting 2.0-day 93^{238} which is formed in the deuteron bombardment of uranium. The production of these isotopes is described in another report.[2] The yield of 2.0-day 93^{238} is about 10 microcuries per microampere-hour of 15 Mev. deuterons, and the corresponding yield of 94^{238} is, therefore, about 10^{-3} microcuries per microampere-hour. A 1000-microampere-hour bombardment produces about 1 microcurie of 94^{238}, corresponding to about 1×10^6 counts per min. (on a chamber with 45% counting efficiency), which is a sufficient amount of activity to serve as a tracer in a very large number of chemical experiments. There will be mixed with about 1 microcurie of 94^{238} about 0.02 microcurie of 94^{239} which is also formed during the deuteron bombardment of uranium. This other isotope of 94, namely, 94^{239}, might conceivably be used as a tracer, but the intensity of readily prepared samples is considerably less. In the bombardment with neutrons of a rather large amount, about 2 kg., of uranyl nitrate hexahydrate, placed directly behind the beryllium target of the Berkeley 60-inch cyclotron we have found that the yield of 94^{239} is about 0.02 microcurie per 1000 microampere-hours of deuterons. Thus, it is seen that the best tracer isotope for 94 is the 50-year 94^{238} formed in the deuteron bombardment of uranium.

On the other hand, it is the neutron bombardment of uranyl nitrate rather than the deuteron bombardment of uranium which is the more suitable for the production of radioactive 93 for tracer experiments. The yield of 93^{239} in the neutron bombardment of two kilograms of uranyl nitrate hexahydrate amounts to about 80 microcuries per microampere-hour of deuterons. The yield of 93^{239} in the direct deuteron bombardment of uranium is about 80 microcuries per microampere hour, which is about the same as that obtained in the bombardment of kilogram amounts of uranyl nitrate with neutrons; however, the 93 formed in the deuteron bombardment of uranium, being a complex mixture of some 90% 93^{239} and 10% 93^{238}, may be undesirable for some experiments involving 93 as a tracer because of the growth, during the experiments, of the highly alpha-active 94^{238} from the 2.0-day 93^{238}. In addition, it is more convenient to perform neutron bombardment of uranium; for example, an easily performed bombardment, 100 microampere-hours of beryllium plus 15 Mev. deuteron neutrons on 200 g. of uranyl nitrate hexahydrate, produces of the order of a millicurie of 93^{239}, which is ample for a set of tracer experiments. For these reasons we believe that the best tracer isotope for 93 is the 2.3-day 93^{239} formed by the neutron bombardment of uranyl nitrate hexahydrate.

S. G. English and J. W. Gofman have given us valuable help in some of the experiments described in this paper.

Summary[13]

The chemical properties of elements 94 and 93 have been studied by means of the tracer technique using the radioactive isotopes 94^{238} and 93^{239}. Plutonium is suggested as the name for element 94 following the convention used in the naming of neptunium (element 93) and uranium. The chemical symbols Pu and Np are suggested for plutonium and neptunium. In the reduced states the precipitation reactions of neptunium and plutonium are similar to those of the tripositive rare earths and actinium, and of the quadripositive cerium, thorium and uranium. Neptunium and plutonium resemble actinium, thorium and +4 uranium in that their fluorides, iodates and hydroxides are insoluble in water; their sulfides are soluble in acid; and their metals are electropositive. Neptunium and plutonium exhibit a higher oxidation state with properties similar to those of uranium of oxidation state +6.

Probably the reduced state of both elements has an oxidation number of +3 or +4 and the formulas of the fluorides are NpF_3 and PuF_3 or NpF_4 and PuF_4. For both elements the standard oxidation–reduction potential from the metal to the reduced ionic state is greater than +0.5 v. For the reduced to the oxidized ionic state the standard potential for neptunium is about −1.35 v. and for plutonium, −1.0 to −1.4 v. Probably PuO_2 and NpO_2 are the oxides formed by electrodeposition.

There is practically no resemblance in chemical properties between neptunium and plutonium and rhenium and osmium. The chemical properties of neptunium and plutonium indicate that a "rare earth" type group of elements is starting at the upper end of the periodic table, and from the present data we can just as well consider the group to be starting with actinium or thorium, rather than with uranium which has been previously suggested as the starting point.

BERKLEY 4, CALIFORNIA RECEIVED JANUARY 16, 1948

---

(13) Summary was written at time of publication, since the original report contained no summary.

[CONTRIBUTION FROM THE GULF RESEARCH & DEVELOPMENT COMPANY FELLOWSHIP, MELLON INSTITUTE]

The Adsorption of Butane on Glass Spheres

BY R. T. DAVIS[1a] AND T. W. DEWITT[1b]

The Brunauer–Emmett–Teller theory of multilayer adsorption has had a considerable success in supplying a foundation for interpreting adsorption data. It has also been of great practical value in providing a relatively simple and reliable method for estimating the surface area of a wide variety of finely divided materials. While the theory admirably accounts for the major features of multilayer adsorption its more detailed behavior is not entirely satisfactory. It is well known that its range of applicability extends only over a relative pressure range of about 0.05 to 0.35 and that it consistently predicts excessive adsorption in the higher relative pressure range. In the low relative pressure region the theory predicts too low an adsorption and this has been generally[1c] attributed to neglect of a varying heat of adsorption over the first layer. Further than this, however, the heat of adsorption predicted by the theory is invariably appreciably lower than that measured calorimetrically or by use of the Clapeyron equation. It was suggested by Cassie[2] that this latter difficulty might arise from a constant entropy term associated with the adsorption energy and not determinable separately from it in the theory.

In the course of some other work rather extensive data have been obtained on the adsorption of butane on glass spheres. These data were extended to cover the region of very low partial pressures in order to obtain values for the heat of adsorption at very low surface coverages. There were thus obtained adsorption data over a wide range of partial pressures, surface coverages and temperatures. It was hoped that comparison of thermodynamic quantities, experimentally obtained, with those predicted by the Brunauer–Emmett–Teller theory might provide some clue to the origin of some of the difficulties mentioned above. Of particular interest is the form of the heat of adsorption curve at low surface coverages.

The system butane–glass is very convenient for such studies. The vapor pressure of butane is such that the system is readily investigated over the rather wide temperature interval of −78 to 0°. The net heat of adsorption is sufficiently low so that (at these temperatures) very low surface coverages are easily studied. Finally, glass beads produced by fusion would be expected to provide an inert and (it was hoped) a relatively smooth surface.

Experimental

The glass spheres were made by the method of Bloomquist and Clark.[3] Electron microscope pictures showed them to be for the most part well-formed spheres with only an occasional irregularly shaped particle. With the exception of a few thread-like appendages the surface appeared perfectly smooth. This does not, of course, eliminate the possibility of surface cracks of molecular dimensions. The beads were not sized. Particles were observed with diameters ranging from a few tenths of a micron up to as high as eight microns, with the average about 3 microns.

The butane used in the experiments was obtained from a tank of C. P. *n*-butane purchased from the Ohio Chemical Company. The gas was purified by condensing it at −78° and pumping off about a third of it. The remainder was used for the adsorption measurements. The vapor pressure of the purified gas at 0° checked satisfactorily with that given by Aston.[4]

Two adsorption systems were employed. One was of conventional design for operation up to pressures of one atmosphere,[5] except that all stopcocks were replaced by mercury cut-off valves. A separate system, equipped with two McLeod gages, was used for measurements in the pressure range 0.0005 to 17.0 mm. Hg pressure. Mercury cut-offs were also used in the low-pressure system. Approximately 10 g. of the glass spheres was used in the adsorption bulb of the high pressure system and about 3 g. in the low pressure sample tube. Samples were degassed for several hours at room temperature prior to adsorption measurements. Dead space calibrations were carried out in the usual way with helium.

Temperature control was achieved through the use of appropriate low temperature baths. A stirred ice-bath was used for 0°, a mixture of solid–liquid chlorobenzene was used for −46°, and a Dry Ice–acetone bath for −78°.

Results

Figure 1 is a plot of the adsorption of nitrogen at −195° on the glass spheres, together with a BET plot, from which the surface area may be calculated.

Figures 2, 3, 4, and 5 are plots of the adsorption of butane on the glass spheres. In Fig. 6 all the data are plotted on a single graph as log p/p_0 against log v/g. Only by such a plot can the wide range of values for p/p_0 be covered in a single figure of reasonable size. Straight line BET plots are shown in Fig. 7 and in Table I are collected the areas and heat values calculated from these plots, along with the corresponding quantities obtained from the nitrogen isotherm. The straight line form of the BET equation is

$$\frac{p/p_0}{v(1 - p/p_0)} = \frac{1}{v_m c} + \frac{c - 1}{v_m c} p/p_0 \qquad (1)$$

where v is the volume of gas adsorbed at pressure p, v_m is the volume of gas required to form a monolayer on the surface of the adsorbent, p_0 is the vapor pressure of the liquid adsorbate, and

$$c = \frac{a_1 b_2}{a_2 b_1} e^{(E_1 - E_L)/RT}$$

[1a] Present address: Juniata College, Huntingdon, Pa.

[1b] Present address: Clinton Laboratories, Oak Ridge, Tenn.

[1c] Brunauer, Emmett and Teller, THIS JOURNAL, **60**, 309 (1938).

[2] Cassie, *Trans. Faraday Soc.*, **41**, 450 (1945).

[3] Bloomquist and Clark, *Ind. Eng. Chem.*, *Anal. Ed.*, **12**, 61–62 (1940).

[4] Aston and Messerly, THIS JOURNAL, **62**, 1917 (1940).

[5] Emmett, "Advances in Colloid Science," Vol. I, Interscience Publishers, Inc., New York, 1942, pp. 1–36.

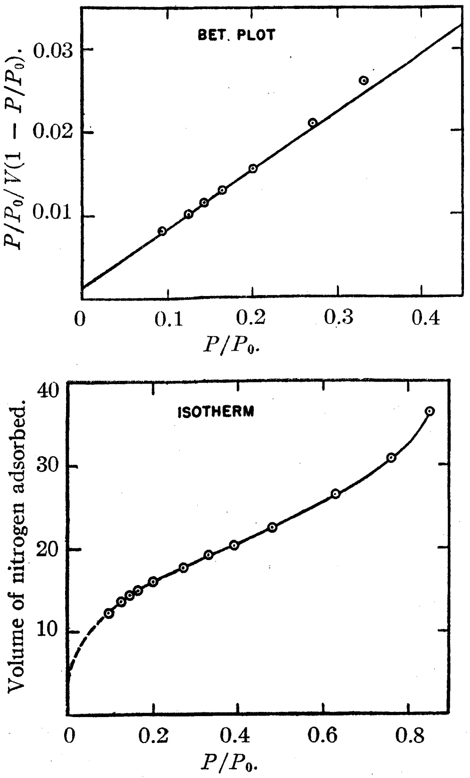


Fig. 1.—Adsorption of nitrogen on glass spheres at −195°.

The constant a_1b_2/a_2b_1 is the ratio of the evaporation–condensation coefficients for the first and higher layers. E_1 is the heat of adsorption in the first layer and E_L is the heat of condensation of the adsorbate. Areas are calculated from v_m, the volume of adsorbate corresponding to a monolayer, by obtaining cross-sectional areas for the adsorbate molecules from the liquid density and assuming hexagonal packing on the surface. For butane the value of 32 sq. Å. was used as the cross-sectional molecular area.

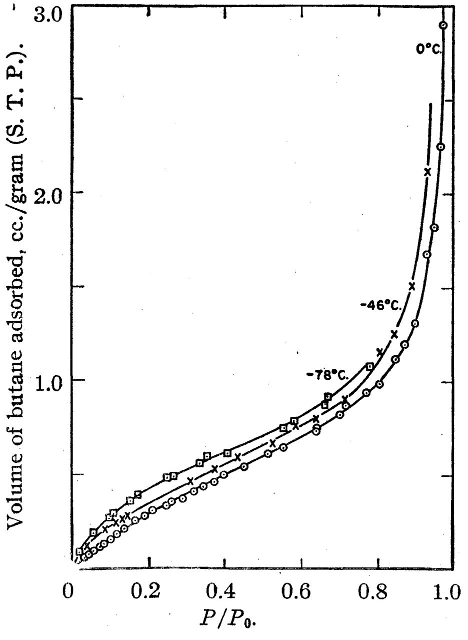


Fig. 2.—Adsorption of butane on glass spheres.

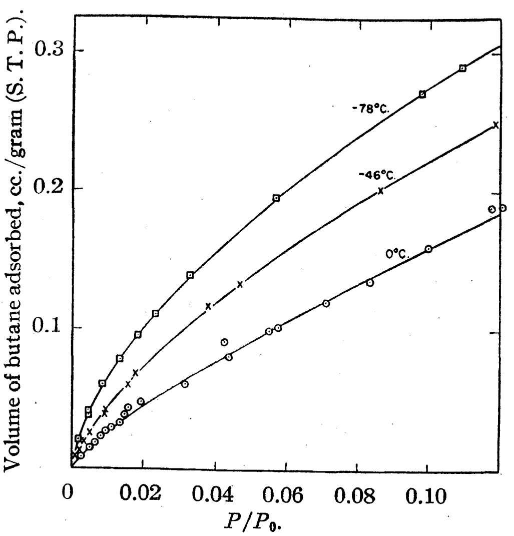


Fig. 3.—Adsorption of butane on glass spheres.

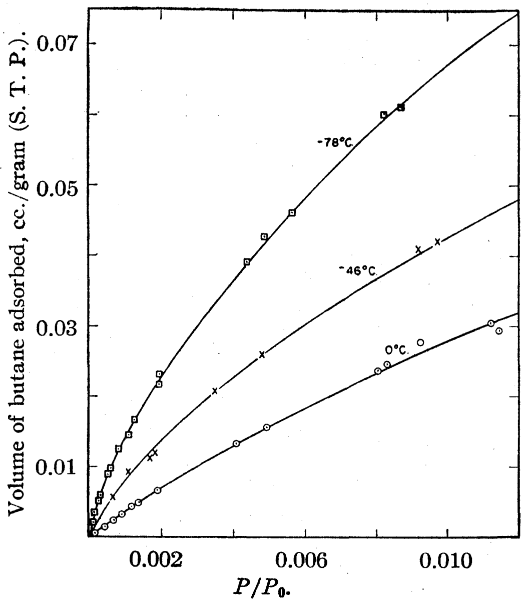


Fig. 4.—Adsorption of butane on glass spheres.

Harkins and Jura have used a method of calculating the surface area of various non-porous solids[6] which involves plotting the adsorption data according to the equation

$$\log \frac{p}{p_0} = B + \frac{A}{v^2} \qquad (2)$$

where A and B are constants. The square root of the slope of the straight line is proportional to the surface area. The proportionality constant was determined empirically for several gases by cali-

---

[6] Harkins and Jura, This Journal, **66**, 1366 (1944).

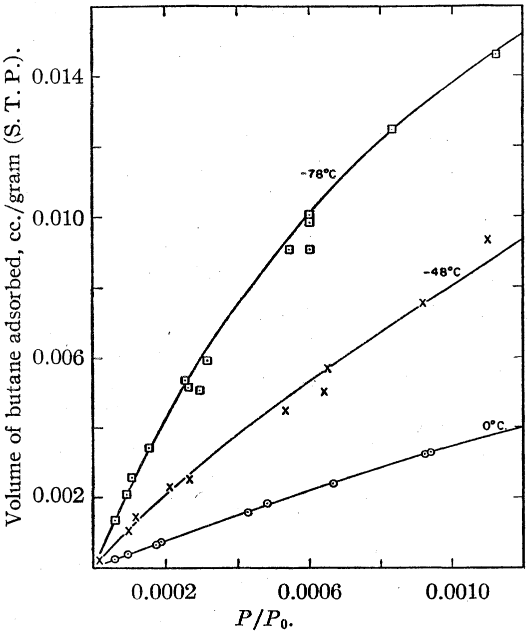


Fig. 5.—Adsorption of butane on glass spheres.

TABLE I

SURFACE AREA OF GLASS SPHERES

Gas	Temperature, °C.	c	Area, sq. m./g. by BET[a] method	Area, sq. m./g. by H. and J. method
C_4H_{10}	− 78	11.55	3.56	5.36[b] (4.51)
C_4H_{10}	− 46	8.47	3.34	4.81[b] (4.37)
C_4H_{10}	0	5.40	3.35	4.69[b] (4.69)
N_2	−195	55	5.82	4.47 ..

[a] Corrected for temperature variation of density of liquid butane. Cross-sectional area at 0° assumed to be 32 ss. Å. [b] Calculated using factor of 13.6 for all temperatures. Figures in parentheses calculated assuming factor is 13.6 for 0° and varies inversely with square root of absolute temperature. The factor 13.6 is equivalent to a cross-sectional area of 56.6 Å.[2]

bration against an absolute determination of the area.[7] The factor for butane at 0° is 13.6, which corresponds to a cross-sectional area for butane of 56.6 sq. Å. The butane data are plotted in this fashion in Fig. 8. Below relative pressures of 0.3 to 0.4 the plots are distinctly curves, but points in the higher pressure ranges yield reasonably straight lines from which areas may be calculated. The areas calculated using the Harkins and Jura method are given in Table I. The derivation of the Harkins and Jura equations involves a transformation through the Gibbs adsorption equation. This transformation inserts the absolute temperature in the denominator of the term involving $1/v^2$. It would be therefore expected that the constant relating the slope of the plot to the surface area, would vary inversely as the square root of the absolute temperature. For the figures in parentheses in Table I, it has been assumed that the constant 13.6 applies only to 0° and areas for −46° and −78° have been calculated assuming the constant varies as $1/\sqrt{T}$. The correction appears to be in the right direction and of approximately the right size since it yields fairly consistent area values for all three temperatures.

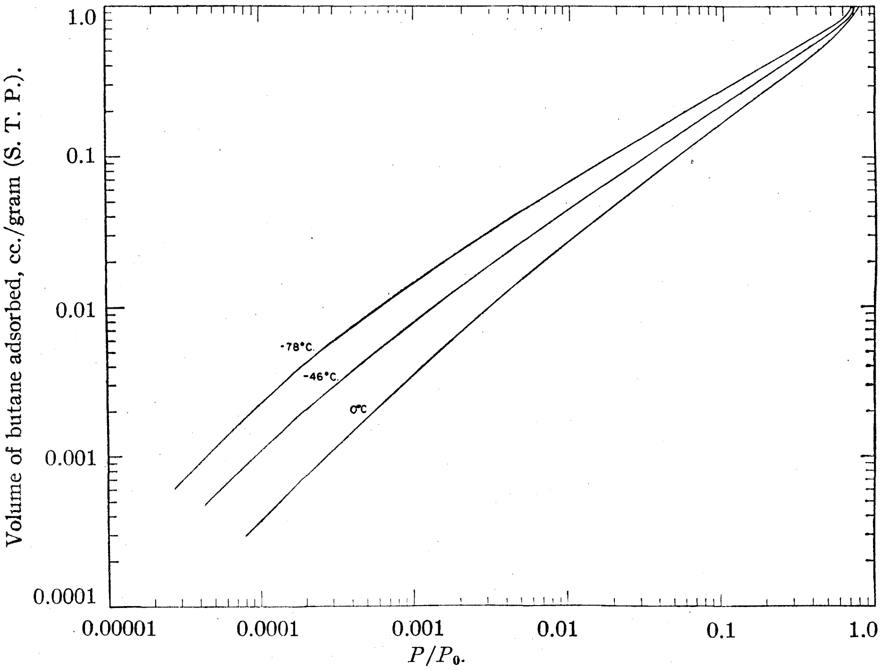


Fig. 6.—Adsorption of butane on glass spheres.

Thermodynamic Data.—The Clausius–Clapeyron equation is used for calculating the heat of adsorption. For convenience the equation was used in the form

$$\log\left(\frac{p}{p_0}\right)_2 - \log\left(\frac{p}{p_0}\right)_1 = \frac{-\Delta H_R}{2.303R}\left[\frac{1}{T_1} - \frac{1}{T_2}\right] \quad (3)$$

where $(p/p_0)_2$ is the relative pressure for a given value of volume adsorbed at T_2, $(p/p_0)_1$ that at T_1, and ΔH_R is the heat of adsorption referred to normal liquid. This equation directly incorporates the heat of liquefaction of the adsorbate, and the heats thus calculated are therefore not absolute but relative to the heat of liquefaction of normal liquid. Figure 6 provides a very easy way

---

(7) Harkins and Jura, THIS JOURNAL, **66**, 1362 (1944).

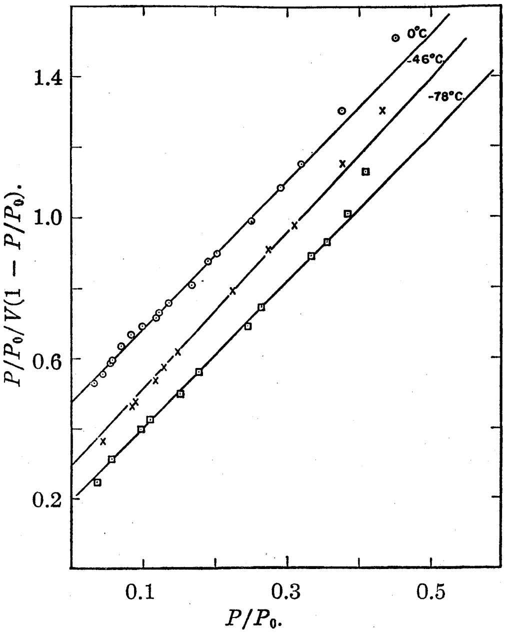


Fig. 7.—Adsorption of butane on glass spheres, B. E. T. plot.

of graphically carrying out these calculations. The heat of adsorption, ΔH_R, is directly proportional to log $(p/p_0)_2$ − log $(p/p_0)_1$. In Fig. 6 this quantity is proportional to the horizontal distance between any two isotherms at a given value of v. This distance then, multiplied by a factor determined by $2.303RT_1T_2/(T_2 - T_1)$ and the length of the logarithmic cycle, immediately gives the desired heat of adsorption. The heat values were obtained in this way from a large logarithmic plot of the data. The values thus obtained are shown in Fig. 9 on a logarithmic plot to spread out the values in the region of low p/p_0. The cross-hatching indicates the estimated limits of error. The tendency to constant values in the very low range will be noted. For comparison with these experimentally determined values, the heats of adsorption have been calculated from the BET equation with the appropriate values of c and v_m. The integral energy of adsorption, ΔE_I, relative to the energy of normal condensation is

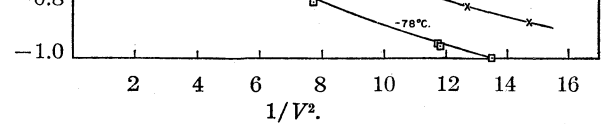


Fig. 8.—Adsorption of butane on glass spheres, Harkins and Jura plot.

$$[\Delta E_I = (E_1 - E_L)v_1] \qquad (4)$$

where E_1 is the molal energy of adsorption in the first layer, E_L the molal energy of liquefaction of normal liquid and v_1 is the number of moles of adsorbate in the first layer at the relative pressure at which the integral heat is desired. Differentiation of equation (4) with respect to V, the total number of moles of adsorbate, gives $\Delta E_R = (E_1 - E_L)\mathrm{d}v_1/\mathrm{d}V$, the differential molal energy of adsorption relative to normal liquid as a function of the total amount of gas adsorbed. This value should be directly comparable to ΔH_R determined experimentally since we are dealing with condensed phases throughout and there should be no difference between ΔH and ΔE. The quantity $E_1 - E_L$ was obtained in the usual way from the c value of the BET plots and $\mathrm{d}v_1/\mathrm{d}V$ was obtained by differentiation of the expression given by Hill[8] for the number of moles of adsorbate in the first layer as a function of total amount adsorbed. The experimental and calculated curves for the heat of adsorption are compared in Fig. 10.

The free energy change in going from condensed liquid having a vapor pressure p_0 to the adsorbed phase having a vapor pressure p, is given by $\Delta F = RT \ln p/p_0$. Free energy of adsorption values were thus calculated directly from the data and also from the BET equation. Of course, over the range of applicability of the BET equation, the experimental and calculated free energies must agree. From these free energy values and the corresponding heat values previously determined, entropies of adsorption, experimental and theoretical, were calculated through the relation $\Delta S = (\Delta H - \Delta F)/T$. Experimental and theoretical entropy values are compared in Fig. 11.

If values for c in the BET equation are available over a temperature range it becomes possible to determine separately the quantities a_1b_2/a_2b_1 and $E_1 - E_L$. Since

$$c = \frac{a_1b_2}{a_2b_1}\, e^{\frac{E_1 - E_L}{RT}}$$

a plot of log c against $1/T$ should be a straight line (assuming $E_1 - E_L$ is not strongly dependent on temperature). The slope of this plot serves for the evaluation of $E_1 - E_L$ and the intercept for

---

(8) T. L. Hill, *J. Chem. Phys.*, **14**, 268 (1946). Hill showed that the BET derivation leads to the conclusion that the number of moles of gas V_1 adsorbed in the first layer is given by the equation

$$\frac{V_1}{V_m} = \frac{c(V/V_m + 1) - [(1 - V/V_m)^2c^2 + 4V/V_mc]^{1/2}}{2(c - 1)} \qquad (5)$$

where the symbols are the molal equivalents of those used in equation (1). Differentiation with respect to the total number of moles of gas adsorbed gives

$$\frac{\mathrm{d}V_1}{\mathrm{d}V} = \frac{c}{2(c-1)}\left\{1 - \frac{V/V_m - 1 + 2/c}{[(1 - V/V_m)^2 4/cV/V_m]^{1/2}}\right\} \qquad (6)$$

Equations (4) and (6) were used to calculate the differential heats of adsorption that one would expect from the BET theory.

that of a_1b_2/a_2b_1. Such a plot for the butane on glass data is shown in Fig. 12. Values of $E_1 - E_L$ and a_1b_2/a_2b_1 determined from this plot are listed in Table II. The range of values shown indicates the outside limits obtainable from different straight lines through the three points, which are not quite in a straight line. Evidently the ratio a_1b_2/a_2b_1 is essentially unity and the slope of the plot yields a value for $E_1 - E_L$ in reasonable agreement with those obtained in the usual way from the individual c values.

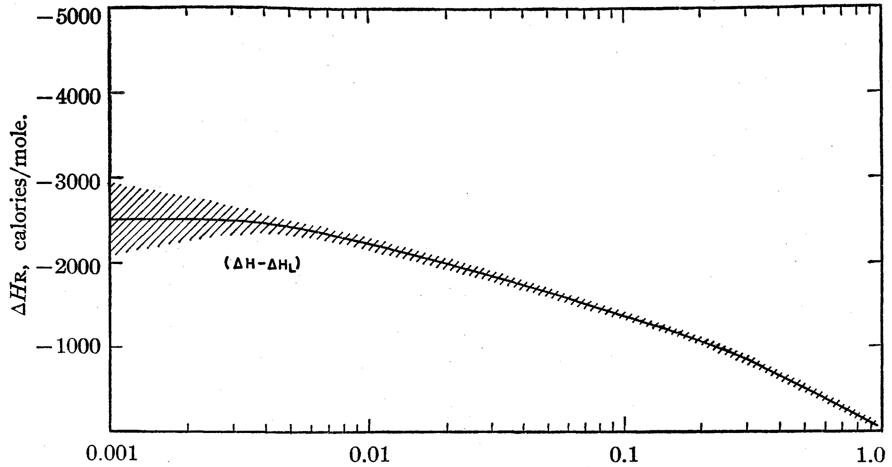


Fig. 9.—Adsorption of butane on glass spheres and heat of adsorption.

TABLE II

CALCULATION FROM "c" VALUES

($E_1 - E_L$) from "c" values assuming a_1b_2/a_2b_1 is unity	−78°	947 calories/mole
	−46°	962 calories/mole
	0°	962 calories/mole
($E_1 - E_L$) from slope of plot of log "c" vs. $1/T$	881 to 1165 calories/mole Mean = 1015 calories/mole	
a_1b_2/a_2b_1 from intercept of plot of log "c" vs. $1/T$	0.7 to 1.2	

Discussion

The system is quite normal in its behavior, and when viewed from the point of view of its pressure–volume adsorbed relations, requires little comment. The BET method for determining surface areas leads, as usual, to considerably lower surface area values, when the calculations are based on the butane isotherm than when they are based on the nitrogen isotherm, provided the values 32 and 16.2 Å.^{2} are used for the cross-sectional areas of the molecules of butane and nitrogen, respectively. With a smooth glass adsorbing surface it does not seem reasonable to assign this discrepancy to a screening out of the larger butane molecules from small holes. It must be that butane occupies a larger area on the surface than would be calculated from the liquid density. In calculating the area values recorded in Table I, corrections for the thermal expansion of the liquid were applied.

In the Harkins and Jura plots there is no straight line relation between the logarithm of the relative pressure and the reciprocal square of the volume adsorbed, as required in their theory, if the data in the relative pressure range 0.05 to 0.35, which is the region of usual validity of the BET equation, is used. For relative pressures above 0.3–0.4, however, the plots are relatively good straight lines and a reliable slope can be determined. The values for the areas thus determined are seen, from Table I, to be quite reasonable. It is interesting that the temperature correction demanded by the theory seems to operate in the right direction and to approximately the right extent. The factor 13.6 is equivalent to assuming a cross-sectional area for butane of about 56.6 Å.^{2} rather than the 32 Å.^{2} calculated from the liquid density and usually used in the application of the BET

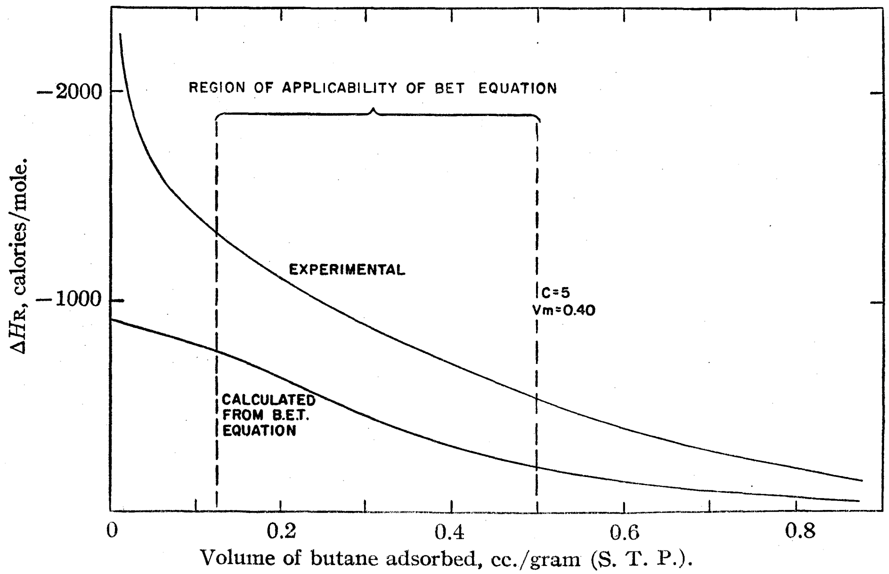


Fig. 10.—Adsorption of butane on glass spheres and heat of adsorption.

method. If a cross-sectional area of 56.6 Å.^{2} is used for butane in applying the BET method to the present work, good agreement with the nitrogen area is obtained but, as will be seen from Table I, the Harkins and Jura factor of 13.6 gives areas about 25% too low compared to the BET nitrogen area. The reason for this is readily seen to be that the BET and Harkins and Jura nitrogen areas do not agree. Nitrogen adsorption on glass beads has a low "c" value (55) and this constitutes a case wherein the nitrogen values for the two methods do not agree.[9] It will be noted from the table that there is good agreement between the area values calculated from butane and nitrogen data if the Harkins and Jura method and constants are used for both. Of course this should not be surprising since the constants were empirically determined to give such agreement. As has already been pointed out, equally good agreement could be obtained between the two gases using the BET method if a comparable procedure is used and the cross-sectional area of butane is chosen to give agreement with the nitrogen area. At the moment there seems to be no basis for making a choice between the BET method and the Harkins and Jura method for obtaining areas, if the Harkins and Jura method is applicable and yields a single straight line. The BET method when used to obtain absolute surface areas involves the assumption that the cross-sectional area of a molecule is independent of the substrate; the Harkins and Jura method assumes the same for its empirically chosen conversion factor. Probably such an assumption is not strictly justified for either method. Perhaps the best that can be done at the present is to admit that absolute areas cannot be relied on to better than 20–30% and regard both methods as adequate within these limits.

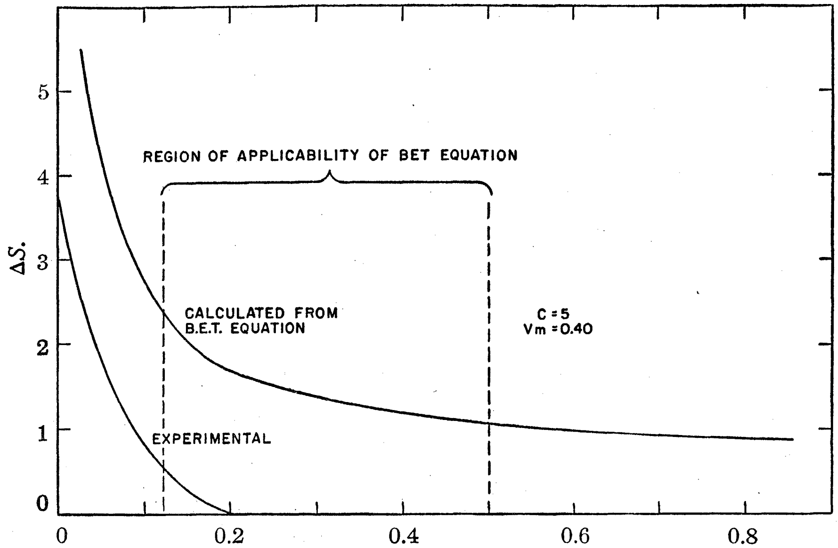


Fig. 11.—Adsorption of butane on glass spheres and entropy of adsorption.

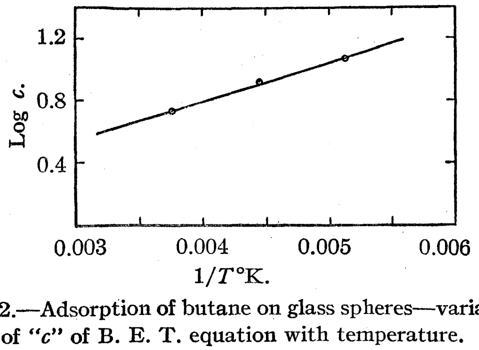


Fig. 12.—Adsorption of butane on glass spheres—variation of "c" of B. E. T. equation with temperature.

Thermodynamics.—The form of the heat curve is interesting, particularly at low surface coverages. Below about one per cent. coverage the heat appears to be constant at a rather high value. Beyond this it drops off at least approximately logarithmically with increasing adsorption. There is some uncertainty in the data in the low ranges; an unmistakeable departure, however, from its behavior at higher coverages occurs in this region. This is best illustrated by the logarithmic plot of Fig. 6 which spreads out the data at low partial pressures. It is also reflected in the nearly parallel straight line portions of the isotherms at the left in Fig. 6. Clausius–Clapeyron computations from parallel straight lines in this type of plot, of course, lead to constant heat values.

The sharp drop-off in the heat after about one per cent. of the surface is covered is difficult to explain. Roberts and Orr[10] and Orr[11] have made extensive theoretical calculations on the heat of adsorption of argon on alkali halide crystals and on the variation of the heat with amount adsorbed. Orr[12] determined the heats experimentally for the adsorption of oxygen, nitrogen and argon on potassium chloride and cesium iodide. Lateral van der Waals interaction invariably (as would be expected) contributes only in a way to increase the heat with surface coverage; only in the case of adsorption on the cesium positive ion faces of the crystal was there an electrostatic repulsive energy, arising from the oriented induced dipoles of the adsorbed atoms, sufficiently large to balance out the van der Waals attractive forces and give a net decrease in the energy of adsorption with increas-

---

[9] P. H. Emmett, THIS JOURNAL, **68**, 1784 (1946).

[10] Roberts and Orr, *Trans. Faraday Soc.*, **34**, 1346 (1938).

[11] Orr, *ibid.*, **35**, 1247 (1939).

[12] Orr, *Proc. Royal Soc.* (*London*), **A173**, 349 (1939).

ing coverage. In general, except for regions of very low coverage, agreement between experiment and theory was quite good. It is quite improbable that induced dipoles in butane adsorbed on glass could account for the observed decrease in heat of adsorption; indeed, the decrease in heats starts at such low surface coverages that no kind of lateral interaction would be expected to come into play. Frankenburg, in his study[13] of the adsorption of hydrogen on tungsten at elevated temperatures and also one of the authors (Davis) in the study of nitrogen adsorption on tungsten[13a] found the same behavior of the heat of adsorption at low surface coverages. Indeed, the behavior of the butane–glass system is so similar to that of the hydrogen–tungsten system that one is led to suspect the presence of something fundamentally general. In an attempt to account for the decreasing heat of adsorption, Frankenburg postulated a repulsive force operating between adsorbed atoms even at high dilutions that had its origin in the electron cloud that was assumed to exist in the substrate metal in the neighborhood of each adsorbed atom. No such device can be appealed to in the case of the butane–glass system, yet the experimental similarity of the data in the two cases tempts one to seek a common explanation. It does not seem probable that it will be found in the existence of lateral repulsive forces. Perhaps one is forced to the view that a heterogeneous set of adsorption sites is responsible. If so, the distribution of such sites must be of a remarkably universal form.

Reference to Figs. 10 and 11 makes it immediately apparent that the BET equation does not do too well in predicting individually the heat and entropy of adsorption. Although the form of the calculated heat curve approximates that of the experimental curve, it is everywhere much too low. Since the equation fits the data, and therefore the experimental and calculated free energies must agree, at least over the range of applicability, the entropy is everywhere correspondingly high. Experimentally, the entropy contribution has almost disappeared before a monolayer is completed and the heat contribution accounts for the free energy of adsorption thereafter. In the case of the BET equation the heat soon drops to a rather low value and the entropy continues to make an appreciable contribution to the adsorption free energy. It looks as though the theory incorporates too large an entropy contribution: this may be the origin of the excessive adsorption predicted by the theory for higher layers. A further indication of some basic difficulty is the recognized fact that the value for $E_1 - E_L$ obtained from the c value of the BET equation is so much smaller than the Clausius–Clapeyron heat. This cannot be blamed on a deviation of the factor a_1b_2/a_2b_1 from unity, at least in the present case, since it has been independently determined to be essentially unity. Even more disturbing is the result of plotting log c against $1/T$ for some other data. If the data of McGavack and Patrick[14] for the adsorption of sulfur dioxide on silica gel is thus plotted, the constant a_1b_2/a_2b_1 turns out to be about 6 and $E_1 - E_L$ about 700 calories instead of around 1700 as obtained directly from the c value. Several sets of data for the adsorption of nitrogen[15] at low temperature yield an average value of about 10 for a_1b_2/a_2b_1 and a value of about 400 calories for $E_1 - E_L$. Normally $E_1 - E_L$ determined from the c values for low temperature nitrogen adsorption is in the neighborhood of 700–800 calories. Thus in these cases, separate evaluation of a_1b_2/a_2b_1 has made agreement between $E_1 - E_L$ and the measured heat of adsorption considerably worse, rather than better.

Just wherein improvements are to be made to the simple BET theory is not clear. One obvious thing to do would be to attempt to take molecular interactions into account. Such a refinement has been approached by Hill.[16] The resulting equations are quite complicated and no application to experimental data has yet been published. As adsorption data accumulate, deficiencies in the simple theory become more apparent and the need for satisfactory refinements grows. The BET theory is theoretically sound and improvements will probably come through the use of an improved adsorption model and the incorporation of hitherto consciously ignored factors.

Summary

Data for the adsorption of butane on glass spheres has been reported for a relative pressure range from below 0.0001 up to near saturation at temperatures of −78, −46 and 0°. From these data heats of adsorption have been calculated through the Clausius–Clapeyron equation. The heat of adsorption tends to remain constant up to several per cent. surface coverage after which it decreases approximately logarithmically with increasing adsorption. Experimental heats and entropies of adsorption have been compared with the corresponding quantities calculated from the BET equation. The theory was found somewhat deficient in its ability to predict individually these thermodynamic functions. A plot of log c against $1/T$ was used for the independent evaluation of $E_1 - E_L$ and the coefficient a_1b_2/a_2b_1 in the expression for the constant c of the BET theory. In the case of butane on glass, a_1b_2/a_2b_1 was essentially unity. Some other data were thus treated and a_1b_2/a_2b_1 found to be larger than unity and $E_1 - E_L$ correspondingly lower than usual.

PITTSBURGH, PA. RECEIVED OCTOBER 9, 1947

---

(13) Frankenburg, THIS JOURNAL, **66**, 1827 (1944); **66**, 1838 (1944).

(13a) Davis, *ibid.*, **68**, 1395 (1946).

(14) McGavack and Patrick, *ibid.*, **42**, 946 (1920).

(15) Brunauer and Emmett, *ibid.*, **60**, 309 (1938).

(16) Hill, Presented at the Symposium on the Adsorption of Gases, Colloid Division, 110th meeting of the American Chemical Society, Chicago, Ill., September, 1946.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Magnetic Studies on the Dissociation and Disproportionation of Some Hexaarylethanes

BY WARD BYERLY,[1] HOWARD G. CUTFORTH AND P. W. SELWOOD

Previous communications from this Laboratory[1a] have given the heats of dissociation of hexylphenylethane, di-*o*-tolyltetraphenylethane, di-α-naphthyltetraphenylethane, and tetra-*o*-tolyldiphenylethane. Rate constants and activation energies have been given for the disproportionation of di-*o*-tolyltetraphenylethane.[2] To these results the present paper adds heats of dissociation and other thermodynamic constants for di-*o*-chlorophenyltetraphenylethane and for di-β-naphthyltetraphenylethane. Rate constants are given for the disproportionation of di-*p*-tolyltetraphenylethane. All the previously published results on heats of dissociation have been recalculated to correct an error in the method of calculating degrees of dissociation. Reference to this error has already been made.[2] Some of the data in Table I are not directly comparable with those published in 1941 because more experience with the magnetic susceptibility method has led us to reject certain data which we formerly believed were accurate. The conclusions drawn from the corrected results do not differ greatly from those originally reported, but all the reliable data, old and new, have been assembled in one table in the present paper.

Experimental

The magnetic measurements and the preparation of free radicals have already been described.[1,2] Again the authors are indebted to Professor Carl S. Marvel of the University of Illinois for supplying the triarylmethyl chlorides. All solutions were in toluene.

Results

All results on the five ethanes are summarized in Table I. Table II shows the best average values for free energy, heat and entropy changes for the various ethanes, as derived from the data of Table I.

These results confirm the general conclusions previously reached. It appears that the entropy change associated with dissociation is not independent of substituent, although the difference between hexaphenylethane and the other ethanes is not so large in this respect as previously reported.

It is also confirmed that the heats of dissociation are substantially independent of the substituent. On the other hand, large differences in percentage dissociation are produced by what must obviously be steric effects. However, the difference in de-

TABLE I

APPARENT DEGREE OF DISSOCIATION AND EQUILIBRIUM CONSTANTS FOR SOME HEXAARYLETHANES IN TOLUENE SOLUTION AT SEVERAL CONCENTRATIONS AND TEMPERATURES

The data are given in the following order: ethane, molal concentration, temperature, degree of dissociation [α], and equilibrium constant, $K \times 10^3$.

Hexaphenylethane.—0.0163 *M;* 60°, 0.200, 3.27; 70°, 0.257, 5.81; 80°, 0.296, 8.09.—0.0231 *M;* 60°, 0.199, 4.58; 70°, 0.241, 7.08; 80°, 0.300, 11.9.—0.0497 *M;* 60°, 0.134, 4.12; 80°, 0.204, 10.4.

Di-o-tolyltetraphenylethane.—0.0156 *M;* 30°, 0.426, 19.7; 40°, 0.518, 34.7; 50°, 0.622, 63.7.—0.0397 *M;* 30°, 0.349, 29.7; 40°, 0.433, 52.4; 50°, 0.523, 91.2; 60°, 0.601, 143; 70°, 0.644, 209; 80°, 0.704, 266; 90°, 0.699, 257.—0.0649 *M;* 10°, 0.184, 10.7; 20°, 0.243, 18.5; 30°, 0.312, 36.6; 40°, 0.395, 66.8; 50°, 0.485, 118.

Di-α-naphthyltetraphenylethane.—0.0109 *M;* 10°, 0.285, 4.94; 20°, 0.483, 19.7; 30°, 0.562, 31.4; 50°, 0.743, 93.5.—0.0278 *M;* −10°, 0.150, 2.96; 0°, 0.203, 5.73; 10°, 0.271, 11.2; 20°, 0.351, 21.1; 30°, 0.459, 43.2; 40°, 0.553, 76.0; 50°, 0.615, 109.—0.0410 *M;* 20°, 0.324, 25.4; 30°, 0.373, 36.3; 40°, 0.488, 76.1; 50°, 0.570, 123.

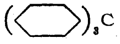
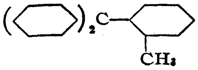
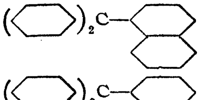
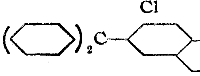
Tetra-o-tolyldiphenylethane.—0.0239 *M;* −10°, 0.678, 137; 0°, 0.728, 186; 10°, 0.802, 311.—0.0699 *M;* −10°, 0.692, 435; 0°, 0.777, 757.

Di-o-chlorophenyltetraphenyl.—0.0399 *M;* −10°, 0.043, 0.31; 0°, 0.062, 0.65; 10°, 0.083, 1.19; 20°, 0.115, 2.37; 30°, 0.152, 4.32; 40°, 0.196, 7.60; 60°, 0.325, 24.9.

Di-β-naphthyltetraphenylethane.—0.0246 *M;* 30°, 0.105, 1.22; 40°, 0.143, 2.34.—0.436 *M;* 30°, 0.0938, 1.69; 40°, 0.119, 2.53; 50°, 0.161, 5.42; 60°, 0.211, 9.88; 80°, 0.333, 29.1.—0.0821 *M;* 30°, 0.0656, 1.51; 40°, 0.089, 2.85; 50°, 0.123, 5.72; 60°, 0.142, 8.13; 70°, 0.192, 14.9.

TABLE II

PROBABLE VALUES FOR THE PERCENTAGE DISSOCIATION (100α FOR 0.03 MOLAL SOLUTION AT 20°), THE FREE ENERGY, HEAT, AND ENTROPY CHANGE

Free radical	100 α for 0.03 *M* solution at 20°	ΔF_{20}, kcal./mole	ΔH_{20} kcal./mole	ΔS_{20}, cal./mole °C.
	1.7	4.7	10.9	21.2
	30	2.4	11.2	30.0
	34	2.2	10.4	28.0
	11.5	3.1	11.2	26.2
	2.5	4.2	12.0	26.6

---

[1] Ward Byerly died at Oak Ridge, Tennessee, January 13, 1943.

[1a] Preckel and Selwood, THIS JOURNAL, **63**, 3397 (1941).

[2] Selwood and Preckel, *ibid.*, **65**, 895 (1943).

gree of dissociation produced by an α-naphthyl group as compared with an *o*-chloro group might be interpreted as being due to resonance. The difference between α-naphthyl and β-naphthyl supports the resonance theory of free radical stability.

The results obtained on di-*o*-tolylphenylmethyl are of little significance because of the high rate of disproportionation shown by this radical.

We turn now to a rate study on the disproportionation of *p*-tolyldiphenylmethyl. The problem is one of some difficulty because the solutions must be prepared and handled below 0°. It is complicated in another way. In our previous study on the dipproportionation of *o*-tolyldiphenylmethyl the ethane was at least 90% dissociated at the beginning of each run. But the degree of dissociation for *p*-tolyldiphenylmethyl is much less, and the changes in paramagnetism are correspondingly slight.

In Fig. 1 we show free radical concentrations plotted against time. The initial concentrations of ethane, and the temperatures at which disproportionation was observed are as follows: 0.0632 molal at 10°, and 0.0632 molal at 25°. For time intervals not in excess of ten hours these results give reasonably consistent velocity constants.

No difficulty is found in calculating the free radical concentration at any time, from the magnetic data, by the method previously used. But there is a difficulty in calculating the velocity constants because of the equilibrium, ethane $\rightleftarrows$ 2 radicals. The constants have been evaluated in the following way: Let $[A_2]$ be the concentration of the ethane, [B] and [C] those of the disproportionate.

We have

$$A_2 \underset{k_2}{\overset{k_1}{\rightleftarrows}} 2A \xrightarrow{k_3} B + C \tag{1}$$

$$d[A]/dt = k_1[A_2] - k\,[A]^2 - k_3[A]^2 \tag{2}$$

and

$$k_1/k_2 = [A]^2/[A_2] \tag{3}$$

eliminating A_2

$$d[A]/dt = -k_3[A]^2 \tag{4}$$

and integrating

$$1/[A]_2 - 1/[A]_1 = k_3(t_2 - t_1) \tag{5}$$

where $[A]_2$, $[A]_1$ are concentrations of free radical at times t_2, t_1.

Rate constants derived in this way from the first few hours of disproportionation are as follows: 0.0632 M at 10°, $k_3 = 12.92$; 0.0632 M at 25°, $k_3 = 41.8$. We find the activation energy to be 13.1 kcal. per mole of free radical. It seems probable that this is a maximum value, because disproportionation of *o*-tolyldiphenylmethyl required an activation energy of only 11.4 kcal. per mole, and the experiments and calculations in that case were much less complex.

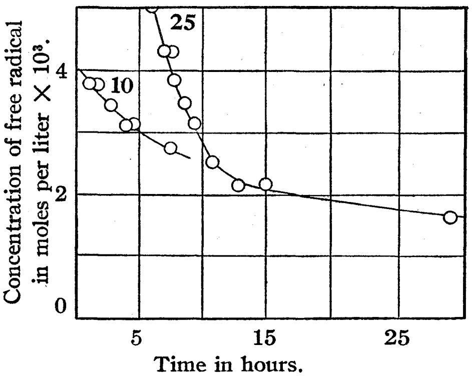


Fig. 1.—Disproportionation of *p*-tolyldiphenylmethyl.

An interesting observation was made during the work on *p*-tolyldiphenylmethyl. It will be recalled that the complete disproportionation of *o*-tolyldiphenylmethyl leaves the solution colored almost the same as when the free radical is present. The disproportionation of the *p*-tolyl also leaves the solution strongly colored *provided that the reaction is carried out in the dark.* If the disproportionation is carried out in the light, the loss of color parallels the loss of paramagnetism. But in the dark the solution remains colored even though all the free radical is destroyed. If now the solution is exposed to light the color fades in a few moments.

An attempt was made during this work to obtain the activation energy of the dissociation process by magnetic measurements on certain ethanes. The experimental difficulties proved insurmountable.

EVANSTON, ILLINOIS

RECEIVED JULY 16, 1947

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Water Absorption of Proteins. II. Lack of Dependence of Hysteresis in Casein on Free Amino Groups[2]

BY EDWARD F. MELLON, ALFRED H. KORN AND SAM R. HOOVER

Introduction

A series of benzoylated casein samples containing different amounts of free amino groups was used previously[3] to show that the amino group is responsible for the absorption of about one quarter of the total amount of water absorbed by casein, throughout the entire range of relative humidities. Furthermore, it appeared that the water absorbed by the amino group could be subdivided into three distinct portions. Since the amino group accounted for such a large proportion of the total water absorbed, we thought it would be interesting to know whether any of the water absorbed on the amino group is involved in the hysteresis phenomena. Therefore, the same series of benzoylated caseins was used to study the desorption phenomena of casein.

Experimental

The preparation of the benzoylated caseins, their analyses, the manipulations necessary to obtain a reproducible dry weight, and a detailed description of the apparatus and method for measuring the absorption or desorption over saturated salt solutions are given in the earlier paper.[3] The desorption experiments were made only at 30.0 ± 0.1°. The samples were thoroughly dried at 70° and then equilibrated at one of the higher humidities (51, 75, 84 or 93%). The water absorbed at these higher humidities was the same as that absorbed in the previous absorption experiments, where the absorption proceeded gradually from the lower to the higher humidities. The samples were then put into an atmosphere of the next lower relative humidity. It took the desorption samples about eighteen days to reach equilibrium—three times as long as the absorption samples—and there was a greater fluctuation in the equilibrium values obtained for different specimens of the same sample run at different times. When equilibrium was achieved at one humidity, the samples were moved to the next lower humidity until the value at 6% relative humidity was obtained. Then the samples were dried to check the starting weight.

Results and Discussion

Four desorption isotherms were determined for each of the benzoylated caseins. Each began at a different point on the absorption isotherm. From two to four determinations, made at different times, were averaged to determine each point on each isotherm. Figure 1 shows the four desorption isotherms of sample 1 only (purified casein) as compared with the absorption isotherm. The curves for the benzoylated samples are similar. All these curves show clearly that there is a marked hysteresis in the water-sorption phenomenon. It is also apparent that the total water content of the sample approaches a characteristic or limiting desorption curve regardless of the initial water content. Sets of isotherms similar to these have been obtained for wool by Speakman and Cooper[4] and for titania gels by Rao.[5]

Because the desorption isotherms from the higher humidities become identical at lower humidities, we can discuss the main desorption characteristics by discussing the upper limiting curve for each material. The data which fall on this upper curve for each sample at each humidity have been averaged, and the average value for each is reported in Table I. The standard deviation from these average values ranges from 0.002 to 0.004 g./g. of total nitrogen. The average values for the water content on absorption and the hysteresis values are also included in Table I. The water contents are reported on the basis of a gram of total nitrogen because this value relates the water content to the protein content and frees the calculations from the effects of the different weights of the benzoyl groups in the different samples. We have assumed that the benzoyl group does not absorb water.

TABLE I

WATER CONTENT OF BENZOYL CASEINS

Sample	NH_2-N, %[a]	Curve[b]	Water content[c] at relative humidity, % 5.9	11.8	31.4	50.9	75.1	83.6	93.3
1	0.93	A	159	227	465	660	981	1149	1441
		D	233	310	584	786	1064	1194	..
		H	74	83	119	126	83	45	
2	0.58	A	140	204	423	603	892	1040	1288
		D	218	290	540	729	989	1106	
		H	78	86	117	126	97	66	
3	0.36	A	126	186	394	559	841	978	1193
		D	204	268	509	690	938	1041	
		H	78	82	115	131	97	63	
4	0.26	A	124	183	386	547	820	943	1146
		D	193	257	490	674	912	1007	
		H	69	74	104	127	92	64	

[a] Moisture-free basis. [b] A = absorption, D = desorption, H = hysteresis. [c] g. H_2O/g. N × 1000.

The absolute magnitude of the hysteresis reaches an observed maximum of about 2.0 g. of water per 100 g. of protein at 51% R.H. This value is relatively large and wholly reproducible. The rapid approach of the 84% R.H. desorption isotherm to that of the 93% R.H. curve argues that the desorption curve would not be displaced

---

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(2) Presented before the Division of Colloid Chemistry, 112th Meeting of the American Chemical Society, New York City, September, 1947.

(3) Mellon, Korn and Hoover, THIS JOURNAL, **69**, 827 (1947).

(4) Speakman and Cooper, *J. Textile Inst.*, **27**, 183T (1936).

(5) Rao, *J. Phys. Chem.*, **45**, 506 (1941).

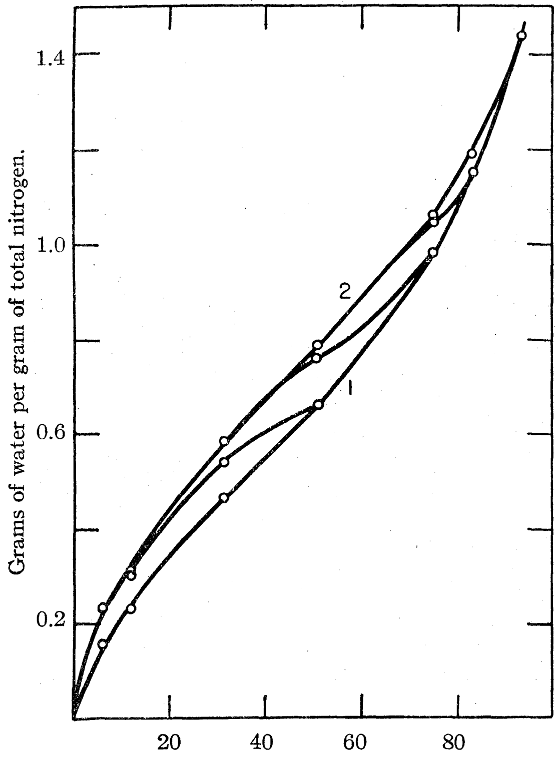


Fig. 1.—Absorption and desorption isotherms for casein: (1) absorption, (2) desorption.

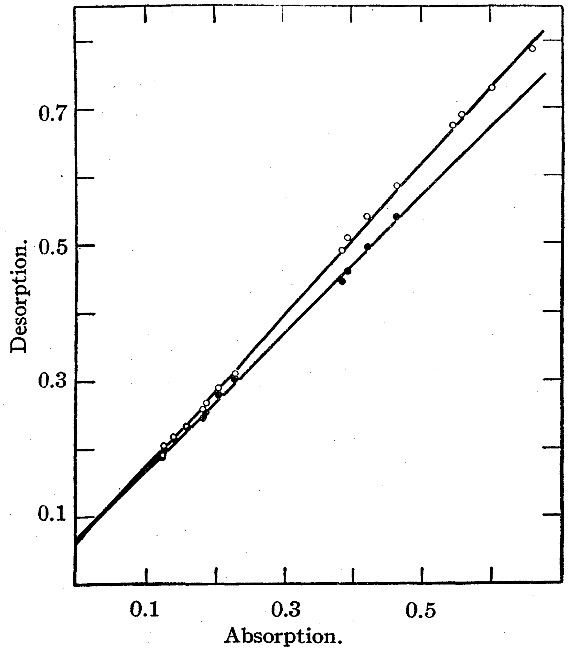


Fig. 2.—Relationship between absorption and desorption water contents: O, limiting desorption values; ●, desorption values from 51% R.H.

appreciably if desorption data from 100% R.H. were available. In our experience, reliable sorption data in the range 95–100% R.H. were difficult to obtain. The relative magnitude of the hysteresis is a maximum at the lowest humidity studied, where the hysteresis value is one half the amount absorbed. At intermediate humidities, the samples on desorption reach the same water content at relative humidities about 10–12% lower than on absorption. Speakman and Cooper[4] reported a comparable displacement of about 18% R.H. for wool.

The hysteresis values for the four samples are of similar magnitude, and, except for sample 1 at high humidities and sample 4 at low humidities, the variation is well within the experimental error (Table I), indicating that the amount of hysteresis is independent of the amino content of the sample and, therefore, cannot be due to the presence of the amino groups. This is in marked contrast to the high percentage of the water content held by the amino group both on absorption and desorption.

The nature of the hysteresis can be shown more clearly if the limiting desorption data for all four samples at the lower humidities are plotted (Fig. 2) against the absorption data. The data for the limiting curve of all four samples fall on a straight line with a slope of 1.12 and an extrapolated intercept of 0.059 (g. H_2O/g. N). This intercept is about half the magnitude of the maximum hysteresis obtained in these experiments. This would indicate that the water involved in the hysteresis consists of two types—a constant amount and a portion proportional to the amount absorbed.

The desorption data from 51% R.H., which do not approach the upper curve in Fig. 1 as rapidly as the higher humidity data, now become of particular importance. When these desorption values are plotted against the absorption values (Fig. 2), they fall on a straight line with a slope of 1.0 and an extrapolated intercept of 0.067 g. H_2O/g. N. The difference between these two slopes is statistically significant.

The intercept values appear to be associated with a type of water which is bound firmly at relatively low humidities. Its quantity is independent of the humidity from which the desorption is begun. The slope of 1.0 shows that it is the only type of water involved in the hysteresis, if desorptions are started from below about 60% relative humidity. This type of hysteresis has not been treated in any of the previous literature on the phenomenon.

The hysteresis indicated by the difference of the slope (Fig. 2) from 1.0 is associated with water absorbed above the upper break in the absorption curve, but it persists at the lower humidities, where it is proportional to the amount absorbed. Therefore, it might be attributed either to the capillary phenomena of Zsigmondy[6] and McBain[7] or to the swelling of the gel according to Urqu-

[6] Zsigmondy, *Z. anorg. Chem.*, **71**, 356 (1910).

[7] McBain, THIS JOURNAL, **57**, 699 (1935).

hart.[8] Smith[9] has recently proposed an extension of Urquhart's treatment, and applied it to cellulose, nylon and wool. However, our absorption and desorption data do not give the linear extrapolation characteristic of the approximate method of Smith. The excellent data of Wiegerink[10] on the sorption of wool give a curve of similar shape to that obtained from our data when plotted according to Smith; and it is quite possible that the protein gels require a more complicated swelling function than the simple weight function used by Smith. Moreover, several observations have been made which seem to indicate that the structure of casein is fairly open and most of the groups should be freely available to water vapor without swelling. The first of these is that even though the large benzoyl group has been introduced to modify the amino group there is apparently little disruption of the remainder of the molecule, as shown by the strict linearity of the absorption *versus* amino-content plots of the earlier paper.[3] This situation does not prevail in the cellulose–cellulose acetate system, where opening of the structure by intermediate degrees of acetylation is clearly demonstrable.[11] Secondly the lack of hysteresis in the absorption of the amino group indicates that no new amino groups are made available by swelling.

Summary

Desorption isotherms have been obtained for a number of benzoylated casein samples with various amounts of free amino groups.

A definite hysteresis in the sorption phenomena of about one-half the absorption value at 6% R.H. and about one-fifth at 50% R.H. was observed.

The hysteresis was independent of the content of free amino groups in the samples, although the amino group is responsible for one-fourth the water absorption in casein.

The hysteresis appears to be of two types: a constant hysteresis independent of the humidity from which desorption was started, and a hysteresis proportional to the amount absorbed and due only to absorption above the upper break in the absorption curve. This appears to be the first demonstration of the two-fold nature of the hysteresis phenomena.

(8) Urquhart, *J. Textile Inst.*, **20**, 125T (1929).

(9) Smith, THIS JOURNAL, **69**, 646 (1947).

(10) Wiegerink, *Textile Research*, **10**, 357 (1940).

(11) Hoover and Mellon, *Textile Research J.*, **17**, 714 (1947).

PHILADELPHIA 18, PA. RECEIVED SEPTEMBER 27, 1947

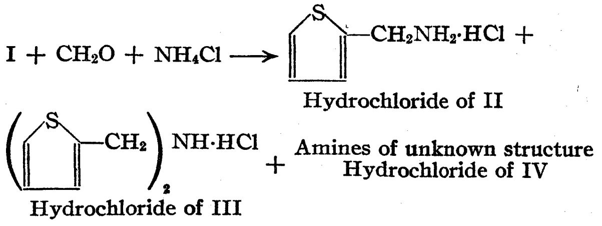
[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES, A DIVISION OF SOCONY-VACUUM OIL CO., INC., RESEARCH AND DEVELOPMENT DEPARTMENT]

Aminomethylation of Thiophene. I. The Reaction of Thiophene with Formaldehyde and Ammonium Salts

BY HOWARD D. HARTOUGH, SIGMUND J. LUKASIEWICZ AND EVERETT H. MURRAY, JR.[1]

Recently the authors reported that thiophene possessed alpha hydrogens of sufficient reactivity to undergo a type of Mannich reaction.[2] At the same time Holdren and Hixon reported that the Mannich reaction had been extended to 2-methylfuran.[3] They also reported that only resinous products were obtained from the use of ammonium chloride with formaldehyde. Bachman and Heisey reported that pyrroles, azoles and their benzalogs which contain the —NH— group in the heterocyclic ring will undergo the Mannich reaction.[4]

The reaction of thiophene, I, with ammonium chloride and formaldehyde has been investigated and found to give a variety of products. Besides the formation of complex amines of unknown structure, IV, 2-thenylamine (2-aminomethylthiophene), II, and di-(2-thenyl)-amine, III, have been isolated.



The yields of II and III leave much to be desired and many unsuccessful attempts were made to improve the yields over those previously reported.[2] Lower yields were obtained when the reaction quantities were increased five-fold. Yields obtained from various molar ratios of reactants are listed in Table I.

TABLE I

EFFECT OF MOLAR CONCENTRATION ON YIELDS OF AMINES II, III AND IV

Moles of reactants				Weight % of total product		
C_4H_4S	CH_2O (Aqueous)	NH_4Cl	Mole ratio	II	III	IV
5	10	5	1:2:1	17.6	5.3	77
2	2	2	1:1:1	15.6	3.1	80
4	2	2	2:1:1	17.7	20.3	62
5	4	4	1.25:1:1	22.2		77
1	1	3	1:1:3	36.8	15.2	48

Hexamethylenetetramine in the presence of concentrated hydrochloric acid was found to react

---

[1] Present address: Owens-Illinois Glass Co., Glassboro, N. J.

[2] Hartough, *et al.*, THIS JOURNAL, **68**, 1389 (1946).

[3] Holdren and Hixon, *ibid.*, **68**, 1198 (1946).

[4] Bachman and Heisey, *ibid.*, **68**, 2496 (1946).

with thiophene in the same manner as ammonium chloride and formaldehyde.

In an effort to determine the molar ratios involved in the basic reaction, excess amounts of both ammonium chloride and thiophene were used with trioxymethylene and the unreacted portions recovered. Within reasonable limits the basic reaction was found to involve one mole of thiophene, one mole of ammonium chloride and two moles of formaldehyde. These observations are summarized in Table II.

TABLE II

DETERMINATION OF MOLAR RATIOS IN BASIC REACTION

Reactants used, moles			Reactants recov., moles			Mole ratio of basic reaction		
I	CH_2O	NH_4Cl	I	CH_2O	NH_4Cl	I	CH_2O	NH_4Cl
4	2	1	2.9	0	0	1.1	2	1
5	10	5	1.0	0	1.0	1	2.5	1
2	2	2	1.0	0	0.95	1	2	1
4	2	2	3.0	0	1.13	1	2	0.9

No successful degradation of polymeric amine IV types could be carried out by oxidation similar to the oxidation of polymers obtained from hydroxylamine, thiophene and formaldehyde.[5]

It is probable, however, that the polymeric linking takes place through the 2- and 5-positions. The structure of these polymeric materials will be discussed in later publications. The position of the —CH_2NH_2 group in the thenylamine was proven by oxidation of the 2-thenylamine to 2-thiophenecarboxylic acid.

No tri-(2-thenyl)-amine has been isolated. The failure to isolate this amine may be due to the fact that sub-resinous polymeric amines (IV) decompose to hard resinous masses at 180–210°. This is below the calculated boiling point of the tertiary amine under the reduced pressures used.

Blocking one of the reactive 2,5-positions in the thiophene nucleus leads to a somewhat less complicated reaction. 2-Methylthiophene reacts similarly to I in that the primary amine, 5-methyl-2-thenylamine (VI) as the hydrochloride, the secondary amine, di-(5-methyl-2-thenyl)-amine (VII) as the hydrochloride, are formed, along with a smaller amount of amines of unknown structure (X) as the hydrochloride. However, at 88° there were obtained appreciable amounts of the tertiary amine, tri-(5-methyl-2-thenyl)-amine (VIII) as the hydrochloride, and di-(5-methyl-2-thienyl)-methane (IX).

Not all the factors influencing this reaction are understood since it has been found that if the reaction is controlled at a lower temperature, 60–70°, less X is formed and VIII could not be isolated.

2-Chlorothiophene failed to react with aqueous formaldehyde and ammonium chloride but reacted with trioxymethylene and ammonium chloride to give di-(5-chloro-2-thenyl)-amine, XI. No other simple amine could be isolated and the reaction was complicated with amines of type IV.

A reaction with 2-*t*-butylthiophene, formaldehyde and ammonium chloride gave tri-(5-*t*-butyl-2-thenyl)-amine hydrochloride, XII. None of the secondary amine was isolated but a small amount of an unidentified product believed to be of type IV was obtained.

3-Methylthiophene was not investigated other than to determine that it reacted similarly to thiophene giving a series of amines including the sub-resinous type IV.

The alkylamine hydrochlorides have not been investigated to any great extent but in general they cause condensation of thiophene with aqueous formaldehyde. 2-Methylthiophene reacted with formaldehyde in the presence of dimethylamine hydrochloride to give a 45% yield of di-(5-methyl-2-thienyl)-methane, IX, along with higher polymers and a small amount of an unidentified amine containing sulfur. Similar reactions with thiophene gave high yields of polymers. Caesar and Sachanen reported that salts of weak bases and strong acids caused condensation of formaldehyde with thiophene thereby producing polymers.[6] No study has been made with polymeric formaldehyde and the alkylamine hydrochlorides and this may give the desired products rather than direct condensation of the formaldehyde and thiophene.

Superficially, at least, this reaction can be classified as a modified Mannich reaction. Although this reaction proceeds very readily with ammonium chloride to give the products listed above when alkylamine hydrochlorides are used it proceeds with reluctance and further investigation is needed to completely typify it.

Resins were obtained from the condensation of thiophene and formaldehyde with urea, ethylenediamine, and aniline (low yields) and with ammonium chloride. Morpholine hydrochloride caused no condensation with thiophene. A reaction occurred with thiourea but the oils obtained were so unstable and possessed such a stench that identification work was abandoned.

In general, when ammonium chloride is used, II, III, and IV are always obtained if the formaldehyde is used in amounts of two moles or less per mole of thiophene and ammonium chloride. Paraformaldehyde gave comparable results. For example, 11% II, 11% III, and 78% sub-resinous IV were obtained from a reaction involving 18 moles of thiophene, 18 moles of paraformaldehyde and 15 moles of ammonium chloride. II and III are not obtained when more than two moles of paraformaldehyde per mole of thiophene is used.

Ammonium chloride, ammonium bromide and, presumably, ammonium iodide undergo this reaction but other ammonium salts such as the acetate, phosphate, diacid phosphate, sulfate and acid sulfate do not react.

Experimental

Reaction of Thiophene, Aqueous Formaldehyde and Ammonium Chloride.—To a well-stirred mixture of 84

---

(5) Hartough, THIS JOURNAL, **69**, 1355 (1947).

(6) Caesar and Sachanen, Paper presented at 110th Meeting of the American Chemical Society, Chicago, September 9, 1946.

g. (1 mole) of thiophene and 162 g. (3 moles) of ammonium chloride was added 81 g. (1 mole) of 37% formaldehyde solution. After fifteen minutes heating at the reflux temperature, 72°, a yellow color appeared indicating the start of the reaction. The mixture was heated at reflux for one hour, cooled, the condenser inverted and the excess thiophene distilled off; 51 g. (0.63 mole) was recovered. The reaction mixture was then filtered to remove excess ammonium chloride, the filter washed with alcohol until colorless, the filtrate concentrated on the steam-bath to remove alcohol, cooled, made alkaline with 100 g. of 40% sodium hydroxide solution, and extracted three times with 50 ml. of benzene. The benzene was removed by distillation and the amines distilled *in vacuo;* 17.5 g. of 2-thenylamine, II, b. p. 82° at 17 mm.[7,8]; 7.0 g. di-(2-thenyl)-amine, III, b. p. 134–135° at 3 mm.; and 23 g. of sub-resinous amines, IV, were obtained. Refractionation of II and III through a 12-plate column to effect higher purity gave the following refractive indices; II, n^{20}D 1.5615; III, n^{20}D 1.6032. These products correspond to yields of 42% of II and 18.3% III based on the 0.37 mole of thiophene used in the reaction.

Anal. Calcd. for C_5H_7NS (II): N, 12.39. Found: N, 12.33. Calcd. for $C_{10}H_{11}NS_2$ (III): S, 30.62; N, 6.69. Found: S, 30.43; N, 6.65.

Analysis of typical samples of IV indicated that the nitrogen and sulfur ratios varied from 2:3 to 1:1.

II reacts rapidly with carbon dioxide in the air and a thin film on glass quickly forms a white solid, presumably the carbamate. II is soluble in water in all proportions but can be salted out conveniently with sodium chloride.

Oxidation of II with alkaline permanganate gave 2-thiophenecarboxylic acid, XIV, m. p. 129.5–130°. A mixed melting point with an authentic sample gave no depression.

The hydrochloride of II was prepared and crystallized from 20% hydrochloric acid solution by cooling in an ice-salt-bath; m. p. 188–189°.

Anal. Calcd. for C_5H_8ClNS: N, 9.30. Found: N, 9.30.

The hydrochloride of III was prepared and recrystallized from water; m. p. 252–253° with decomposition.

Anal. Calcd. for $C_{10}H_{12}ClNS_2$: S, 26.07; N, 5.66. Found: S, 25.59; N, 5.59.

The N-(2-thenyl)-N′-phenylthiourea, XV, was prepared by standard procedures from phenyl isothiocyanate and 2-thenylamine. After two recrystallizations from water and alcohol the product melted at 123.5–124°.[9]

Anal. Calcd. for $C_{12}H_{12}N_2S_2$: N, 11.28. Found: N, 11.36.

The di-(2-thenyl)-amine did not give a crystalline derivative with phenyl isothiocyanate.

The N-(2-thenyl)-benzamide, XVI, was prepared according to standard procedures, from II and benzoyl chloride; m. p. 121–122°.

Anal. Calcd. for $C_{12}H_{11}NOS$: N, 6.4. Found: N, 6.3.

The N-(2-thenyl)-stearamide, XVII, was prepared by refluxing 20 g. (0.177 mole) of 2-thenylamine and 50 g. (0.177 mole) of stearic acid in 200 ml. of xylene until 2.5 ml. (3.5 ml. calcd.) of water was collected in a water trap. After cooling, the white crystalline XVII was filtered off and recrystallized twice from benzene; 42 g. (67% yield), m. p. 92.5–93°.

Anal. Calcd. for $C_{23}H_{41}NOS$: N, 3.7. Found: N, 3.9.

Preparation of N-(2-Thenyl)-phthalimide, XVIII, and N,N′-Di-(2-thenyl)-phthalamide, XIX.—A mixture of 22 g. (0.2 mole) of 2-thenylamine and 14.8 g. (0.1 mole) of phthalic anhydride in 100 ml. of xylene was refluxed until 1.4 ml. (1.8 ml. calcd.) of water was collected in the water trap. Upon cooling 20 g. of XIX was filtered off, washed with cold benzene, and recrystallized twice from benzene, m. p. 169–169.5°. Removal of the xylene yielded 9 g. of XVIII, which after two recrystallizations from alcohol melted at 126–127°.

Anal. Calcd. for $C_{13}H_9NO_2S$ (XVIII): N, 5.76. Found: N, 5.65. Calcd. for $C_{18}H_{16}N_2O_2S_2$ (XIX): N, 7.81. Found: N, 7.86.

Preparation of N-(2-Thenyl)-urea, XX, and N,N′-Di-(2-thenyl)-urea, XXI.—A mixture of 20 g. (0.177 mole) of 2-thenylamine, 50 ml. of water, 17.6 g. of concentrated hydrochloric acid, and 12 g. (0.20 mole) of urea was heated at reflux for nine hours at the reflux temperature, 106°. The hot aqueous solution was decanted from the bottom organic layer (8 g., XXI), and 15 g. of XX was obtained by crystallization from the water solution. XX was purified by three treatments with decolorizing charcoal and recrystallization from hot water; m. p. 129.5–130.5°. XXI was purified by digesting once with water and three recrystallizations from hot alcohol; m. p. 164–165°.

Anal. Calcd. for $C_6H_8N_2OS$ (XX): N, 17.95; S, 20.51. Found: N, 17.45; S, 20.66. Calcd. for $C_{11}H_{12}N_2OS_2$ (XXI): N, 11.11; S, 25.39. Found: N, 11.01; S, 25.21.

The Reaction of Thiophene, Hexamethylenetetramine and Hydrochloric Acid.—To a well-stirred mixture of 168 g. (2 moles) of thiophene and 70 g. (0.5 mole) of hexamethylenetetramine was added 200 g. of hydrochloric acid (36%) over a period of forty minutes. After addition of the acid the mixture was maintained at a reflux temperature of 76–80° for one hour. The procedure from this point follows that previously described. Thirty-three grams of 2-thenylamine, II (identity established by mixed melting point of the N-(2-thenyl)-N′-phenylthiourea), 16 g. of di-(2-thenyl)-amine, III, and 100 g. of sub-resinous amine, IV, were obtained.

The Reaction of Thiophene, Formaldehyde and Ammonium Chloride.—To a mixture of 18 moles (1312 g.) of thiophene and 15 moles (803 g.) of ammonium chloride was added 18 moles (1460 g.) of 36% formaldehyde. The mixture was heated slowly over a two-hour period to 72° whereupon the reaction became vigorous and was controlled by means of an ice-bath. After twenty minutes the reaction was completed. The reaction mixture was cooled, 12 moles of sodium hydroxide as a 40% aqueous solution was added, the salt filtered off by suction, the oil layer decanted from the filtrate, the filter washed with thiophene (or benzene) and the filtrate extracted once with thiophene. The thiophene, I, was recovered by distillation and 123 g. of II, 97 g. of III, and 660 g. of IV were obtained.

Reaction of Thiophene, Urea and Hydrochloric Acid.—To a cooled mixture of 30 g. (0.5 mole) of urea, 42 g. (0.5 mole) of thiophene and 41 g. (0.5 mole) of formaldehyde (36%) was slowly added 50 g. of concentrated hydrochloric acid. A white solid material began to form immediately. The reaction mixture was heated to reflux for six hours, cooled, the resin washed with water, dilute sodium hydroxide, and then digested with hot water. The resin, 93 g., analyzed as follows: S, 14.2; N, 20.6.

Reaction of Thiophene, Formaldehyde and Ethylenediamine Dihydrochloride.—To 30 g. (0.5 mole) of ethylenediamine, cooled in an ice-bath, was added 100 g. of concentrated hydrochloric acid. To this dihydrochloride of ethylenediamine was added 84 g. (1 mole) of thiophene and 83 g. (1 mole) of formaldehyde (36%) and the mixture was refluxed for two hours at 75°. After cooling, the resinous material was washed with hot water several times, dried in an oven and analyzed (S, 19.0; N, 5.98).

Reaction of 2-Methylthiophene, Formaldehyde and Ammonium Chloride. Procedure A.—To a well-stirred mixture of 196 g. (2 moles) of 2-methylthiophene and 161 g. (3 moles) of ammonium chloride was added 162 g.

---

(7) Blicke and Burckhalter, THIS JOURNAL, **64**, 478 (1942).

(8) Putokhin and Egorova, *J. Chem. Soc.* (*U.S.S.R.*), **10**, 1873 (1940); *C. A.*, **35**, 4377 (1941), gave b. p. of 88° at 26 mm., 77° at 16 mm.; n^{15}D 1.5678; d^{15}_4 1.1370.

(9) v. Braun, Fussgänger and Kühn, *Ann.*, **445**, 218 (1925), prepared this compound from the reaction of 2-thenyl isothiocyanate with aniline, m. p. 123°.

(2 moles) of formaldehyde (36%). The mixture was warmed to 40° where the reaction started and the temperature rose to 87° without further heating. When the rate of reaction decreased sufficiently the mixture was heated at the reflux temperature (85°) an additional thirty minutes, cooled, 200 ml. of benzene added, and the reaction mixture neutralized with 40% sodium hydroxide solution. After three more extractions with 100 ml. of benzene, the benzene was removed by distillation and the products fractionated under reduced pressure to yield 21 g. of 5-methyl-2-thenylamine, VI, b. p. 68–69° at 4 mm., $n^{20}\text{D}$ 1.5518; 21 g. of di-(5-methyl-2-thienyl)-methane, IX, b. p. 135–136° at 4 mm.; 39 g. of di-(5-methyl-2-thenyl)-amine, VII, b. p. 161–162° at 4 mm., $n^{20}\text{D}$ 1.5832; 32 g. of tri-(5-methyl-2-thenyl)-amine, VIII, b. p. 207–214° at 3 mm., m. p. 81–81.5°; and 83 g. of residue X. Extraction of the residue with boiling alcohol yielded an additional 10 g. of VIII.

Anal. Calcd. for $C_{12}H_{15}NS_2$, VII: S, 27.00; N, 5.91. Found: S, 27.03; N, 5.98.

Anal. Calcd. for $C_{18}H_{21}NS_3$, VIII: S, 27.68; N, 4.01. Found: S, 27.73; N, 4.04.

Anal. Calcd. for $C_{11}H_{12}S_2$, IX: S, 30.7. Found: S, 30.4.

The N-(5-methyl-2-thenyl)-N′-phenylthiourea, XXII, was prepared in order to properly identify VI since it picked up carbon dioxide from the air too rapidly to obtain good analyses. XXII melted at 133–134°.

Anal. Calcd. for $C_{13}H_{14}N_2S_2$, XXII: N, 10.69. Found: N, 10.45.

While VII appeared to form a thiourea derivative with phenyl isothiocyanate, no crystalline product could be obtained.

Procedure B.—To a well-stirred mixture of 490 g. (5 moles) of 2-methylthiophene and 535 g. (5 moles) of ammonium chloride was added 425 g. (5 moles) of 36% formaldehyde. The mixture was warmed to 40°, the heat was discontinued and the temperature controlled at 60–70° by means of an ice-bath. Crystals began to form and within a few minutes a slurry developed which became very hard to stir. After thirty minutes the ice-bath was no longer necessary and the reaction mixture was stirred an additional one and one-half hours. After cooling to 10° the mixture was filtered, the precipitate washed with benzene and recrystallized from six liters of water to yield 379 g. (56% yield) of di-(5-methyl-2-thenyl)-amine hydrochloride, XXIII, m. p. 216–217° with decomposition.

Anal. Calcd. for $C_{12}H_{16}ClNS_2$ (XXIII): S, 23.40; N, 5.12. Found: S, 23.54; N, 5.36.

The filtrate contained the benzene layer which upon evaporation yielded 82 g. of IX. A water and benzene insoluble oil, 66 g. XA, was not identified. It contained 16.3% S and 4.1% N, which cannot be reconciled with any simple structure. Neutralization of the water layer with sodium hydroxide followed by extraction of the products gave 15 g. of VI, and 109 g. of a light red viscous oil, XB (analysis showed S, 22.98; N, 7.87). Only a trace of VIII could be extracted from XB with hot alcohol.

Reaction of 2-Chlorothiophene, Paraformaldehyde and Ammonium Chloride.—To 119 g. (1 mole) of 2-chlorothiophene was added 30 g. (1 mole) of paraformaldehyde, 54 g. (1 mole) of ammonium chloride and 10 ml. of acetic acid. The mixture was heated with stirring at 85–90° for one and one-half hours, cooled, 50 ml. of water added and 34 g. of di-(5-chloro-2-thenyl)-amine hydrochloride, XI, was filtered off. After digesting twice in 700 ml. of hot water the product melted at 240–242° with decomposition.

Anal. Calcd. for $C_{10}H_{10}Cl_3NS_2$: S, 20.35; N, 4.45. Found: S, 20.30; N, 4.72.

The filtrate was neutralized with 40% sodium hydroxide solution, extracted three times with 50 ml. of benzene, the extracts combined, and upon evaporation of the solvent 19 g. of a viscous red oil was obtained (*Anal.* Found: S, 17.9; N, 5.04). This product reacted with phenyl isothiocyanate but no crystalline products could be obtained.

Reaction of 2-*t*-Butylthiophene, Formaldehyde and Ammonium Chloride.—To a mixture of 276 g. (2 moles) of 2-*t*-butylthiophene[10] and 161.5 g. (3 moles) of ammonium chloride heated to 75° was added 84 g. (1 mole) of formaldehyde (36%) over a period of thirty minutes. The mixture was heated at 85–90° for one hour, cooled and the organic layer separated. Upon dilution of the organic layer with petroleum ether 14 g. of XII separated out and was recrystallized from alcohol; m. p. 204–206° with decomposition. Recovery of 2-*t*-butylthiophene by distillation yielded an additional 44 g. of tri-(5-*t*-butyl-2-thenyl)-amine hydrochloride, XII, as a residue.

Anal. Calcd. for $C_{27}H_{40}ClNS_3$: S, 19.20; N, 2.81. Found: S, 18.94; N, 2.83.

Neutralization of the water layer with 40% sodium hydroxide solution followed by extraction with benzene yielded 4.5 g. of light yellow oil (*Anal.* Found: S, 15.9; N, 8.5).

Acknowledgments.—The authors wish to thank Dr. D. E. Badertscher for his advice and interest in this problem and Mrs. Josephine Sindoni Piel and Miss Loretta G. Conley for technical assistance.

Summary

Thiophene, formaldehyde and ammonium salts have been found to undergo a type of Mannich reaction to yield 2-thenylamine (2-aminomethylthiophene), di-(2-thenyl)-amine, and polymeric amines of unknown structure.

With 2-methylthiophene, formaldehyde, and ammonium chloride, 5-methyl-2-thenylamine, di-(5-methyl-2-thenyl)-amine, tri-(5-methyl-2-thenyl)-amine, two complex amines of unknown structure, and di-(5-methyl-2-thienyl)-methane have been isolated.

2-Chlorothiophene and 2-*t*-butylthiophene reacted to give both simple and complex amines.

The alkylamine hydrochlorides such as dimethylamine hydrochloride do not react in a similar manner to ammonium chloride. While unidentified amines were formed the major reaction is a coupling action of formaldehyde with thiophene forming polymers containing no nitrogen.

In addition to sixteen new aminomethyl derivatives of thiophene, N-thenylstearamide, -benzamide, -phthalamide, -phthalimide, N-(2-thenyl)-urea, di-N,N′-(2-thenyl)-urea, N-(2-thenyl)-N′-phenylthiourea and N-(5-methyl -2′-thenyl)-N′-phenylthiourea have been prepared and characterized.

PAULSBORO, NEW JERSEY RECEIVED SEPTEMBER 9, 1947

---

[10] Sample received from P. D. Caesar of these laboratories; data will be published later.

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

The Preparation and Some Reactions of Ethyl α-Acetamidoacetoacetate

BY N. F. ALBERTSON, B. F. TULLAR, J. A. KING,[1] B. B. FISHBURN AND S. ARCHER

During the course of our investigations on useful intermediates for amino acid synthesis, we had occasion to prepare and study ethyl α-acetamidoacetoacetate, II. This compound was prepared in quantitative yield by reduction of ethyl α-oximinoacetoacetate, I, in acetic acid–acetic anhydride solution in the presence of a palladium–charcoal catalyst. Zinc dust reduction of I in the same solvent gave 79% of the theoretical yield of II, m. p. 47°.

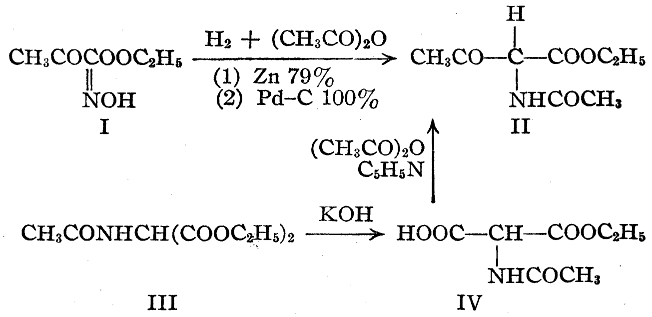
Cerchez and Colesiu[2] reported the preparation of II, m. p. 141°, by reduction of the acetate of I with aluminum amalgam. In view of the discrepancy in melting points we attempted to repeat this work, but were unable to obtain a substance whose properties corresponded with those of the one described. Aluminum amalgam reduction of acetyloximinoacetoacetic ester in the presence of moist ether gave 2,5-dimethyl-3,6-dicarbethoxypyrazine when the suggested method[3] of Cerchez and Colesiu[2] was followed. However, simultaneous addition of acetic anhydride and water to the reaction mixture gave II.[4]

Convincing proof that this low-melting solid, II, was indeed ethyl α-acetamidoacetoacetate was furnished by a fourth method of synthesis. Ethyl acetamidomalonate (III) was saponified to its half-ester with one equivalent of potassium hydroxide. The ester, IV, was then treated with acetic anhydride in the presence of pyridine according to the method of Dakin[5] for converting amino acids to acetamido ketones. The desired compound was obtained as a crystalline solid identical in all respects with the compound obtained in the other preparations. The reactions involved are given in the scheme.

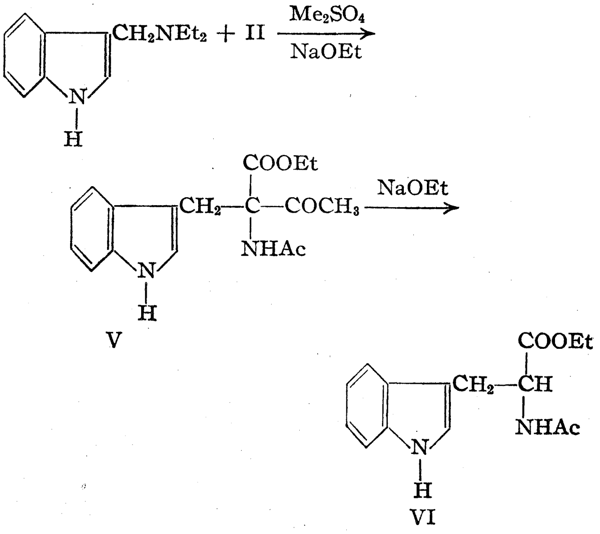
For the preparation of larger quantities of the ester, II, a method was employed whereby the isolation of the oximino-ester, I, was avoided. Aside from possessing the obvious advantage of eliminating several manipulations, the procedure is safer since it obviates the necessity of isolating the oxime. In one experiment the oxime, I, decomposed with explosive violence while being heated on the steam-bath to remove the last traces of solvent. It was possible to obtain II in 70% of the theoretical yield based on ethyl acetoacetate by following the zinc dust reduction procedure described in the experimental part.

The zinc dust method of reduction was also applied to the preparation of α-propionamidoacetoacetic ester.

When the acetamido ester, II was alkylated



with diethylaminomethylindole methosulfate under conditions similar to those used with ethyl acetamidomalonate and gramine[6] the alkylation product, V, was isolated in 83% yield. However,



when there was a delay in adding the dimethyl sulfate to the reaction mixture, no ester, V, could be obtained. When α-acetamidoacetoacetate was warmed with an alcoholic solution of sodium ethylate it cleaved into ethyl acetate and aceturic ester. It was found that V also underwent the same type of cleavage to give N-acetyl tryptophan ethyl ester, VI. This compound was also prepared from ethyl (3-indolylmethyl)-acetamidomalonate for purposes of comparison. Attempts to alkylate

---

(1) Present address: Warner Institute for Therapeutic Research, 113 West 18th Street, New York, N. Y.

(2) Cerchez and Colesiu, *Compt. rend.*, **194**, 1954 (1932).

(3) No experimental details were given, but previous publications by these authors give details for aluminum amalgam reduction. However, the authors point out[2] that conditions must be determined for each preparation.

(4) After the cessation of hostilities in Europe one of us (B. F. T.) was able to communicate with Dr. Cerchez at the University of Bucharest. He stated that the m. p. in the literature was a misprint and that the results which he and Colesiu obtained were in agreement with ours.

(5) Dakin, *J. Biol. Chem.*, **78**, 91 (1928).

(6) Albertson, Archer and Suter, THIS JOURNAL, **67**, 36 (1945).

II with benzyl chloride resulted only in cleavage to aceturic ester even when the sodium ethylate was added to the other reactants. Similar cleavage reactions have been observed with other substituted keto-esters.[7]

The behavior of ethyl α-acetamidoacetoacetate on catalytic reduction was examined, since Adkins and Reeve[8] reported that on reduction and subsequent hydrolysis ethyl O-ethyloximinoacetoacetate yielded a mixture of *dl*-threonine and *dl-allo*-threonine which was separated into its diastereomeric components by fractional crystallization from water and ethanol.

It was possible to reduce II in the presence of either Raney nickel or Adams catalyst so that hydrolysis of the intermediate hydroxy-ester led to a mixture of amino acids of approximately the same proportions of threonine and *allo*-threonine in each case. The fractional crystallization method of Adkins was used to separate the mixture into a more soluble fraction, m. p. 225–228°, and a less soluble fraction, m. p. 245–246°. The latter was largely *dl-allo*-threonine, since on benzoylation it gave a monobenzoyl derivative identical with that reported by Carter.[9] Some threonine could be separated from the soluble fraction by benzoylating and using β-phenethylamine according to the procedure of Carter,[10] but more than 75% of the crude hydrolysis mixture was recovered as substantially pure *dl-allo*-threonine. This method is a convenient one for preparing *dl-allo*-threonine since it is possible to obtain over-all yields of 43% based on ethyl acetoacetate via the catalytic reduction route and 41% by the somewhat shorter chemical reduction method.

Experimental[11]

Ethyl α-Oximinoacetoacetate (I).—The procedure of Adkins and Reeve[6] gave 75% yield when petroleum ether (b. p. 60–90°) was added to the toluene to decrease the solubility of the product.

Ethyl α-Acetamidoacetoacetate (II). A. Catalytic Reduction of Ethyl α-Oximinoacetoacetate.—One-tenth mole of ethyl α-oximinoacetoacetate was dissolved in a mixture of 50 ml. of acetic anhydride and 150 ml. of acetic acid, 1 g. of 5% palladium–charcoal catalyst[12] added and the mixture subjected to hydrogenation at 50 lb. pressure. After ninety minutes at room temperature the theoretical amount of hydrogen was absorbed. The catalyst and solvent were removed and the residual oil was triturated with petroleum ether (b. p. 60–90°). The crystalline solid thus obtained weighed 18.7 g. (yield quantitative). On crystallization from toluene at −15° it melted at 41–42°.

Anal. Calcd. for $C_8H_{13}NO_4$: N, 7.48. Found: N, 7.35.

When treated with 2,4-dinitrophenylhydrazine the ester yielded a yellow crystalline solid which melted at 199–200° after crystallization from ethanol. Analysis indicated that the derivative was a pyrazolone.

Anal. Calcd. for $C_{12}H_{11}N_5O_6$: N_{total}, 21.80: N_{NO_2}, 8.72. Found: N_{total}, 22.06; N_{NO_2}, 8.96 (by $TiCl_3$ reduction).

B. Reduction of Ethyl α-Oximinoacetoacetate with Zinc Dust.—To a cooled, well-stirred solution of 159 g. of ethyl α-oximinoacetoacetate in 250 ml. of acetic anhydride and 750 ml. of acetic acid, 275 g. of zinc dust was added portionwise during the course of thirty minutes. The temperature was kept at 40° by the addition of the metal. The suspension was stirred for an additional ten minutes and then 750 ml. of water was added at such a rate that the temperature remained at 40°. After stirring for an additional two hours the mixture was filtered and the filter cake washed with two 250-ml. portions of water. The filtrate was extracted with five 250-ml. portions of chloroform and the organic layer then washed with two 200-ml. portions of water. The chloroform was removed by distillation at 30 mm. pressure and the residue triturated with petroleum ether (b. p. 60–90°). The oil crystallized on cooling. The crystals were filtered and air dried, yield, 148 g., 79%, m. p. 47–49°. The dinitrophenylhydrazine derivative melted at 196–197°, undepressed on admixture with the sample prepared above.

C. From Ethyl Acetoacetate Directly.—The oximation of 64 ml. (0.5 mole) of ethyl acetoacetate was carried out according to the method of Adkins and Reeve[8] except that the mixture was not diluted with water. Instead 125 g. of ice and 100 ml. of acetic anhydride were added and the mixture was cooled in an ice-bath. During the course of one hour 125 g. of ice, 50 ml. of acetic anhydride and 65 g. of zinc dust were added to the stirred mixture, while the temperature was maintained below 20°. The product was isolated as in the previous experiment. The yield was 54–59% of the theoretical. When the amount of zinc was increased to 150 g., the yield increased to 71%. The product when recrystallized from acetone or ether melted at 47–49° and was identical with the compounds prepared by methods A or B.

D. From Ethyl Acetamidomalonate.—The ester, IV, was prepared by allowing a solution of 0.1 mole of ethyl-acetamidomalonate, 0.1 mole of potassium hydroxide in 50 ml. of water and 125 ml. of alcohol to stand for two days. The solvent was then removed, the residue partitioned between 50 ml. of chloroform and 20 ml. of water and the aqueous phase acidified with hydrochloric acid. The solid was collected on a filter, washed with ice water and air dried, m. p. 126–128° (d.).

Anal. Calcd. for $C_7H_{11}O_5N$: N, 7.40. Found: N, 7.15.

Nine and one-half grams of the above acid ester, IV, were slowly added to a mixture of 25 ml. of pyridine and 37 ml. of acetic anhydride with swirling. There was a yellow color produced immediately and carbon dioxide was evolved. The solution was allowed to stand overnight at room temperature and was then diluted with ice. The solvents were removed *in vacuo* to leave 9.2 g. of oil. This was distilled giving 6 g. of product boiling at 93–98° at approximately 1 mm. This product, m. p. 47°, was identical with the samples previously prepared.

When the pyridine and acetic anhydride were distilled from the reaction mixture without prior addition of ice the N-diacetylated compound was obtained as an oil. This gave the same derivative with 2,4-dinitrophenylhydrazine as the monoacetylated compound and could be converted to the monoacetylated compound by warming with sodium bicarbonate.

E. By Aluminum Amalgam Reduction.—Ten and three-tenths grams of Baker aluminum foil was amalgamated by the method of Vogel[13] and covered with 350 ml. of ether. A solution of 34.2 g. of acetyloximinoacetoacetic ester[2] and 35 ml. of acetic anhydride in 50 ml. of ether was dropped in over a ten minute period with simultaneous addition of 6 ml. of water. Two hours later an additional 10 ml. of water was added and the reaction allowed to

---

(7) Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 269.

(8) Adkins and Reeve, THIS JOURNAL, **60**, 1328 (1938).

(9) Carter, *et al.*, *J. Biol. Chem.*, **129**, 363 (1939).

(10) Carter and Risser, *ibid.*, **139**, 255 (1941).

(11) All m. p.'s are uncorrected.

(12) Mozingo, "Organic Syntheses," vol. 26, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 78D.

(13) Vogel, *J. Chem. Soc.*, 597 (1927).

stand overnight. It was then filtered and the insoluble material washed with ether. When several milliliters of the ether solution were shaken with an aqueous solution of ferric chloride the aqueous layer was colored a deep reddish purple color similar to that obtained with acetamidoacetoacetic ester prepared by the preceding methods.

The ether layer was dried and concentrated to give 17.7 g. of light orange oil. This gave a derivative with 2,4-dinitrophenylhydrazine melting at 201–202.5° and not depressed when mixed with the pyrazolone obtained from acetamidoacetoacetic ester. Nearly all of the oil distilled at 103–106° at 1 mm. and readily crystallized on cooling. It did not depress the m. p. of acetamidoacetoacetic ester prepared by other methods.

When the acetic anhydride was omitted in the above reaction no color with ferric chloride could be obtained and the only product which could be isolated was 2,5-dimethyl-3,6-dicarbethoxypyrazine. When five times as much aluminum was used and no acetic anhydride added, a small amount of *allo*-threonine (m. p. 249° after two recrystallizations from aqueous acetone) separated from the ether solution.

Ethyl α-Propionamidoacetoacetate.—Zinc dust reduction of α-oximinoacetoacetate in the presence of propionic acid and propionic anhydride gave α-propionamidoacetoacetate, m. p. 57° from acetone; b. p. 101–103° at slightly less than 1 mm.

Anal. Calcd. for $C_9H_{15}NO_4$: N, 6.96. Found: N, 7.14.

Ethyl α-Acetamido-α-(3-indolylmethyl)-acetoacetate (V).—To a solution of 0.58 g. of sodium in 50 ml. of absolute alcohol there were added in the order indicated 4.7 g. of ethyl α-acetamidoacetoacetate, 5.1 g. of diethylaminomethylindole and 4.7 ml. of methyl sulfate. The clear solution was warmed on a steam-bath and allowed to stand overnight. It was poured onto dilute acetic acid and the separated solid collected and air-dried, yield, 6.5 g. (83%), m. p. 152–154.5°. Crystallization from dilute ethanol raised the m. p. to 156–159°.

Anal. Calcd. for $C_{17}H_{10}O_4N_2$: N, 8.86. Found: N, 9.06.

Ethyl Aceturate.—To a solution of 1.6 g. of sodium in 40 ml. of ethanol was added 12.5 g. of acetamidoacetoacetic ester. The solution was warmed on a steam-bath. A precipitate started to form within several minutes and the solution darkened in color. After one hour the solution (strong odor of ethyl acetate) was poured onto crushed ice containing some acetic acid and the resulting solution extracted with chloroform. The product was distilled at 92–95° at about 0.5–1 mm. It melted at 44.5–47.5° (lit.[14] b. p. (2 mm.) 106°, m. p. 48°).

N-Acetyl-*dl*-tryptophan Ethyl Ester. (VI). A. From Ethyl Acetamido-(3-indolylmethyl)-malonate.—A mixture of 19.6 g. of ethyl acetamido-3-indolylmethylmalonate, 60 ml. of ethanol, 60 ml. of water and 3.2 g. of potassium hydroxide was allowed to stand at room temperature for two days. It was then concentrated *in vacuo* and partitioned between water (50 ml.) and chloroform. The water layer was acidified with 5 ml. of concentrated hydrochloric acid and the malonic acid collected and washed with water. It was decarboxylated at 160° and the residue taken up in chloroform and washed with 10% sodium carbonate solution and water. Removal of the chloroform gave crystals melting at 128–130°. Recrystallization from aqueous ethanol raised the m. p. to 133.5–135.5°.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: N, 10.21. Found: N, 10.20.

B. **From Ethyl α-Acetamido-α-(3-indolylmethyl)-acetoacetate.**—This reaction was similar to the preparation of aceturic ester except that the reaction mixture was refluxed for six hours and the product isolated by pouring onto ice and acetic acid and filtering. It proved to be identical with product "A" above.

dl-allo-**Threonine. A. Reduction with Raney Nickel Catalyst.**—A quantity of 319 g. of ethyl α-acetamidoacetoacetate in 500 ml. of alcohol was reduced at 1000 lb. pressure in the presence of approximately 10 g. of Raney nickel catalyst. The temperature rose to 68° in the course of the reaction, which was complete in ninety minutes. The catalyst was filtered off (filter-cel) and the solvent removed by distillation at 30 mm. pressure. There remained 315 g. of a colorless, viscous oil, $n^{25}D$ 1.4625. Concentrated hydrochloric acid (800 ml.) was added to this hydroxy ester and the mixture was heated under reflux for three and one-half hours before being concentrated to dryness *in vacuo*. One hundred milliliters of water was added and the mixture taken to dryness again. The crude mixture of hydrochlorides was dissolved in 300 ml. of water in which 70 g. of sodium hydroxide had been dissolved. The solution was made faintly acid to litmus with acetic acid, cooled to 10° and then filtered to yield 85 g. of crude *dl-allo*-threonine, m. p. 245–246°. The mother liquor was diluted with 500 ml. of alcohol and then set in ice for several hours. The crystals that separated were collected on a filter and dried, wt. 70 g., m. p. 225–228°.

The more soluble fraction was then taken up in 150 ml. of hot water, filtered (charcoal) and diluted with 200 ml. of alcohol. On cooling 14 g. more of the *allo* isomer, m. p. 245–248°, separated. The filtrate from this crop was concentrated to dryness and the crystallization repeated several times more. In this way it was possible to obtain a total of 40 g. of the higher-melting compound from the original, more soluble fraction. The crude crops were combined and recrystallized from aqueous ethanol to yield 117 g. of *dl-allo*-threonine, m. p. 251–252° (yield, 58%).

No *dl*-threonine could be isolated directly from the low-melting residue.

In another experiment the low-melting solid from the initial separation was benzoylated according to Carter's method.[9] The crude monobenzoate, m. p. 159–165°, was crystallized several times to raise the m. p. to 172–174°. The substance did not depress the m. p. of an authentic specimen of monobenzoyl-*dl-allo*-threonine. A sample of *dl*-threonine gave a monobenzoate, m. p. 147°, in agreement with the value reported by Carter.

B. **Reduction with Adams Catalyst.**—When 18.7 g. of ethyl α-acetamidoacetoacetate in 100 ml. of acetic acid was reduced in the presence of 0.3 g. of Adams catalyst, the theoretical amount of hydrogen was absorbed in six hours at room temperature. Removal of the catalyst and evaporation of the solvent left 18.9 g. of the hydroxy ester, $n^{25}D$ 1.4625. Hydrolysis and crystallization by the procedure described above gave 6.9 g. (55%) of pure *dl-allo*-threonine, m. p. 251–252°.

Summary

1. Ethyl α-acetamidoacetoacetate was prepared from ethyl α-oximinoacetoacetate by (a) reduction with hydrogen in the presence of palladium on charcoal in acetic acid–acetic anhydride solution, (b) reduction with zinc dust in acetic acid–acetic anhydride solution, and (c) reduction with aluminum amalgam in the presence of acetic anhydride. In addition it was prepared directly from acetoacetic ester and also from ethyl hydrogen acetamidomalonate by reaction with pyridine and acetic anhydride.

2. Alkylation of ethyl α-acetamidoacetoacetate with diethylaminomethylindole methosulfate gave ethyl α-acetamido-α-(3-indolylmethyl)-acetoacetate. Attempted alkylation with benzyl chloride resulted only in the formation of aceturic ester which was also produced when ethyl α-acetamidoacetoacetate was treated with sodium ethylate.

---

[14] Cherbuliez and Plattner, *Helv. chim. acta*, **12**, 320 (1929).

3. Reduction of ethyl α-acetamidoacetoacetate with either Raney nickel or Adams catalyst afforded, after hydrolysis, *dl-allo*-threonine in 55–58% yield. No *dl*-threonine could be isolated directly.

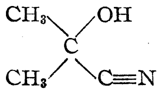
Rensselaer, New York Received September 16, 1947

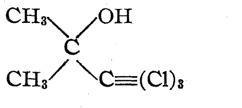
[Contribution from the Grosvenor Laboratory]

The Synthesis of α-Alkoxyisobutyric Acids and Alkyl Methacrylates from Acetonechloroform

By Ch. Weizmann, M. Sulzbacher and E. Bergmann

From the similarity of acetonecyanohydrin and acetonechloroform the latter appears a possible





starting material for the preparation of α-hydroxy-isobutyric and methacrylic acid. Equally, its analogs and homologs could be used for the synthesis of the analogs and homologs of these acids.

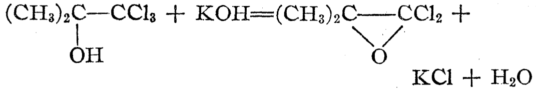
Literature data regarding the hydrolysis of acetonechloroform and similar compounds are scanty and contradictory: the formation of α-hydroxy-,[1] α-chloro-isobutyric acid and methacrylic acid,[2] *e. g.*, has been observed from acetonechloroform,[3,4] but most of the latter suffers undefined decomposition to acetone, carbon monoxide, phosgene and formic acid.[5]

When acetonechloroform is treated with a solution of four moles of potassium hydroxide or sodium butoxide in *butyl alcohol* at 0°, a vigorous reaction takes place; the alkaline reaction disappears, potassium (or sodium) chloride precipitates in the expected quantity, and the salt of a monobasic acid $C_8H_{16}O_3$ is formed which was identified as *α-butoxy-isobutyric acid.* Every alcohol investigated has given the same reaction which can be formulated as

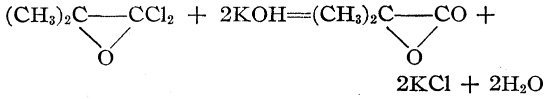
$$(CH_3)_2C(OH)CCl_3 + 4KOH + ROH = (CH_3)_2C(OR)COOK + 3KCl + 3H_2O$$

As it is surprising that under these conditions a tertiary alcoholic hydroxyl group should be alkylated, the following mechanism is suggested

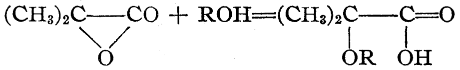
(A)



(B)

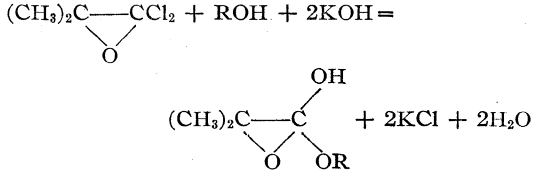


(C)

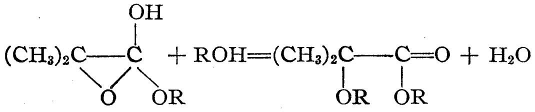


Analogously, the product of step (A) can be attacked by the alcohol ROH

(B′)

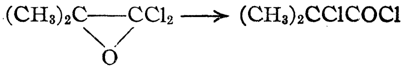


(C′)



Such esters, indeed, in which the alkyl radicals of the ester and of the ether group are identical, have been observed as by-products.[6]

The intermediary formation of an ethylene oxide from such trichlorinated alcohols and alkaline reagents has already been assumed by Jozicz[4] in order to explain the formation of α-chloroacids in the hydrolysis; this would be due to a pinacolonic re-arrangement, *e. g.*



One might be tempted to assume that the α-alkoxy acids in the above synthesis are formed through the intermediate of these α-chloroacids; however, the high yields obtained would imply that the rearrangement proceeds almost quantitatively, which is unlikely. Moreover, one would rather expect α-chloroacids of such structure to give the corresponding unsaturated acids, upon treatment with alcoholic potassium hydroxide. Methyl methacrylate does not add alcohols under the experimental conditions employed here.

That the acids obtained are actually the α- and not the isomeric β-alkoxy-compounds, can be

---

(1) Willgerodt and Schiff, *J. prakt. Chem.*, [2] **41**, 519 (1890).

(2) Ostropjatow, *Ber.*, **29**, Ref. 908 (1896).

(3) The observations of Thomas and Oxley (British Patent 505,103 (1937) *C. A.* **33**, 7821 (1939)) could not be confirmed; they are theoretically most unlikely.

(4) Trichloromethyl-phenylcarbinol: Jozicz, *Chem. Zentrl.*, **68**, I, 1013 (1897). Rapson, Saunder and Stewart, *J. Chem. Soc.*, **74** (1944). It is doubtful whether the trichloromethylisopropylcarbinol studied by Jozicz actually had that structure; see Howard, This Journal, **49**, 1068 (1927).

(5) Compare Bressanin and Segre, *Gazz. chim. ital.*, **41**, I, 671 (1911). See also Peser, *C. A.*, **42**, 514 (1948).

(6) The opening of lactone rings by alcohols to form alkoxy acids is not without analogies. See F. E. Küng, U. S. Patent 2,352,641 (*C. A.*, **38**, 5500 (1944)). We owe this observation to one of the Referees. Compare also Aston and Greesburg, This Journal, **62**, 2590 (1940).

concluded from the observation that trichloromethylphenylcarbinol gives α-alkoxyphenylacetic acids. In this case, no β-alkoxylation is possible.

Primary alcohols give higher yields in alkoxyacids than secondary, secondary higher ones than tertiary alcohols in the reaction with acetonechloroform. The reaction is, also, not specific for acetonechloroform, but is applicable to its homologs and analogs. A number of examples are given in the Experimental Part.

"De-alkoxylation" of the α-alkoxyisobutyric acids to methacrylic acid is best carried out by heating the esters with the equivalent amount of phosphorus pentoxide. Oxalic acid and zinc chloride cause the same transformation with a lower rate of conversion and somewhat lower yield. Heating with anilinium hydrobromide is without effect on the alkoxyesters. Heating with alcoholic sulfuric acid also causes de-alkoxylation; therefore, frequently in the esterification of the alkoxyacids, some alkyl methacrylate is formed, and its quantity increases with increasing stringency of the conditions of esterification. The alkoxyacids containing secondary alkyl radicals are more easily converted into unsaturated compounds, and in the case of *t*-alkyl compounds, no alkoxy ester has been isolated from the esterification with alcoholic sulfuric acid.

The alkoxyacids are fairly stable; they are viscous liquids which can be characterized by crystalline derivatives, *e. g.*, the phenylhydrazides. Amides are best prepared from the esters; thus α-methoxyisobutyr-(β-hydroxyethyl)-amide was synthetized. An attempt to prepare the acid chlorides in pure state failed; however, the crude chlorides, obtained by means of thionyl chloride, can be used for the preparation of such substances as *phenyl α-butyoxyisobutyrate;* in this reaction, however, and still more in the preparation of phenyl α-isobutyoxyisobutyrate, substantial quantities of phenyl methacrylate were formed. This is somewhat surprising as the α-acyloxyisobutyric acids can easily be converted into the corresponding acid chlorides.[7]

An interesting parallel to our reaction is to be seen in the observation by Banti[8] that in presence of alcoholic potassium hydroxide solution, acetonechloroform and aniline give an anilinoisobutyric acid, m. p. 185°, or its anilide, m. p. 155–157°. The anilino-anilide (m. p. 122°) which is formed from methacrylic acid or methacrylanilide and aniline at 190°[9] is undoubtedly the β-anilino-compound, Banti's anilide, therefore, the α-anilino-anilide, also formed from α-bromoisobutyrylanilide and aniline at low temperature.[10,11]

Experimental

The experiments in the **α-methoxyisobutyric acid** series are described in detail; the analogous ones with its homologs are summarized in the tables.

To a cold and vigorously stirred solution of 448 g. of potassium hydroxide in 250 cc. of water and 1000 cc. of methyl alcohol, which was contained in a three-necked flask, fitted with mercury-sealed stirrer, reflux condenser and dropping funnel, a solution of 355 g. of acetonechloroform in 700 cc. of methyl alcohol was slowly added. The violent reaction, which was accompanied by the precipitation of potassium chloride, was checked by energetic cooling. The mixture was stirred for one hour at room temperature and then for two hours at boiling temperature. The inorganic salt was filtered off and washed with methyl alcohol (441 g., calcd. 447.1 g.).

The clear filtrate was freed from methyl alcohol at ordinary pressure and from most of the water *in vacuo*, and the residue was treated with a slight excess of dilute sulfuric acid (congo red). The inorganic precipitate was filtered, thoroughly washed with ether and the aqueous solution extracted with the same solvent. The residue of the combined and dried extracts distilled at 98–99° (20 mm.); yield, 167 g. (70.8%).[12,13] The same result is obtained when instead of aqueous-methanolic potassium hydroxide solution, methyl alcoholic sodium methoxide is used.

Anal. Calcd. for $C_5H_{10}O_3$: C, 50.8; H, 8.5; OCH_3, 26.3; mol. wt., 118. Found: C, 50.5; H, 8.6; OCH_3, 25.9; mol. wt., 117 (by titration).

Phenylhydrazide from 3 g. of the acid and 3.5 g. of phenylhydrazine at 120° (two hours): the melt solidified upon cooling. The product crystallized from boiling water in needles of m. p. 103°.

Anal. Calcd. for $C_{11}H_{16}O_2N_2$: C, 63.5; H, 7.7; N, 13.5; OCH_3, 14.9. Found: C, 63.2; H, 7.9; N, 13.2; OCH_3, 14.6.

Methyl Ester.—The solution of 118 g. of α-methoxyisobutyric acid in 125 cc. of methyl alcohol, containing 25 cc. of concentrated sulfuric acid, was refluxed for twelve hours. The excess of methyl alcohol was distilled off and the cold residue poured into the double volume of concentrated brine. The ester layer, which separated, was washed again with an equal volume of brine and dried over calcium chloride; b. p. 134–135° (lit. 144.8–145° (767 mm)); yield, 105 g. (79.6%). The use of larger quantities of sulfuric acid produced a dark resinous by-product.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.5; H, 9.1; OCH_3, 47.0. Found: C, 54.1; H, 9.2; OCH_3, 46.9.

Methacrylates from α-Methoxyisobutyric Acid.—(a) A mixture of 39.6 g. of methyl α-methoxyisobutyrate and 30 g. of phosphorus pentoxide was heated in the presence of some hydroquinone for two hours. The liquid was directly distilled off from the brown resinous mass and redistilled. The methyl methacrylate boiled at 99–100°; yield, 28.4 g. (95%).

(b) A mixture of 39.6 g. of methyl α-methoxyisobutyrate and 20 g. of freshly fused zinc chloride was heated in presence of some hydroquinone for two hours. Fractional distillation in a Widmer column gave: b. p. 98–102°, methyl methacrylate, 18.0 g. (60%); b. p. 130–135°, methyl α-methoxyisobutyrate, 8.0 g. (20.4% of initial amount).

(c) A mixture of 39.6 g. of methyl α-methoxyisobutyrate and 30 g. of anhydrous oxalic acid was heated in the

---

(7) Blaise, *Compt. rend.*, **154**, 1087 (1912); **155**, 47 (1913); **175**, 1216 (1922); **176**, 1148 (1923); *Bull. soc. chim.*, [4] **15**, 666 (1914); Blaise and Herzog, *Compt. rend.*, **184**, 1332 (1927), and further publications.

(8) Banti, *Gazz. chim. ital.*, **59**, I, 819 (1929).

(9) Autenrieth and Pretzel, *Ber.*, **36**, 1262 (1903); Autenrieth, *ibid.*, **38**, 2534 (1905).

(10) Compare the formation of α-anilinoisobutyronitrile (reduction to isopropylaniline) from acetonecyanohydrin and aniline: Bucherer and Grolée, *Ber.*, **39**, 990 (1906). See Mulder, *Rec. trav. chim.*, **26**, 181 (1907); Bucherer, German Patent 157,710 (*Chem. Zentr.*, **76**, I, 415 (1905); v. Walther and Huebner, *J. prakt. Chem.*, [2] **93**, 126 (1916).

(11) Ethyl α-bromoisobutyrate and aniline give at 160° the esters of both the isomeric anilinoisobutyric acids: Bischoff and Mintz, *Ber.*, **25**, 2326 (1892).

(12) The acid had been prepared before by Barker and Skinner, THIS JOURNAL, **46**, 407 (1924); b. p. 81.5–83° (8–9 mm.).

(13) Compare Madsen, *Z. physik. Chem.*, **92**, 107 (1918).

TABLE I

α-ALKOXYISOBUTYRIC ACIDS

Acetone chloroform, g.	ROH, R	Cc.	Alkali[a]	G.	Acid formed, -butyric	Formula	B. p., °C.	Mm.	Yield, g.	%	Carbon, %		Hydrogen, %		Mol. wt.	
											Calcd.	Found	Calcd.	Found	Calcd.	Found[b]
35.5	Ethyl	350	$NaOC_2H_5$	54.4	α-Ethoxyiso-[14,15,16]	$C_6H_{12}O_3$	97	19	18.5	70.1[c]	54.5	53.9	9.1	9.0	132	131
35.5	Ethyl	200	KOH	45	α-Ethoxyiso-	$C_6H_{12}O_3$	99	20	18.0	68.2					132	131
35.5	Butyl	350	$NaOC_4H_9$	76.8	α-Butoxyiso-	$C_8H_{16}O_3$	121	20	23.0	71.9	60.0	59.8	10.0	9.8	160	158
35.5	Butyl	400	KOH	45	α-Butoxyiso-	$C_8H_{16}O_3$	111	8	25.0	78.1					160	159
177.5	Isobutyl	1220	KOH	224	α-Isobutoxyiso-[17]	$C_8H_{16}O_3$	116	20	98.0	61.2	60.0	59.7	10.0	10.0	160	160
177.5	Isobutyl	1250	KOH	250	α-Isobutoxyiso-	$C_8H_{16}O_3$	116	20	120.0	75.0					160	159
71.0	2-Ethylhexyl	600	KOH	90	α-(2-Ethylhexoxy)-iso-	$C_{12}H_{24}O_3$	133	4	61.0	70.5[d]	66.6	67.0	11.1	11.2	216	214
88.7	Dodecyl[e]	700	KOH	112	α-Dodecoxyiso-	$C_{16}H_{32}O_3$	200	16	32.0	23.5[f]	70.5	70.4	11.8	11.3	272	278
88.7	Allyl[g]	430	KOH	112	α-Allyloxyiso-	$C_7H_{12}O_3$	115	22	50.0	69.4	58.3	58.5	8.3	8.6	144	145
35.5	2-Ethoxyethyl	250	KOH	45	α-(2-Ethoxyethoxy)-iso-	$C_8H_{16}O_4$	136	12	17.0	48.3	54.6	55.0	9.1	9.6	176	170
71.0	2-Butoxyethyl	540	KOH	90	α-(2-Butoxyethoxy)-iso-	$C_{10}H_{20}O_4$	140	5	44.0	50.0	58.8	58.6	9.8	10.3	204	200
44.5	2-Ethoxyethoxyethyl	230	KOH	56	α-(2-Ethoxyethoxyethoxy)-iso-	$C_{10}H_{20}O_5$	178	12	9.0	16.3	54.5	54.5	9.1	8.9	220	216
88.7	Isopropyl	1000	KOH	112	α-Isopropoxyiso-	$C_7H_{14}O_3$	106	15	32.0	43.8	57.5	57.8	9.6	9.9	146	145
88.7	*t*-Amyl	650	KOH	112	α-*t*-Pentoxyiso-	$C_9H_{18}O_3$	115	20	17.5	20.1	62.1	62.5	10.4	10.6	174	172

[a] The quantities of potassium hydroxide are "pure KOH." The technical product, containing about 13% of water, was used. [b] By titration. [c] The crude product contained a small amount of ethyl ester, which was removed by treatment with soda solution and extraction with ether. Re-acidification gave the pure acid. Calcd.: OC_2H_5 34.1. Found: 33.9. [d] Small quantities of 2-ethylhexyl α-2-ethylhexoxyisobutyrate of b. p. 168° (4 mm.) were isolated. When the reaction was brought to completion at 130° (instead of 100°) and the crude product extracted with ether, before acidification, one third of the total reaction product consisted of that ester. [e] The reaction was begun at 35° and completed at 70°. [f] Besides the acid, 38 g. (17.3%) of dodecyl α-dodecoxyisobutyrate of b. p. 276° (15 mm.) were isolated. [g] The reaction was started at 0° and completed at room temperature.

TABLE II

α-ALKOXY ACIDS

Chlorinated alcohol	G.	ROH, R	Cc.	Alkali	G.	Acid formed	Formula	B. p. °C.	Mm.	Yield, G.	%	Carbon, %		Hydrogen, %		Mol. wt.,	
												Calcd.	Found	Calcd.	Found	Calcd.	Found
Methyl ethyl ketone chloroform	96	Isobutyl	800	KOH	112	α-Isobutoxymethyl ethyl acetic	$C_9H_{18}O_3$	123	20	54.0	62.1	62.1	62.5	10.4	10.6	174	177
Cyclohexanone-chloroform	109	Isobutyl	800	KOH	112	1-Isobutoxycylcohexanecarboxylic	$C_{11}H_{20}O_3$	165	30	61.0	61.0	66.0	66.4	10.0	10.2	200	211
2-Ethylhexanal-chloroform	111	Isobutyl	800	KOH	101	2-Isobutoxy-2-ethylheptoic	$C_{13}H_{26}O_3$	172	20	59.5	57.4	67.8	68.0	11.3	11.7	230	232

presence of some hydroquinone for two hours. The liquid product was directly fractionated: b. p. 98–102°, methyl methacrylate, 10.0 g. (33.3%); b. p. 130–135°, methyl α-methoxyisobutyrate, 24.0 g. (60.6% of initial amount).

(d) When the amount of oxalic acid was doubled, the yield in methyl methacrylate rose to 13.0 g. (43.4%).

(e) **(β-Butoxyethyl) Methacrylate.**—A mixture of 32 g. of α-methoxyisobutyric acid with 120 cc. of butyl cellosolve and 10 cc. of concd. sulfuric acid was heated at 130° in presence of tannic acid for twelve hours. The reaction product was poured into water (in which butyl cellosolve and the methoxyacid are soluble) and the supernatant ester layer extracted with ether. (β-Butoxyethyl) methacrylate boiled at 122° under 12 mm. pressure; yield, 48 g. (80%). A small head fraction, b. p. 69–70° (13 mm.), was identified as butyl methacrylate. No ester of α-methoxyisobutyric acid was observed.

Table I lists the homolog α-alkoxyisobutyric acids, prepared from acetonechloroform.

The **phenylhydrazide of α-ethoxyisobutyric acid** was prepared, as described for the methoxy compound. It boiled at 195–200° (24 mm.) and solidified upon cooling. From dilute alcohol or isoöctane it crystallized in prisms, m. p. 84°.

Anal. Calcd. for $C_{12}H_{18}O_2N_2$: C, 64.1; H, 8.9; N, 12.6; OC_2H_5, 20.3. Found: C, 64.9; H, 7.9; N, 12.7; OC_2H_5, 19.9.

The **phenylhydrazide of α-butoxyisobutyric acid** boiled at 210° (24 mm.) and crystallized from petroleum ether in form of needles, m. p. 108–109°.

Anal. Calcd. for $C_{14}H_{22}O_2N_2$: C, 67.2; H, 8.8; N, 11.2. Found: C, 67.0; H, 8.7; N, 11.0.

Table II summarizes the preparation of analogous α-alkoxy acids from chlorinated alcohols.

The experiment, leading from trichloromethylphenylcarbinol (benzaldehydechloroform) to **α-methoxyphenylacetic** acid, is described in detail.

A solution of 56.4 g. of benzaldehydechloroform[18] in

---

(14) See Bischoff, *Ber.*, **32**, 1758 (1899); Schreiner, *ibid.*, **12**, 179 (1879).

(15) Hell and Waldbauer, *ibid.*, **10**, 448 (1877).

(16) Blaise and Picard, *Bull. soc. chim.*, [4], **11**, 587 (1922).

(17) Prepared before from iodoform and sodium isobutoxide (b. p. 141–144° (34 mm.)); Gorbow and Kessler, *Ber.*, **20**, ref. 776 (1887).

(18) Prepared from chloral and benzene in the presence of aluminum chloride (b. p. 145° (15 mm.); m. p. 37°); Dinesmann, *Compt. rend.*, **141**, 201 (1905).

TABLE III

ESTERS OF α-ALKOXYISOBUTYRIC ACIDS

$(CH_3)_2C(OR)COOH$ R	G.	R'OH R'	Cc.	H_2SO_4 conc., cc.	Temp. °C.	Time, hr.	Product, -isobutyrate	Formula	B. p. °C.	B. p. Mm.	Yield, G.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen % Calcd.	Hydrogen % Found
Ethyl	79.2	Ethyl	90	15	Reflux	13	Ethyl α-ethoxy-	$C_8H_{16}O_3$	55	13	84.0	87.5[a]	60.0	59.8	10.0	9.9
Butyl	160.0	Methyl	200	2	Reflux	20	Methyl α-butoxy-	$C_9H_{18}O_3$	60	6	130.5	75.0	62.1	62.1	10.4	10.8
Butyl	32.0	Butyl	50	6	Reflux	12	Butyl α-butoxy-	$C_{12}H_{24}O_3$	218	760	33.6	77.7[b]	66.6	66.2	11.2	11.0
Butyl	40.0	2-Ethoxyethyl	120	0.5	110	5	2-Ethoxyethyl α-butoxy-	$C_{12}H_{24}O_4$	122	13	46.0	80.0[c]	62.1	62.2	10.3	10.6
Butyl	40.0	2-Ethoxyethoxyethyl	180	0.5	110	5	2-Ethoxyethoxyethyl α-butoxy-	$C_{14}H_{28}O_5$	152	12	42.0	62.0[d]	60.9	61.2	10.1	10.4
Butyl	30.0	2-Butoxyethoxyethyl	130	0.4	110	5	2-Butoxyethoxyethyl α-butoxy-	$C_{16}H_{32}O_5$	176	11	48.0	90.0	63.2	63.5	10.5	10.8
Isobutyl	64.0	Butyl	200	2	Reflux	12	Butyl α-isobutoxy-	$C_{12}H_{24}O_3$	103	12	65.0	75.2	66.6	66.6	11.2	11.0
Isobutyl	80.0	Isobutyl	125	20	Reflux	13	Isobutyl α-isobutoxy-	$C_{12}H_{24}O_3$	204	760	77.0	71.2[e]	66.6	66.4	11.2	11.1
Isobutyl	128.0	2-Ethylhexyl	360	40	130	10	2-Ethylhexyl α-isobutoxy-	$C_{16}H_{32}O_3$	115	13	44.0	20.0[f]	70.6	70.4	11.8	11.7
2-Ethylhexyl	100.0	Butyl	230	2	Reflux	20	Butyl α-2-ethylhexoxy-	$C_{16}H_{32}O_3$	155	10	110.0	87.3	70.6	70.8	11.8	11.7
2-Ethylhexyl	...	See Table I Note *d*			....	..	2-Ethylhexyl α-2-ethylhexoxy-	$C_{20}H_{40}O_3$	168	4	...	...	73.0	72.5	12.2	11.4
2-Ethylhexyl	40.0	*n*-Dodecyl	120	1	120	24	Dodecyl α-2-ethyl-hexoxy-	$C_{24}H_{48}O_3$	232	10	61.1	86.0[g]	75.0	74.7	12.5	13.1
n-Dodecyl	...	See Table I Note *f*			....	..	Dodecyl α-dodecoxy	$C_{28}H_{56}O_3$	276	15	...	...	76.4	76.8	12.8	12.6
Allyl	28.8	Allyl	50	3	Reflux	6	Allyl α-allyloxy-	$C_{10}H_{16}O_3$	190	760	25.5	69.3[h]	65.2	65.4	8.9	8.7
2-Ethoxyethyl	22.0	2-Ethoxyethyl	60	0.3	110	5	2-Ethoxyethyl α-2-ethoxyethoxy-	$C_{12}H_{24}O_5$	138	12	24.0	77.5	58.1	58.5	9.7	10.1
2-Ethoxyethyl	23.0	2-Ethoxyethoxyethyl	90	0.3	120	5	2-Ethoxyethoxyethyl α-2-ethoxyethoxy-	$C_{14}H_{28}O_6$	163	12	25.0	65.5	57.5	57.1	9.6	9.8
Isopropyl	29.2	Butyl	50	10	Reflux	10	Butyl α-isopropoxy-	$C_{11}H_{22}O_3$	181	760	7.0	17.3[i]	65.3	65.5	10.9	10.9

[a] 6.9 g. (10.0%) of ethyl methacrylate was formed. [b] 6.0 g. (21.1%) of butyl methacrylate was formed. With 10 cc. of sulfuric acid, the quantity of butyl methacrylate rose to 18.0 g. (63.3%) while that of the butoxy ester decreased to 15.2 g. (35.2%). [c] The same result was obtained by ester interchange reaction when methyl α-butoxyisobutyrate was heated with ethyl cellosolve in a column until no more methanol distilled over. [d] The same result was obtained by ester interchange reaction between methyl α-butoxyisobutyrate and ethyl carbitol. [e] 8.5 g. (12.0%) of isobutyl methacrylate was formed. [f] 112.0 g. (70.0%) of 2-ethylhexyl methacrylate was formed. [g] The ester solidified slightly below room temperature and could be recrystallized by precipitation of its acetonic solution with alcohol. [h] 5.1 g. (20.2%) of allyl methacrylate was formed. This was resinified when the heating time and the amount of sulfuric acid were doubled; under these conditions, only 18.4 g. (50.0%) of allyl α-allyloxyisobutyrate was obtained. [i] 21.0 g. (73.9%) of butyl methacrylate was formed. This tendency of de-alkoxylation is still more outspoken for α-*t*-pentoxyisobutyric acid which (17.4 g.) with butyl alcohol (30 cc.) in presence of concentrated sulfuric acid (6 cc.) gave only butyl methacrylate (90.1%).

100 cc. of methanol was slowly added to a solution of 56 g. of potassium hydroxide in 200 cc. of methanol, the temperature being maintained at about 45°. The mixture was stirred for one hour at boiling temperature, allowed to cool and filtered from potassium chloride (56 g.). The clear solution was evaporated *in vacuo*, and the residue was treated with a slight excess of dilute sulfuric acid. The oily layer was separated and combined with the ether extract of the aqueous solution. α-Methoxyphenylacetic acid of b. p. 165° (18 mm.) and m. p. 72° (from ligroin) was obtained in a yield of 30 g. (72.2%).

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.1; H, 6.0; OCH_3, 18.7. Found: C, 65.3; H, 6.2; OCH_3, 18.6.

The esters of the α-alkoxyisobutyric acids are listed in Table III. They were prepared by direct esterification of the acids with an excess of the alcohols in the presence of a small quantity of concentrated sulfuric acid as catalyst and of about 0.5% of tannic acid as polymerization inhibitor. It is, however, not necessary to isolate the α-alkoxyacids for the preparation of these esters. The following example shows that the same ultimate yields can be obtained without such isolation.

The solution obtained from 156.8 g. of potassium hydroxide in 750 cc. of butyl alcohol and 124.2 g. of acetonechloroform in 250 cc. of butyl alcohol (0°, two hours), and filtered from the potassium chloride (154.0 g.) formed, was acidified with concentrated sulfuric acid at 0° (congo red) and filtered again. The filtrate, containing the free α-butoxyisobutyric acid, was boiled with 50 cc. of concentrated sulfuric acid, 5 g. of tannic acid and 300 cc. of carbon tetrachloride (azeotropic distillation). After nine hours, the amount of water liberated became negligible. The greater part of the organic solvents was distilled off and the residue washed with water, 20% sodium carbonate solution and water, and dried. Fractional distillation gave three fractions: butyl alcohol, butyl methacrylate (20.0 g., 20.1%) and butyl α-butoxyisobutyrate (70.0 g., 46.3%).

The esterification of 52.2 g. of α-isobutoxymethylethylacetic acid with 80 cc. of isobutanol in the presence of 14 cc. of concentrated sulfuric acid gave 54.0 g. (78.2%) of isobutyl-α-isobutoxy methylethylacetate of b. p. 220° and 5.7 g. (12.2%) of isobutyl tiglate.

The esterification of 50.0 g. of 1-isobutoxycyclohexane-

TABLE IV

UNSATURATED ESTERS

Starting material	Conditions	Unsaturated ester	Yield, %	B. p. °C.	B. p. Mm.	Remarks
Ethyl α-ethoxyisobutyrate	P_2O_5, 80°, 2 hr.	Ethyl methacrylate	90.0	120	760	See Table III, note *a*
Butyl α-butoxyisobutyrate	P_2O_5, 60°, 1 hr.	Butyl methacrylate	100.0	160	760	See Table III, notes *b*, *i*
Butyl α-isopropoxyisobutyrate	P_2O_5, 60°, 1 hr.	Butyl methacrylate	95.0	160	760	
Isobutyl α-isobutoxyisobutyrate	P_2O_5, 60°, 1 hr.	Isobutyl methacrylate[19]	91.0	56	18	See Table III, note *e*
2-Ethylhexyl α-isobutoxyisobutyrate	P_2O_5, 100°, 2 hr.	2-Ethylhexyl methacrylate[20]	90.0	120	18	See Table III, note *f*
Methyl methacrylate	2-Ethylhexanol, 1% H_2SO_4, column	2-Ethylhexyl methacrylate	75.0	120	18	Alkyl exchange
Methyl methacrylate	Ethylcellosolve, 1% H_2SO_4, column	2-Ethoxyethyl methacrylate[19]	75.0	70	22	Alkyl exchange
Methyl methacrylate	Butylcellosolve, 1% H_2SO_4, column	2-Butoxyethyl methacrylate	76.0	112	15	Alkyl exchange
Allyl α-allyloxyisobutyrate	P_2O_5, 60°, 1 hr.	Allyl methacrylate[21]	90.0	82	17	See Table III, note *h*
Methyl methacrylate	Diethylamino ethanol, 1% Na, column	β-Diethlaminoethyl methacrylate[22]	40.0	112	25	Alkyl exchange
Isobutyl α-isobutoxy-methylethylacetate	P_2O_5, 70°, 1 hr.	Isobutyl tiglate	95.0	180	760	See also esterification of acids
Isobutyl 1-isobutoxycyclohexanecarboxylate	P_2O, 100°, 2 hr.	Isobutyl 1-cyclohexenecarboxylate	85.0	140	28	
Isobutyl 2-isobutoxy-3-ethylheptoate	P_2O_5, 100°, 2 hr.	Isobutyl 3-ethyl-2-heptenoate	85.0	135	20	

carboxylic acid with 100 cc. of isobutanol and 15 cc. of concentrated sulfuric acid gave 18.5 g. (28.9%) of isobutyl 1-isobutoxycyclohexanecarboxylate of b. p. 154° (28 mm.) and 32 g. (70.3%) of isobutyl 1-cyclohexenecarboxylate.

The esterification of 46.0 g. of 2-isobutoxy-3-ethylheptoic acid with 100 cc. of isobutanol and 15 cc. of concentrated sulfuric acid gave 42.0 g. (73.4%) of isobutyl 2-isobutoxy-3-ethylheptoate of b. p. 155° (23 mm.) and 8.5 g. (20.0%) of isobutyl-3-ethyl-2-heptenoate.

The unsaturated esters, mainly methacrylates, encountered in this investigation, are listed in Table IV. It includes some esters of methacrylic acid which have not been prepared through the intermediary of α-alkoxyisobutyric esters but through alkyl exchange with methyl methacrylate.

In order to identify the unsaturated ester from isobutyl α-isobutoxymethylethylacetate, a sample was saponified with methyl alcoholic potassium hydroxide solution. The free acid obtained distilled at 197–203°, solidified and had m. p. 60°. These constants point to **tiglic acid** for which the literature records m. p. 65° and b. p. 199°.

When a carbon disulfide solution of the acid was kept for three days in the sunlight with a slight excess of bromine, an oily dibromide was formed which was brought to crystallization by the following treatment: dissolution in sodium carbonate solution, extraction with ether, acidification, re-extraction with carbon disulfide and evaporation, m. p. 85°.[23]

Of course, under these experimental conditions, angelic acid would also give the dibromide of its *trans*-isomer tiglic acid. The m. p. of the dibromide, however, excludes the possibility that the unsaturated ester formed was isobutyl α-ethyl-acrylate. The m. p. of the dibromide of α-ethylacrylic acid is 75°.[24]

α-Butoxy-isobutyryl Chloride and its Esterification with Phenol.—To a solution of 32 g. of freshly distilled α-butoxyisobutyric acid in 25 cc. of dry chloroform, 25 g. of thionyl chloride was slowly added, and the solution was kept at 18° during sixteen hours. After this time, the gas development had practically ceased. The weight increase of a trap showed that hydrogen chloride and sulfur dioxide had been liberated in a quantity of about 97%. The reaction mixture was a clear, brown liquid.

At 0°, a solution of 19.7 g. of phenol in 40 cc. of pyridine was added gradually. After twenty-four hours at room temperature, the product was diluted with 50 cc. of benzene, washed with water, dilute sulfuric acid and cold sodium hydroxide solution, and dried. The solvent was removed and the residue distilled under 20 mm. pressure in presence of hydroquinone. The liquid boiled, practically without residue, between 90 and 145°. It consisted of (a) b. p. 95–100° (16 mm.), phenyl methacrylate,[19] 10 g. (30.9%); (b) b. p. 138–140° (14 mm.), **phenyl α-butoxyisobutyrate**, 20 g. (42.4%).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.2; H, 8.5. Found: C, 71.4; H, 8.7.

When the same reaction was carried out with 32 g. of α-isobutoxyisobutyric acid, 26 g. (80.2%) of phenyl methacrylate was the only product.

Aminolysis of Methyl α-Methoxyisobutyrate with Ethanolamine.—A mixture of 27.7 g. of methyl α-methoxyisobutyrate and 12.2 g. of monoethanolamine was heated on the steam-bath. After about fifteen minutes, it homogenized, and gentle refluxing (methyl alcohol) started. After three hours, the reaction was not yet quite complete, and fractional distillation gave: at 30–35° (10 mm.), methyl α-methoxyisobutyrate, 8.0 g. (28.7% of the initial quantity); at 63–70° (10 mm.), ethanolamine, 3.0 g. (24.5% of the initial quantity) and at 150–152° (16 mm.), **α-methoxyisobutyr-(β-hydroxyethyl)-amide**, 24.0 g. (74.5%).

The amide is a colorless, highly viscous oil which solidifies to a white crystalline mass at 0°.

Anal. Calcd. for $C_7H_{15}O_3N$: C, 52.1; H, 9.3; N, 8.7. Found: C, 51.8; H, 9.2; N, 8.7.

Summary

Acetonechloroform, when treated at 0°, with an alkali alkoxide or a solution of alkali hydroxide in an alcohol, gives the salt of an α-alkoxyisobutyric acid in good yield. Ten such α-alkoxyisobutyric acids have been prepared and their reac-

---

(19) Du Pont de Nemours & Co., *Ind. Eng. Chem.*, **28**, 1160 (1936).

(20) Roehm and Haas, French Patent 801,658; *Chem. Zentr.*, **108**, I, 429 (1937).

(21) Rehberg, Fisher and Smith, THIS JOURNAL, **65**, 1003 (1943); Rutovski and Zabrodina, *C. A.*, **35**, 4121 (1941).

(22) du Pont, British Patent 475,131; *Chem. Zentr.*, **109**, I, 2963 (1938).

(23) The dibromides of tiglic and angelic acid have the same m. p.: Wislicenus, *Ann.*, **272**, 12 (1893). Tiglic acid dibromide does not coalesce with water.

(24) Faworski, *J. prakt. Chem.*, [2] **51**, 541 (1895).

tions investigated. The reaction appears to be general for all analogs and homologs of acetonechloroform; three new α-alkoxyacids have thus been synthesized. A reaction mechanism has been suggested for this somewhat surprising reaction, and the analogous reaction of acetonechloroform and aniline has been discussed.

The dealkoxylation of the esters of the α-alkoxyacids to α,β-unsaturated esters has been investigated and a number of known and new esters of this series have been prepared.[25]

(25) (Note added February 19, 1948): In the November, 1947, issue of THIS JOURNAL (p. 2667), McElvain and Stevens describe the formation of ethyl α-ethoxyisobutyrate from acetonechloroform and 3 moles of sodium ethoxide in absolute alcohol. They also quote the British Patent 578,082 corresponding to the present paper (*C. A.*, **41**, 2075 (1947); applied in 1943; compare Weizmann, British Patent 587,545, applied in 1944).

LONDON, S. W. 1

RECEIVED APRIL 29, 1947

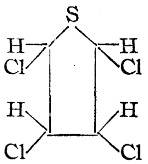
[CONTRIBUTION FROM RESEARCH AND DEVELOPMENT DEPARTMENT OF SOCONY-VACUUM LABORATORIES, A DIVISION OF SOCONY-VACUUM OIL CO., INC.]

The Chlorination of Thiophene. I. Addition Products

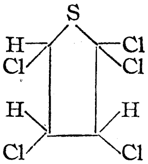
BY HARRY L. COONRADT AND HOWARD D. HARTOUGH

A study of the reaction of thiophene with chlorine was undertaken in these Laboratories when it became evident that the reaction was much more complex than had been indicated in the literature. Prior investigators reported[1] that when the reaction products were distilled, hydrogen chloride was evolved throughout the distillation and the presence of addition products was indicated since the substitution products distilled without decomposition. A study of addition products formed in the reaction was made by the present authors in order to determine, in part, their chemical potentialities since these compounds had been destroyed in the past by the methods used in processing the chlorinated mixtures.

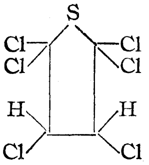
The addition compounds isolated from the reaction mixture were α-2,3,4,5-tetrachlorothiolane,[2] m.p. 111.5–113.5°, (I), β-2,3,4,5-tetrachlorothiolane, m.p. 44.5–46°, (II), 2,2,3,4,5-pentachlorothiolane (III), and 2,2,3,4,5,5-hexachlorothiolane (IV).



I, m. p. 111.5–113.5°
II, m. p. 44.5–46°



III



IV

The addition products were described previously by Steinkopf and Köhler[3] as "hydrogen chloride addition products." The assumption of addition products was based on the separation of a liquid material from exhaustively chlorinated thiophene, 2-thiophenecarboxylic acid or 4,5-dibromo-2-thiophenecarboxylic acid to which was assigned the structure of 2,3,4,5,5-pentachloro-2-thiolene or 2,3,4,4,5-pentachloro-2-thiolene. We isolated no such addition product from exhaustively chlorinated thiophene, and it seems probable that the material of Steinkopf and Köhler was not a single compound. The present work indicates that the addition compounds are chlorine addition products. Hydrogen chloride did not form addition products with 2,5-dichlorothiophene at 0° or −40° nor with 2,3,4,5-tetrachlorothiophene at 0°.

There are six possible geometrical isomers of 2,3,4,5-tetrachlorothiolane. Two were isolated and identified. These compounds may be viewed as the products of the addition of chlorine to thiophene. The *alpha* isomer, I, was obtained as a white crystalline product when partially chlorinated thiophene was cooled and filtered. The *beta* isomer, II, was obtained when partially chlorinated thiophene was distilled to remove the more volatile components, the residue cooled to crystallize and separate I, and the filtrate fractionated under reduced pressure. The higher boiling fractions contained II.

The structures of I and II were indicated by the method of synthesis and analysis. Further evidence for the structure assigned to I was obtained by dehydrohalogenation. Pyrolysis yielded hydrogen chloride and dichlorothiophenes composed of about 50% 2,3-dichlorothiophene, and 50% 2,4-dichlorothiophene with a trace of 2,5-dichlorothiophene. However, when I reacted with ethanolic potassium hydroxide, dichlorothiophenes composed of approximately 54% 3,4-dichlorothiophene, 44% 2,4-dichlorothiophene, 2% 2,5-dichlorothiophene, and no 2,3-dichlorothiophene were obtained. This conversion of I to all four possible dichlorothiophenes is evidence for the structure assigned. II upon treatment with ethanolic potassium hydroxide yielded a mixture of dichlorothiophenes.

The 2,2,3,4,5-pentachlorothiolane (III) was separated in low yield by the fractionation under reduced pressure of chlorinated thiophene. A superior method of preparation was found to be

---

[1] W. Steinkopf, "Die Chemie des Thiophens," Theodor Steinkopff, Dresden, 1941, p. 35.

[2] This terminology is in accord with that in Patterson, "The Ring Index," Reinhold Publishing Corp., New York, N. Y., 1940, p. 44. Other terminology, except that derived from thiacyclopentane, is cumbersome and occasionally misleading. The *alpha* and *beta* isomers of tetrachlorothiolane have been so designated by the present authors.

[3] Steinkopf and Köhler, *Ann.*, **532**, 250 (1937).

the chlorination of 2-chlorothiophene at low temperatures and subsequent crystallization of III at low temperatures from the reaction mixture. The structure assigned to III was based on the latter synthesis and on analysis. Further evidence for the structure assigned was the conversion of III to trichlorothiophenes by pyrolysis and by dehydrohalogenation with ethanolic potassium hydroxide. Of the trichlorothiophenes formed by pyrolysis, infrared absorption spectra indicated that 92% was 2,3,5-trichlorothiophene and 8% was 2,3,4-trichlorothiophene. However, of the trichlorothiophenes formed by the reaction of III with ethanolic potassium hydroxide similar analysis showed that 35% was 2,3,5-trichlorothiophene and 65% was 2,3,4-trichlorothiophene.

The 2,2,3,4,5,5-hexachlorothiolane (IV) was obtained from chlorinated thiophene by fractionation under reduced pressure. The same compound, IV, also was prepared by the direct addition of chlorine to 2,5-dichlorothiophene. The position of the two hydrogen atoms was indicated by the latter synthesis, and by the formation of 2,5-dichlorothiophene by the action of zinc on IV. IV reacted with ethanolic potassium hydroxide to give 2,3,4,5-tetrachlorothiophene. Pyrolysis of IV yielded hydrogen chloride and 2,3,4,5-tetrachlorothiophene.

The formation of the addition product, IV, as the principal product of the exhaustive chlorination of thiophene at 80–130° showed that at the latter stage of the reaction the ratio of addition to substitution products increased markedly. This is in contrast to the early stages of the chlorination where more chlorine reacted to form substitution than addition products. When two moles of chlorine was treated with one mole of thiophene at 70–80°, only 20% of the chlorine reacted to form addition products. The balance of the chlorine reacted to form substitution products as calculated from the weight of chlorine added and the weight of the reaction products.

The effect of temperature on the ratio of addition to substitution products was determined in part. When two moles of chlorine per mole of thiophene was used, the chlorine that reacted to form addition products was 20% at 70–80°, 30% at 30°, and 40% at −30°; the balance of the chlorine reacted to form substitution products. When the exhaustive chlorination of thiophene was conducted at reflux temperatures up to 200°, with concomitant pyrolysis, the yield of the addition product, IV, was low due to its dehydrohalogenation to tetrachlorothiophene. When the exhaustive chlorination was conducted at 80–130°, IV was obtained directly by distillation of the reaction product and was purer than the IV obtained when the chlorination was conducted at a lower temperature. This was clarified when I was found to react with chlorine at 115°, but not at 40°. The impurity in IV formed by chlorination near room temperature was thus indicated to be I and possibly other addition products which accumulated in the reaction mixture at lower temperatures and decomposed when IV was fractionated. I was found to react more readily than IV with cold sodium carbonate solution. Treatment of the crude reaction product with the alkaline solution destroyed the more unstable addition products so that IV could be distilled satisfactorily.

The purity of the addition products reported in this paper was indicated by the melting point, and infrared absorption spectrograms of carbon tetrachloride solutions of I, II and IV. Similar absorption spectrograms for I, II, IV and thiolane were obtained. The white crystalline addition products isolated had relatively high vapor pressures at room temperatures, but were quite stable under such conditions as was indicated by a constant melting point on standing. The addition products had a slight vesicant and lachrymatory action.

Experimental

Chlorination.—Thiophene of better than 99.5% purity, as determined by infrared absorption analysis, was used. The chlorinations were conducted in a flask fitted with stirrer, efficient condenser, thermometer and chlorine gas inlet tube that led below the surface of the liquid. The chlorine was measured by a rotameter.

α-2,3,4,5-Tetrachlorothiolane, I.—Five moles (420 g.) of thiophene was chlorinated at 30° with from two and one-half to ten moles of chlorine. The products were placed in stoppered flasks and immersed in a Dry Ice–acetone-bath at −70° for four hours. The cold reaction mixtures were filtered and the precipitates washed with cold petroleum ether. The white crystalline products so obtained had melting points of about 106–112° which were not substantially changed by repeated recrystallizations from ASTM naphtha. The moles of chlorine used per mole of thiophene and the yields of I, m. p. 106–112°, based on chlorine were as follows: 0.5, 9.9%; 0.8, 13.2%; 1.0, 11.1%; 2.0, 8.2%. The best yield of I based on thiophene was obtained with two moles of chlorine per mole of thiophene. The effect of the temperatures of chlorination on the yields under such conditions was as follows: 70–80°, 3.5%; 30°, 8.2%; −30°, 3.8%. Addition of petroleum ether to the more highly chlorinated mixtures before crystallization reduced coprecipitation and facilitated separation of I. Under such conditions the moles of chlorine used and the yields of I, m. p. 106–112°, based on chlorine were as follows: 3.0, 1.9%; 4.0, 0.0%. I of m. p. 111.5–113.5° was obtained by fractional crystallization from carbon tetrachloride by the addition of ASTM naphtha or from benzene by the addition of petroleum ether. I boiled at 111.5° (3.4 mm.) with partial decomposition, as was indicated by hydrogen chloride evolution and a distillate with a lower melting point. I gave an immediate precipitate with alcoholic silver nitrate.

Anal. Calcd. for $C_4H_4Cl_4S$: C, 21.26; H, 1.79; Cl, 62.8; S, 14.2; mol. wt., 226. Found: C, 21.27; H, 1.78; Cl, 62.5; S, 14.8; mol. wt., 226.

β-2,3,4,5-Tetrachlorothiolane, II.—Ten moles of chlorine was added to ten moles (840 g.) of thiophene over a two-hour period during which time the temperature was allowed to rise at a constant rate from 50 to 100°. Then nitrogen was passed through the reaction mixture for forty minutes while the mixture was heated at 90°. The cold reaction mixture was washed in turn with water, 5% sodium carbonate solution and water, and then dried over sodium sulfate. The mixture was distilled until the vapor temperature reached 150°. Hydrogen chloride was evolved during the distillation. The 404 g. of residue was divided. One-half (202 g.) was distilled directly under 4 mm. pressure. The major portion of the distillate was chlorine substitution products. In addition, there was a higher boiling fraction consisting of 8 g. of liquid, b. p. 112° (4 mm.), from which no II was obtained, and 74 g. of black tarry residue from which 7 g. of I was isolated by recrystallization from ASTM naphtha.

The other one-half (202 g.) of the mixture was kept at −30° for eighteen hours and then at room temperature for twenty-four hours. The precipitate, I (25 g.) that formed was separated by filtration. The filtrate was fractionated under reduced pressure (5 mm.) and gave, in addition to the chlorine substitution products, 47 g. of II, b. p. 110–118° (5 mm.), and 12 g. of black crystalline residue. The residue was recrystallized from ASTM naphtha and gave 2 g. of white crystalline product, m. p. 64–69°. II was recrystallized from ASTM naphtha; m. p. 44.5–46°; $n^{50}\mathrm{D}$ 1.5688.

Anal. Calcd. for $C_4H_4Cl_4S$: C, 21.26; H, 1.79; Cl, 62.8; S, 14.2. Found: C, 21.26; H, 1.87; Cl, 62.9; S, 14.2.

Pyrolysis of α-2,3,4,5-Tetrachlorothiolane, I.—Forty grams of I was refluxed at about 180° for thirteen hours. Hydrogen chloride was evolved throughout the heating period. The liquid product had a refractive index, $n^{30}\mathrm{D}$, of 1.5698. Distillation at atmospheric pressure gave 22 g. of dichlorothiophenes, b. p. 160–168°, and 8 g. of residue. The dichlorothiophene fraction was analyzed by infrared spectrograms which indicated the composition was 50% 2,3-dichlorothiophene and 50% 2,4-dichlorothiophene which contained a trace of 2,5-dichlorothiophene.

Reaction of α-2,3,4,5-Tetrachlorothiolane with Ethanolic Potassium Hydroxide.—A solution of 168 g. (3 moles) of potassium hydroxide in 504 g. of absolute ethanol was heated to 65–70°. The heater was removed and 226 g. (1 mole) of I, m. p. 106–110°, was added over a two-hour period so that the temperature was maintained at 65–70°. Considerable heat was evolved. The mixture then was refluxed at 80° for twenty-two hours. Water was added and the mixture was steam distilled into approximately 250 ml. fractions. Water was added to each fraction to precipitate an oil. The oily layers from the first three fractions were combined. The water layers were extracted twice with petroleum ether; the petroleum ether solution was distilled and the residual oil, 15 ml., added to the main body of the oil. The combined oil was washed with water to remove alcohol and then treated again with a mixture of 10 g. of sodium hydroxide and 10 g. of potassium hydroxide at 100–125° for five hours to react with any I that might remain. The excess alkali and any salt formed was removed by filtration and 124 g. (81%) of dichlorothiophenes was obtained as filtrate. The dichlorothiophenes, b.p. 155–185°, were separated by fractionation and analyzed by infrared absorption spectrograms. The analysis indicated a dichlorothiophene composition of approximately 2% 2,5-dichlorothiophene, 44% 2,4-dichlorothiophene, no 2,3-dichlorothiophene, and 54% 3,4-dichlorothiophene.

Reaction of α-2,3,4,5-Tetrachlorothiolane with Chlorine.—One mole of chlorine was passed into a solution of 34 g. (0.15 mole) of I, m.p. 110–112°, in 500 ml. of carbon tetrachloride at 40° during a two-hour period. The resultant product was evaporated on a steam-bath, and the crystalline residue, 34 g., m.p. 104–110°, showed no depression of the melting point with I.

Anal. Calcd. for $C_4H_4Cl_4S$: Cl, 62.8. Found: Cl, 63.3.

Four moles of chlorine was passed into 113 g. (0.5 mole) of I, m.p. 110–112°, at 115° during a one hundred-minute period. The product was a liquid which weighed 120 g., 7 g. more than the original I. The product was washed in turn with water, 5% sodium carbonate solution and water. The product gave 80 g. of distillate, b.p. 57–113° (4 mm.), and 10 g. of residue.

2,2,3,4,5-Pentachlorothiolane, III.—Two moles of chlorine was passed into 1 mole (119 g.) of 2-chlorothiophene at −30 to −35° during an eighty-minute period. Nitrogen was passed through the cold mixture for five minutes. The mixture was transferred to a stoppered flask and placed in a Dry Ice–acetone-bath at −70°, but crystallization was slow. The addition of 25 ml. of petroleum ether facilitated crystallization. After four hours the cold mixture was filtered. The precipitate (46 g.) after recrystallization from petroleum ether melted at 31–32°; $n^{35}\mathrm{D}$ 1.5755; $\Delta n\mathrm{D}/\Delta t = -0.0005$. The calculated refractive index, $n^{20}\mathrm{D}$, was 1.5830.

Anal. Calcd. for $C_4H_3Cl_5S$: C, 18.45; H, 1.16; Cl, 68.1; S, 12.3. Found: C, 18.32; H, 1.09; Cl, 67.9; S, 12.5.

Pyrolysis of 2,2,3,4,5-Pentachlorothiolane, III.—Twelve grams of III with refractive index, $n^{33}\mathrm{D}$, of 1.5740 was refluxed for twenty-four hours. Evolution of hydrogen chloride had practically ceased after that time. The condenser was inverted and 9 g. of light red oil was obtained by distillation. Redistillation gave a colorless product, b.p. 190–195°. Infrared absorption analysis indicated that of the trichlorothiophenes present 92% was 2,3,5-trichlorothiophene and 8% 2,3,4-trichlorothiophene.

Reaction of 2,2,3,4,5-Pentachlorothiolane, III, with Ethanolic Potassium Hydroxide.—Twelve grams of pentachlorothiolane with refractive index, $n^{33}\mathrm{D}$, of 1.5740 was refluxed with 50 ml. of 20% ethanolic potassium hydroxide for eight hours. The mixture was diluted with 100 ml. of water and steam distilled. The steam distillate was extracted with ether; the ether solution was washed with water, dried over calcium chloride, and then distilled. The distillate, b.p. 198–212°, weighed 8 g. and infrared absorption analysis indicated that of the trichlorothiophenes present 65% was 2,3,4-trichlorothiophene and 35% was 2,3,5-trichlorothiophene.

2,2,3,4,5,5-Hexachlorothiolane, IV.—Twenty-six and one-half moles of chlorine was added to 420 g. (5 moles) of thiophene over a five and one-half hour period. The temperature was maintained at 40° except during the last hour when it was lowered to 5°. The mixture evolved some chlorine at room temperature. A 400-g. sample of the 1284 g. of product was washed in turn with water, 5% sodium carbonate solution, and water. The alkaline and water solutions were extracted with carbon tetrachloride. The organic material was combined and dried over sodium sulfate. The carbon tetrachloride was distilled and the residue fractionated; the yield of IV was 354 g. (77%); b.p. 100–105° (1 mm.). The compound was recrystallized by adding just sufficient petroleum ether to dissolve the crystals and then cooling the solution slowly to 0°. The white crystalline product melted at 45–46°; $n^{50}\mathrm{D}$ 1.5590, $\Delta n\mathrm{D}/\Delta t = -0.0005$. IV gave an immediate precipitate with alcoholic silver nitrate.

Anal. Calcd. for $C_4H_2Cl_6S$: C, 16.29; H, 0.69; Cl, 72.2; S, 10.9. Found: C, 16.31; H, 0.64; Cl, 71.8; S, 10.8.

Chlorination of 2,5-Dichlorothiophene.—Five moles of chlorine was passed, during a two-hour period, into 100 g. (0.65 mole) of 2,5-dichlorothiophene at 5–10°. The product weighed 130 g. There was 20 g. of distillate, b.p. 115–120° (5 mm.), which after recrystallization from petroleum ether had a m.p. 45–46°. This material gave no depression of the melting point with IV prepared from thiophene as described above.

Pyrolysis of 2,2,3,4,5,5-Hexachlorothiolane, IV.—Forty-five grams of IV was refluxed (about 215°) for seventy-two hours. Hydrogen chloride evolution was rapid at first, but very slow near the end. Upon distillation there was obtained 7 g., b.p. 76–83 (3 mm.), and 17 g. of 2,3,4,5-tetrachlorothiophene, b.p. 75–77° (2 mm.), m. p. 29°. The latter material gave no depression of the melting point with pure tetrachlorothiophene, m. p. 29.09°.

Reaction of 2,2,3,4,5,5-Hexachlorothiolane, IV, with Ethanolic Potassium Hydroxide.—A solution of 20 g. of potassium hydroxide in 180 g. of absolute alcohol was heated to 60° and 45 g. of IV added over a ten-minute period. The mixture was refluxed for eighteen hours.

Water was added and the mixture steam distilled. The organic layer was separated and the water layer extracted four times with 30-ml. portions of petroleum ether. The combined organic material was dried over calcium chloride, filtered and fractionated. The 2,3,4,5-tetrachlorothiophene weighed 7 g., mixed m.p. 29°.

Reaction of 2,2,3,4,5,5-Hexachlorothiolane, IV, with Zinc.—A suspension of 150 g. of 90% zinc dust in 500 ml. of water was heated to 95°, and 250 g. of IV added over a one and one-quarter hour period. The unreacted metal was removed by filtration and the organic layer separated. The water layer was extracted with ether and yielded 21 g. of product. The organic material was combined and the ether distilled. The distilled 2,5-dichlorothiophene weighed 85 g.; b.p. 160–163°; $n^{20}D$ 1.5624.

Acknowledgment.—The authors are grateful to Dr. D. E. Badertscher and Dr. C. C. Price for their advice and interest in this problem, to Miss Emily Burns who carried out a great many of the laboratory experiments, and to Mr. J. G. Ehlers for infrared spectrographic analyses.

Summary

Thiophene reacts with chlorine to produce both addition and substitution products in proportions dependent upon the reaction conditions and the ratio of chlorine to thiophene.

Chlorine addition products were isolated. These are identified as α-2,3,4,5-tetrachlorothiolane, β-2,3,4,5-tetrachlorothiolane, 2,2,3,4,5-pentachlorothiolane and 2,2,3,4,5,5-hexachlorothiolane. The compounds are white crystalline materials stable at room temperature.

Pyrolysis of α-tetrachlorothiolane and of pentachlorothiolane gave mixtures of dichlorothiophenes and trichlorothiophenes, respectively, varying in composition from the chlorothiophenes formed by dehydrohalogenation with ethanolic potassium hydroxide.

PAULSBORO, N. J.

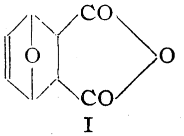
RECEIVED JULY 28, 1947

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Reaction of Furan with Maleic Anhydride[1]

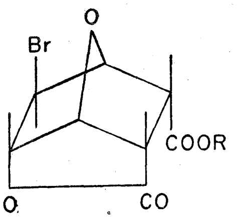
BY R. B. WOODWARD AND HAROLD BAER

In an attempt to synthesize cantharidine or cantharidine-like compounds, Diels and Alder[2] undertook the study of the reaction of furan with maleic anhydride. The two substances reacted in ether solution to give a crystalline adduct, m.p. 125°, which was shown to have the structure (I).

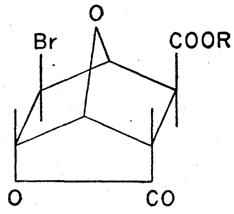


I

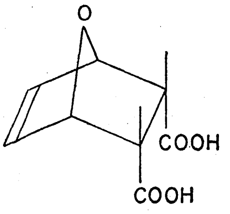
Subsequently, the same authors[3] observed that an aqueous solution of maleic acid dissolved furan on long shaking. When the resultant solution was treated with bromine a substance, $C_8H_7O_5Br$, m.p. 205°, was precipitated, to which the structure (II, R = H) was assigned. This bromolactonic acid was converted by diazomethane to a monomethyl ester (II, R = Me), m.p. 175°. Hydrobromic acid at 100° converted (II) to an isomer (III, R = H), from which an ester (III, R = Me), m.p. 168°, was obtained, while the same agent, at 160–170°, converted (II) to *o*-phthalic acid. These observations indicated that the solution of furan in aqueous maleic acid contained *endo-cis*-1,4-endoxo-Δ^5-cyclohexene-2,3-dicarboxylic acid (IV). It is significant that the German authors presented no evidence of the actual isolation from the solution of an adduct. *On the assumption that the acid obtained by the hydrolysis of the crystalline anhydride (I) was identical with the acid contained in the aqueous solution of furan in maleic acid, Diels and Alder assigned the structure (V) to the adduct, m.p. 125°.*



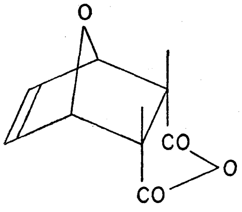
II



III

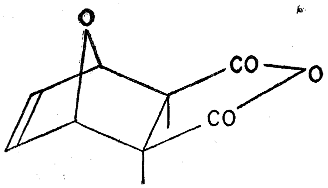


IV



V

In this communication, it is shown that that assumption was incorrect and that, in fact, the product of the addition of maleic anhydride to furan is *exo-cis*-3,6-endoxo-Δ^4-tetrahydrophthalic-anhydride (VI). When the anhydride, m.p.



VI

---

[1] This paper is the third in a series of studies on diene addition reactions. For II, see Woodward and Baer, THIS JOURNAL, **66**, 645 (1944).

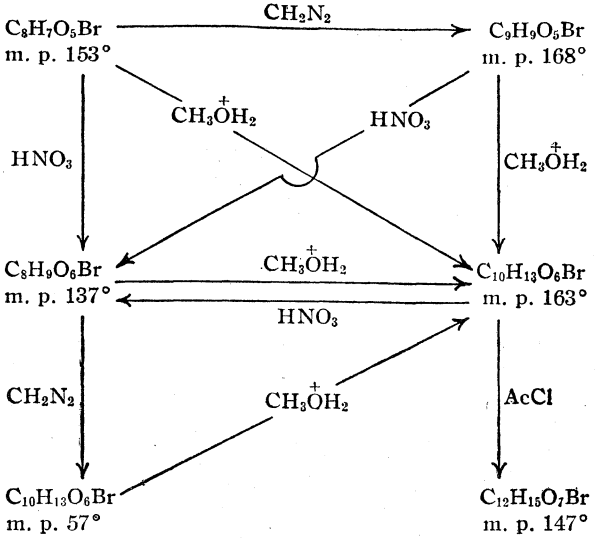
[2] Diels and Alder, *Ber.*, **62**, 557 (1929).

[3] Diels and Alder, *Ann.*, **490**, 243 (1931).

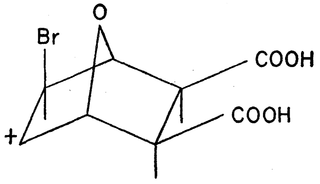
125°, is dissolved in water or dilute base and the resultant solution is treated with bromine, a new colorless crystalline substance $C_8H_7O_5Br$, m.p. 153° (d.), is precipitated,[4] in the latter case after acidification with hydrochloric acid. Careful evaporation of the mother liquor from the reaction yields a dibromide of the adduct acid, $C_8H_7O_5Br_2$, m.p. 155°. This substance, which was converted by catalytic esterification to a dimethyl ester, $C_{10}H_{12}O_5Br$, m.p. 116°, is of no great interest and needs no further comment.

Esterification of the new monobromo compound, m.p. 153°, with diazomethane gives a monomethyl ester, $C_9H_9O_5Br$, m.p. 168° (dec.) which is not identical with either of the isomeric esters, m.p. 175° and 168°, of Diels and Alder (*vide supra*) as evidenced by mixed melting point determinations and, further, by the striking differences between the chemical properties of the new ester, as contrasted with those of the previously described isomers. The latter melt without decomposition to clear liquids, which resolidify on cooling; they are stable to dilute alkalies, and to alkaline permanganate, and do not reduce Fehling solution or Tollens reagent. By contrast, the new ester melts with complete decomposition, it decolorizes cold aqueous permanganate instantly, reduces Tollens and Fehling solution readily when warmed slightly, and it is rapidly destroyed, with the formation of dark-colored intractable material, by the action of cold dilute weak bases or by short warming with dilute acids. Base liberates bromide ion instantaneously from the new ester, but, significantly, alcoholic silver nitrate fails to yield a precipitate of silver bromide.

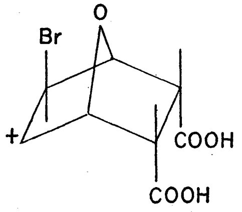
Catalytic esterification, with methanol and sulfuric acid, converts either the monobromo compound, $C_8H_7O_5Br$, or the new ester, m.p. 168°, into a new substance, $C_{10}H_{13}O_6Br$, m.p. 163° (d.), from which an acetyl derivative, $C_{12}H_{15}O_7Br$, m.p. 147°, may be obtained. Any of the three substances, when boiled with dilute nitric acid,[5] is converted to an acid, $C_8H_9O_6Br$, m.p. 137° (d.). This acid is transformed by the action of methanol and sulfuric acid to the compound $C_{10}H_{13}O_6Br$, m.p. 163°, but *by the action of diazomethane, an isomeric substance, $C_{10}H_{13}O_6Br$, m.p. 57° (dec.) is obtained.* The new compound is inordinately unstable. It decomposes spontaneously within an hour, and it is the first substance of this series to yield a precipitate of silver bromide with alcoholic silver nitrate. Methanol containing sulfuric acid converts the 57° compound into its isomer, m.p. 163°. The accompanying chart will clarify this somewhat involved series of changes.



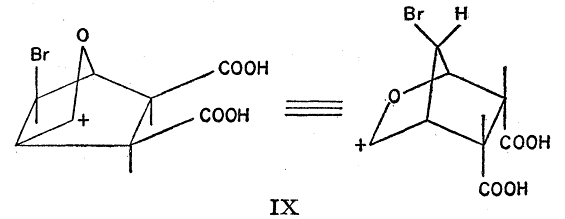
These transformations are explicable only on the basis that the original adduct (I), m.p. 125°, has the *exo-cis* configuration (VI). Attack at the double bond by bromine produces a carbonium ion (VII) or its equivalent. Unlike the corresponding *endo-cis* ion (VIII), which can undergo spontaneous stabilization by lactonization, to give (II, R = H), VII is incapable of direct lactonization, since the oxygen bridge blocks union between the positively charged carbon atom and an oxygen of the carboxyl group. However, after a normal Wagner–Meerwein rearrangement to (IX), the hitherto inaccessible carboxyl group may participate in lactonization, with the formation of (X, R = H); this expression represents the monobromo compound $C_8H_7O_5Br$, m.p. 153°, of the new series. This change is comparable to that involved in the transformation of *exo-cis*-Δ^5-bicyclo-[1,2,2]-heptene-2,3-dicarboxylic acid (XI) into the lactone (XII) on treatment with acid.[6] In our case, the circumstances are even more favorable for rearrangement, since the oxygen atom tends to stabilize the rearranged ion, through contributions



VII



VIII



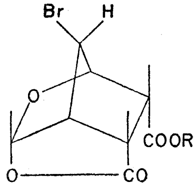
IX

---

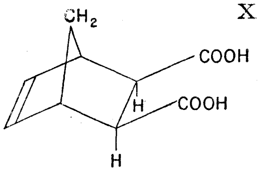
(4) Observation of Mrs. Virginia (Williams) Eager.

(5) Nitric acid only, of all acids tried, is effective, presumably because it oxidizes the decomposition products which are usually formed in reactions involving these very sensitive substances, and permits ready isolation of the desired product from reaction mixtures free of otherwise inseparable contaminants.

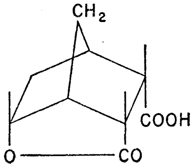
(6) Alder and Stein, *Ann.*, **514**, 1 (1934).



X



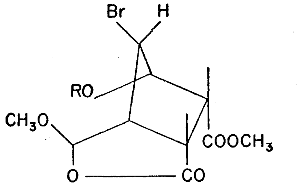
XI



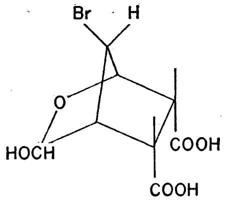
XII

of the type $-\overset{|}{C}=\overset{+}{O}-$. The presence in the rearranged ion of a carboxyl group in a position in which it may participate in lactonization undoubtedly provides additional driving force for the rearrangement; on the other hand the similar rearrangement in the hydration of dicyclopentadiene[7] indicates that this factor is not a necessary one. The occurrence of a Wagner–Meerwein rearrangement during bromination is not unexpected in the light of current views on the mechanism of halogenation[8] and, in any event, has been observed in other cases, *e.g.* in the reaction of pinene with bromine to give 2,6-dibromo-camphane.[9]

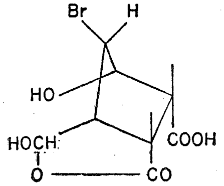
The structure (X, R = H) is compatible with all of the observed reactions of the 153° compound. The formulation of the mono-ester, m.p. 168°, as (X, R = CH_3) follows directly, while the compound $C_{10}H_{13}O_6Br$, m.p. 163°, may be represented as the pseudo-ester (XIII, R = H), a formulation supported by the formation of a mono-acetyl derivative (XIII, R = CH_3CO—). The acid, $C_8H_9O_6Br$, m.p. 137°, is (XIV) (or its ring-chain tautomer, XV), and finally, the isomeric substance $C_{10}H_{13}O_6Br$, m.p. 57° is the normal diester (XVI).



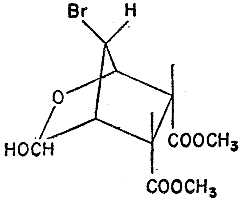
XIII



XIV

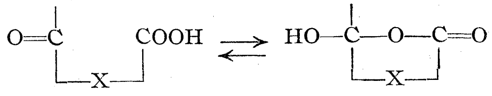


XV



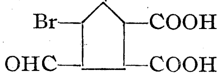
XVI

The formation of the isomeric esters, $C_{10}H_{13}O_6Br$, provides proof of the presence of a (potential) carbonyl group in this series, and in particular, the formation of the pseudo-ester (XIII, R = H) and the normal ester (XVI) respectively under catalytic esterification conditions and through the action of diazomethane, is consonant with the usual properties of substances capable of participation in ring-chain equilibria of the type XVII$a \rightleftarrows$ XVIIb.[10]

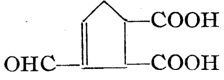


XVIIa XVIIb

The great sensitivity of the entire series arises from the circumstance that all of the substances are derived from the cyclopentane aldehyde (XVIII); once the lactone ring of any of the compounds is opened (say by alkali) with liberation of

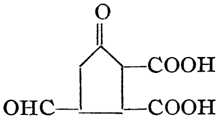


XVIII



XIX

the free aldehyde group, the β-halogen atom is eliminated with extreme ease. The resultant unsaturated aldehyde (XIX), itself very probably an unstable substance, may readily isomerize[11] to



XX

XX, which possesses manifold possibilities for auto-condensation.[12]

The ready elimination of bromide ion, and possibly also the potential aldehyde group, accounts for the facile oxidation by dilute permanganate solution, while the latter feature is responsible for the observed reducing action toward warm Fehling solution and Tollens reagent. In that connection, it is significant that while the substances are immediately oxidized by permanganate in the presence of the merest trace of base, dilute acid suppresses the reduction of that agent considerably; the somewhat greater stability of the acids of the series as compared with the esters is another consequence of the same effect. Finally, the fact that the ester of m.p. 57° is by far the most unstable compound of the entire series is a consequence of the fact that in it the potential aldehyde group is masked only as a simple hemiacetal function; mere prototropic change is necessary to initiate the series of degenerative reactions, while in

---

[7] Bartlett and Schneider, THIS JOURNAL, **68**, 7 (1946).

[8] Roberts and Kimball, *ibid.*, **59**, 947 (1937).

[9] Aschan, *Ber.*, **61**, 42 (1928).

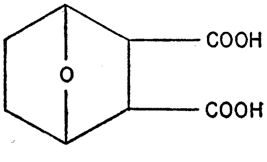
[10] *Cf.*, *i. a.*, Meyer, *Monatsh.*, **26**, 1295 (1905); Blaise and Courtot, *Bull. soc. chim.*, [3] **35**, 999 (1906).

[11] *Cf.* Woodward and Blout, THIS JOURNAL, **65**, 562 (1943).

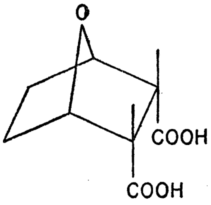
[12] *Cf.* the behavior of levulinic aldehyde, a simple analog of XX. When the acetal of the aldehyde is warmed with dilute acids the free aldehyde is liberated; attempts to neutralize the solutions with sodium carbonate result in very rapid and complete destruction of the substance [Harries, *Ber.*, **31**, 37 (1898)].

the other compounds, a more difficult reaction, initiated by an external reagent, must take place prior to decomposition.

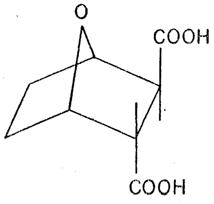
In addition to its ready elimination in the presence of base, the bromine atom in these compounds is remarkable in two further ways. The stability to alcoholic silver nitrate is traceable to the circumstance that while the bi-(or tri)-cyclic ring system is retained, stabilization of the carbonium ion intermediate which might otherwise result from the attack of silver ion is impossible. Finally, the bromine atom in (X) and its derivatives is stable toward zinc under conditions which normally transform dibromides and bromohydrin derivatives into olefins. However, it is known that this reaction is highly stereospecific, in that *trans* elimination takes place exclusively.[13] For instance, *dl*-2,3-dibromobutane gives only *cis*-butene-2, while *meso*-2,3-dibromobutane gives only the *trans*-olefin. No data are available on the reaction of zinc with a cyclic dibromide or bromohydrin derivative of known *cis*-configuration, but the above facts strongly indicate that the reaction, in such a case, in which the groups to be eliminated cannot assume a *trans* position with respect to one another, will proceed with difficulty, or not at all. Now in the formation of X, it is most probable that the initial attack of the bromine on the adduct (VI) takes place on the *exo* side[14]; consequently the bromine atom in (X), and the substances derived from it, will be *cis* to the oxygen attached to the contiguous carbon atom, and the sluggishness toward zinc may be accepted as confirmatory of the assigned structures.



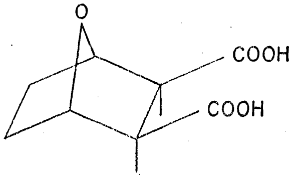
XXI



XXII



XXIII



XXIV

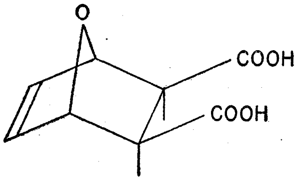
We turn now to a consideration of the configurations of the acids of the structure XXI. Three stereoisomeric forms, *viz.*, *endo–cis* (XXII), *trans* (XXIII) and *exo–cis* (XXIV), are possible. Alder and Backendorf, starting from the furan–maleic anhydride adduct (I or VI) have prepared three acids of the structure XXI, and *on the basis of the assignment of the erroneous configuration* (*V*) *to the original adduct*, deduced the configuration of the three saturated acids.[15] It is now clear that the previous configurational assignments, except for that of the intermediary *trans* acid, are invalid and must be revised. In Table I, the correct configurations are presented. In this connection it is noteworthy that the German workers were led to believe that in the *endoxo*-cyclohexane series, the melting point regularities observed in other (*e.g.* the [1,2,2]bicycloheptane) series were reversed, and that further, addition reactions (*e.g.*, hydrogenation), which normally occur with addition from the *exo* side,[16] also took an abnormal course, with *endo* addition. It is now clear that both the melting point regularities and the *exo* addition rule are obeyed in the *endoxo* cyclohexane series, and that the only reversal necessary is that which we have made in the configurational assignments.

TABLE I

CONFIGURATIONS OF THE 3,6-*endoxo*-HEXAHYDROPHTHALIC ACIDS AND ANHYDRIDES

		M. p., °C. Acid	Anhydride
exo–cis	(XXIV)	122–123	116–117
trans	(XXIII)	180	.....
endo–cis	(XXII)	169–170	158–159

The work described here demonstrates that the reaction of furan with dienophiles is similar to that of the fulvenes previously studied[1] in this Laboratory in that both *exo* and *endo* adducts may be formed, depending on the reaction conditions, and, in this particular case, on the nature of the addend. We are not prepared to discuss at this point the theoretical implications of the present work, but in any future discussion, the following points must be borne in mind. In the furan series, both addition reactions are readily reversible. Further, *the order of stabilities of the isomers is the same as that in the fulvene case*, as evidenced by the fact that while the *exo–cis* acid (XXV), obtained from the anhydride (VI), can be purified by recrystallization from warm water, all attempts so far made to isolate the *endo–cis* acid (IV) from its solutions have failed; since maleic acid is the only solid product obtained it



XXV

---

(13) Young and Lucas, THIS JOURNAL, **52**, 1970 (1930); Young and Winstein, *ibid.*, **58**, 103 (1936); Wilson and Lucas, *ibid.*, **58**, 2396 (1936).

(14) *Cf.* Alder and Stein, *Ann.*, **515**, 185 (1935); **525**, 183 (1936).

(15) Alder and Backendorf, *ibid.*, **535**, 113 (1938).

(16) It is worthy of note that the prevalence of *exo* addition in the catalytic hydrogenation of these bicyclic substances provides an excellent example of the operation of the catalyst hindrance effects postulated by Linstead, *et al.*, THIS JOURNAL, **64**, 1985 (1942).

appears that the furan–maleic acid reaction is extraordinarily readily reversible, with the result that attempts at removal of solvent, or extraction, result preferentially in removal of furan, by volatilization or extraction, with continuous displacement of the equilibrium until no adduct remains.

Experimental

Furan–Maleic Anhydride Adduct.—This substance was prepared according to the directions of Diels and Alder.[2] It is impractical to recrystallize the adduct because of the ease with which it dissociates in warm solvents.

Bromolactonic Acid (X, R = H).—Thirty-six grams of the furan–maleic anhydride adduct was dissolved in a solution containing 19 g. of sodium hydroxide in 600 ml. of water. The solution was cooled to about 8°, and bromine was added dropwise with constant stirring until a faint color persisted. Acidification with hydrochloric acid produced 49.5 g. of a white needle-like crystalline substance whose melting point was 153° (dec.) after recrystallization from water (not warmer than 40°). It is necessary to place the melting point capillary in the bath not more than 10° below the decomposition point or reproducible results cannot be obtained.

Anal. Calcd. for $C_8H_7O_5Br$: C, 36.5; H, 2.66. Found: C, 36.6, 36.3; H, 2.73, 2.70.

Concentration of the mother liquor *in vacuo* yielded 5.5 g. of the normal dibromide, m. p. 155° (from water).

Anal. Calcd. for $C_6H_6OBr(COOH)_2$: C, 27.9; H, 2.33; neut. equiv., 172. Found: C, 29.2, H, 2.79; neut. equiv., 170, 172.

Esterification of the dibromo acid (500 mg.) with 10 ml. of absolute methanol containing a few drops of fuming sulfuric acid (30%) yielded the dimethyl ester which, after two recrystallizations from water melted at 115.9–116.3°.

Anal. Calcd. for $C_{10}H_{12}O_5Br_2$: C, 32.3; H, 3.23. Found: C, 32.6; H, 3.51.

In order to obtain a maximum yield of the 153° compound it is necessary to add the bromine slowly and with rapid stirring as will be illustrated by Table II. The yield of dibromide is variable and of little significance because of the difficulty encountered in its isolation.

TABLE II

Adduct, g.	153° cpd.	Dibromide (155°)
9.2	8.2	2.2
30	28	7.3
36 rapid stirring	49.5	5.5

The 153° compound may also be obtained by dissolving the adduct directly in warm water (40–50°) and after cooling to 0° adding bromine until a slight color persists; the product, which has precipitated from the solution, is filtered off. In two typical experiments the weight of 153° compound obtained was approximately equal to that of the adduct used, and *ca.* one third as much dibromide was isolated.

If a small quantity of the 153° compound is dissolved in water and neutral or acid potassium permanganate added, no oxidation is observed. The addition of the slightest excess of carbonate results in instant decoloration of the solution.

Attempts at solution in caustic alkali or soda result in complete destruction of the compound if warmed; if the solution is kept cold, no decomposition is apparent until the solution is acidified, when a brown, amorphous solid is precipitated.

Schiff reagent fails to react but both Tollens solution and Fehling reagent give positive tests if the solution is warmed gently on the steam-bath. The addition of silver nitrate solution to a hot aqueous solution of the 153° compound produces an immediate precipitate of silver bromide; in alcoholic solution no reaction is observed.

Half-methyl Ester (X, R = CH_3).[4]—Diazomethane is distilled onto an ether suspension of the 153° acid (1 g.). After the reaction has ceased, the ether is boiled off and the solid that remains is recrystallized from methanol: 0.75 g. of fine, cotton-like needles, m. p. 167–168° (d.).

Anal. Calcd. for $C_9H_9O_5Br$: C, 39.1; H, 3.25. Found: C, 39.1, C, 39.1; H, 3.31, H, 3.39.

This substance is moderately stable to weakly acid permanganate solutions but once again, the addition of the merest trace of alkali results in instant decolorization of the permanganate.

This ester cannot be dissolved either in alkali or dilute sulfuric, hydrochloric, or acetic acids without complete decomposition. The reaction with nitric acid will be described under the preparation of the 137° compound.

If, however, nitrogen is bubbled through a saturated barium hydroxide solution and then the 168° ester rapidly added, the residue remaining, after warming for a half-hour to 50°, is mainly barium carbonate. While no organic product could be isolated from the solution, this result would indicate the presence of a β-keto acid in the solution which presumably resulted from the action of the base on the 168° ester. This observation may be considered as evidence for the change XVIII → XIX.

Pseudoester (XIII, R = H).—Into 10 ml. of methanol, containing a few drops of 30% fuming sulfuric acid, is placed 500 mg. of the 153° acid. After heating under reflux for three hours the solution is poured onto ice, whereupon the ester crystallizes (yield 300 mg.). After recrystallization from methanol the ester is obtained as plates, m. p. 163° (d.).

Anal. Calcd. for $C_{10}H_{13}O_6Br$: C, 38.9; H, 4.21. Found: C, 38.3, 38.3; H, 4.18, 4.14.

By making use of the above procedure the 168° ester (500 mg.) may be converted to the 163° ester (350 mg.); the 57° ester (*vide infra*) is also converted to the 163° ester by this procedure.

This ester is sensitive to alkali and alkaline potassium permanganate but relatively stable to acid and neutral permanganate.

Heating the 163° ester in methanol with zinc for twenty-four hours resulted in no change.

Acetyl Derivative (XIII, R = CH_3CO^-).—The 163° ester is dissolved in acetyl chloride and the solution heated under reflux for one hour. The solution was decomposed on ice and cooled in an ice-bath overnight: needles were obtained which, on recrystallization from methanol, melted at 146.5–147°.

Anal. Calcd. for $C_{12}H_{15}O_7Br$: C, 41.0; H, 4.27. Found: C, 41.1; H, 4.54.

Acid (XIV or XV).—Two grams of the 163° ester is added to a mixture of 10 ml. of concentrated nitric acid and 20 ml. of water and the mixture warmed in a water-bath (50°) with constant stirring until solution is complete. After warming for one more hour the solution is concentrated, by distillation *in vacuo*, and then cooled; the precipitated acid (600 mg.) is twice recrystallized from water and obtained as needles, m. p. 136–137° (d.) (this is not a true melting point and consequently varies somewhat with the rate of heating).

Anal. Calcd. for $C_8H_9O_6Br$: C, 34.1; H, 3.20. Found: C, 34.2, 34.0; H, 3.28, 3.56.

The same acid is obtained by treatment of either the 168° ester or the 158° acid in an analogous manner. From 1.4 g. of the 168° compound one obtains 450 mg. of acid.

Alkaline potassium permanganate attacks this substance with vigor. The Schiff test is negative but positive Tollens and Fehling tests are obtained.

This acid is readily converted to the 163° ester. To a solution of 300 mg. of acid in 10 ml. of methanol is added a few drops of fuming sulfuric acid (30%) and the whole heated under reflux for several hours. Decomposition of the solution on ice produces the characteristic silky plates of the 163° ester, m.p. 160° (d.).

Normal Ester (XVI).—Onto a suspension of 400 mg. of the 137° acid in ether diazomethane is distilled; the mixture is permitted to stand in ice until the evolution of nitrogen ceases. Removal of most of the ether on the steam-bath followed by cooling in ice results in the formation of 300 mg. of solid ester. Recrystallization from ether containing a little methanol produces clusters of transparent needles, m. p. 57° (dec.). This ester is estremely unstable, decomposing slowly in the cold room (5°) and very rapidly at room temperature (about an hour).

Anal. Calcd. for $C_{10}H_{13}O_6Br$: C, 38.9; H, 4.21; Br, 25.9. Found: C, 38.9; H, 4.43; Br, 26.3.

The Schiff test on this ester is negative but positive Fehling and Tollens tests are very readily obtained on only slight warming. Silver nitrate in alcoholic solution reacts slowly in the cold but rapidly on warming to produce a copious quantity of silver bromide.

Acid potassium permanganate does not effect a rapid oxidation but in an alkaline solution this reagent is instantly decolorized.

Summary

The reaction between furan and maleic acid in water, and that between furan and maleic anhydride in ether, take different stereochemical courses. In the former case, an *endo–cis* adduct is formed, while in the latter, an *exo–cis* product is obtained.

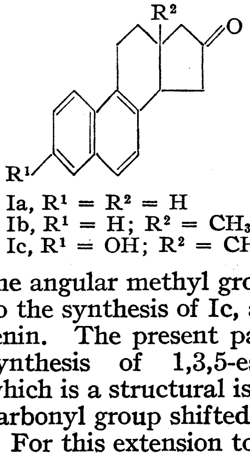
CAMBRIDGE, MASS. RECEIVED SEPTEMBER 23, 1947

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

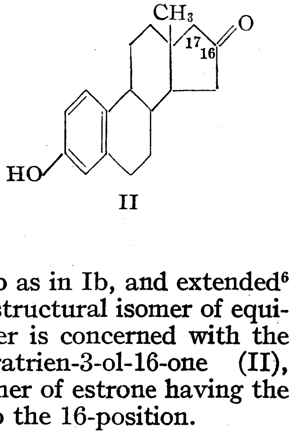
The Synthesis of 1,3,5-Estratrien-3-ol-16-one, A Structural Isomer of Estrone[1]

BY A. L. WILDS AND THOMAS L. JOHNSON[2,3]

Several years ago[4] a method of synthesis was developed for the ketone Ia, which possesses the basic ring system of the female sex hormones but with the ketone group at the 16 rather than the 17-position, and lacking the angular methyl and 3-hydroxyl groups. More recently[5] this synthetic approach was modified to permit incorporation of the angular methyl group as in Ib, and extended[6] to the synthesis of Ic, a structural isomer of equilenin. The present paper is concerned with the synthesis of 1,3,5-estratrien-3-ol-16-one (II), which is a structural isomer of estrone having the carbonyl group shifted to the 16-position.



Ia, R¹ = R² = H
Ib, R¹ = H; R² = CH₃
Ic, R¹ = OH; R² = CH₃



II

For this extension to compounds having ring B hydrogenated the key intermediate was the ketone VII,[7] for which an improved synthesis was developed by Bachmann, Kushner and Stevenson.[8]

In the present work the over-all yield in the conversion of the substituted malonic ester III to V could be raised from 28 to 45% by eliminating distillation of the intermediate keto ester IV and carrying out the cyclization with anhydrous hydrogen fluoride.[9] The remaining steps involving reduction of the dibasic acid to VI, conversion to the methyl ester, Dieckmann cyclization and methylation of the cyclic β-keto ester, followed by hydrolysis and decarboxylation, proceeded well to give mainly the crystalline isomeride of the octahydro ketone VII. Similar treatment of V led to the related hexahydro ketone VIII.[8] In each case the over-all yield of ketone from dibasic acid was 75–78%, or about 6.5 and 7.4%, respectively, for the 14–15 step synthesis from *m*-aminophenol.

In the earlier synthesis of the desoxy tetracyclic ketone Ib,[5] an acetic acid residue was introduced into the 2-position of 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene by preparing the sodium enolate of the ketone with sodium amide and alkylating with methyl bromoacetate. Preliminary attempts to apply this procedure to the methoxy ketones VII or VIII (on a 0.5 g. scale) led to oily acidic mixtures after hydrolysis, from which no pure crystalline products could be isolated. Further work in the tetrahydro desoxy series showed that the original procedure, although quite satisfactory on a moderately large scale (71% yield on a 20 g. scale) was poor for small scale experiments (35–39% on a 0.5 g. scale). Triphenylmethylsodium, however, proved to be satisfactory as an enolizing agent even on a small scale, and when the optimum conditions for the reaction were developed it was possible to prepare the crystalline acetic acid derivatives IXa and Xa in 55–59% yields from the methoxy ketones VII and VIII.

With the hexahydroketone VIII the most probable position of alkylation was the 2-position.

---

[1] Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

[2] Eli Lilly Research Fellow, 1945–1946.

[3] Present address: Sterling-Winthrop Research Institute, Rensselaer, N. Y.

[4] Wilds, THIS JOURNAL, **64**, 1421 (1942).

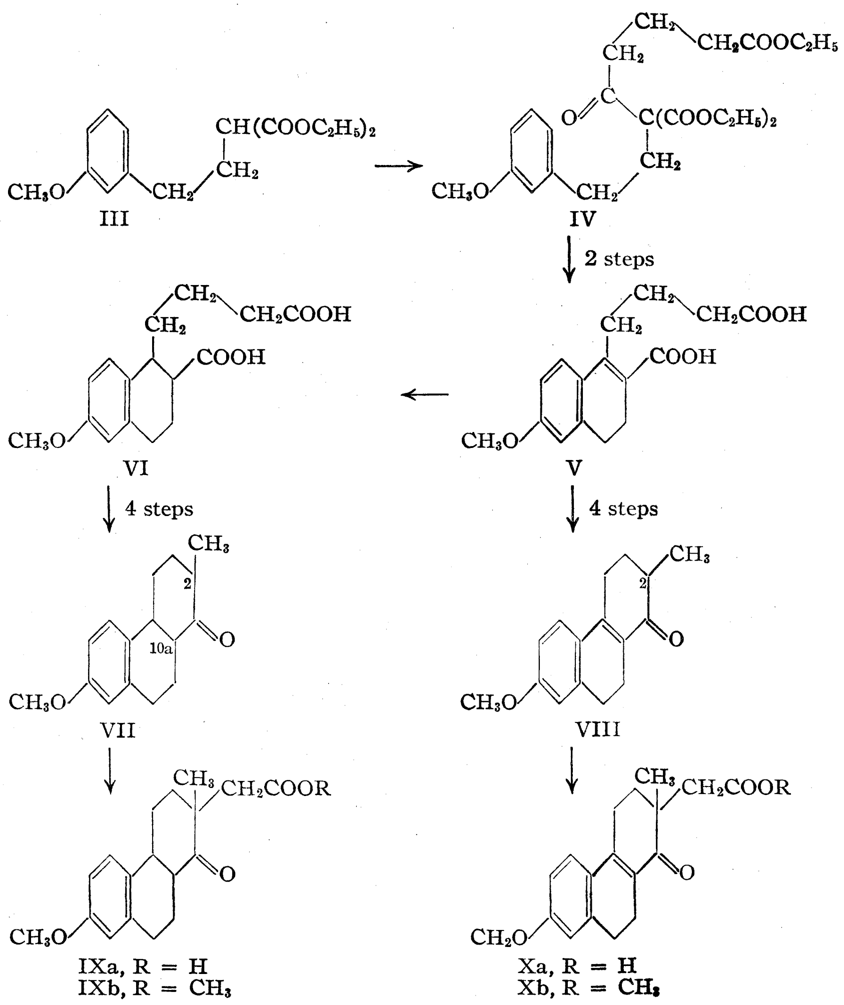
[5] Wilds and Beck, *ibid.*, **66**, 1688 (1944).

[6] Wilds and Close, *ibid.*, **69**, 3079 (1947).

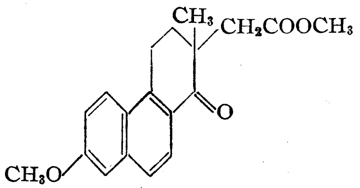
[7] Robinson and Walker, *J. Chem. Soc.*, 183 (1938).

[8] Bachmann, Kushner and Stevenson, THIS JOURNAL, **64**, 974 (1942).

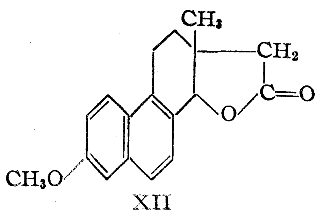
[9] Adkins and Hager have found this to be an excellent reagent for effecting the cyclization of somewhat analogous β-keto esters; Glenn F. Hager, Ph.D. Thesis, University of Wisconsin, 1943.



This structure for the acid Xa was proved by selective dehydrogenation of the methyl ester at 150° to the tetrahydro ester XI, which has been prepared[6] by a similar alkylation of the tetrahydro analog of VIII. The structure Xa for the acid also was supported by the ultraviolet absorption spectrum of the ester Xb, which was almost identical with that of the ketone VIII.



XI

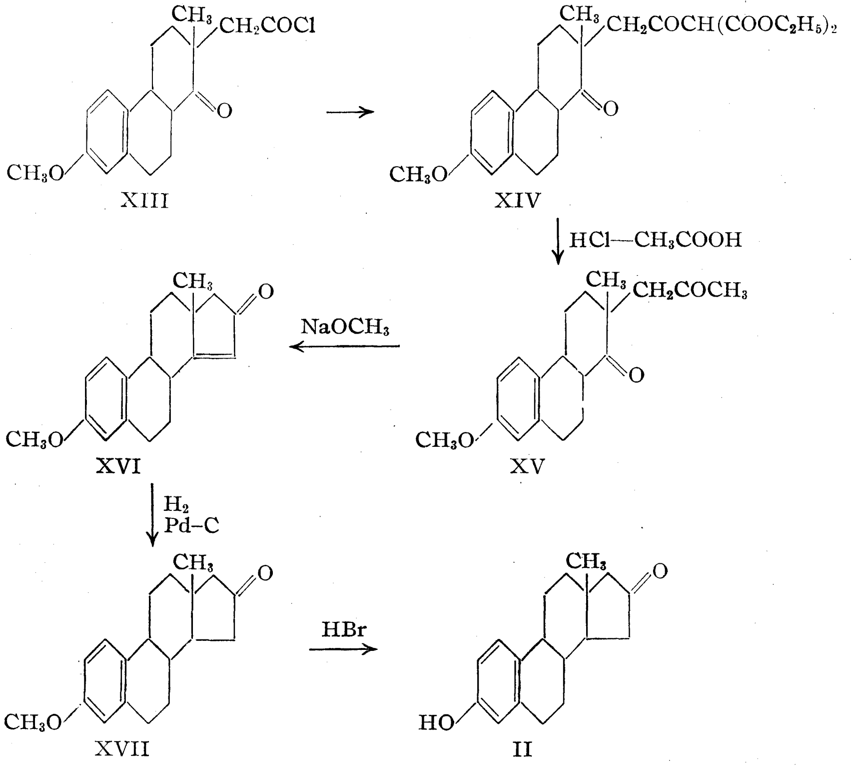


XII

In the case of the octahydro ketone VII not only the 2-position but also the angular 10a-position is available for alkylation. The results of dehydrogenation of the octahydro ester IXb were not so definitive as those for the hexahydro ester. The product after hydrolysis of the dehydrogenated ester contained considerable lactonic as well as acidic material. A small amount (5%) of the tetrahydro ester XI could, however, be isolated from the acidic product. The crystalline lactone, surprisingly enough, had the composition $C_{18}H_{20}O_3$ and thus apparently contained two hydrogen atoms more than the tetrahydro lactone XII, which was prepared by aluminum isopropoxide reduction of the ester XI. On the other hand, the ultraviolet absorption spectrum which closely resembled that of the tetrahydro lactone XII would indicate the presence of a naphthalene nucleus. Further work will be necessary to establish its structure.

Regardless of its own structure, however, the lactone obtained from the octahydro ester furnishes additional support for structure IXb, since a small amount of the same lactone was obtained by dehydrogenation of the hexahydro ester Xb at 225°. And finally, the hexahydro and octahydro series were linked by hydrogenation of the ester Xb. While the reaction was complex, it was possible to isolate a small amount (3%) of the crystalline octahydro ester IXb. Another product was the tetrahydro lactone XII, identical with that obtained from XI. Although in each of these reactions to establish the structure of IXa the yield of the critical derivative was low, the combined evidence affords reasonably good proof for the formula assigned.

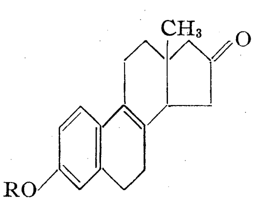
The next step of the synthesis involved converting the substituted acetic acids (IXa and Xa) into the corresponding methyl ketones. The reactions,[5] which involved formation of the acid chloride, condensation with sodiomalonic ester and acid hydrolysis of this intermediate to the diketone, proceeded well (78–83% yield) in the tetrahydro desoxy series regardless of the scale of the run (0.15 g. to 24 g.). Initial experiments in both the hexahydro and octahydro methoxy series, however, were unsuccessful and no crystalline products could be isolated. In the hexahydro series, starting with Xa, a large amount of *acidic* oil was obtained at the stage of the acyl malonic ester derivative. Part of the difficulty can be attributed to the step involving formation of the supposed acid chloride, for after hydrolysis of the latter, prepared with thionyl chloride or oxalyl chloride, only a small fraction of the starting acid could be recovered.



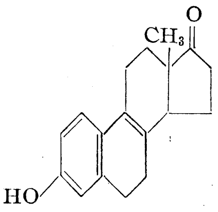
Early experiments with the octahydro acid IXa, using thionyl chloride to prepare the acid chloride, likewise led to an oily product at the diketone stage. However, in one run employing oxalyl chloride, 20% of the crystalline diketone XV was obtained. Here, too, the major difficulty consisted in forming the acid chloride. When the supposed acid chloride was hydrolyzed with water most of the product was a *neutral* oil, from which some of the starting acid could be obtained by alkaline hydrolysis. This indicated that the major product of this step was the ***enol*** lactone of IXa, rather than the acid chloride. By employing the sodium salt of the acid with oxalyl chloride,[10] the reaction was improved and the yield of the diketone increased to 42%. The sodium salt method, however, was unsuccessful in the hexahydro series, as were attempts to block the carbonyl group of IXb by conversion to a ketal with ethyl orthoformate or ethylene glycol.[11,12]

The cyclization of the diketone XV to the unsaturated ketone XVI was markedly influenced by the reaction conditions. The yield of the crystalline product was 90% using sodium methoxide in methanol as the condensing agent and heating for two and three-quarters hours. With shorter or longer times the yield was markedly decreased, in the latter case probably through isomerization of the crystalline ketone XVI. The ultraviolet absorption spectrum of the ketone (Fig. 1) showed bands typical for an α,β-unsaturated ketone (max. 227 mμ)[13] and for a phenol ether (max. 280 mμ).

Demethylation of the methoxy ketone XVI with hydrobromic and acetic acids gave a mixture from which a crystalline phenolic ketone could be isolated in 37% yield. The ultraviolet absorption spectrum of the latter (Fig. 1, max. at 273 mμ), different from that of the original methyl ether, indicated that the double bond had shifted from ring D into conjugation with ring A, most probably as shown in XVIIIa. This compound is then the 16-keto isomer (*dl*) of Hirschmann and Wintersteiner's isoequilin A (XIX, max. at 273 mμ)[14] which was prepared by a similar acid isomerization of the 7–8 double bond of equilenin to the 8–9 position.



XVIIIa, R = H
XVIIIb, R = CH_3



XIX

By hydrogenation with a palladium-on-carbon catalyst the unsaturated methoxy ketone XVI was converted into one of the isomeric forms of the reduced ketone XVII in 90% yield. Demethylation of this compound gave one of the eight possible racemic forms of the phenolic ketone II, m.p. 177.5–178°. The ultraviolet absorption

---

[10] *Cf.* Adams and Ulich, THIS JOURNAL, **42**, 599 (1920).

[11] Salmi, *Ber.*, **71**, 1803 (1938).

[12] Serini and Köster, *ibid.*, **71**, 1766 (1938).

[13] The predicted value for a five-membered ring ketone having two β-substituents and an exocyclic double bond is about 229 mμ [*cf.* Woodward, THIS JOURNAL, **64**, 76 (1942) and Gillam and West, *J. Chem. Soc.*, 486 (1942)].

[14] Hirschmann and Wintersteiner, *J. Biol. Chem.*, **126**, 737 (1938).

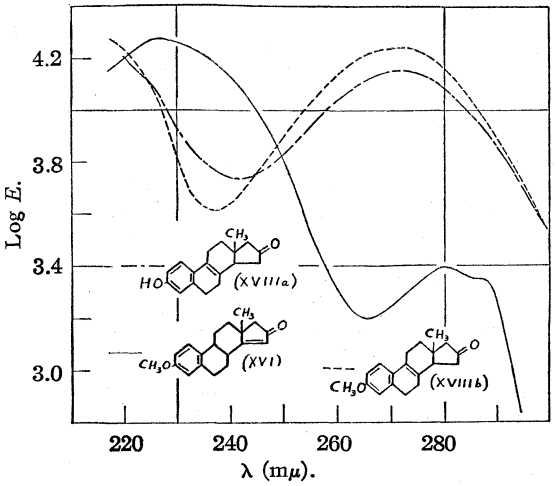


Fig. 1.

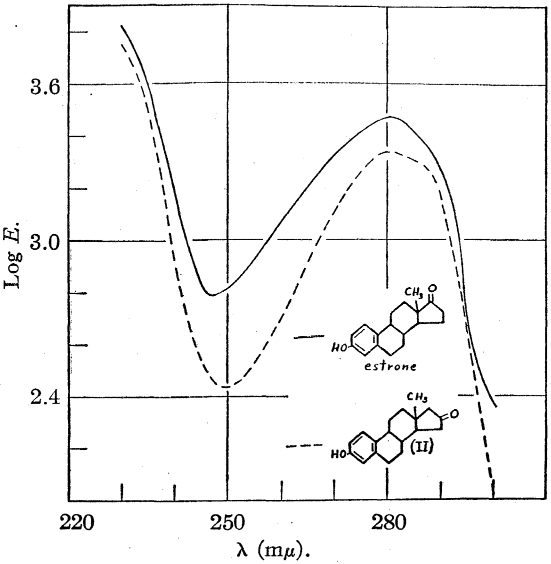


Fig. 2.

spectrum of the reduced phenolic ketone was in reasonably good agreement with that for estrone as can be seen from Fig. 2.

Tests for estrogenic activity, for which we are indebted to Drs. J. A. Leighty and E. D. Campbell of Eli Lilly and Co., indicated that this isomer of the phenolic ketone II possesses a low order of activity in ovariectomized mice. When injected as a solution in cottonseed oil, about 500 γ was equivalent to one mouse unit of estrone (0.066 γ). Since in the case of the analogous structural isomer of equilenin, reported recently,[6] the decrease in activity was much less (to about one-third that of *dl*-equilenin), it seems apparent that the present isomer of II does not possess the same stereochemical configuration as estrone. The unsaturated phenolic ketone XVIIIa was considerably more active, with one mouse unit equal to about 30 γ. This activity is the same as that for one of the isomers of Ic,[6] but is much lower (of the order of one-hundredth) than that for isoequilin A, which was reported[14] to be about one-fifth as active as estrone. Further work is in progress to prepare other stereoisomers of II by isomerization at various stages of the synthesis and by other suitable variations. The introduction of a keto group at C-17[5] in XVI with the goal of synthesizing the structures of estriol and estrone also is being investigated.

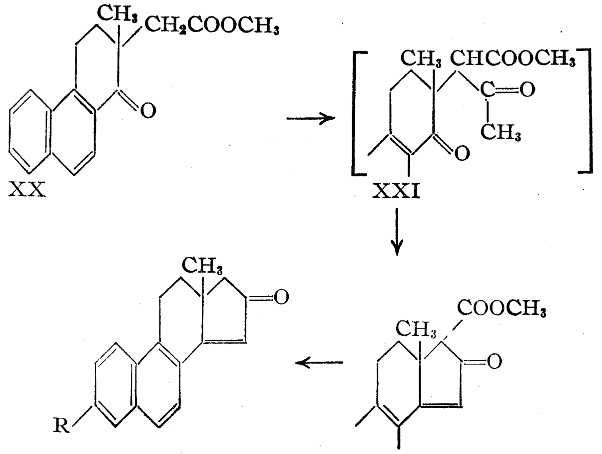
In view of the low yield at the stage of converting the acetic acid derivative IXa to the diketone XV, and the failure of the reaction in the hexahydro series, other approaches to the diketone and cyclic ketone which did not involve formation of the acid chloride, were investigated. Trial experiments were carried out first with the more readily available tetrahydro desoxy derivatives. Attempts to prepare the diketone directly from the ketone (corresponding to VII) by alkylation of the enolate with chloroacetone or iodoacetone were unsuccessful. Another route which appeared to offer considerable promise was the acetoacetic ester type of condensation between the keto ester XX and esters of acetic acid. Condensation reactions with ethyl acetate or acetonitrile, using sodium methoxide as the condensing agent, gave no positive results. Consequently the stronger base triphenylmethylsodium was used to prepare the enolate of the ester XX which was then condensed with phenyl acetate, a method employed with considerable success by Hauser and co-workers.[15] This led to an initial alkali-soluble product which underwent hydrolysis and decarboxylation with acid to give the cyclic ketone XXIIIa (in 23% yield) instead of the diketone. The yield could be raised by a retreatment of the neutral fraction to 37% (or 52% when corrected for recovered starting acid). The intermediate alkali-soluble material appears to be the cyclic keto ester XXII, previously prepared by Wilds and Beck[5] from XXIIIa through the glyoxalate reaction. The ultraviolet absorption spectrum of the compound closely resembled that of XXIIIa and other compounds having the same ring and conjugated double bond system.[16] The reaction of acetyl chloride with the enolate of the ester XX also was investigated. In this case the product (presumably XXI) was neutral, and after acid hydrolysis and decarboxylation the diketone corresponding to this was isolated in 19% yield using Girard's reagent P.

Application of the triphenylmethylsodium–phenyl acetate reaction to the methoxy hexahydro ester Xb gave an initial alkali-soluble product which led to a neutral oil upon hydrolysis and decarboxylation. Apparently this product unlike that in the tetrahydro desoxy series was not completely cyclized (if at all); upon heating with

---

(15) Reviewed by Hauser and Hudson in "Organic Reactions," John Wiley and Sons, Vol. 1, New York, N. Y., 1942, pp. 266–302.

(16) See Wilds, Beck, Close, Djerassi, J. A. Johnson, T. L. Johnson and Shunk, THIS JOURNAL, **69**, 1985 (1947).



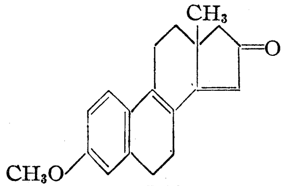
XX

XXI

XXII

XXIIIa, R = H
(XXIIIb, R = CH_3O)

alkali, however, it gave the crystalline cyclic ketone XXIV in 11% yield. This material, a yellow solid, was not obtained entirely pure, judging from the melting point range, but the ultraviolet absorption spectrum, with the main maximum at 360 mμ, supports the structure with the double bonds as shown. Upon standing the filtrate from this ketone slowly deposited a small amount of a higher melting ketone which proved to be the dehydrogenated naphthalenic analog XXIIIb.[6] The reaction of acetyl chloride with the enolate of Xb gave after hydrolysis and cyclization about 2% of the same ketone XXIV as obtained from the phenyl acetate reaction.



XXIV

In the octahydro series the yields were even lower. In one run the reaction of phenyl acetate with the enolate of IXb gave after hydrolysis and decarboxylation 6% of the crystalline diketone XV, identical with that from the acid chloride–malonic ester procedure. In another run no crystalline diketone could be isolated, but after cyclization the crystalline compound obtained was similar in melting point and analysis to the cyclic ketone XVI; the mixed melting point, however, showed a 25° depression. The ultraviolet absorption spectrum (Fig. 1) indicated that in this isomer the double bond had shifted away from the carbonyl group and into conjugation with the aromatic ring as shown in XVIIIb.

Experimental[17]

Preparation of 1-Keto-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene and 1-Keto-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene.[18]

—The method of Bachmann, Kushner and Stevenson[8] was employed for preparing these ketones with some modification in certain of the steps.

Ethyl 5-Keto-6,6-dicarbethoxy-8-*m*-anisyloctanoate (IV).—To 7.85 g. of powdered sodium in 230 cc. of dry, thiophene-free benzene was added 100 g. of diethyl β-*m*-anisylethylmalonate (III)[8] and the mixture was stirred and refluxed for twenty hours. Then the solution was cooled in an ice-bath and 76 g. of the acid chloride of ethyl hydrogen glutarate[8] was added. After four hours at room temperature and one hour at reflux the mixture was cooled and water added. The benzene layer and the ether extract of the aqueous layer were combined, washed with sodium bicarbonate solution and dried over sodium sulfate. Then the solvents and low boiling material were removed *as rapidly as possible* under reduced pressure (25 mm.), warming the residue finally to 100° in an oil bath. The residual yellow oil (134 g. corresponding to an apparent yield of 91%) was used in the next step without further treatment.[19]

γ-(6-Methoxy-2-carboxy-3,4-dihydro-1-naphthyl)-butyric Acid (V).[8]—To 25 g. of the crude undistilled keto ester (from the above procedure) in a 500-cc. platinum beaker cooled in an ice–salt mixture to −10°, was added approximately 150 g. of anhydrous, liquid hydrogen fluoride.[9] The mixture was kept in the bath at −10° for five hours, then the hydrogen fluoride was removed in a stream of air. Ice was added, most of the residual acid was neutralized with solid sodium bicarbonate, and the mixture was extracted twice with ether, washing the latter with water and evaporating. The residual triester was refluxed for three hours with 100 cc. of 45% potassium hydroxide and 100 cc. of methanol, most of the methanol was evaporated in a stream of air and the diluted mixture extracted with ether. The alkaline layer was acidified by pouring onto a mixture of ice and 110 cc. of concentrated hydrochloric acid and the tribasic acid was extracted with three portions of ether. Following removal of the ether the residue was heated with 250 cc. of water on the steam-bath for twelve hours. After cooling, the oily solid was filtered, triturated with about 30 cc. of ether, refiltered and washed with cold benzene, giving 8.15 g. of the dibasic acid, m. p. 185–187.5° (d.). A second crop of 0.10 g., m. p. 175–182°, brought the total yield to 50%, based upon the crude keto-ester, or an over-all yield of 45%, based on the diethyl β-*m*-anisylethylmalonate.

A third crop of 0.85 g., m. p. 135–143° (d.), proved to be β-*m*-anisylmalonic acid. After recrystallization from dioxane–benzene the compound melted at 143–144° (d.) and showed no m. p. depression when mixed with an authentic sample.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.5; H, 5.9. Found: C, 60.5; H, 6.0.

The above conditions represent the optimum determined from a number of cyclizations in which the time of standing with hydrogen fluoride and the temperature were varied.

1-Keto-2-carbomethoxy-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene.[8]—The dibasic acid (20 g., m. p. 185–188°) was converted to the dimethyl ester with diazomethane in ether (prepared from 30 g. of N-nitroso-N-methylurea), the ether was removed by distillation and the absence of water insured by adding dry benzene and again distilling the solvent. Meanwhile

---

(17) All melting points are corrected unless otherwise indicated; those marked "vac." were determined in sealed Pyrex melting point tubes evacuated to at least 0.5 mm.

18) Some of the early experiments in this section were carried out by Dr. Lloyd W. Beck.

(19) The earlier procedure[8] for this reaction included further purification by flash distillation at 340° (0.05 mm.) followed by fractional distillation. We have observed that this purification results in lower and more variable over-all yields of the dibasic acid V after cyclization, as indicated by the following example: crude keto ester obtained in 86% apparent yield gave a 43% over-all (from III) yield of the acid V; after the flash distillation the over-all yield of V dropped to 38%, after the fractional distillation to 16%, and after a second fractional distillation to 7%.

sodium methoxide was prepared from 3.2 g. of sodium and 70 cc. of anhydrous methanol, removing the excess solvent under reduced pressure at 100°. Dry benzene was added to the solid and again removed. The cake of sodium methoxide was broken up, the system filled with nitrogen, and the dimethyl ester was added in 250 cc. of dry benzene. The suspension was refluxed with occasional vigorous swirling; in one hour the sodio derivative of the cyclic keto ester began to separate as a voluminous precipitate. After eighteen hours at reflux, the mixture was cooled and 25 cc. of methyl iodide in 25 cc. of anhydrous methanol was added. After twenty-four hours at room temperature, the solid had completely dissolved, and an additional 10 cc. of methyl iodide and 10 cc. of methanol were added and the solution refluxed for one hour. The mixture was acidified with acetic acid, water and ether added and the organic layer was washed with sodium bicarbonate solution, dried and evaporated. The residue readily crystallized from methanol giving 15.6 g. of the keto ester, m. p. 96–97.5° and an additional 1.85 g., m. p. 90–96.5°, for a total yield of 84%. The pure compound is reported[8] to melt at 98–100°.

1-Keto-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (VIII).—A mixture of 20.1 g. of the above keto ester, 200 cc. of acetic acid, 200 cc. of hydrochloric acid and 100 cc. of water was refluxed under nitrogen for two hours, then cooled, diluted and extracted twice with ether, washing with water, dilute potassium hydroxide and acid. From the ether extract by recrystallization from petroleum ether (b. p. 60–68°) was obtained 14.8 g. (91%) of the ketone, m. p. 67–69°. Further recrystallization gave material melting at 68–69° (reported 66–67°[8] and 67–68°[7]). The ultraviolet absorption spectrum was reported earlier.[16]

From the potassium hydroxide washings was obtained 0.52 g. of phenolic material, m. p. 183–189°. Two recrystallizations from methanol gave colorless prisms of what appears to be 1-keto-2-methyl-7-hydroxy-1,2,3,4,-9,10-hexahydrophenanthrene, m. p. 187–189°.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1. Found: C, 78.8; H, 7.0.

γ-(6-Methoxy-2-carboxy-1,2,3,4-tetrahydro-1-naphthyl)-butyric Acid (VI).—Reduction of the recrystallized unsaturated dibasic acid (5.03 g.) was carried out as described by Bachmann, Kushner and Stevenson,[8] with palladium-on-carbon catalyst.[20] A total of 4.64 g. (92%), m. p. 155–157.5°, of the reduced acid was obtained by crystallization from benzene (reported,[8] m. p. 156–157.5°).

1-Keto-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (VII).—The Dieckmann reaction was carried out on the dimethyl ester of the reduced dibasic acid (from 12.4 g. of acid and diazomethane) as described for the unsaturated analog, allowing twenty-one hours at reflux and using 25 cc. of methyl iodide in 50 cc. of methanol for the first addition and 10 cc. of methyl iodide in 25 cc. of methanol for the second. The mixture was allowed to stand for another twenty hours, followed by three hours at reflux, and the intermediate keto ester was isolated as an oil.[21] It was hydrolyzed and decarboxylated by refluxing with 120 cc. of acetic acid, 120 cc. of hydrochloric acid and 60 cc. of water for one and one-half hours under a nitrogen atmosphere. The cooled mixture, which showed an intense green fluorescence, was worked up as described for the hexahydro ketone. The product crystallized from methanol giving 5.74 g. of colorless ketone, m. p. 107–114°. The filtrate contained a preponderance of oily diastereoisomers which were partially converted to the crystalline isomeride by a repetition of the acid treatment for one and one-half hours using one-half the original quantity of reagents. In this manner an additional 1.71 g. of the crystalline ketone, m. p. 114–116°, was obtained, and from a third acid treatment another 0.26 g., m. p. 102–112°, for a total crude yield of 74%. Two recrystallizations of this material from methanol gave 5.1 g. of ketone, m. p. 116–118°, which was used in the subsequent reactions. By further recrystallization material of m. p. 118.5–119° was obtained (reported 116–117.5°[8] and 119–120°[7]).

Syntheses in the Desoxy Series (with 1-Keto-2-methyl-1,2,3,4-tetrahydrophenanthrene)

1-Keto-2-methyl-1,2,3,4-tetrahydrophenanthrene-2-acetic Acid.—For the preliminary experiments in the methoxy series it was essential to have a procedure suitable for small-scale runs. The procedure previously described by Wilds and Beck,[5] in which sodium amide was used in ether[22] suspension to enolize the ketone, gave considerably lower yields (35–39%) when the amount of ketone was reduced to 0.5 g.; with potassium amide (and allowing only 0.75 hour for enolization) the yield was slightly improved (49%). Triphenylmethylsodium[15] proved to be a suitable reagent for runs on a small scale, giving 74% yield of the acid in 0.5 g. runs (by a procedure similar to that described below in the octahydro series).

Condensation of Methyl 1-Keto-2-methyl-1,2,3,4-tetrahydrophenanthrene-2-acetate with Phenyl Acetate.—To a solution of 1 g. of the methyl ester XX (m. p. 72–73.5°) in 10 cc. of dry ether was added triphenylmethylsodium solution[25] in slight excess (11 cc. of 0.4 *M*) under nitrogen followed by 0.5 cc. of phenyl acetate.[23] The mixture was allowed to stand at room temperature for four hours with occasional swirling. Dilute acetic acid and ether were then added and the ether solution was washed with water and three times with 10% potassium hydroxide solution (the latter constitutes fraction a). The ether solution was evaporated and a crop of triphenylmethane (0.5 g., m. p. 91–93°) was crystallized from benzene. The filtrate was dried by repeated addition of dry benzene and distillation under reduced pressure, then the residue was treated again with the triphenylmethylsodium solution until a permanent red color remained (9 cc.). Phenyl acetate (0.5 cc.) was added and the above procedure repeated, giving a second portion of material in the alkaline extract (fraction b). Both fractions were worked up separately. The potassium hydroxide solution containing fraction a was acidified, extracted with ether and the latter washed with sodium bicarbonate solution. Evaporation of the ether left 0.48 g. of oil which was refluxed for two hours with 10 cc. of acetic acid, 10 cc. of hydrochloric acid and 4 cc. of water. After cooling, extracting with ether and washing with alkali and water, 0.23 g. of a yellow oil was obtained which crystallized immediately when stirred with petroleum ether, giving 0.203 g., m. p. 142.5–148°.

Fraction b gave in a similar manner an additional 0.120 g., m. p. 133–144°. This material proved to be $\Delta^{1,1'}$-2'-keto-2-methyl-3,4-dihydro-1,2-cyclopentenophenanthrene (XXIIIa); a recrystallized sample had the m. p. 148–150° alone and when mixed with a known sample.[5] From the neutral fraction after the second treatment was obtained 0.283 g. (30%), m. p. 148–151.5°, of the starting acid by alkaline hydrolysis and recrystallization of the bicarbonate-soluble fraction. The yield of the cyclic ketone corresponded to 37%, or 52% taking into account the recovered acid.

In another run, starting with 2 g. of the methyl ester, the intermediate alkali-soluble product was investigated. This material (950 mg. of oil which contained phenol)

---

[20] Linstead and Thomas, *J. Chem. Soc.*, 1130 (1940).

[21] Recently Anner and Miescher [*Helv. Chim. Acta*, **30**, 1427 (1947)] have reported isolation of three of the four possible crystalline *dl*-forms of this compound.

[22] Subsequent work has indicated toluene to be a more suitable solvent than ether for this reaction on a large scale, and in this case also the size of run can be reduced to at least 2 g. without lowering of yield. Using toluene at 55° for seven hours for the enolization of the ketone with sodium amide, the yield of crystallized acid (m. p. 148–150.5°) amounted to 71%; 5% of the starting ketone was recovered and none of the high melting by-product (m. p. 255–256°) was formed.

[23] Ethyl acetate was much less satisfactory, resulting in a lower yield of cyclic ketone, a trace of the uncyclized diketone and an appreciable amount of lactonic material.

would not crystallize until seeded in methanol with methyl $\Delta^{1,1'}$-2′-keto-2-methyl-3,4-dihydro-1,2-cyclopentenophenanthrene-3′-carboxylate (XXII, m. p. 148–154°) prepared earlier.[5] A total of 0.30 g. of yellow solid was obtained, m. p. 141–150°, which gave a green color with alcoholic ferric chloride. Repeated recrystallization from methanol gave a sample with the m. p. 149.5–158°. This material apparently retained solvent of crystallization since the analysis showed a low carbon value (76.4%). After drying at 80° and 0.1 mm. for forty hours, satisfactory analytical values were obtained.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.4; H, 5.9. Found: C, 78.3; H, 5.9.

The ultraviolet absorption spectrum[24] was very similar to that of the cyclic ketone XXIIIa[16] and showed maxima at 219 mμ (log E = 4.33), 238.5 mμ (4.10), 267 mμ (4.48), 276 mμ (4.56) and 315.5 mμ (4.40); minima at 230.5 mμ (4.05), 249 mμ (4.08), 270 mμ (4.45) and 287.5 mμ (4.06); and points of inflection at 245 mμ (4.09) and 360 mμ (3.75).

Syntheses in the Hexahydro Series (with 1-Keto-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene)

1-Keto-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-acetic Acid (Xa).—The hexahydro ketone VIII (5.04 g.) was alkylated using triphenylmethyl sodium and methyl bromoacetate following the same procedure as described below for the octahydro ketone VII, except that ten minutes was allowed between the addition of the base and the bromo ester. The acid was crystallized from benzene to give 3.40 g. of acid (m. p. about 90–100°) containing benzene of crystallization. An additional 0.26 g. of crystalline material was obtained by chromatographic fractionation of the remaining acidic oil as the methyl ester (see below). The solvent of crystallization could be removed only by heating for one to two days at 70° and 0.2 mm., then giving a product melting at 105.5–106.5°. The loss in weight (10.4%) corresponded approximately to one-half molecule of benzene of crystallization (calcd. 11.5%). The yield of product, corrected for the benzene of crystallization, was 52%. Recrystallization of the combined acid from carbon tetrachloride (which is not suitable for crystallizing the crude product) gave 2.82 g. (45%) of nearly colorless, solvent-free material, m. p. 105.5–106.5° with slight softening at 104°. The purest sample was obtained from methanol as colorless clumps of prisms, m. p. 106.5–107.5°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7. Found: C, 71.9; H, 6.9.

The **methyl ester Xb**, prepared with an ethereal solution of diazomethane, was obtained in practically quantitative yield as colorless blades from methanol, m. p. 66.5–68°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.6; H, 7.1. Found: C, 72.3; H, 6.9.

The ultraviolet absorption spectrum[24] of the ester showed maxima at 240 mμ (log E = 4.04) and 329 mμ (4.34) and a minimum of 262.5 mμ (3.04).

In addition to the acid some phenolic material also was obtained which crystallized when stirred with benzene, 360 mg. (7%), m. p. 119–125°. Repeated recrystallization from benzene raised the m. p. of the product to 124–126.5°; from the analytical values this material appears to be **2-methyl-7-methoxy-9,10-dihydro-1-phenanthrol**.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 79.8; H, 6.6.

Chromatographic fractionation of the residual oily acid (as the methyl ester) was carried out on alumina. Elution with 60% benzene (in petroleum ether) gave 430 mg. of a nearly colorless oil which crystallized when stirred with petroleum ether; 204 mg., m. p. 140–160°. After two recrystallizations from methanol a compound, isomeric with the desired methyl ester, was obtained as colorless prisms, m. p. 161.5–163°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.6; H, 7.1. Found: C, 72.5; H, 7.0.

The ultraviolet absorption spectrum[24] of this ester was quite different from that of the methyl ester Xb, showing a maximum at 261 mμ (log E = 4.23), a minimum at 233 mμ (3.63) and a point of inflection at 292 mμ (3.51).

Subsequent eluates of the chromatogram, finally using pure benzene, gave material which upon saponification yielded 0.26 g. of the acetic acid derivative Xa mentioned above.

Dehydrogenation of the Hexahydro Methyl Ester Xb.—The ester (100 mg., m. p. 64–66°) and 100 mg. of palladium-on-carbon catalyst[20] were heated under nitrogen at 130–150° for a total of twenty minutes. The product was crystallized from methanol to give a total of 54 mg. of solid, m. p. 94–96°; after a second recrystallization the product melted at 97.5–99° alone and when mixed with a sample of the tetrahydro methyl ester XI (m. p. 98.5–99.5°).[6] Saponification gave the corresponding acid, m. p. 145–147° alone and when mixed with an authentic sample.[6]

In another run the same quantities of the methyl ester and catalyst were heated for five minutes in a bath preheated to 225°. The crude product gave 46 mg. of the tetrahydro ester, m. p. 94.5–97.5°. The material in the filtrate was hydrolyzed with 5% potassium hydroxide, extracted with ether and acidified. After warming the suspension of acid for one-half hour on the steam-bath it was taken up in ether and washed with sodium bicarbonate solution. The latter gave 22 mg. of acidic material and from the ether was obtained 16 mg. of neutral, lactonic material. Crystallization gave 11 mg. of a mixture, m. p. 123–133.5° (softening at 117°), from which a small amount of material, m. p. 131.5–134°, was obtained after five recrystallizations from benzene–petroleum ether. This showed no depression in m. p. when mixed with the lactone obtained below by dehydrogenation of the methyl ester of the octahydro acid.

$\Delta^{1,1'}$-2′-Keto-2-methyl-7-methoxy-3,4,9,10-tetrahydro-1,2-cyclopentenophenanthrene (XXIV).—To a solution of 634 mg. of the hexahydro methyl ester Xb (m. p. 64–66°) in 10 cc. of dry, thiophene-free benzene was added 1.4 equivalents of triphenylmethylsodium solution[25] (9 cc. of 0.3 *M*) under nitrogen; the red color of the reagent did not persist. Phenyl acetate (0.4 cc.) was added and the mixture allowed to stand for eighteen hours. Then it was worked up as described above for the desoxy series and the potassium hydroxide-soluble portion isolated. A retreatment of the neutral fraction (5 cc. of triphenylmethylsodium and 0.4 cc. of phenyl acetate) gave additional alkali-soluble material. These were hydrolyzed in a nitrogen atmosphere with acid; as the neutral fraction was not crystalline it was heated for fifteen hours under nitrogen with 2 cc. of 45% potassium hydroxide and 8 cc. of methanol, and the neutral portion was evaporatively distilled at 180–200° (0.1 mm.). The yellow distillate (105 mg.) was crystallized from methanol yielding 50 mg., m. p. 120–127°, and 14 mg., m. p. 116–127°, corresponding to an 11% yield. A sample with a sharp melting point could not be obtained. Repeated recrystallization of the cyclic ketone from methanol gave yellow prisms, m. p. 122.5–128° with a small residue remaining to 135°.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.2. Found: C, 81.1; H, 7.2.

The ultraviolet absorption spectrum[24] showed maxima at 257.5 mμ (log E = 4.03) and 360 mμ (4.44); minima at 230 mμ (3.74) and 293 mμ (3.53); and an inflection at 280 mμ (3.70).

The methanol filtrate from which the ketone XXIV had crystallized slowly deposited a small amount of solid which was filtered after five months. This material, which melted at 120–130° but with a residue up to 185°, gave after two recrystallizations from methanol a small sample of cream colored solid, m. p. 202–203°, which gave

---

[24] The ultraviolet absorption spectra were all determined in absolute alcohol solution using a Beckman quartz photoelectric spectrophotometer; $E = (1/c) \log (I_0/I)$ for a 1-cm. cell, where c = concentration in moles per liter.

no melting point depression (m. p. 202–204°) when mixed with $\Delta^{1,1'}$-2′-keto-2-methyl-7-methoxy-3,4-dihydro-1,2-cyclopentenophenanthrene (XXIIIb).[6]

Basic hydrolysis of the initial neutral material containing triphenylmethane gave 272 mg. of acidic oil from which 71 mg. of the starting acid could be crystallized using benzene.

Synthesis in the Octahydro Series (with 1-Keto-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene)

1-Keto-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-acetic Acid (IXa).—The following procedure represents the best of a number of runs in which the conditions were varied. To a solution of 5.47 g. of the octahydro ketone VII in 50 cc. of dry, thiophene-free benzene was added[25] at room temperature under nitrogen a 10% excess of triphenylmethylsodium[15] in ether (61 cc. of 0.4 *M*). After twenty minutes the reaction flask was cooled in ice, transferred to a nitrogen-filled condenser attached to a mercury trap and 10 cc. of methyl bromoacetate was added *all at once* through the condenser with swirling. The mixture was refluxed for one and one-half hours, then the ether and benzene were evaporated and the residue was saponified by refluxing for twelve hours with 75 cc. of 45% potassium hydroxide and 75 cc. of methanol. After evaporating most of the methanol, the alkaline solution was washed twice with ether and acidified. The product was extracted with ether and crystallized from carbon tetrachloride to give 4.96 g. of the acid containing solvent of crystallization; the latter was removed by heating at 65° for twelve hours, giving 3.40 g. of acid, m. p. 132.5–138°. The mother liquors were evaporated and the residue was treated with 25 cc. of saturated sodium bicarbonate solution and allowed to stand; more of the acid separated as the insoluble sodium salt from which, after acidifying and extracting with ether, an additional 0.41 g. of the crystalline acid, m. p. 136.5–140°, was obtained. By a second treatment with a smaller volume of bicarbonate solution another 0.15 g. of the acid, m. p. 127–135°, was obtained, bringing the total yield to 59%. The ether washings contained 0.18 g. of phenolic oil which could not be crystallized. The purest sample of the acid was obtained by recrystallization from methanol, giving clumps of colorless prisms, m. p. 139.5–140.5°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3. Found: C, 72.0; H, 7.5.

The **methyl ester** IXb, obtained in 91% yield with diazomethane, crystallized from methanol as colorless leaflets, m. p. 97–97.5°.

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.1; H, 7.6. Found: C, 72.0; H, 7.6.

Dehydrogenation of the Octahydro Methyl Ester IXb.—A mixture of 100 mg. of the ester (m. p. 94–96°) and 100 mg. of palladium-on-carbon catalyst[20] was heated at 200–205° for twenty-five minutes. Crystallization of the product from benzene–petroleum ether (b. p. 60–68°) gave 46 mg., m. p. 110–128°; after four recrystallizations was obtained 12 mg. of material, m. p. 133.5–134.5°, which proved to be a lactone. It gave no depression in m. p. when mixed with the lactone obtained by dehydrogenation of the hexahydro ester (see above), but showed depression to 110–120° with the tetrahydro lactone XII (m. p. 145–145.5°).

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.0; H, 7.1; for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4; for $C_{18}H_{22}O_3$: C, 75.5; H, 7.8. Found: C, 76.1, 75.9; H, 7.1, 7.1.

The ultraviolet absorption spectrum[24] showed maxima at 229 mμ (log E = 4.66), 265 mμ (3.70), 274 mμ (3.71), 320 mμ (3.29), and 334 mμ (3.39); minima at 252–258 mμ (3.60), 269 mμ (3.66), 298 mμ (2.81) and 324 mμ (3.21); and inflections at 284 mμ (3.54), 308 mμ (3.01) and 329 mμ (3.26).

In another experiment 100 mg. of the ester was heated with the catalyst for ten minutes at 250°. A total of 37 mg. of the crude lactone and 32 mg. of acid, m. p. 125–131°, were obtained. The acid was treated with diazomethane and recrystallized five times from methanol to give about 5 mg. of the methyl ester of the tetrahydro acid XI, m. p. 95.5–96°. The mixed m. p. with an authentic sample[6] was 95.5–98.5°, while with the octahydro ester IXb (m. p. 94–96°) the m. p. was depressed to 72–96°.

Hydrogenation of the Hexahydro Methyl Ester Xb.—A solution of 489 mg. of the hexahydro ester Xb (m. p. 64–66°) in 16 cc. of purified dioxane was stirred with 200 mg. of palladium-on-charcoal catalyst[20] and hydrogen at atmospheric pressure and room temperature. After seven hours, when 1.1 mole-equivalents of hydrogen had been absorbed, reduction was still taking place at a steady rate and the reaction was stopped. The catalyst and solvent were removed, the residue hydrolyzed with 5 cc. of 45% potassium hydroxide and 20 cc. of methanol and separated into acidic (250 mg.) and lactonic (210 mg.) material as described above. A small portion (50 mg.) of the lactone crystallized from methanol, m. p. 114–138°. Recrystallization from benzene–petroleum ether gave a mixture of needles and clumps of microscopic crystals which were separated by hand. The former had the m. p. 162–171°, the latter 143–145°. A mixture of the latter with the lactone of 1-hydroxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-acetic acid (XII; see below) gave no m. p. depression. Apparently this lactone was formed by disproportionation.[26] The higher melting material was not investigated further.

The acidic fraction was dissolved in 5 cc. of hot sodium bicarbonate solution (saturated at room temperature) cooled and seeded with a trace of the sodium salt of the octahydro acid. After two days at 0° a small amount of precipitate had formed from which was obtained 15 mg. of acid which readily crystallized, m. p. 118–130°. The melting point was raised to 125–138° when the crude sample was mixed with the octahydro acid IXa. The crude acid was converted to the methyl ester (diazomethane) and recrystallized twice from methanol giving material melting at 95–97°. A mixture with the methyl ester of the octahydro acid IXb (m. p. 95.5–97°) showed no m. p. depression, while with the tetrahydro methyl ester XI (m. p. 98.5–99.5°)[6] the m. p. was depressed to 76–90°.

Aluminum Isopropoxide Reduction of the Tetrahydro Methyl Ester XI.—A solution of 100 mg. of the methyl ester[6] (m. p. 97.5–98.5°), and 300 mg. of aluminum isopropoxide in 5 cc. of anhydrous isopropyl alcohol was refluxed for sixteen hours. The solution was cooled, dilute acid added and the product was extracted with ether. The residue after evaporating the solvent was heated for two hours with 1 cc. of 45% potassium hydroxide and 4 cc. of methanol, diluted, acidified and warmed on the steam-bath for one-half hour. The product was extracted with ether, washed with bicarbonate solution (only 5 mg. of acidic material obtained) and crystallized from alcohol, giving 63 mg. of lactone, m. p. 144.5–145.5°, and an additional 11 mg., m. p. 142–144°, for a yield of 82%. The melting point of the pure lactone XII was 145–145.5°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4. Found: C, 76.3; H, 6.4.

The ultraviolet absorption spectrum[24] showed maxima at 236 mμ (log E = 4.84), 266.5 mμ (3.75), 275.5 mμ (3.77), 314 mμ (3.21), and 329 mμ (3.27); minima at 253.5 mμ (3.63), 270.5 mμ (3.73), 306 mμ (3.05) and 324

---

[25] The apparatus, designed by Dr. C. David Gutsche, was a convenient modification of that described by Baumgarten and Hauser [THIS JOURNAL, **66**, 1039 (1944)], which permitted the reagent reservoir and buret to be closed off from the rest of the system while this and the reaction flask were evacuated and filled with nitrogen. Measured amounts of the reagent solution were then added to the reaction flask from the buret.

[26] Disproportionation accompanying hydrogenation of somewhat related compounds has been observed before with equilin by Dirscherl and Hanusch, *Z. physiol. Chem.*, **233**, 13 (1935); **236**, 131 (1935), and with dihydroequilin by Serini and Logemann, *Ber.*, **71**, 186 (1938); for a recent example see Anner and Miescher, *Helv. Chim. Acta*, **29**, 1889 (1946).

mμ (3.08); and inflections at 285 mμ (3.62), 308 mμ (3.07), and 321 mμ (3.11).

1-Keto-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-acetone (XV).—The octahydro acid IXa (1.34 g.) was converted to the sodium salt by means of 0.374 g. of sodium bicarbonate in 5 cc. of water, the water was evaporated in a stream of air and the solid residue was powdered and dried in an oven at 100° for twelve hours. Dry benzene (15 cc.), a drop of pyridine and 4 cc. of oxalyl chloride (b. p. 63–64°) were added to the sodium salt[10] at 0°. Immediate reaction took place and after standing at room temperature for two and one-half hours, the solvent was removed under reduced pressure without heating, and an additional 10 cc. of benzene was added and removed as before. The acid chloride was dissolved in 30 cc. of dry benzene and filtered through a plug of cotton into a suspension of sodiomalonic ester (from 0.5 g. of sodium powder and 5 cc. of diethyl malonate in 50 cc. of dry ether). After stirring at room temperature for fifteen hours and at reflux for two, the mixture was acidified with dilute acetic acid, extracted with ether, the ether removed and the residue heated for one and one-half hours under nitrogen with 10 cc. of water, 25 cc. of acetic acid and 25 cc. of hydrochloric acid. The cooled mixture, which showed an intense green fluorescence, was diluted, extracted with ether and washed with water, 10% potassium hydroxide and dilute acid. From the ether was obtained 1.02 g. of brown oil which crystallized from methanol to give 471 mg. of the diketone, m. p. 115–122°. Evaporative distillation of the material in the filtrate at 170–190° (0.05 mm.) and recrystallization from methanol gave an additional 76 mg., m. p. 114–117.5° and 18 mg., m. p. 107–117° for a total yield of 42%. One recrystallization of the combined material gave 422 mg. of the diketone, m. p. 121–122.5°. The pure compound crystallized from methanol as colorless blades, m. p. 122–122.5°.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 76.0; H, 8.1. Found: C, 75.9; H, 8.1.

Acidification of the potassium hydroxide extracts gave 410 mg. of oil, from which 282 mg. of starting acid, m. p. 131–136°, was recovered through the insoluble sodium salt. The yield of crude diketone corrected for this recovered acid was 54%. When the acid chloride was prepared from the free acid, rather than the salt, the yield of crude diketone was only 20%.[27]

Condensation of Methyl 1-Keto-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-acetate with Phenyl Acetate.—This reaction was carried out with 750 mg. of the octahydro ester IXb (m. p. 95–97°) in the same manner as described above for the hexahydro ester Xb, except that ether was used instead of benzene to dissolve the ester originally, and the reaction mixture was allowed to stand for six hours. After hydrolysis and decarboxylation of the potassium hydroxide-soluble material, the neutral oil was evaporatively distilled at 185–200° (0.1–0.4 mm.) giving 130 mg. of oil from which 41 mg. (6%) of solid diketone, m. p. 105–118°, could be crystallized using methanol. Recrystallization from methanol gave 19 mg. of material, m. p. 121.5–122.5°, which showed no depression in m. p. when mixed with the diketone XV prepared by the malonic ester procedure.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 76.0; H, 8.1. Found: C, 75.5; H, 8.0.

A retreatment of the initial neutral fraction with triphenylmethylsodium and phenyl acetate gave only 7 mg. more of the crystalline diketone, m. p. 113–120.5°.

From another run starting with 700 mg. of the ester, the only variations being that benzene was used as the initial solvent and the reaction time was sixteen hours instead of six, no crystalline diketone was obtained. The oily diketone (135 mg., after evaporative distillation) was cyclized by heating with 1 cc. of 45% potassium hydroxide and 5 cc. of methanol for fifteen hours under nitrogen; 95 mg. of neutral oil was obtained which crystallized from methanol upon cooling to Dry Ice temperature, giving 26 mg. of solid, m. p. 103–109°. Recrystallization from methanol gave 7 mg., m. p. 108–111°. A mixture of this material with the cyclic ketone XVI (m. p. 110–111°) prepared by cyclization of the crystalline diketone XV (see below) gave a depression in melting point to 84–95°.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.8; H, 7.9. Found: C, 80.3; H, 7.7.

The ultraviolet absorption spectrum[24] of this substance (Fig. 1), which supported the structure XVIIIb as a result of a shift of the double bond, showed a maximum at 273 mμ (log E = 4.25) and a minimum at 237.5 mμ (3.62); a lower maximum and minimum in the region 320–370 mμ (log E = 2.7–2.9) were indicated but were not measured accurately.

3-Methoxy-1,3,5,14-estratetraen-16-one (XVI).—The optimum conditions for cyclizing the diketone XV were as follows: To a solution of 0.7 g. of sodium in 14 cc. of absolute methanol was added 284 mg. of the diketone (m. p. 120.5–122.5°) and the mixture was refluxed on the steam-bath in a nitrogen atmosphere for exactly two and three-quarters hours. The cooled mixture was diluted and extracted twice with ether and the extracts washed with water and dilute acid. After evaporating the ether the residue was stirred with petroleum ether (b. p. 60–68°), giving 239 mg. (90%) of solid, m. p. 107.5–111°. Recrystallization from alcohol gave 195 mg. of colorless blades, m. p. 110–111°, and 39 mg., m. p. 106.5–109°. The melting point of the first crop was not raised by further recrystallization.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.8; H, 7.9. Found: C, 80.8; H, 7.8.

The ultraviolet absorption spectrum[24] (Fig. 1) showed maxima at 227 mμ (log E = 4.27) and 280 mμ (3.40); a minimum at 265 mμ (3.21); and an inflection at 287 mμ (3.36).

The great importance of time in the above procedure was demonstrated by the following experiments, using the same concentration of sodium methoxide in methanol and starting with 100 mg. of diketone: two hours, 54% yield of crystalline cyclic ketone; two and three-quarters hours (above run on 284 mg.), 90%; three hours, 71%; four hours, 48%; and eight hours, no crystalline cyclic ketone isolated. In the last case the oily product was refluxed under nitrogen with 2 cc. of water, 5 cc. of acetic acid and 5 cc. by hydrochloric acid for one and one-half hours in order to effect isomerization if possible. When the neutral fraction was evaporatively distilled at 180–200° (0.05 mm.) and stirred with petroleum ether, it partially crystallized giving 22 mg. of an impure yellow solid, m. p. 110–145°. Further recrystallization from methanol gave material, m. p. 145–165°, which was still impure (*Anal.* Found: C, 79.1; H, 6.5); the ultraviolet absorption spectra suggested that it contains some of the methyl ether XXIIIb.

1,3,5,8(9)-Estratetraen-3-ol-16-one (XVIIIa).—A mixture of 75 mg. of the methoxy cyclic ketone XVI (m. p. 110–11°), 2.5 cc. of acetic acid and 2.5 cc. of 42% hydrobromic acid was refluxed under nitrogen for two and one-half hours. The cooled mixture, which exhibited a bright blue fluorescence, was diluted and made distinctly basic with 45% potassium hydroxide solution. Extraction with ether removed 12 mg. of oily neutral material. From the alkaline solution was obtained 60 mg. of phenolic oil which crystallized when stirred with a small amount of methanol yielding 26 mg. (37%) of a gray solid, m. p. 182–186°. Two recrystallizations from methanol gave the sample used for analysis which still melted over the range 188–193.5° (vac.).

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5. Found: C, 80.3; H, 7.5.

---

[27] Hydrolysis of the acid chloride prepared from the free acid gave only 17% of acidic material and 82% of a neutral oil, from which 24% of the solid starting acid was recovered by alkaline hydrolysis. When acid chloride prepared from the sodium salt was hydrolyzed, the acidic fraction was 40% and the neutral 56%. The latter probably is the enol lactone of the keto acid.

The ultraviolet absorption spectrum[24] (Fig. 1) showed maxima at 273 mμ (log E = 4.16), 336 mμ (2.36) and 362.5 mμ (2.22) and minima at 241.5 mμ (3.73), 332 mμ (2.35) and 355 mμ (2.20). The non-crystalline phenolic material, evidently a mixture, did not give crystalline material when converted to the benzoate.

3-Methoxy-1,3,5-estratrien-16-one (XVII).—A suspension of 200 mg. of palladium-on-carbon catalyst[20] in 10 cc. of purified dioxane was saturated with hydrogen at room temperature and atmospheric pressure, then 192 mg. of the methoxy ketone XVI, dissolved in 6 cc. of dioxane, was introduced and stirring continued for twenty hours until one mole-equivalent of hydrogen was absorbed. After removal of the catalyst and solvent, the product crystallized readily upon stirring with petroleum ether to give 168 mg. of colorless solid, m. p. 146–148°. An additional 6 mg., m. p. 143–148°, from the filtrate brought the yield to 90%. The pure material crystallized from absolute alcohol as colorless blades, m. p. 147.5–148°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.2; H, 8.5. Found: C, 80.3; H, 8.4.

The compound was shown to be a ketone by reaction with Girard reagent P; 48 mg. (from 50 mg.) was recovered from the water-soluble fraction, m. p. 144–147.5°.

1,3,5-Estratrien-3-ol-16-one (II).—A mixture of 62 mg. of the saturated methoxy ketone XVII (m. p. 147–148°), 2 cc. of acetic acid and 2 cc. of 42% hydrobromic acid was refluxed under nitrogen for three hours. The cooled mixture (intense blue fluorescence) was diluted, extracted twice with ether, and the latter washed with water and three times with 10% potassium hydroxide; acidification of the alkaline layers and extraction with ether gave 52 mg. of phenolic product which crystallized upon stirring with petroleum ether to give 41 mg. (70%) of gray solid, m. p. 166–174.5°. An additional 2 mg., m. p. 158–170°, was obtained from the filtrate. Two recrystallizations of the material in the first crop from methanol gave the phenol II as colorless, irregular blades, m. p. 177.5–178°. Indications of polymorphism were obtained for this substance. When one sample was introduced in a bath preheated to 140°, it melted and immediately resolidified to melt again at 174–176°. If inserted at 100° and heated rather rapidly, the solid partially melted at 166–168°, followed by resolidification and remelting at 174–177°; if this melt was allowed to resolidify it remelted at 174–176.5° with no apparent change at the lower temperature.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2. Found: C, 79.7; H, 8.1.

The ultraviolet absorption spectrum[24] (Fig. 2) showed a maximum at 280.5 mμ (log E = 3.34) and a minimum at 249.5 mμ (2.43). For estrone the maximum was found at 279.5 mμ (3.48) and the minimum 247 mμ (2.79). The values for the extinction coefficient were somewhat higher than those found by Mayneord and Roe[28] and Dannenberg[29]—maximum at 280 mμ (log E = 3.3 and 3.36 respectively) and minimum at 248 mμ (2.5 and 2.58).

Digestion of the residue from the original ether extracts with 10% potassium hydroxide gave an additional 5 mg. of solid phenolic material, m. p. 135–150°, and 8 mg. of neutral oil.

The **benzoate** was prepared from the total crude phenolic material from demethylation of 50 mg. of the methyl ether by refluxing for three hours under nitrogen with a mixture of 0.25 cc. of benzoyl chloride and three drops of pyridine in 5 cc. of dioxane. After cooling and allowing to stand for several hours, the semi-solid material was filtered and washed well with water and alcohol, giving 43 mg. of nearly colorless benzoate, m. p. 213–225° (vac.). An additional 8 mg., m. p. 218–226° (vac.) was obtained from the filtrate for a total yield of 77% (from the methoxy ketone). Recrystallization of the material from acetone gave 32 mg., m. p. 227–229° (vac.). Another recrystallization gave the benzoate as colorless leaflets, m. p. 228–229.5° (vac.).

Anal. Calcd. for $C_{25}H_{26}O_3$: C, 80.2; H, 7.0. Found: C, 79.8; H, 7.0.

Summary

A twenty-step total synthesis of an isomer (II) of estrone having the keto group at C-16 instead of C-17 has been accomplished. Several alternative routes to 3-methoxy-1,3,5,14-estratetraene-16-one (XVI) from 1-keto-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a - octahydrophenanthrene - 2 - acetic acid (IXa) were explored. Hydrogenation and demethylation of XVI gave one of the eight possible isomers of II. Demethylation of the unsaturated ketone XVI resulted in a shift of the double bond to the 8–9 position, giving the 16-keto isomer (XVIIIa) of isoequilin A. The estrogenic activity of II was low (about 1/7600th that of estrone) indicating it to differ from estrone stereochemically as well as in the position of the keto group. XVIIIa was about 1/450th as active as estrone. The preparation of other stereoisomers is being investigated.

MADISON 6, WIS. RECEIVED SEPTEMBER 8, 1947

---

[28] Mayneord and Roe, *Proc. Roy. Soc.* (*London*), **A158**, 634 (1937).

[29] Dannenberg, *Abhandl. preuss. Akad. Wiss., Math.-nat. Klasse*, No. 21 (1939).

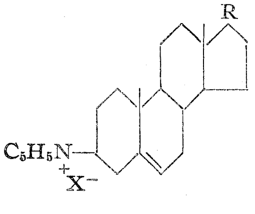
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Preparation and Structure of Cholesteryl Quaternary Salts

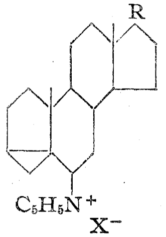
BY L. CARROLL KING, R. M. DODSON AND LEE A. SUBLUSKEY

Cholesterylpyridinium *p*-toluenesulfonate (I) was prepared in two ways: (a) by action of pyridine on cholesteryl *p*-toluenesulfonate and (b) by action of pyridine and *p*-toluenesulfonic acid on *i*-cholesteryl methyl ether. Cholesteryl isothiuronium *p*-toluenesulfonate (II)[1] was prepared (a) by action of thiourea on cholesteryl *p*-toluenesulfonate and (b) by action of thiourea and *p*-toluenesulfonic acid on *i*-cholesteryl methyl ether in alcoholic solution. Compound I was converted to the corresponding iodide on treatment with sodium iodide or on treatment with hydriodic acid. It was unchanged on refluxing twenty-four hours with pyridine and *p*-toluenesulfonic acid and displayed qualitative evidence for unsaturation. Compound II was converted to cholesteryl mercaptan and this in turn was converted to cholesteryl disulfide. These compounds were identical with the corresponding compounds reported by Wagner-Jauregg and Lennartz.[2]

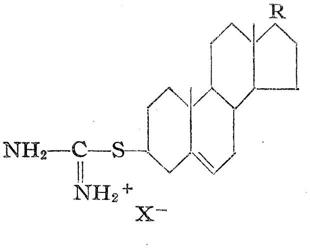
Of the structures considered for these quaternary salts, I and II are preferred over Ia and IIa.



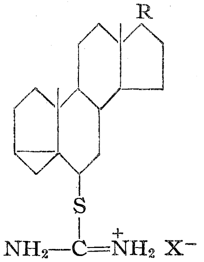
I



Ia



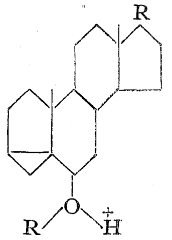
II



IIa

$X = CH_3C_6H_4SO_3^-$
$R = C_8H_{17}^-$

This preference is based on the fact that a single levorotatory salt is obtained from each of the reactions and on the fact that the salt when prepared from *i*-cholesteryl methyl ether is produced under conditions favoring rearrangement of the *i*-steroid structure. Structures Ia and IIa are further considered to be unlikely in view of their similarity to an oxonium structure such as III which may be involved when an *i*-steroid ether is rearranged to the normal steroid structure.[3]



III

Both cholesteryl *p*-toluenesulfonate and *i*-cholesteryl methyl ether are known to react readily with alcohol when a trace of acid is present. In the present paper they are shown to react selectively with thiourea in the presence of alcohol. A further study of this observation is in progress.

This investigation was partially supported by a Grant-in-Aid from the National Cancer Institute.

Experimental[4]

Cholesterylpyridinium *p*-Toluenesulfonate (I).—(a) A solution of 5.4 g. (0.01 mole) of cholesteryl *p*-toluenesulfonate[5] in 40 cc. of pyridine was heated on the steam-bath for five and one-half hours. The solution was diluted with acetone, cooled in ice, the product separated by filtration and washed with acetone-hexane. From this reaction 4.0 g. of product, m. p. 227–229°, was obtained. Two crystallizations from a mixture of chloroform and carbon tetrachloride raised the melting point to 231–232°; $[\alpha]^{26}\text{D}$ −6.1° in chloroform.

Anal. Calcd. for $C_{39}H_{57}O_3NS \cdot H_2O$: C, 73.44; H, 9.01; N, 2.20. Found: C, 73.73, 73.34; H, 9.10, 9.44; N, 2.56.

This compound is slightly soluble in acetone, soluble in chloroform but insoluble in carbon tetrachloride. It forms a colloidal solution on heating with water and can be crystallized from dilute alcohol. In chloroform solution this compound reacts rapidly with bromine forming a light yellow solution. A suspension of this compound in water slowly decolorized permanganate.

(b) A solution consisting of 1.0 g. of *i*-cholesteryl methyl ether,[6] 1.0 g. of *p*-toluenesulfonic acid and 10 cc. of pyridine was refluxed for two hours, then cooled and diluted with acetone. The crystalline material which was isolated from this reaction mixture was identical in all respects with the compound I; m. p. 230–232°, $[\alpha]^{25}\text{D}$ −4.5° in chloroform, yield 0.9 g.

Cholesterylpyridinium Iodide.—(a) A solution of 1.4 g. of cholesterylpyridinium *p*-toluenesulfonate (I) in absolute alcohol was treated with 2 g. of sodium iodide in alcohol. The cholesterylpyridinium iodide precipitated

---

(1) Cholesteryl isothiuronium halides were prepared and converted to cholesteryl mercaptan: Rosenberg and Turnbull, U. S. 2,375,873; U. S. 2,375,874, *C. A.*, **39**, 5049 (1945).

(2) Wagner-Jauregg and Lennartz, *Ber.*, **74**, 27 (1941).

(3) R. M. Dodson and Byron Riegel, *J. Org. Chem.*, in press, (1948); E. W. Meyer, Ph. D. Thesis, Northwestern University, 1943, pp. 49, 54.

(4) All melting points were observed on a Fisher-Jones melting point block. All rotations were determined with 100–105 mg. of sample in 3 cc. of solvent using a 1-dcm. tube of 2.5 cc. capacity. Analysis by P. Craig.

(5) Freudenberg and Hess, *Ann.*, **448**, 128 (1926).

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

at once. It was crystallized from alcohol; m. p. 260–261° dec., $[\alpha]^{27}D$ −7.4° in chloroform; yield 1.3 g.

Anal. Calcd. for $C_{32}H_{50}NI$: C, 66.75; H, 8.79; N, 2.44. Found: C, 66.59; H, 8.66; N, 2.12.

(b) A solution of 1.1 g. of I in absolute alcohol was treated with concentrated hydriodic acid. The iodide precipitated at once. It was crystallized from alcohol and was identical with that above, m. p. 260–261°; $[\alpha]^{25}D$ −7.8° in chloroform; yield 0.9 g.

Attempted Rearrangement of Cholesterylpyridinium *p*-Toluenesulfonate.—A solution consisting of 1.0 g. of cholesterylpyridinium *p*-toluenesulfonate and 1 g. of *p*-toluenesulfonic acid in 15 g. of pyridine was heated at the reflux temperature for twenty-four hours. The reaction mixture was worked up as described under the preparation of I. There was no evidence of decomposition and 0.9 g. of the starting substance was recovered unchanged; m. p. 229–231°. This was converted to the iodide, m. p. 260–261°; $[\alpha]^{24}D$ −7.5° in chloroform.

Cholesterylisothiuronium *p*-Toluenesulfonate (II).—(a) A solution of 5.4 g. (0.01 mole) of cholesteryl *p*-toluenesulfonate, 9.0 g. of thiourea and 5 cc. of pyridine in 50 cc. of absolute ethanol was heated under reflux for three hours. The resulting solution was diluted with water until a precipitate started forming, cooled and filtered. The residue was then suspended in acetone, the acetone heated to boiling, and the insoluble product filtered from the solution; yield 4.0 g. (65%) of salt; m. p. 230–234°. Recrystallization from alcohol raised the melting point to 233–235°; $[\alpha]^{24}D$ −27.1° in pyridine.

Anal. Calcd. for $C_{35}H_{56}N_2O_3S_2$: C, 68.15; H, 9.15; N, 4.54. Found: C, 68.26; H, 9.16; N, 4.31.

(b) From a similar reaction using 0.01 mole of cholesteryl *p*-toluenesulfonate, 0.02 mole of thiourea and 50 cc. of 95% alcohol, 2.26 g. (40%) of II, m. p. 231–233°, was obtained. This reaction mixture was acid to litmus and contained some cholesteryl ethyl ether, m. p. and mixed m. p. 89.0–89.5°.

(c) A reaction mixture consisting of 2.0 g. of *i*-cholesteryl methyl ether,[6] 2.0 g. of *p*-toluenesulfonic acid, 4.0 g. of thiourea in 50 cc. of ethyl alcohol was refluxed four hours. Compound II was isolated as described above; m. p. 233°; yield 1.3 g. (42%); $[\alpha]^{24}D$ −26.9° in pyridine. From this reaction mixture 0.3 g. of unchanged *i*-cholesteryl methyl ether, m. p. 75–77°, was also obtained.

Cholesteryl Mercaptan.—A solution of 2.46 g. (0.004 mole) of II and 0.68 g. (0.012 mole) of sodium hydroxide in 50 cc. of ethyl alcohol was heated under reflux. After the solution became homogeneous 5 cc. of water was added and the heating continued for two hours. The reaction mixture was then poured into 100 cc. of ice water and the resulting suspension acidified with 1 cc. of glacial acetic acid and stirred until the precipitate coagulated. The compound was separated and crystallized from acetone–methanol; m. p. 94–96°; yield 1.5 g. (93%). Recrystallization from acetone raised the melting point to 97.0–97.5°; $[\alpha]^{25}D$ −26.6° in chloroform.[7]

Anal. Calcd. for $C_{27}H_{46}S$: C, 80.53; H, 11.51. Found: C, 80.25; H, 11.80.

Cholesteryl Disulfide.—A solution consisting of 0.50 g. (0.00125 mole) of cholesteryl mercaptan in 10 cc. of hexane was oxidized with 0.32 g. (0.00125 mole) of iodine. Ten cubic centimeters of 5% potassium hydroxide was added and the mixture shaken. The mixture was then diluted and extracted with hexane. The hexane was then evaporated and the residue crystallized from benzene–ethyl alcohol and from acetone–benzene; m. p. 141–143°.[7]

Summary

Cholesterylpyridinium *p*-toluenesulfonate was prepared from cholesteryl *p*-toluenesulfonate and from *i*-cholesteryl methyl ether. Cholesterylisothiuronium *p*-toluenesulfonate was prepared from the same substances. The evidence indicates that these salts are derivatives of the normal cholesteryl structure.

---

[7] Wagner–Jauregg and Lennartz (ref. 2) reported for cholesteryl mercaptan m. p. 99.5°, $[\alpha]_D$ −23.85°; and for cholesteryl disulfide; m. p. 144.5°.

EVANSTON, ILLINOIS RECEIVED NOVEMBER 12, 1947

[CONTRIBUTION NO. 65 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

Substituted Styrenes. III. The Preparation of Some *m*- and *p*-Substituted α-Methylstyrenes

BY DEXTER SEYMOUR AND KATHERINE B. WOLFSTIRN

In connection with some studies undertaken in this laboratory on the effect of ring substituents in styrenes on their reactivity toward certain types of free radicals,[1a,b] it was necessary to synthesize a series of substituted α-methylstyrenes. *p*-Bromo, *p*-chloro and *p*-methoxy-α-methylstyrenes were synthesized by known methods. Some peculiarities in the preparation of the last mentioned were noted and are discussed further in the experimental part.

p-Fluoro-α-methylstyrene was prepared in a straightforward way from *p*-fluorobromobenzene and acetone through the Grignard reagent. *p*-Cyano-α-methylstyrene was prepared by taking advantage of the rather large difference in reactivity toward the Grignard reagent between a nitrile and a ketone grouping. A somewhat obscure paper[2] which came to our attention later records this fact also. Methylmagnesium bromide was added to a stoichiometric amount of *p*-cyanoacetophenone and the crude alcohol was dehydrated with acetic anhydride. Careful fractionation of the product gave 44% of *p*-cyano-α-methylstyrene, 20% of unreacted *p*-cyanoacetophenone and about 25% of non-volatile polymeric material. *m*-Bromo-α-methylstyrene was prepared in 54% yield by addition of two moles of methylmagnesium bromide to methyl *m*-bromobenzoate followed by dehydration with acetic anhydride.

Although the reaction is reported in the literature,[3] we were unable to prepare the Grignard reagent from *p*-dimethylaminobromobenzene even

---

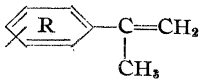
[1] (a) Walling, Seymour and Wolfstirn, THIS JOURNAL, in press; (b) Walling, Seymour and Wolfstirn, *ibid.*, submitted for publication.

[2] Carter, *Iowa State Coll. J. Sci.*, **15**, 63 (1940); *cf. British Chem. Abs.*, **AII**, 254 (1941).

[3] Ehrlich and Sachs, *Ber.*, **36**, 4297 (1903).

TABLE I

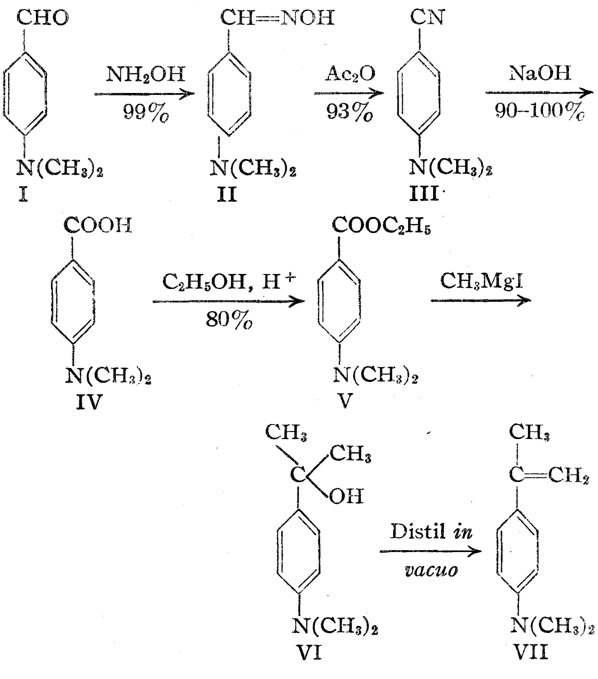
PHYSICAL PROPERTIES OF SUBSTITUTED α-METHYLSTYRENES



R	Yield, %	M. p., °C.	B. p., °C.	Pressure, mm.	$n^{20}D$	d^{20}_4	Calcd. %C	Calcd. %H	Calcd. %N	Found %C	Found %H	Found %N
p-F	55		97.5–101.5	95	1.5120	1.0150	79.40	6.66		78.66	6.71	
p-Cl	70	3.5	78.0–80.0	8	1.5559	1.0723	70.85	5.94	..[a]	71.04	6.03	..
p-Br	37		114.5–117.5	24	1.5834	1.3623	54.84	4.60		54.54	4.66	
m-Br	54		68–72	2	1.5779	1.3560	54.84	4.60		54.12	4.54	
p-OCH₃	66	34	63.0–65.5	0.5	....	0.9860[b]	...	..		...	..	
p-N(CH₃)₂	69	75.0–76.5	....	..	....	....	81.95	9.37	8.69	82.08	9.40	8.64
p-CN	44		86.0–87.5	2	1.5680	1.0017	83.90	6.34	9.78	83.98	6.31	9.72

[a] Calcd. for C_9H_9Cl: Cl, 23.23. Found: C, 23.22. [b] Density at 40° referred to water at 4°.

employing measures such as the "entrainment" method, and an alternative synthesis of *p*-dimethylamino-α-methylstyrene was carried out. The reactions employed were all straightforward and proceeded with the yields indicated. Several attempts to effect acid catalyzed alcoholysis of the nitrile III to produce the ester V directly met with no success and recourse was had to hydrolysis followed by Fisher esterification. The intermediate alcohol VI was not isolated but was dehydrated directly by vacuum distillation to the styrene VII. The over-all yield of recrystallized VII from V was 69%. The styrenes prepared, together with yields and physical properties, are listed in Table I.



Experimental[4]

***p*-Chloro-α-methylstyrene.**—This compound was prepared in 70% yield essentially by the method of Mowry, Huber and Ringwald.[5] The carbinol was dehydrated by refluxing sixty-four hours with about 100 mg. of iodine in toluene. After purification the product had b. p. 78.0–80.0° (8 mm.), $n^{20}D$ 1.5559, d^{20}_4 1.0723, *MR*D (calcd.) 44.56, *MR*D (found) 45.70.

***p*-Bromo-α-methylstyrene.**—This compound was prepared in 37% yield from *p*-bromophenylmagnesium bromide and acetone.[6] The best fraction had b. p. 114.5–117.5° (24 mm.), $n^{20}D$ 1.5834, d^{20}_4 1.3623, *MR*D (calcd.) 47.46, *MR*D (found) 48.34. Bergmann and Weigmann[6] give: b. p. 58–60° (2 mm.); $n^{20}D$ 1.5778.

***p*-Methoxy-α-methylstyrene.**—This compound was prepared from 249 g. (1.50 moles) of methyl anisate, 305 g. (3.20 moles) of methyl bromide and 81.6 g. (3.40 atoms) of magnesium.[6] The crude carbinol was dehydrated by distillation at reduced pressure.[7] The crude styrene so obtained was carefully redistilled through 17 cm. of glass helices with traces of *t*-butylcatechol and trinitrobenzene added as inhibitors. There was obtained 147 g. (66%) of pure product which had b. p. 63.0–65.5° (0.5 mm.), m. p. 34°, d^{40}_4 0.9860. The substance was observed to polymerize after several months even in the refrigerator in a brown bottle.

When methylmagnesium iodide was used in the preparation of the carbinol, or iodine or acetic anhydride were employed as dehydrating agents, the product was always what appeared to be the dimer of *p*-methoxy-α-methylstyrene with the following properties: b. p. 195–199° (1.5 mm.); $n^{20}D$ 1.5753.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.07, H, 8.11; mol. wt., 296. Found: C, 80.97; H, 8.91; mol. wt. (cryoscopic in benzene), 260.

Previous workers[6,7] apparently experienced little difficulty in this respect, however.[8]

***p*-Fluoro-α-methylstyrene.**—To the Grignard reagent prepared from 25.2 g. (1.05 atoms) of magnesium and 175 g. (1.00 mole) of *p*-fluorobromobenzene in 350 ml. of dry ether was added 63.8 g. (1.10 moles) of acetone in 700 ml. of ether and the mixture was allowed to stand two and one-half days. The mixture was hydrolyzed with saturated ammonium chloride solution and the ether removed from the product by distillation. Then 500 ml. of toluene and 100 mg. of iodine were added and the mixture was refluxed nineteen and one-half hours under a water separator. Fifteen milliliters (83%) of water separated. The toluene solution was washed with sodium thiosulfate and water and dried by distillation. The toluene was removed through a 17 cm. column packed with 1/8" single turn glass helices and the residue fractionated. The middle fraction had b. p. 97.5–101.5° (95 mm.), $n^{20}D$ 1.5120, d^{20}_4 1.0150, *MR*D (calcd.) 39.59, *MR*D (found) 40.20. The yield was 74.5 g. (55%).

Anal. Calcd. for C_9H_9F: C, 79.40; H, 6.66. Found: C, 78.66; H, 6.71.

---

[4] All melting and boiling points are uncorrected.

[5] Mowry, Huber and Ringwald, THIS JOURNAL, **69**, 851 (1947).

[6] Bergmann and Weizmann, *Trans. Faraday Soc.*, **32**, 1327 (1936), and earlier references given there.

[7] Skraup and Freundlich, *Ann.*, **431**, 267 (1923).

[8] Yamashita, *J. Chem. Soc. Japan*, **62**, 1216 (1941); *cf. Chem. Abs.*, **41**, 3070 (1947), reports, however, that *p*-methoxy-β-methylstyrene readily forms a dimer on treatment with iodine in toluene.

A bromine analysis indicated the presence of not more than 2 wt. per cent. *p*-fluorobromobenzene as impurity.

p-**Cyano-α-methylstyrene.**—In a 2-liter three-necked flask previously flushed with dry nitrogen the Grignard reagent was prepared from 135 g. (0.95 mole) of methyl iodide and 24.0 g. (1.00 atom) of magnesium in 1250 ml. of dry ether. When reaction was complete, the reagent was filtered under nitrogen into a 2-liter dropping funnel attached to one neck of a 5-liter three-necked flask equipped with a Hershberg stirrer and a reflux condenser protected by a "Drierite" tube. In the flask was placed 133 g. (0.918 mole) *p*-cyanoacetophenone dissolved in 750 ml. of dry ether. The Grignard reagent was added to this solution dropwise over a period of one and one-half hours and the mixture was stirred two and three-quarter hours longer. The reaction mixture was worked up in the usual way and the crude carbinol dehydrated by boiling two hours with about 300 ml. of acetic anhydride. After hydrolysis of the excess anhydride, the products were taken up in chloroform, the solution dried, and the chloroform removed through 85 cm. of $^1/_8''$ glass helices. The residue was distilled at 1.5 mm. to separate volatile material from any polymeric products. The distillate was collected from 86–120° and there remained about 25 g. of non-distillable material in the flask. The distillate was fractionated at 2 mm. pressure using an 80-cm. 15-plate low hold-up column designed by Dr. H. Sargent of these Laboratories.[9] Three fractions were collected: (1) b.p. 82.0–86.0° (2 mm.), n^{20}_{D} 1.5618, wt. 4.4 g.; (2) b.p. 86.0–87.0° (2 mm.), n^{20}_{D} 1.5680, wt. 29.8 g.; (3) b. p. 87.0–87.5° (2 mm.), n^{20}_{D} 1.5680, wt. 28.0 g. The pot residue weighed 26.1 g. and gave 20.9 g. (15.7%) of *p*-cyanoacetophenone on crystallization from hexane-benzene. Fractions (2) and (3) of the distillate above which decolorized potassium permanganate in acetone and bromine in carbon tetrachloride were combined to yield 57.8 g. (44%) of *p*-cyano-α-methylstyrene, d^{20}_4 1.0017, MR_{D} (calcd.) 44.05, MR_{D} (found) 46.68.

Anal. Calcd. for $C_{10}H_9N$: C, 83.90; H, 6.34; N, 9.78. Found: C, 83.76, 83.98; H, 6.32, 6.31; N, 9.72.

m-**Bromo-α-methylstyrene.**—The Grignard reagent was prepared from 67.8 g. (2.83 atoms) of magnesium and 265 g. (2.79 moles) of methyl bromide and to this was added an ether solution of 294 g. (1.40 moles) methyl *m*-bromobenzoate. The reaction mixture was worked up in the usual way and the carbinol was dehydrated by the acetic anhydride technique. After hydrolysis of the excess anhydride, the neutral products were extracted with chloroform, dried and the solvent removed through 17 cm. of glass helices. Fractionation of the residue gave 150 g. (54%) of *m*-bromo-α-methylstyrene, b. p. 68.0–72.0° (2 mm.), n^{20}_{D} 1.5779, d^{20}_4 1.3560, MR_{D} (calcd.) 47.46, MR_{D} (found) 48.20.

Anal. Calcd. for C_9H_9Br: C, 54.86; H, 4.60. Found: C, 54.12; H, 4.54.

p-**Dimethylaminobenzaldoxime.**—This material was prepared from 75 g. (0.50 mole) *p*-dimethylaminobenzaldehyde by the method of Sachs and Steinert.[10] There was obtained 80.9 g. (99%) of oxime melting at 142.5–144.0° and it was used without purification.

p-**Dimethylaminobenzonitrile.**—Following the method of Sachs and Steinert,[10] 73.8 g. (0.45 mole) of *p*-dimethylaminobenzaldoxime was dehydrated with 300 ml. of 95% acetic anhydride to yield 61 g. (93%) of crude nitrile, melting at 74–75°. It was used directly in the next step.

p-**Dimethylaminobenzoic Acid.**—One-hundred twenty-eight grams (0.877 mole) of *p*-dimethylaminobenzonitrile was refluxed for nineteen hours with a mixture of 750 ml. of 2 *M* sodium hydroxide and 450 ml. of 95% ethyl alcohol. Most of the alcohol was removed by distillation and 500 ml. of water was added. The warm solution was acidified to *p*H 2 with concentrated hydrochloric acid and the suspension was allowed to stand for thirty-six hours. The acid was collected by filtration and washed with water. Neutralizing to about *p*H 7 with ammonia afforded a further small amount of product. The dry *p*-dimethylaminobenzoic acid weighed 148 g. (102%, probably due to inorganic salts), and was esterified without further purification.

Ethyl *p*-**Dimethylaminobenzoate.**—A mixture of 196.5 g. (1.19 mole) of crude *p*-dimethylaminobenzoic acid and 2 liters of absolute ethanol was saturated with dry hydrogen chloride and refluxed overnight. Most of the alcohol was distilled and the residue was thrown into iced sodium hydroxide solution (200 g. in 1 liter of water) with good stirring. The crude ester was collected by filtration; after drying it weighed 172.7 g. (79% based on recovered acid). From the mother liquor there was recovered 9.1 g. (4.6%) of unreacted acid.

The crude ester was distilled at 1–2 mm., the fraction boiling at 125–142° being collected. This weighed 159 g. and was crystallized from 400 ml. of 66% by volume ethanol. The first crop of shiny white plates weighed 124 g. (57%) and melted at 65–66°. A second crop of less pure material, weighing 27.0 g. (12%) and melting at 58–61°, was obtained, by concentration of the mother liquor.

p-**Dimethylamino-α-methylstyrene.**—The Grignard reagent was prepared from 341 g. (2.40 moles) of methyl iodide and 62.4 g. (2.60 atoms) of magnesium in 1200 ml. dry ether. To this refluxing solution was added 154.4 g. (0.800 mole) of ethyl *p*-dimethylaminobenzoate in 1200 ml. of ether over a period of one and one-half hours and refluxing was continued for twenty-one and one-half hours longer. The mixture was hydrolyzed with saturated ammonium chloride solution and worked up in the usual way. After removal of the ether, the crude product was distilled *in vacuo*, which caused the elimination of water. The styrene was collected from 95–121° at 1 mm.; it weighed 91.8 g. (71%). Recrystallization from 250 ml. of hexane gave 74.2 g. (58%) of *p*-dimethylamino-α-methylstyrene melting at 75.0–76.5°.

Anal. Calcd. for $C_{11}H_{15}N$: C, 81.95; H, 9.37; N, 8.69. Found: C, 82.08; H, 9.40; N, 8.64.

A further 14.6 g. (11%) of product melting at 72.0–74.0° was obtained from the mother liquor.

Summary

1. The preparation of *p*-chloro, *p*-bromo and *p*-methoxy-α-methylstyrenes is described.

2. *p*-Fluoro, *m*-bromo, *p*-cyano and *p*-dimethylamino-α-methylstyrenes have been prepared and their physical properties recorded for the first time.

PASSAIC, NEW JERSEY

RECEIVED OCTOBER 29, 1947

---

[9] A description of this column will appear in a forthcoming article by Dr. Sargent.

[10] Sachs and Steinert, *Ber.*, **37**, 1740 (1904).

[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, MONSANTO CHEMICAL COMPANY]

The Use of Liquid Phase Oxidation for the Preparation of Nuclearly Substituted Styrenes. IV.[1] *m*-Chlorostyrene

BY WILLIAM S. EMERSON AND VICTOR E. LUCAS[2]

m-Chlorostyrene has been prepared by heating *m*-chlorophenylmethylcarbinol with potassium bisulfate at reduced pressure[3,4,5] in yields as high as 83%.[4] The carbinol was prepared by treating *m*-chlorobenzaldehyde with methylmagnesium iodide[4,5] or by treating acetaldehyde with *m*-chlorophenylmagnesium bromide.[3]

We have found that chlorobenzene can be alkylated with ethylene in the presence of aluminum chloride to give *m*-chloroethylbenzene in 37% conversion and 80% yield. Oxidation of *m*-chloroethylbenzene with air at 100 p. s. i, pressure in the presence of a chromium oxide catalyst gave *m*-chloroacetophenone in 26% conversion and 76% yield. This ketone was hydrogenated to *m*-chlorophenylmethylcarbinol in 94% yield by means of hydrogen and copper chromite. While this preparation of the carbinol from chlorobenzene involves three steps, the yields are good and the use of such difficultly available intermediates as *m*-chlorobenzaldehyde and *m*-chlorobromobenzene is avoided. The 84% yield of *m*-chlorostyrene, obtained by dehydrating *m*-chlorophenylmethylcarbinol in the vapor phase over alumina, is comparable to the 83% reported for the potassium bisulfate method.[4]

A still better method of synthesis was found to involve the chlorination of *m*-chloroethylbenzene in the presence of light and a phosphorus trichloride catalyst to give α,*m*-dichloroethylbenzene in 44% conversion and 91% yield. When the vapors of the latter compound, together with steam, were passed over a calcium sulfate catalyst, *m*-chlorostyrene was obtained in 93% yield.

Experimental

***m*-Chloroethylbenzene.**—Chlorobenzene was treated with ethylene in the presence of aluminum chloride in an autoclave equipped with a stirrer and gas inlet. The charge consisted of 3178 g. of chlorobenzene, 45.4 g. of ethyl chloride and 90.8 g. of anhydrous aluminum chloride. While the temperature was held at 100°, 454 g. of ethylene was introduced over a two-hour period. The mixture was then cooled, removed from the autoclave and poured into 5 kg. of ice water containing 100 cc. of concentrated hydrochloric acid. After the complex had decomposed, the organic layer was separated, dried over anhydrous potassium carbonate and distilled. In this way there was obtained 1702 g. (53.7% recovery) of chlorobenzene, b. p. <68° at 14 mm., $n^{25}\mathrm{D}$ 1.5213–1.5201; 1478 g. (37.3% conversion and 80.2% yield) of *m*-chloroethylbenzene, b. p. 68–74° at 14 mm.,[6] $n^{25}\mathrm{D}$ 1.5181–1.5160 (1103 g., b. p. 68–72° at 14 mm., $n^{25}\mathrm{D}$ 1.5171–1.5168); and 361 g. (7.6% calculated as chlorodiethylbenzene) of more highly alkylated material. The residue was 21 g.

***m*-Chloroacetophenone.**—Into a stirred autoclave equipped with a reflux condenser and gas outlet, thermowell and air inlet there was placed 500 g. of *m*-chloroethylbenzene and 5 g. of chromium oxide. While this mixture was stirred at a temperature of 140–155°, 3 cu. ft./hr. of air at 100 p. s. i. was introduced for a six-hour period. After cooling, the autoclave was opened, and the reaction mixture removed and filtered. By washing the solution with aqueous alkali and acidifying the extract there was obtained 8.1 g. (1.4%) of *m*-chlorobenzoic acid. The organic layer was distilled to obtain 331.5 g. (66.2% recovery) of *m*-chloroethylbenzene, b. p. 65–69° at 13 mm., $n^{25}\mathrm{D}$ 1.5181–1.5161, and 140.6 g. (25.6 % conversion and 76.0% yield) of *m*-chloroacetophenone, b. p. 76–92° at 3 mm., $n^{25}\mathrm{D}$ 1.5462–1.5491. The tarry residue weighed 13.7 g. (2.5%).

***m*-Chlorophenylmethylcarbinol.**—A standard American Instrument Company hydrogenation autoclave was charged with 100 g. of *m*-chloroacetophenone and 10 g. of copper chromite. The initial hydrogen pressure was 980 p. s. i. at 27°. Hydrogenation was conducted at 140° for seven hours. After the catalyst was removed by filtration, the product was distilled to give 94.9 g. (94%) of *m*-chlorophenylmethylcarbinol, b. p. 85–89° at 2 mm. (102–104° at 3 mm.),[4] $n^{25}\mathrm{D}$ 1.5418 ($n^{20}\mathrm{D}$ 1.5438).[4]

***m*-Chlorostyrene.**—A pyrolysis tube[7] was packed with activated alumina. Over a forty-minute period 74 g. of *m*-chlorophenylmethylcarbinol, together with some steam, was passed through the tube at 90 mm. pressure and 313–340°. Upon cooling, the tube was washed out with benzene and the distillate extracted with the same solvent. The combined washings and extracts were distilled from a trace of sulfur and hydroquinone to give 55 g. (84%) of *m*-chlorostyrene, b. p. 75–79° at 15 mm. (62–63° at 6 mm.),[4] $n^{25}\mathrm{D}$ 1.5612 ($n^{20}\mathrm{D}$ 1.5619).[4]

α,*m*-Dichloroethylbenzene.—A 1-liter three-necked flask equipped with a stirrer, condenser, thermometer and gas inlet tube was charged with 562 g. of *m*-chloroethylbenzene and 3 g. of phosphorus trichloride. While the temperature was maintained at 10–15° by means of an ice–salt-bath and the flask was illuminated with ultraviolet light, chlorine was introduced until a gain of 85 g. was observed. Direct distillation of the reaction mixture yielded 292.6 g. (52.1% recovery) of *m*-chloroethylbenzene, b. p. 70° at 17 mm.–74° at 16 mm., $n^{25}\mathrm{D}$ 1.5172–1.5183 and 306.2 g. (43.6% conversion and 91.4% yield) of α,*m*-dichloroethylbenzene, b. p. 63–70° at 2 mm., $n^{25}\mathrm{D}$ 1.5401–1.5423. The tarry residue weighed 8.7 g. (1.0%).

***m*-Chlorostyrene.**—The pyrolysis tube was packed with calcium sulfate (Drierite). Over a one hundred sixty-minute period 250 g. of α,*m*-dichloroethylbenzene, together with about three (liquid) volumes of steam, was passed through the tube at 90 mm. pressure and 425–475°. Upon cooling, the tube was washed out with 50

---

[1] For the preceding paper in this series see Emerson, Heyd, Lucas, Lyness, Owens and Shortridge, THIS JOURNAL, **69**, 1905 (1947).

[2] Present address: Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina.

[3] Marvel and Schertz, THIS JOURNAL, **65**, 2054 (1943).

[4] Brooks, *ibid.*, **66**, 1295 (1944).

[5] Ushkov and Matuzov, *J. Gen. Chem.*, **14**, 120 (1944); *Chem. Abstr.*, **39**, 916 (1945).

[6] Dreisbach, U. S. Patent 2,159,370; *Chem. Abstr.*, **33**, 6875 (1939), describes the ethylation of chlorobenzene. He obtained about 80% of *m*-chloroethylbenzene contaminated with 20% of the *ortho* isomer. Some of our *m*-chloroethylbenzene was redistilled through a four-foot Vigreux column. The middle cut (88%) boiled at 65–68° (13 mm.), $n^{25}\mathrm{D}$ 1.5172. Oxidation of this fraction gave *m*-chlorobenzoic acid, m. p. 157–158° (cor.) after one crystallization from aqueous ethanol (Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1943, Vol. I, p. 439, gives m. p. 158°.)

[7] Emerson and Agnew, THIS JOURNAL, **67**, 518 (1945).

cc. of benzene and the combined distillate and washings were extracted three times with benzene. These combined extracts were washed free of acid with aqueous sodium bicarbonate and then distilled from a trace of sulfur and hydroquinone to give 183 g. (92.5%) of *m*-chlorostyrene, b. p. 76–81° at 17 mm. (62–63° at 6 mm.),[4] n^{25}_D 1.5616 (n^{20}_D 1.5619).[4]

Summary

The preparation of *m*-chlorostyrene from *m*-chloroethylbenzene by two routes has been described. The first involves oxidation to *m*-chloroacetophenone, hydrogenation to *m*-chlorophenylmethylcarbinol and dehydration in the vapor phase to *m*-chlorostyrene. The second involves chlorination to α,*m*-dichloroethylbenzene followed by dehydrochlorination in the vapor phase to *m*-chlorostyrene.

DAYTON, OHIO RECEIVED NOVEMBER 3, 1947

[CONTRIBUTION NO. 148 FROM THE GOODYEAR TIRE & RUBBER CO., RESEARCH LABORATORY]

The Synthesis and Reactions of Disazodicarboxylates[1]

BY NORMAN RABJOHN

The azo group in esters of azodicarboxylic acid is very reactive and will add to numerous compounds possessing active hydrogen atoms. Alder, Pascher and Schmitz[2] have shown that ethyl azodicarboxylate forms adducts with natural and synthetic rubbers.

The facility with which azo compounds of this type add to rubber and related polymers suggested that compounds containing two such active groups in the same molecule should be useful cross-linking agents. If current hypotheses concerning the nature of vulcanization are correct, then such compounds ought to be effective vulcanizing agents. They conceivably could be of value in quantitative vulcanization studies since they offer the possibility of introducing controlled numbers of cross-linkages between rubber molecules, or other similarly unsaturated polymers, by a comparatively simple addition reaction. Accordingly, the synthesis of disazodicarboxylates and the investigation of their properties was undertaken as described in the present paper.

A number of these azo esters have been obtained by the following series of reactions

$$\mathrm{HOROH} + 2\mathrm{COCl_2} \longrightarrow \mathrm{ClCO_2ROCOCl}\ (\mathrm{I}) + 2\mathrm{HCl}$$

$$\mathrm{H_2NNH_2} + (\mathrm{R'O})_2\mathrm{CO} \longrightarrow \mathrm{H_2NNHCO_2R'}(\mathrm{II}) + \mathrm{R'OH}$$

$$\mathrm{ClCO_2ROCOCl} + 2\mathrm{H_2NNHCO_2R'} \xrightarrow{\mathrm{R_3''N}} (\mathrm{R'OCONHNHCO_2})_2\mathrm{R}\text{—}\ (\mathrm{III}) + 2\mathrm{R_3''N{\cdot}HCl}$$

$$(\mathrm{R'OCONHNHCO_2})_2\mathrm{R}\text{—} \xrightarrow{[\mathrm{O}]} (\mathrm{R'OCON{=}NCO_2})_2\mathrm{R}\text{—}\ (\mathrm{IV}) + 2\mathrm{H_2O}$$

The nature of the R and R′ groups has been varied and their combinations are shown in Table II. The dichlorocarbonates (I) were prepared by two different procedures. Aromatic dichlorocarbonates were obtained by the method of Oesper, Broker and Cook[3]; aliphatic dichlorocarbonates were synthesized by merely adding a glycol to an excess of liquid phosgene. All of the aliphatic dichlorocarbonates are high-boiling liquids which can be distilled in some cases under reduced pressure without appreciable decomposition. Since they could not be obtained in an analytically pure condition, they were converted to the corresponding diurethans (Table I) for the purpose of identification.

The esters of hydrazine monocarboxylic acid were prepared according to the procedure of Diels.[4] The bis-hydrazodicarboxylates (III) (Table II) are all relatively high melting solids which were obtained in yields of 80–90%. They were oxidized to the corresponding disazodicarboxylates (IV) in good yields by means of nitric acid or hypochlorous acid. The dis-azo esters are in most instances viscous, orange-colored oils which are thermally unstable above 125° and cannot be distilled without decomposition; however, they appear to be stable at room temperature. The dis-azo esters prepared from aromatic dichlorocarbonates are solids. They decomposed within a few hours at room temperature or during attempts to purify them by crystallization. Only those disazodicarboxylates which are listed in Table III were obtained in a satisfactory state of purity. They absorbed the theoretical amount of hydrogen when shaken over platinum oxide catalyst, being regenerated to the bis-hydrazodicarboxylates.

All of the disazodicarboxylates reacted rapidly with natural and synthetic rubbers at relatively low temperatures; good vulcanizates were obtained without the aid of other ingredients. The vulcanization studies will be reported elsewhere.[5]

To gain an insight into the manner in which these dis-azo esters vulcanize rubber, a study was made of the reaction between ethyl azodicarboxylate (V) and 2-methyl-2-butene (VI). Although the former is monofunctional, its mode of addition should be analogous to that of a disazodicarboxylate. The 2-methyl-2-butene may be considered to be representative of an isoprene unit in natural

---

(1) Presented in part at the September, 1946, Meeting of the American Chemical Society.

(2) Alder, Pascher and Schmitz, *Ber.*, **76**, 27 (1943).

(3) Oesper, Broker and Cook, THIS JOURNAL, **47**, 2609 (1925).

(4) Diels, *Ber.*, **47**, 2183 (1914).

(5) Flory, Rabjohn and Shaffer, forthcoming publication.

TABLE I

ALIPHATIC DIURETHANS ($H_2NCO_2ROCONH_2$)

R	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$-(CH_2)_2-$	165–166	$C_4H_8O_4N_2$	32.43	32.73	5.41	5.61
—(CH$_2$ $_3$—	168–169	$C_5H_{10}O_4N_2$	37.04	37.01	6.17	6.39
$-(CH_2)_4-$	198–199	$C_6H_{12}O_4N_2$	40.91	41.08	6.82	6.80
$-(CH_2)_6-$	187–188	$C_8H_{16}O_4N_2$	47.06	47.19	7.84	7.93
$-(CH_2)_{10}-$	171–172	$C_{12}H_{24}O_4N_2$	55.38	55.38	9.23	9.36
$-(CH_2CH_2)_2-O-$	150–151	$C_6H_{12}O_5N_2$	37.50	38.00	6.25	6.35

TABLE II

BIS-HYDRAZODICARBOXYLATES ($R'OCONHNHCO_2ROCONHNHCO_2R'$)

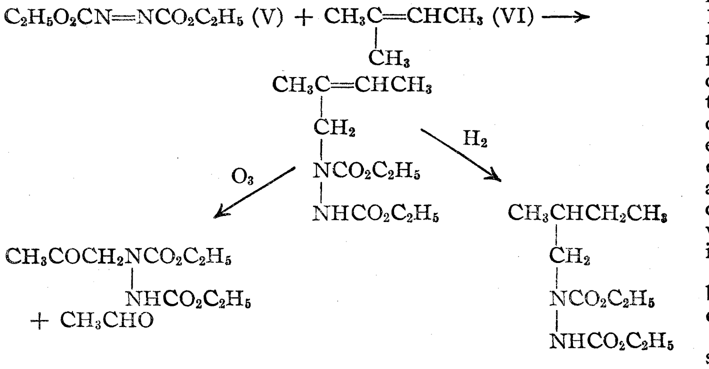
R'	R	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$-C_2H_5$	$-(CH_2)_2-$	104–105	$C_{10}H_{18}O_8N_4$	37.27	37.35	5.59	5.68
$-C_2H_5$	$-(CH_2)_4-$	178–179	$C_{12}H_{22}O_8N_4$	41.14	41.28	6.29	6.28
$-C_2H_5$	$-(CH_2)_6-$	154–155	$C_{14}H_{26}O_8N_4$	44.44	44.67	6.88	7.09
$-C_2H_5$	$-(CH_2)_{10}-$	87–88	$C_{18}H_{34}O_8N_4$	49.77	50.05	7.83	7.98
$-CH_2C_6H_5$	$-(CH_2)_{10}-$	79–80	$C_{28}H_{38}O_8N_4$	60.21	59.90	6.81	6.89
$-C_{10}H_{21}$	$-(CH_2)_{10}-$	91–92	$C_{34}H_{66}O_8N_4$	62.01	62.29	10.03	10.05
$-C_2H_5$	$-(CH_2CH_2)_2-O-$	129–130	$C_{12}H_{22}O_9N_4$	39.34	39.40	6.01	6.09
$-C_2H_5$	$-C_6H_4-$	191–192	$C_{14}H_{18}O_8N_4$	45.41	45.61	4.87	4.99
$-C_2H_5$	$-C_6H_4-C(CH_3)_2-C_6H_4-$	222–224	$C_{23}H_{28}O_8N_4$	56.56	56.26	5.74	5.94

TABLE III

DISAZODICARBOXYLATES ($R'OCON{=}NCO_2ROCON{=}NCO_2R'$)

R'	R	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$-C_2H_5$	$-(CH_2CH_2)_2-O-$	80–85 (10^{-4} mm.)	$C_{12}H_{18}O_9N_4$	39.78	40.04	4.97	5.13
$-CH_3$	$-(CH_2)_{10}-$	38–39	$C_{16}H_{26}O_8N_4$	47.76	47.83	6.47	6.52
$-C_{10}H_{21}$	$-(CH_2)_{10}-$	35–36	$C_{34}H_{62}O_8N_4$	62.39	62.75	9.48	9.60

rubber. The following reactions indicate that the azodicarboxylate system adds to the olefin by attacking a carbon atom *alpha* to a double bond.



It can be argued then that the disazodicarboxylates vulcanize rubber by the establishment of cross-links between polymer chains caused by the attachment of azodicarboxylate systems at *alpha* methylenic carbon atoms. This agrees with the findings of Farmer[6] that many reagents undergo reaction with rubber at this position.

Experimental

Preparation of Dichlorocarbonates.—The following procedure is representative of the method employed for the preparation of aliphatic dichlorocarbonates. Twenty grams (0.22 mole) of tetramethylene glycol was added dropwise to 150 g. (1.5 moles) of liquid phosgene which was cooled in an ice-bath. The addition of the glycol was regulated so that the temperature remained below 10°. The excess phosgene was allowed to evaporate and the residue was warmed at 40–50° (20 mm.) to remove traces of phosgene and hydrogen chloride. There was obtained 47.5 g. (99%) of tetramethylene dichlorocarbonate as an almost colorless, slightly viscous liquid. Due to a tendency to decompose at the high temperature required for distillation, it was impossible to obtain a sample pure enough for analysis. The dichlorocarbonate was identified by shaking a small sample with aqueous ammonia to obtain the corresponding diurethan (Table I).

All of the aliphatic dichlorocarbonates prepared by this procedure were obtained in essentially quantitative yields.

The aromatic dichlorocarbonates were synthesized by condensing the diphenols with phosgene in the presence of a tertiary amine according to the method of Oesper, Broker and Cook.[3]

Preparation of bis-Hydrazodicarboxylates.—The procedure employed for the preparation of decamethylene bis-methyl hydrazodicarboxylate is general for this class of compounds. To a solution of 12 g. (0.134 mole) of hydrazine monocarboxylic acid methyl ester in 200 cc. of dioxane were added dropwise 20 g. (0.067 mole) of decamethylene dichlorocarbonate and 13.5 g. (0.134 mole) of triethylamine. The dichlorocarbonate was kept in excess during the addition. The reaction mixture was allowed to stir until it had cooled and the precipitate of triethylamine hydrochloride was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was dissolved in a mixture of ethyl acetate and

---

(6) Farmer, *Trans. Faraday Soc.*, **38**, 340 (1942).

hexane. Upon standing for several hours a white solid precipitated; m. p. 109–111°; yield 23 g. (85%). After recrystallization from a mixture of ethyl acetate and hexane, the product melted at 112–113°.

Anal. Calcd. for $C_{16}H_{30}O_8N_4$: C, 47.29; H, 7.39. Found: C, 47.34; H, 7.59.

Preparation of Disazodicarboxylates.—The oxidation of decamethylene bis-methylhydrazodicarboxylate to the corresponding azo compound is typical. Sixteen grams of decamethylene bis-methylhydrazodicarboxylate was dissolved in 130 cc. of concentrated nitric acid. A slow oxidation took place and within about ten minutes an orange-colored oil formed as an upper layer. When this layer no longer appeared to increase, the reaction mixture was poured onto 500 g. of crushed ice. The azo compound was removed by extraction with benzene. The extract was washed with water, several times with 10% sodium bicarbonate solution and again with water. It was dried over anhydrous sodium sulfate and then concentrated under reduced pressure on a steam-bath. The residue was crystallized from a mixture of ethyl acetate and hexane. There was obtained 13 g. (82%) of decamethylene dis-methylazodicarboxylate as a bright, orange-colored solid; m. p. 38–39°.

Anal. Calcd. for $C_{16}H_{26}O_8N_4$: C, 47.76; H, 6.47. Found: C, 47.83; H, 6.52.

This compound was prepared also in satisfactory yield by passing chlorine into a well-stirred mixture of the bis-hydrazodicarboxylate and water.

Many of the disazodicarboxylates prepared by the nitric acid oxidation procedure did not form oil layers during the oxidation step. In such cases, the reaction became quite vigorous and was stopped by pouring onto ice.

Only those disazodicarboxylates which are solids (with the exception of diethylene dis-ethyl azodicarboxylate which was distilled at approximately 10^{-4} mm.) could be purified sufficiently for analysis. All of the disazodicarboxylates decomposed with the evolution of a gas when heated above 125°.

Preparation of Hydrazine Monocarboxylic Acid Esters.—The methyl and ethyl esters were obtained by the method of Diels.[4] The benzyl ester was prepared in a similar manner except that the condensation was carried out at steam-bath temperature and the ester was isolated as the hydrochloride salt; m. p. 186–187°. Neut. equiv. Calcd. for $C_8H_{11}O_2N_2Cl$: 202.5. Found: 205. Upon treating the hydrochloride with concentrated sodium hydroxide solution, the free ester resulted in 75% overall yield; m. p. 69–70°. It was purified by crystallization from a mixture of ethyl acetate and hexane. *Anal.* Calcd. for $C_8H_{10}O_2N_2$: C, 57.83; H, 6.02. Found: C, 57.83; H, 5.96. Hydrazine monocarboxylic acid *n*-decyl ester was obtained in 65% yield by heating di-*n*-decyl carbonate and 85% hydrazine hydrate at 115° for seventy-two hours. After crystallization from dilute alcohol, it melted at 58–59°. *Anal.* Calcd. for $C_{10}H_{24}O_2N_2$: C, 61.11; H, 11.11. Found: C, 61.35; H, 11.16.

Reduction of Decamethylene dis-Methyl Azodicarboxylate.—Two grams of the azo compound was dissolved in 100 cc. of dioxane and shaken with 0.1 g. of platinum oxide catalyst under hydrogen at a pressure of 50 lb./sq. in. The hydrogen uptake was rapid and within twenty minutes the solution was colorless. The drop in pressure corresponded to the theoretical amount of hydrogen required for reduction. The catalyst was removed by filtration and the filtrate was concentrated. The residue was dissolved in a mixture of ethyl acetate and hexane. There was obtained 1.9 g. of a white solid which melted at 112–113°. The melting point of a mixture of this substance and a known sample of decamethylene *bis*-methyl hydrazodicarboxylate was not depressed.

Condensation of Ethyl Azodicarboxylate with 2-Methyl-2-butene.—The ethyl azodicarboxylate was prepared according to the method of Ingold and Weaver.[7] 2-Methyl-2-butene was synthesized by dehydrating *t*-amyl alcohol after the procedure of Norris and Reuter.[8] The dehydration product (b. p. 36.5–38.5°) was purified[9] by careful fractionation with methyl alcohol through a 25 mm. × 72″ Podbielniak column. The product was washed with water to remove the methyl alcohol, dried over anhydrous potassium carbonate and then refractionated though a 13 mm. × 72″ Podbielniak column; $n^{20}D$ 1.3874.

A mixture of 41.5 g. (0.24 mole) of ethyl azodicarboxylate and 50 g. (0.71 mole) of 2-methyl-2-butene was allowed to stand at room temperature for nine days. The excess 2-methyl-2-butene was removed and the residue was distilled *in vacuo*. There was obtained 54 g. (92%) of a viscous, colorless oil which boiled at 128–129° (3 mm.); $n^{20}D$ 1.4613. *Anal.* Calcd. for $C_{11}H_{20}O_4N_2$: C, 54.10; H, 8.19. Found: C, 53.94; H, 8.22.

A 10-g. sample of this material was dissolved in 100 cc. of alcohol and reduced with hydrogen over Adams catalyst. The resulting product boiled at 115–116° (2 mm.); $n^{20}D$ 1.4507. *Anal.* Calcd. for $C_{11}H_{22}O_4N_2$: C, 53.66; H, 8.94. Found: C, 53.63; H, 9.01.

Seven grams of the adduct of ethyl azodicarboxylate and 2-methyl-2-butene was dissolved in 100 cc. of chloroform. A stream of ozonized air, containing about 2% of ozone, was bubbled through the solution for six hours at 0°. The solvent was removed under reduced pressure and the residue was boiled with 50 cc. of water for three hours. The flask was equipped with a column to keep back the water and the gases were led below the surface of 50 cc. of alcohol. After decomposition of the ozonide had been completed, the alcohol solution was treated with 2,4-dinitrophenylhydrazine. A yellow colored solid was obtained which melted at 147–148°. The melting point of a mixture of this material and a known sample of acetaldehyde 2,4-dinitrophenylhydrazone showed no depression.

The residue was extracted with chloroform and the extract was washed with water, with sodium bicarbonate solution and again with water. It was dried over anhydrous sodium sulfate and the solvent removed. The residue amounted to about 6 g. It was distilled *in vacuo*; b. p. 150–151° (3 mm.); $n^{20}D$ 1.4543.

Anal. Calcd. for $C_9H_{16}O_5N_2$: C, 46.55; H, 6.89. Found: C, 47.05; H, 7.14.

Summary

1. A method of synthesis of disazodicarboxylates has been described. These substances are capable of vulcanizing both natural and synthetic rubbers.

2. The condensation of ethyl azodicarboxylate with 2-methyl-2-butene has been studied. It has been shown that the azo ester system undergoes reaction at an α-methylenic carbon atom.

3. Accordingly, disazodicarboxylates must produce vulcanization by the establishment of cross-linkages between polymer chains.

AKRON, OHIO RECEIVED NOVEMBER 6, 1947

---

[7] Ingold and Weaver, *J. Chem. Soc.*, **127**, 378 (1925).

[8] Norris and Reuter, THIS JOURNAL, **49**, 2624 (1927).

[9] The author wishes to thank Dr. J. R. Long for performing this purification.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Oxidation of Catechol-type Substrates by Tyrosinase

BY MERCHANT L. CUSHING[1]

The fundamental function of the enzyme tyrosinase is thought to be the catalysis of the oxidation of the *ortho*-dihydroxy group of a catechol to an *ortho*-quinone. The enzyme is primed during this oxidation and after this priming is able to bring about the oxidation of monohydric phenols.[2] Robinson and McCance[3] first showed that the enzymatic oxidation of catechol requires two atoms of oxygen per mole. Since the production of an *ortho*-quinone from catechol requires only one atom of oxygen some explanation had to be made as to how the second atom was consumed. Onslow and Robinson[4] suggested that the second atom of oxygen resulted in the formation of hydrogen peroxide

$$C_6H_4(OH)_2 + O_2 \longrightarrow C_6H_4O_2 + H_2O_2$$

Several workers have expressed doubt concerning the validity of this postulate. The arguments advanced by these workers have been summarized in a paper by Dawson and Ludwig[5] who have presented additional evidence against the hydrogen peroxide postulate.

According to Dawson and Nelson[6] the oxidation of catechol takes place in two steps. Only the first step, the oxidation of catechol to *o*-benzoquinone, is catalyzed by the enzyme. This step consumes one atom of oxygen. The quinone reacts with water to form hydroxyhydroquinone, which in turn becomes oxidized to an *o*-quinone, thus consuming the second of oxygen. Later doubt was cast on this mechanism by Mason, Schwartz and Peterson[7] whose examination of the absorption spectrum of catechol undergoing oxidation in the presence of tyrosinase failed to detect hydroxyhydroquinone.

Since the oxidation of a monohydric phenol is through conversion to a catechol-type with the consumption of one atom of oxygen and subsequent oxidation of the catechol with the consumption of two atoms of oxygen, it follows that the oxidation of phenol requires three atoms of oxygen per mole.

Considerable data are recorded in the literature on the extent of oxidation of various phenolic substances but they are scattered and without attempted correlation. This is a natural result of their bit by bit presentation wherein little attention has been given to the effect of structure on the extent of oxidation. It would be an advantage to the advance of the knowledge of enzymatic oxidations if more were understood about the role variation of structure plays in extent and rate of oxidation.

This paper is a report of a study of the effect of variation in structure of the substrate on the extent of its oxidation. In approaching this problem the following postulates were used as guides:

1. It appears to be a general rule that addition to an ortho-quinone results principally in the formation of a 4-substituted catechol.
2. Dawson and Nelson[6] have suggested that water adds in the same way.
3. The use of a second atom of oxygen in the enzymatic oxidation of catechol depends upon the addition of water to *o*-benzoquinone.
4. It seemed likely that if substituents were placed in the 4-position of catechol this might prevent the hydration of the *o*-quinone and thus limit the oxygen consumption to one atom per mole.

Several catechol-type substrates were used to test the above postulates. These were allowed to oxidize in the presence of the enzyme until no more oxygen was consumed. The results are tabulated and discussed in the following section.

The Effect of Substituent Groups on the Total Oxygen Consumption of Catechol-Type Substances.—In Table I there is recorded the result of the oxidation to completion of several catechol-type substances when in the presence of tyrosinase. The oxygen consumption was measured by the technique of the Warburg respirometer, according to Graubard and Nelson.[8]

When the above results are considered in the light of the nature of the groups which are substituents the following generalizations seem permissible:

1. An *ortho*-directing group in the 4-position does not alter the amount of oxygen from that required by catechol.
2. A *meta*-directing group brings about a change in the oxygen consumption, only one atom of oxygen being used in place of the two of catechol.
3. When both the 4- and 5-positions are substituted by *ortho*-directing groups the oxygen consumption is only one atom per mole of substrate.

This would seem to indicate that the 4-position is of great importance in the consumption of the

---

[1] An extract of the thesis submitted by the author to the faculty of Columbia University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Chas. A. Bordner and J. M. Nelson, THIS JOURNAL, **61**, 1507 (1939).

[3] M. E. Robinson and R. A. McCance, *Biochem. J.*, **19**, 251 (1925).

[4] M. W. Onslow and M. E. Robinson, *ibid.*, **20**, 1138 (1926).

[5] C. R. Dawson and B. J. Ludwig, THIS JOURNAL, **60**, 1617 (1938).

[6] C. R. Dawson and J. M. Nelson, "Advances in Enzymology," IV, 99 (1944).

[7] Mason, Schwartz and Peterson, THIS JOURNAL, **67**, 1233 (1945).

[8] Mark Graubard and J. M. Nelson, *J. Biol. Chem.*, **111**, 757 (1935).

TABLE I

OXYGEN CONSUMPTION OF CATECHOL-TYPE SUBSTRATES DURING OXIDATION CATALYZED BY TYROSINASE

Group	Position	Atoms of oxygen per mole substrate		
		Author	Others	Reference
—Cl	4	2.1		
—CH_3	4	...	2.0	(9)
—CHO	4	1.1		
—COOH	4	1.1		(10)
—$COCH_3$	4	1.0		
—$COCH_2Cl$	4	1.1		
—SO_3Na	4	1.0		
—NO_2	4	0.0		
—$SO_2C_6H_5$	4	...	0.0	(9)
—$COCH_2NHCH_3$	4	...	0.0	(11)
—SO_3Na	3	0.0		
—NO_2	3	1.9		
—CH_3	4, 5	1.0		
—Cl	4, 5	1.1		
—Br	4, 5	1.0		
—NO_2	3, 5	0.0		
—Cl	3, 5	1.0		
—Br	3, 5	1.0		
—Cl	3, 4, 5	1.0		
—Br	3, 4, 5, 6	1.1		
—Br, (—CH_3)	3, 5, 6 (4)	1.0		

Measurements were made at 25°. The reaction flasks were of 50 ml. volume and contained as the reaction mixture 1 ml. of enzyme added from the side-arm at zero time, 2 ml. of (0.2 *M*) phosphate–(0.1 *M*) citrate buffer to produce a *p*H of about 7, substrate solution, and water to bring the volume to 8 ml. The enzyme used was purified extract from the common mushroom, *Psalliota campestris*. When the absorption of oxygen ceased fresh enzyme was added. This was repeated until addition of enzyme failed to cause the absorption of more oxygen. The amount of substrate used was 1.0 × 10^{-5} mole, except in a few cases where it was less due to the low solubility of the substrate. The results are the average of three or more determinations.

second atom of oxygen by catechol. In those substances where the 4-position is occupied by a substituent, flanked by a *meta*-directing group, or by two *ortho*-directing groups the consumption of the second atom of oxygen does not occur. The result in all cases is the production of an *o*-quinone, without formation of hydrogen peroxide.

The Effect of Substituent Groups on the Total Oxygen Consumption of Monohydric Phenols.—Since the introduction of substituent groups onto the catechol ring has a marked effect on the extent of oxidation of catechols it was considered of interest to examine the effect of these substituents on the ability of the enzyme to introduce a second hydroxyl group into monohydric phenols.

Data from the literature on the extent of oxidation of monohydric phenols have been used in compiling Table II which classifies the phenols according to the nature and position of the substituent. Only two new substances have been studied here.

TABLE II

OXYGEN CONSUMPTION OF SUBSTITUTED PHENOL DURING OXIDATION CATALYZED BY TYROSINASE

Group in position				Atoms of O_2 per mole	Reference
2	3	4	5		
CH_3	....	.....	..	0	9
CH_3	....	CH_3	..	0	12
CH_3	....	.....	CH_3	0	12
CH_3	CH_3	.....	CH_3	0	12
OCH_3	....	.....	..	0	9, 12
CHO	....	.....	..	0	9
COOH	....	.....	..	0	9
NO_2	....	.....	..	0	9
....	CH_3	.....	..	3	9,12
....	OCH_3	.....	..	3	9
....	Cl	.....	..	0	12
....	C_2H_5	.....	..	2	12
....	CH_3	.....	CH_3	0	12
....	CH_3	CH_3	..	2 Author's obs.	12
....	C_2H_5	.....	CH_3	0	12
CH_3	CH_3	.....	..	2	12
....	COOH	.....	..	0	9
....	....	CH_3	..	3	9,12
....	....	OCH_3	..	3	9,12
....	....	*t*-C_4H_9	..	1	12
....	....	*n*-C_4H_9	..	3	12
....	....	Cl	..	3.0 Author's obs.	
....	....	CHO	..	0^a	
....	....	COOH	..	0^a Author's	13
....	....	$COCH_3$	..	0^a Author's	
....	....				

[a] After eight hours contact with the enzyme no oxidation had taken place. Attempts to prime the enzyme with traces of added catechol failed to bring about oxidation.

By comparison of the results presented in this table with those of Table I it can be seen that the same groups which act to limit the oxidation of catechols to a one-atom-per-mole stage here operate to prevent the introduction of a new or second hydroxyl group by the enzyme. The resulting substituted phenol is inert to tyrosinase oxidation. This seems to be true no matter what is the position of the substituent group. It also may be noted that there are some monohydric phenols which are not subject to the oxidative influence of tyrosinase even when their catechol analogs are substrates.

The oxidation of catechol and a few members of the catechol family by tyrosinase has been longsince well demonstrated. However, if tyrosinase is to play an important part in cellular respiration, as has been recently postulated,[10,14,15] it should possess the ability to catalyze the oxidation of a multitude of diverse and complexly substituted catechols, whose occurrence is widespread. This can now more certainly be considered to be a real property of the enzyme in the light of the findings of this paper.

The enzyme must also possess the property of being primed toward monohydric phenols when it

---

(9) C. E. Pugh and H. S. Raper, *Biochem. J.*, **21**, 1370 (1927).

(10) R. D. H. Heard and H. S. Raper, *ibid.*, **27**, 36 (1933).

(11) D. Baker and J. M. Nelson, *J. Gen. Physiol.*, **26**, 269 (1943).

(12) J. Enselme and J. L. Vigneau, *Bull. soc. chim. biol.*, **27**, 387 (1945).

(13) M. W. Onslow and M. E. Robinson, *Biochem. J.*, **19**, 420 (1925), stated that this gave a positive test for catechol after it had stood twenty-four hours with potato tyrosinase.

(14) E. S. Robinson and J. M. Nelson, *Arch. Biochem.*, **4**, 111 (1944).

(15) E. M. Walter and J. M. Nelson, *ibid.*, **6**, 131 (1945).

catalyzes the oxidation of the more complexly substituted catechols. Without this property the enzyme would be devoid of power to aid in the utilization of the monohydric phenols in nature. The question as to whether the oxidation of a given substrate causes the enzyme to be primed for the oxidation of monohydric phenols must be tested by the use of a substance whose oxidation by tyrosinase alone is negligible. While hydroquinone is not a monohydric phenol it behaves as such toward the enzyme. Its oxidation is very slow and one can note the priming effect of adding traces of catechol. Gregg and Nelson[16] have shown that the oxidation of catechol primed the enzyme so that it could bring about the oxidation of hydroquinone. We have tested the priming of the enzyme during the oxidation of several of the substrates reported in this paper. The results are shown in Table III.

TABLE III

SHOWING THE ABILITY OF TYROSINASE TO EFFECT THE OXIDATION OF HYDROQUINONE DURING OXIDATION OF CATECHOL-TYPE SUBSTRATES

Substrate concentration, 0.25×10^{-5} mole; *p*H 6.40; hydroquinone, 5 mg.; gelatin, 5 mg.; enzyme, 2.75 catecholase units[16]

Substrate	Oxygen (cubic millimeters) Required	Oxygen (cubic millimeters) Consumed (30 min.)
Catechol	56.0	420
3,4-Dihydroxybenzenesulfonate Na	28.0	400
3,5-Dichlorocatechol	28.0	375
3,4,5-Trichlorocatechol	28.0	290
3-Nitrocatechol	56.0	225
3,4-Dihydroxy-ω-chloroacetophenone	28.0	130

The oxygen uptake in excess of that calculated as required for the catechols was consumed in the oxidation of the added hydroquinone. Thus it is seen that regardless of whether the substrate consumes one or two atoms of oxygen it can cause the enzyme to be primed to oxidize monohydric phenols.

Discussion

The question of hydrogen peroxide formation during the oxidation of catechols and phenols has been marked by controversy since the postulate of its formation was first advanced. In recent years the weight of evidence has been such that this postulate is being for the most part rejected. The finding of several substrates whose oxygen consumption is limited to a single atom of oxygen per mole adds confirmation to the work of those who reject the hydrogen peroxide postulate. In all cases where one atom of oxygen was consumed the product was found to behave as an *o*-quinone, and no hydrogen peroxide could be detected. The enzyme being free from catalase, the conclusion that there is no hydrogen peroxide formed appears well justified.

Studies on reaction rates of the system air–tyrosinase–catechol and air–tyrosinase–*p*-cresol are made difficult due to the complex nature of the reaction which each undergoes. The use of a substrate whose oxidation requires only one atom of oxygen per mole should eliminate many of these difficulties.

Experimental Details

Many of the catechol-type substrates used in this study were not available from commercial sources, thus necessitating their preparation according to the methods from previous literature as shown below.

4-Chlorocatechol.—By treating catechol with sulfuryl chloride; m. p. 90–92°.[17]

3,4-Dihydroxybenzaldehyde.—By treating piperonal with phosphorous oxychloride, followed by hydrolysis; yields very small; m. p. 152–153°.[18]

3,4-Dihydroxybenzoic Acid.—By fusion of vanillin with potash; m. p. 197–199°.[19]

3,4-Dihydroxyacetophenone.—By reduction of 4-chloroacetylcatechol; m. p. 116–117°.[20]

3,4-Dihydroxy-ω-chloroacetophenone.—By treatment of catechol with chloroacetic acid and phosphorous oxychloride.[21]

Sodium 3,4-Dihydroxybenzenesulfonate.—By treatment of guaiacol with sulfuric acid; m. p. 97–98°.[22]

4-Nitrocatechol.—By Dakin oxidation of 5-nitrosalicylaldehyde; m. p. 168–170°.[23]

3-Nitrocatechol.—By nitration of catechol; m. p. 86–90°.[24]

4,5-Dimethylcatechol.—From *o*-xylenol.[25]

4,5-Dichlorocatechol.—By treating catechol with sulfuryl chloride.[17]

4,5-Dibromocatechol.—By bromination of catechol in acetic acid.[26]

3,4,5-Trichlorocatechol.—By chlorination of catechol; m. p. 104–105°.[27]

Tetrabromocatechol.—Bromination of catechol; m. p. 192–193°.[28]

3,5,6-Tribromo-4-methylcatechol.—Bromination of 4-methylcatechol; m. p. 163–164°.[29]

3,5-Dibromocatechol.—By Dakin oxidation of 3,5-dibromosalicylaldehyde; m. p. 92–93°.[23]

3,5-Dichlorocatechol.—By Dakin oxidation of 3,5-dichlorosalicylaldehyde; m. p. 85–86°.[23]

3,5-Dinitrocatechol.—By nitration of catechol diacetate; m. p. 160–164°.[30]

Summary

1. It has been shown that the introduction of the *ortho*-directing groups —CH_3 and —Cl into the 4-position of the catechol ring produces a tyrosinase substrate whose oxygen consumption is the same as that for catechol, that is, two atoms of oxygen per mole.

2. The introduction into the 4-position of the catechol ring of such *meta*-directing groups as —CHO, —COOH, —$COCH_3$, —$COCH_2Cl$ and

---

(16) Donald C. Gregg and J. M. Nelson, THIS JOURNAL, **62**, 2500 (1940).

(17) *Ber.*, **44**, 2175 (1911).

(18) *Monatsh.*, **14**, 382 (1883).

(19) *Ber.*, **7**, 617 (1874).

(20) *J. Chem. Soc.*, **105**, 1051 (1914).

(21) THIS JOURNAL, **57**, 1382 (1935).

(22) *Ber.*, **39**, 4093 (1906).

(23) *Am. Chem. J.*, **42**, 492 (1910).

(24) *Bull. soc. chim.*, [3] **9**, 53, 137 (1898).

(25) *Ber.*, **42**, 2922 (1909).

(26) *Ann. chim. phys.*, [7] **13**, 487 (1902).

(27) *Bull. soc. chim.*, [3] **13**, 719 (1902).

(28) *Am. Chem. J.*, **26**, 31 (1894).

(29) *Bull. soc. chim.*, **11**, 735 (1900).

(30) *Ber.*, **26**, 2183 (1893).

—SO_3Na produces substrates whose oxygen consumption is one atom per mole.

3. For those substrates in which both the 4- and 5- positions are substituted the oxygen consumption is one atom per mole.

4. It was shown that the —NO_2 group in the 3-position of the catechol ring produces a substrate which consumes two atoms of oxygen per mole, whereas the —SO_3Na group in this position produces a substance inert to tyrosinase.

5. Leaving the 4-position open and substituting in the 3- and 5-positions produces a substrate which consumes one atom of oxygen per mole.

6. Analysis of the literature shows that the oxidation of a monohydric phenol by tyrosinase fails when there is in the 2-position any group other than —OH.

7. Analysis of the literature shows that an *ortho*-directing group (except —OH) in the 3-position of phenol produces a substrate which consumes three atoms of oxygen, whereas if the group is *meta*-directing the substance is inert to tyrosinase.

8. When there is in the 4-position of the phenol ring an *ortho*-directing group the substance consumes three atoms of oxygen per mole. This was demonstrated with *p*-chlorophenol. When the group is *meta*-directing the substance is inert toward tyrosinase.

9. 4,5-Dimethylphenol was oxidized by tyrosinase with the consumption of two atoms of oxygen per mole.

10. Oxidation of catechol-type substrates enabled the enzyme to bring about the oxidation of hydroquinone.

NEW YORK, N. Y. RECEIVED NOVEMBER 15, 1947

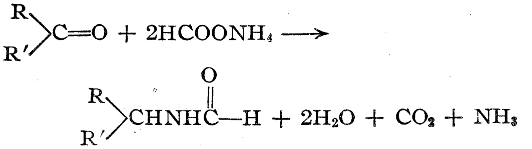
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Studies on the Mechanism of the Leuckart Reaction

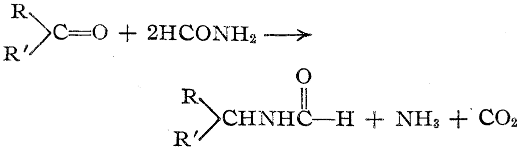
BY ELLIOT R. ALEXANDER AND RUTH BOWMAN WILDMAN

The conversion of carbonyl compounds into the corresponding amino derivatives by means of excess ammonium formate or formamide is usually called the Leuckart reaction. Recently this reaction has been used for the preparation of a rather large number of amines,[1] and the experimental conditions have been developed to the point where good yields can be obtained.

The mechanism of this reaction, however, is not definitely known. Superficially at least the equation may be written as in (1) or (2) in which either ammonium formate or formamide can be considered to be the essential reactant. It is quite interesting that both reagents have been used successfully, although ammonium formate appears to give somewhat better yields than formamide alone[1c,1d] or formamide in the presence of formic acid.[1b] These facts suggested that ammonium formate was the actual reactant, and it was therefore the object of this work to learn if there were conditions such that the reaction could be carried out with ammonium formate but not with formamide.



$$\begin{matrix}R\\R'\end{matrix}\!>\!C{=}O + 2HCOONH_4 \longrightarrow \begin{matrix}R\\R'\end{matrix}\!>\!CHNH\overset{O}{\overset{\|}{C}}{-}H + 2H_2O + CO_2 + NH_3 \quad (1)$$

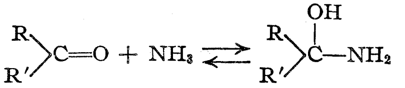


$$\begin{matrix}R\\R'\end{matrix}\!>\!C{=}O + 2HCONH_2 \longrightarrow \begin{matrix}R\\R'\end{matrix}\!>\!CHNH\overset{O}{\overset{\|}{C}}{-}H + NH_3 + CO_2 \quad (2)$$

In Table I are summarized the important data from a number of reactions carried out under different conditions using acetophenone as the carbonyl component. In experiments 4 and 5 it will be observed that when the reaction was carried out in diethylene glycol solution at 120–130°, no reaction occurred with formamide even after as long as fifteen hours, while a yield of 10% was obtained with ammonium formate after four hours. Thus, although formamide is capable of reacting at temperatures greater than 165° (Experiments 1 and 2), at 120–130° ammonium formate appears to the reagent which is both necessary and sufficient for reaction.[2]

One mechanism for the reaction of a carbonyl compound with ammonium formate is the one originally proposed by Wallach[3] which is outlined in equations 3–5.

$$HCOONH_4 \rightleftarrows HCOOH + NH_3 \quad (3)$$



$$\begin{matrix}R\\R'\end{matrix}\!>\!C{=}O + NH_3 \rightleftarrows \begin{matrix}R\\R'\end{matrix}\!>\!\overset{OH}{\overset{|}{C}}{-}NH_2 \quad (4)$$

---

(1) (a) Goodson, Wiegand and Splitter, THIS JOURNAL, **68**, 2174 (1946); (b) Crossley and Moore, *J. Org. Chem.*, **9**, 529 (1944); (c) Novelli, THIS JOURNAL, **61**, 520 (1939); (d) Johns and Burch, *ibid.*, **60**, 919 (1938); (e) Ingersoll, Brown, Kim, Beauchamp and Jennings, *ibid.*, **58**, 1808 (1936).

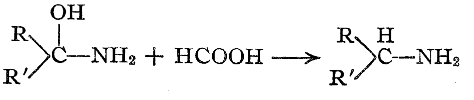
(2) At 165° there may exist an equilibrium between the systems.

$$HCONH_2 + O{=}\underset{|}{C}{-} \rightleftarrows HCON{=}\underset{|}{C}{-} + H_2O$$

$$H_2O + HCONH_2 \rightleftarrows [HCOO]^- + [NH_4]^+$$

In support of this reaction series for the intermediate formation of ammonium formate, it will be observed that the yield was lowered from 30% to 17% by the introduction of anhydrous calcium sulfate into the reaction mixture (Experiments 1 and 2).

(3) Wallach, *Ann.*, **343**, 54 (1905).


(5)

It has also been suggested that an alternative path for primary and secondary alkyl ammonium formates might involve the reduction of an imine formed by the loss of water from the carbonylammonia[1b] (6).

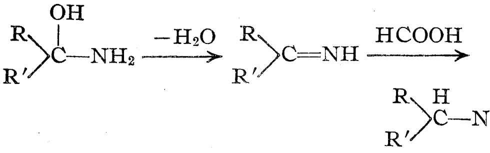

(6)

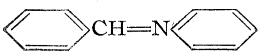
TABLE I

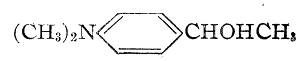
THE LEUCKART REACTION WITH ACETOPHENONE

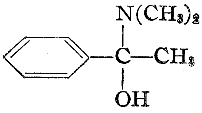
	Mole reactant/mole acetophenone[a]					
No.	Formamide	Ammonium formate	Solvent	Temp., °C.	Time, hr.	Yield, %
1	5.0			165–173	7.5	30[d]
2	5.0[b]			165–170	7.0	17[d]
3		5.2[c]		150–155	8.0	77[d]
4	2.3		Diethylene glycol[f]	120–130	15.0	0[e]
5		2.3	Diethylene glycol[f]	120–130[g]	4.0	10[e]

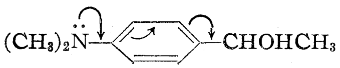
[a] Experiments 1–3 were carried out with 0.5 mole of acetophenone. Experiments 4 and 5 were carried out with 0.33 mole of acetophenone. [b] Anhydrous calcium sulfate (200 g.) was added to the reaction mixture. [c] Preheated at 160° until no more water came off. [d] Isolated as the formyl derivative of *dl*-α-phenylethylamine. [e] Isolated as *dl*-α-phenylethylamine. [f] 50 ml. [g] The reaction mixture became homogeneous at about 90°.

Except for the step involving the reduction of the carbonyl ammonia or imine by formic acid this reaction series seems most reasonable. However, no record of the reduction of a carbon–nitrogen double bond by formic acid could be found, and the reduction of a hydroxyl group by formic acid usually appears to require much more vigorous conditions than were employed in experiment 5. Thus, in a careful study of the minimum decomposition temperature of a number of formic esters, Bowden, Clarke and Harris[4] showed that methyl formate was stable at 440°, and that benzyl formate and benzhydryl formate began to decompose only at 320° and 206°, respectively.[5] Accordingly an investigation was undertaken to determine if intermediates such as those which are shown in equations 5 and 6 can be reduced with formic acid. As a model imine, benzalaniline (I) was chosen. Ketone ammonias, however, are well known to form only unstable addition compounds and for that reason *p*-dimethylaminophenylmethylcarbinol (II) was selected for study. *p*-Dimethylaminophenylmethylcarbinol, it will be observed, is a vinylog of the addition product of acetophenone and dimethylamine (III). Consequently, many of the electrical effects which might be conferred upon the α carbon atom as a result of the electron pair on the nitrogen atom in III would be expected to be relayed to the same atom by the electromeric mechanism shown in IV.


I


II


III


IV

Experiments showed that both benzalaniline and *p*-dimethylaminophenylmethylcarbinol produced resinous materials on boiling with 90% formic acid, but that when the acidity of the reaction mixture was reduced by employing triethylammonium formate, reduction occurred in both cases. Thus, on heating triethylammonium formate and the carbinol at 130–135° for twelve hours, a 6% yield of dimethylaminoethylbenzene was obtained (isolated as the methiodide). When benzalaniline was heated with the same reagent at 140–160° for two hours a 97% yield of N-benzylaniline hydrochloride was obtained. Although the yield in the case of the carbinol was very low, the fact that reduction occurred at all at 130° indicates that compounds of this type are much more susceptible to reduction with salts of formic acid than would normally be supposed.

Experimental[6]

The Leuckart Reaction with Acetophenone.—The procedure used for the runs given in Table I was a modification of the method described by Ingersoll.[7] The product was worked up by two methods. In one of them the formyl derivative of *dl*-α-phenylethylamine was hydrolyzed as described[7] and the product isolated was *dl*-α-phenylethylamine. In the other, the reaction mixture was poured into water and the resulting oil was extracted thoroughly with benzene. The benzene solution was then washed with water and dried over anhydrous magnesium sulfate. Distillation gave the formyl derivative as a thick yellow oil, b. p. 148–156° (4 mm.),[8] $n^{25}\text{D}$ 1.5420–1.5448. The material showed no tendency to crystallize.

Reduction of *p*-Dimethylaminophenylmethylcarbinol with Triethylammonium Formate.—*p*-Dimethylaminophenylmethylcarbinol was prepared by the method of F. Sachs and L. Sachs.[9] After three recrystallizations from high-boiling petroleum ether the material melted at 59–60°.

Triethylammonium formate was prepared by neutralizing 50% formic acid with triethylamine and evaporating the resulting solution on a steam-bath for twelve hours at 20 mm. The crude triethylammonium formate was used without further purification. It was a light brown sirup.

---

(4) Bowden, Clarke and Harris, *J. Chem. Soc.*, 874 (1940).

(5) Triphenylcarbinol, which forms no formate, can be reduced to triphenylmethane by boiling with formic acid; see Kauffmann and Pannwitz, *Ber.*, **45**, 767 (1912).

(6) All melting points and boiling points are uncorrected.

(7) A. W. Ingersoll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 503.

(8) DeLeeuw, *Rec. trav. chim.*, **30**, 241 (1911).

(9) F. Sachs and L. Sachs, *Ber.*, **38**, 512 (1905).

The reaction was carried out by heating 5.0 g. (0.03 mole) of the carbinol with 22.0 g. (0.15 mole) of crude triethylammonium formate in a distilling flask which was equipped with a receiver and water-cooled condenser. The heating was carried out at a temperature of 120–125° for two hours; then it was raised to 130–135° and allowed to run overnight. During the heating period droplets of oil could be observed throughout the reaction mixture and the odor of triethylamine could be detected. A few drops of oil and water collected on the receiver.

On cooling and rinsing the entire apparatus with water into a beaker, a gummy mass separated. This mixture was extracted with ether, evaporated to dryness and stirred thoroughly with three small portions of low-boiling petroleum ether. This solution was again evaporated to dryness and the residue steam distilled. From the distillate a small amount of oil was obtained by extraction with ether and evaporation of the excess solvent. It was characterized by warming with excess methyl iodide and recrystallizing the yellow quaternary salt formed from a mixture of alcohol and ether. After three recrystallizations 0.6 g. (6%) of a very faintly yellow material was obtained, m. p. 219–220° (dec.).[10] A mixed melting point of this material showed no depression with the methiodide of a sample of *p*-dimethylaminoethylbenzene prepared by the high pressure reduction of *p*-dimethylaminophenylmethylcarbinol over Raney nickel.[11]

Reduction of Benzalaniline with Triethylammonium Formate.—Benzalaniline (5.0 g., 0.0276 mole) and triethylammonium formate (13.0 g., 0.0884 mole) were heated with a small flame until the temperature of the reaction mixture reached about 140°. At this point a mild exothermic reaction took place; triethylamine was evolved and the reaction proceeded without further heating. In a very short time the reaction subsided and heating was continued at 140–160° for two hours.

After cooling the reaction mixture was poured into water, an oil separated, and the aqueous layer extracted with two small portions of benzene. The oil and the benzene extracts were then combined and heated with 10 ml. of concentrated hydrochloric acid in such a way that the benzene was allowed to evaporate. The residual oil was hydrolyzed in about ten minutes and the resulting solution was completely homogeneous. On cooling, the hydrolysis mixture completely solidified. It was broken up with a spatula, sucked as dry as possible on a Büchner funnel and rinsed with ice water and ether. After drying thoroughly, 6.9 g. (97.5%) of benzylaniline hydrochloride, m. p. 214–215°[12] was obtained. A second recrystallization from water did not improve the melting point. On regeneration with alkali, the free amine gave a benzamide, m. p. 107–108°, and a benzenesulfonamide, m. p. 118–119°.[13]

Summary

At 120–130° in diethylene glycol solution, acetophenone has been found to undergo the Leuckart reaction with ammonium formate but not with formamide. This indicates that at this temperature ammonium formate and not formamide is the essential reactant for the transformation.

Benzalaniline and *p*-dimethylaminophenylmethylcarbinol were reduced to N-benzylaniline (97%) and *p*-dimethylaminoethylbenzene (6%) by heating with triethylammonium formate at temperatures ranging from 130 to 160°. These compounds are analogous to the intermediates which were postulated by Wallach and by Crossley and Moore for the Leuckart reaction.

---

[10] Davies and Hulbert, *J. Soc. Chem. Ind.*, **57**, 349 (1938).

[11] The decomposition point of a quaternary salt depends somewhat upon the rate of heating. For the mixed melting point, therefore, samples of the material prepared in each way were included in the heating bath to serve as controls.

[12] Brand, *Ber.*, **42**, 3462 (1909).

[13] Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 195.

URBANA, ILLINOIS RECEIVED AUGUST 2, 1947

[CONTRIBUTION FROM THE GROSVENOR LABORATORY]

Preparation of Acetonechloroform and its Homologs

BY CH. WEIZMANN, E. BERGMANN AND M. SULZBACHER

For an investigation which is reported in the preceding paper, acetonechloroform ((trichloromethyl)-dimethylcarbinol) was needed in considerable quantities. Fishburn and Watson[1] concluded from a systematic investigation that the best method for its preparation was the condensation of acetone and chloroform by means of potassium hydroxide in excess acetone as solvent, and reported a yield of 25% under these conditions. Sodamide in anhydrous ether gives a yield of about 75%[2] but it has to be used in 50% excess and under strictly anhydrous conditions.

It has now been found that chloroform will condense with acetone and certain other ketones (see Experimental Part) in solutions of acetals containing potassium hydroxide to yield trichloromethyl carbinols. The yields are quite satisfactory, although some of the chloroform and/or the trichloromethyl carbinol formed reacts with the alkali to give potassium chloride, a side reaction which is the more pronounced the higher the water content of the potassium hydroxide used. The extent to which this side reaction occurs can be further reduced if one does not allow the reaction to go quite to the end.

The reaction can be extended to aldehydes, but only to those which are branched in α-position to the carbonyl group such as 2-ethylhexanal and isobutyraldehyde; straight-chain aldehydes undergo self-condensation more readily than condensation with chloroform. Benzaldehyde condenses with chloroform,[3] benzophenone does not.

While chloroform and bromoform condensed with the carbonyl compounds specified, methylene chloride failed to react at all, and 1,1,1,2,2,3,3-heptachloropropane was simply dehydrohalogenated to hexachloropropylene, even at low tem-

---

[1] Fishburn and Watson, *J. Am. Pharm. Assoc.*, **28**, 491 (1939); see Taffe, *Chem. Zentr.*, **95**, II, 304 (1924).

[2] Schwyzer, "Fabrikation pharmazeutischer und chemisch-technischer Produkte," Berlin, 1931, p. 112.

[3] Rapson and co-workers, *J. Chem. Soc.*, 74 (1944).

TABLE I

Carbonyl compound	Solvent	T,[a] °C.	Carb. cpd. rec., %	% Chloroform		Product	Yield,[b] %	Characteristics B. p., °C. (mm.)
				Rec.	Dec.			
Acetone[c]	Acetal	−1	..	26	13	Acetone-chloroform	80	.....
Acetone[c]	Acetal	−1	..	20	16	Acetone-chloroform	77	.....
Methyl ethyl ketone	Methylal	−5	..	23	24	T[d]-Methylmethylethylcarbinol	67	98–99 (29)[e]
Methyl ethyl ketone	Methylal[f]	−5	..	33	8	T[d]-Methylmethylethylcarbinol	85	.....
Methyl ethyl ketone	Acetal[f]	−5	20	36	7	T[d]-Methylmethylethylcarbinol	89	.....
Cyclohexanone	Methylal	−5	53	20	28	1-T-Methylcyclohexanol	64	120–123[e] (20)[g]
Cyclohexanone	Acetal	−5	51	37	10	1-T-Methylcyclohexanol	85	.....
Acetophenone	Methylal	−5	83	67	16	T-Methylphenylmethylcarbinol	41	[e,h]
Methyl isobutyl ketone	Methylal	−5	90	79	11	1,1,1-T-2,4-Dimethyl-2-pentanol	89	98–100 (22)
2-Ethylhexanal[i]	Methylal	−3	43	34	12	1,1,1-T-3-Ethyl-2-heptanol	82	135–140 (16)[j]
Isobutyraldehyde	Methylal	−4	..	..	..	1,1,1-T-3-Methyl-2-butanol	13	125–130 (760)[k,l]

[a] Temperature of the reaction. [b] Calculated on chloroform entered into reaction. [c] Double quantities used here. [d] T = trichloro-. [e] This condensation has been achieved by means of sodamide by *Chem. Fabrik. Wiernik*, German Patent 515,539 (1931). For the condensation of methyl ethyl ketone and chloroform by means of potassium hydroxide, see the unsuccessful attempts by Ekeley and Klemme, THIS JOURNAL, 46, 1252 (1924). [f] 51 g. of freshly molten, pure potassium hydroxide. [g] M. p. 50–52°. [h] Colorless oil; *Anal.* Calcd. for $C_9H_9OCl_3$: C, 45.0; H, 3.8; Cl, 44.6 Found: C, 44.7; H, 4.0; Cl, 44.6. [i] B. p. 80° (16 mm.). [j] *Anal.* Calcd. for $C_9H_{17}OCl_3$: C, 43.6; H, 6.9; Cl, 43.0. Found: C, 43.9; H, 7.0; Cl, 42.8. [k] This substance was prepared by Howard, THIS JOURNAL, 49, 1068 (1927), from chloral and isopropylmagnesium bromide; b. p. 105° (674 mm.). See also Jozicz, *Chem. Zentr.*, 68, I, 1013 (1897). [l] Considerable quantities (40 g.) of relatively high boiling range (170–230°) were formed.

perature. It had been chosen for these experiments as it contains, according to Rebek and Mandrino, a mobile hydrogen atom.[4]

Experimental

Acetone and Chloroform. (a) **In Methylal** (Formaldehydedimethylacetal).—At −4°, 120 g. of powdered technical potassium hydroxide (102 g. KOH; 1.8 moles) was added to 500 cc. of dry methylal, with vigorous agitation. At about the same temperature (not higher than −1°), a mixture of 215 g. (1.8 moles) of chloroform and 116 g. (2.0 moles) of acetone was added in the course of two hours and the agitation continued for two hours. The pale yellow reaction product was then run into a mixture of crushed ice and dilute sulfuric acid, the top layer separated and the aqueous bottom layer extracted with methylal. Distillation removed the solvent and any unchanged chloroform. The residue, which crystallized at once, was steam-distilled; needles, melting at 91° (after drying). In two parallel experiments, 41.0 and 40.0 g. of chloroform (19.1 and 18.6% of the total quantity employed) were recovered and 175.0 and 177.0 g. of trichloromethyldimethylcarbinol were isolated, corresponding to 67.7 and 68.1% of the chloroform entered into reaction. Titration of the aqueous layer showed that 98 g. of potassium chloride had formed which accounts for 24.3% of the chloroform employed.

When the amount of potassium hydroxide was halved, 108.0 g. (50.2% of the initial) of chloroform was recovered and 130.0 g. of the chlorinated alcohol and 32 g. of potassium chloride were formed, amounting to 81.7 and 8.0%, respectively, of the chloroform entered into reaction. The yield was, therefore, better (the decomposition very much reduced), but the conversion was unsatisfactorily low. If on the other hand the amount of potassium hydroxide was doubled, only 24.0 g. (11.2% of the initial) of chloroform was recovered, but the yield of acetonechloroform was very much reduced.

As already pointed out, freshly molten potassium hydroxide gives considerably better results. In two parallel experiments, conducted as described above, but using 102 g. of freshly molten potassium hydroxide, 82.0 and 80.0 g. of chloroform (38.1 and 37.2% of the total) were recovered and 170.0 and 175.0 g. of acetonechloroform formed (86.0 and 87.2%, calculated on chloroform entered into reaction). Only 7.0 and 6.2% of the chloroform decomposed.

(b) **In Butyraldehydedibutylacetal.**—A suspension of 60 g. of potassium hydroxide flakes (51 g., 0.9 mole KOH) was heated in 300 cc. of butyraldehydedibutylacetal[5] (b. p. 218°; 100–103° (15 mm.)) at 150° until two liquid layers had formed. The mixture was then slowly cooled to −2° with violent agitation which produced a very fine suspension. At this temperature, a mixture of 107.5 g. (0.9 mole) of chloroform and 58 g. (1 mole) of acetone was added slowly, the agitation continued for two more hours, and the product poured into a mixture of cracked ice and dilute sulfuric acid; 32.5 g. (30.2% of the initial) of chloroform were recovered and 97.5 g. of acetonechloroform isolated. This corresponds to 87.5% of the chloroform consumed in the reaction.

All the other experiments are summarized in Table I. It refers to the reaction between 1 mole of carbonyl compound, 10.9 mole of chloroform and if not otherwise stated 60 g. of powdered potassium hydroxide of 85% KOH content.

Acetone and Bromoform.—A mixture of 227.5 g. of bromoform and 58 g. of acetone was slowly added to the suspension of 60 g. of potassium hydroxide (51 g. KOH) in 250 cc. of acetal at −2°. The reaction was extremely violent, and the temperature rose temporarily to +9°; 71.4% of the bromoform used was recovered, but only 10.5 g. of acetonebromoform (from petroleum ether, fine needles, m. p. 168–170°)[6] could be isolated, which corresponds to 13.1% of the bromoform consumed. The balance was decomposed to potassium bromide.

Summary

Good yields of acetonechloroform are obtained when the components are condensed by means of potassium hydroxide in acetals as solvent.

Methyl ethyl ketone, methyl isobutyl ketone, acetophenone, cyclohexanone and α-branched aldehydes (isobutyraldehyde, 2-ethylhexanal) condense with chloroform smoothly under the same

---

(4) Rebek and Mandrino, *Chem. Zentr.*, **109**, II, 1204 (1938). See, however, *C. A.*, **33**, 1266 (1939).

(5) Adkins and co-workers, THIS JOURNAL, **55**, 299 (1933); **56**, 442 (1934).

(6) Aldrich, *ibid.*, **33**, 386 (1911).

conditions. Benzophenone does not react. Straight-chain aldehydes undergo self-condensation.

Acetone could not be condensed with methylene chloride or 1,1,1,2,2,3,3-heptachloropropane.

LONDON, S. W. 1, ENGLAND RECEIVED APRIL 29, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Orienting Effect of Negatively Substituted Vinyl Groups in Aromatic Substitution

BY F. G. BORDWELL AND KENNETH ROHDE[1]

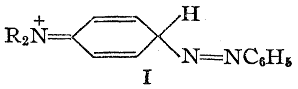
The orienting influence of groups on the course of aromatic substitution reactions was one of the first problems attacked in the development of the "English theory."[2] The directive properties of negatively substituted vinyl groups attracted attention during the early growth of the theory,[3,4] but groups of this nature have since been largely ignored in discussions and reviews. Baker and Wilson in their study of the nitration of ω-nitrostyrene found that the *p*- and *o*-isomers were formed almost exclusively. At that time they believed that the electron attracting effect of the nitro group was "damped out" by the electrons available in the olefinic bond, and that the substituted vinyl group was analogous to a methyl group in its directive properties. Since this early study, additional data concerning the orienting effect of substituted vinyl groups have become available, and the theory has also progressed.

The literature contains no mention of *m*-isomers from the nitration of such negatively substituted vinylbenzenes as α-methoxystyrene,[3] β-bromostyrene,[5] ω-nitrostyrene,[4] cinnamic acid,[6] α-chlorocinnamic acid,[7] α,β-dibromocinnamic acid[7] or 2-phenylethenesulfonyl chloride.[8,9] By careful analysis Baker and Wilson[4] found that the amount of *m*-isomer formed in the nitration of ω-nitrostyrene was less than 2%. Using a similar procedure, we have found that nitration in the *m*-positions of 2-phenylethenesulfonyl chloride also occurs to the extent of less than 2%. These data clearly illustrate the powerful *o*-*p*-directing effect of substituted vinyl groups.

In order to describe completely the orienting effect of a substituent on the course of aromatic substitution, it is necessary to know not only the positions taken by incoming groups under its direction, but also whether the substituent activates or deactivates the benzene nucleus. To determine the latter property for substituted vinyl groups, competitive nitration experiments were carried out by the method developed by Ingold, *et al.*[10] The competitive nitration of 2-phenylethenesulfonyl chloride and benzene was first studied, but the results obtained were not precise. Much better data were obtained from a study of the competitive nitration of cinnamic acid and benzene. The rates of nitration of 2-phenylethenesulfonyl chloride and of cinnamic acid were found to be appreciably lower than that of benzene, and of the same order as that of chlorobenzene. Negatively substituted vinyl groups, therefore, appear to belong with the halogen atoms in the class of strong *o*-*p*-directing groups which deactivate the benzene nucleus toward electrophilic substitution reactions.

Discussion

According to the most recent concepts of the role of orienting groups in aromatic substitution, the ability of a group to produce a more rapid reaction at *o*-*p*- than at *m*-positions is accounted for by assuming a resonance stabilization of the transition state for *o*-*p*- but not *m*-substitution.[11] Thus in the coupling of the benzenediazonium ion with dialkylaminobenzenes, Hughes and Ingold[11] attribute the *o*-*p*-directing influence of the dialkylamino groups to its ability to enhance the stability of the transition state by virtue of the contribution of structure I.



I

This concept of the role of orienting groups can be applied to all common *o*-*p*-directing groups, assuming a hyperconjugation effect for alkyl groups.[11] It is useful in explaining the fact that halogen atoms are strong *o*-*p*-directing groups despite their deactivating effect on the benzene nucleus. Al-

---

[1] Abstracted from the M. S. thesis of Kenneth Rohde, August' 1947.

[2] See, for example, Allan, Oxford, Robinson and Smith, *J. Chem. Soc.*, 401 (1926); Ingold and Ingold, *ibid.*, 1310 (1926); and subsequent papers by Robinson and Ingold and their collaborators.

[3] Ingold and Ingold, *J. Chem. Soc.*, **127**, 870 (1925).

[4] Baker and Wilson, *ibid.*, 842 (1926).

[5] Flürscheim, *J. prakt. Chem.*, **66**, 19 (1902).

[6] Müller, *Ann.*, **212**, 124 (1882); Underwood and Kochman, THIS JOURNAL, **48**, 254 (1926).

[7] Pfeiffer, *Ber.*, **47B**, 1755 (1914).

[8] Bordwell, Colbert and Alan, THIS JOURNAL, **68**, 1778 (1946).

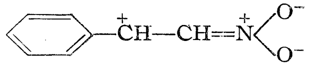
[9] However, nitration of 1-phenyl-1-nitro-2-(*p*-nitrophenyl)-ethene gave 21% of the *meta* isomer,[4] and Moore and Tucker, THIS JOURNAL, **49**, 258 (1927), isolated about 17% of *m*-sulfocinnamic acid from the sulfonation of cinnamic acid.

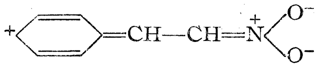
[10] Bird and Ingold, *J. Chem. Soc.*, 918 (1938), and previous papers.

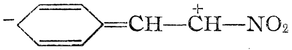
[11] (a) Hughes and Ingold, *ibid.*, 608 (1941); (b) Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, p. 470; (c) Wheland, THIS JOURNAL, **64**, 900 (1942); Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 256.

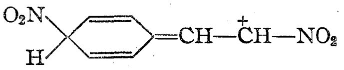
though the withdrawal of electrons from the benzene ring by the halogen atoms lowers the over-all rate of substitution in halobenzenes as compared to benzene itself, the rate of substitution at *o*-*p*-positions is greater than that at *m*-positions by virtue of resonance stabilization in the transition state.[12]

The transition state theory is particularly helpful in accounting for the orienting effects of negatively substituted vinyl groups, since predictions made on the basis of resonance possibilities in the initial states of these molecules are misleading. In the initial state the contribution of structures, such as II and III for ω-nitrostyrene, would be expected to be appreciable and to lead to *m*-substitution. The inductive effect of the nitro group transmitted through a vinyl group should also favor *m*-substitution. These effects are manifested by a lower rate of substitution for negatively substituted vinyl benzenes as compared to benzene. Structures of the type of IV probably would be relatively unimportant. However, in an electrophilic substitution reaction such as nitration of ω-nitrostyrene, which probably involves reaction with the NO_2^+ ion,[13] the energy of the transition state may be lowered appreciably when reaction occurs at the *o*-*p*-positions by the contribution of structures illustrated by V. No such resonance stabilization of the transition state can occur for reaction at the *m*-positions.


II


III


IV


V

Experimental[14]

Percentage of Isomers Formed in the Nitration of 2-Phenylethenesulfonyl Chloride.—In earlier work[8] approximately 50% of the *p*-isomer and 20% of the *o*-isomer have been isolated from a 95% yield of crude nitration mixture. Repetition of the experiment gave a 94% yield of crude nitration product from which fractional crystallization gave 53.4% of *p*-isomer, 19.7% of *o*-isomer, and 10.7% of a mixture. A study was made of the reaction of 2-(*o*- and *p*-nitrophenyl)-ethenesulfonhydrazides with 90% aqueous hydrazine to see whether this reaction could be used to further resolve the mixture. This method has been used[15] to separate isomeric nitrobenzenesulfonhydrazides. The 2-(*o*- and *p*-nitrophenyl)-ethenesulfonhydrazides were readily prepared but not easily purified. The acetone derivatives were prepared for identification purposes. Crude 2-(*p*-nitrophenyl)-ethenesulfonhydrazide, m. p. 142–144°, was converted to the **2-(*p*-nitrophenyl)-ethenesulfonhydrazone of acetone**, m. p. 201–202°.

Anal. Calcd. for $C_{11}H_{13}N_3O_4S$: C, 46.60; H, 4.62. Found: C, 46.75; H, 4.64.

Crude 2-(*o*-nitrophenyl)ethenesulfonhydrazide, m. p. 116–119°, was converted to the **2-(*o*-nitrophenyl)-ethenesulfonhydrazone of acetone**, m. p. 157–159°.

Anal. Calcd. for $C_{11}H_{13}N_3O_4S$: C, 46.60; H, 4.62. Found: C, 46.58; H, 4.50.

Nitrogen was evolved in the reaction of the 2-(*o*- and *p*-nitrophenyl)-ethenesulfonhydrazides with 90% aqueous hydrazine, but no pure products could be isolated from the reaction.

The amount of *m*-isomer in the unresolved 10.7% of nitration product was determined by hydrolysis of the 2-(nitrophenyl)-ethenesulfonyl chlorides followed by oxidation with aqueous potassium permanganate to a mixture of nitrobenzoic acids. The nitrobenzoic acids, obtained in 84% yield, were converted to their barium salts. Fractional crystallization yielded only very small quantities of slightly soluble barium salts, and mixed melting points taken with the acid produced from these salts indicated that the *m*-nitrobenzoic acid thus produced was very impure. The oxidation product was almost exclusively *o*-nitrobenzoic acid, m. p. 128–132°, which gave mixed melting points of 90–95° and 132–134° with *m*- and *o*-nitrobenzoic acids, respectively.

Competitive Nitration of 2-Phenylethenesulfonyl Chloride and Benzene.—The nitrations were run by a method similar to that described by Bird and Ingold.[10] The "R values"[10] in ten determinations ranged from 0.04 to 0.2. The source of error was apparently in the method of separation of the nitration products.

Competitive Nitration of Cinnamic Acid and Benzene.—The nitrations were carried out by keeping a solution consisting of 0.015 mole of benzene, 0.015 mole of cinnamic acid, 0.012 mole of nitric acid and 30 ml. of acetic anhydride at a thermostatically controlled temperature of 25° for eighteen to twenty hours. The reaction mixture was then stirred with about 200 g. of ice and water for one hour, the temperature being kept below 20°. The resulting mixture was extracted with four portions of a 10% solution of benzene in ether, and the cinnamic and nitrocinnamic acids were removed from the combined ethereal solutions by four extractions with aqueous sodium carbonate. The quantity of nitrobenzene and nitrocinnamic acids formed in the reaction was determined by titration of separate solutions containing these substances with titanium trichloride according to the method developed by Francis and Hill.[16] In four determinations the moles of nitrobenzene produced were 0.0034, 0.0028, 0.0039 and 0.0041, respectively, and the moles of nitrocinnamic acids were 0.00043, 0.00034, 0.00048 and 0.00053, respectively. Using the correction formula developed by Ingold and his co-workers,[10] the mean value for the ratio of the rate constants, *k*(cinnamic acid)/*k*(benzene) was found to be 0.111. For the competitive nitration of 2-phenylethene-1-sulfonyl chloride and benzene the ratio of rate constants is approximately 0.07. Bird and Ingold[10] reported a ratio of rate constants of 0.0353 for the competitive nitration of chlorobenzene and benzene at 25°.

Summary

1. Nitration of 2-phenylethenesulfonyl chlo-

---

[12] The calculations of Ri and Eyring, *J. Chem. Phys.*, **8**, 433 (1940), indicate that even in the initial state the charge distribution in chlorobenzene is such as to make the *p*- and *o*-positions more negative than the *m*-positions.

[13] Westheimer and Kharasch, THIS JOURNAL, **68**, 1871 (1946); Bennett, Brand and Williams, *J. Chem. Soc.*, 869 (1946); Goddard, Hughes and Ingold, *Nature*, **158**, 480 (1946).

[14] Microanalyses were by Miss Patricia Craig.

[15] Dann and Davies, *J. Chem. Soc.*, 1050 (1929); Davies, Storries and Tucker, *ibid.*, 624 (1931).

[16] Francis and Hill, THIS JOURNAL, **46**, 2498 (1924).

ride was found to give less than 2% of *m*-isomer, further illustrating the strong *o*-*p*-directing effect of negatively substituted vinyl groups.

2. The mean value for the ratio of rate constants, *k*(cinnamic acid)/*k*(benzene), determined by the competitive nitration of cinnamic acid and benzene was found to be 0.111. This ratio is of the same order as that obtained by Bird and Ingold[10] for the competitive nitration of chlorobenzene and benzene.

3. The *o*-*p*-orienting effect of negatively substituted vinyl groups has been accounted for by the assumption that resonance stabilization in the transition state, involving the electrons of the olefinic bond, is the determining factor.

EVANSTON, ILLINOIS RECEIVED OCTOBER 17, 1947

[CONTRIBUTION FROM THE BIOCHEMISTRY DEPARTMENT, ABBOTT RESEARCH LABORATORIES]

Polysaccharide Acid Esters as Cation Exchange Media

BY FLOYD C. McINTIRE AND JAY R. SCHENCK

In the development of a method for the purification of histamine[1] there arose a need for a cation exchange medium with properties not possessed by the commercially available cation exchangers. It was found that if cotton were *partially esterified* with succinic acid the acid ester so produced would function very nicely as a cation exchanger. The preparation of acid esters by the partial esterification of cellulose and other polysaccharides was then studied further with a view toward a more general use of these materials as cation exchange media.

To this end we have partially esterified cotton with glutaric, maleic, phthalic, and succinic acids and wood cellulose and starch with succinic acid.

Experimental

Esterification of Polysaccharides.—Two methods of esterification were used: (1) The acid anhydride, 0.2 mole, was dissolved in 300 ml. of pyridine. Ten grams of polysaccharide was suspended in this solution and the temperature was maintained at 60° for eighteen to twenty-four hours. The insoluble product was washed successively with water, dilute hydrochloric acid, water and alcohol and then dried *in vacuo;* (2) the acid anhydride, 0.2 to 0.4 mole, and 10 g. of anhydrous sodium acetate were dissolved in 300 ml. of glacial acetic acid. Ten grams of polysaccharide was introduced and the temperature was maintained at 100° for forty-eight hours. The product was washed with dilute hydrochloric acid, water and alcohol and then dried. The latter method is preferable for most purposes as it produces little or no obvious changes in the gross structure of the materials esterified. Satisfactory preparations of cotton acid maleate could be made only by this method. Starch was esterified in this way. During the esterification of wood cellulose and starch the reaction mixture was stirred continuously.

Determination of Cation Binding Capacity and Degree of Esterification.—Free carboxyl groups were determined by shaking a given amount of polysaccharide acid ester with an excess of 0.05 *M* sodium carbonate for fifteen to twenty minutes and titrating an aliquot of the solution for either total sodium or carbonate sodium. In this determination the original concentration of the second sodium ion of sodium carbonate should exceed the sodium ion binding capacity of the acid ester. The values so obtained agreed closely with the values for free carboxyl groups obtained by electrometric titrations. Direct titration with sodium hydroxide in the presence o an indicator was less reliable.

The degree of esterification was calculated from the determination of free carboxyl groups on the assumption that the number of ester linkages was equal to the number of free carboxyls.

Results and Discussion

The esterification of polysaccharides with dicarboxy acids is not new. This was perhaps first claimed by Levy,[2] and since then such esters have been covered in numerous patents.

In nearly all previous reports the polysaccharides were almost completely esterified and the products were soluble in organic solvents as the free acids or in water as the sodium salts. To our knowledge there is no previous report of the partial esterification of polysaccharides with dicarboxy acids for the preparation of cation exchange media. By effecting only partial esterification of the polysaccharides under conditions which minimize changes in mechanical structure, one can obtain products with physical properties which are very desirable for many cation exchange procedures. These partially esterified products do not jel in organic solvents as the free acids or in water as the sodium salts. In appearance they resemble the original polysaccharides very closely. The fibers of cotton acid esters seem more wiry and more brittle than cotton. The starch acid esters have less affinity for water than does the original starch.

Table I shows some representative values for the degree of esterification and the sodium ion binding capacity of the polysaccharide acid esters. The degree of esterification has a rather wide range. As many as one-fourth of the available hydroxyls of cotton have been esterified without noticeable breakdown of the fibers; with starch nearly half of the available hydroxyls were esterified and the product did not jel in water or alcohol either as the sodium salt or as the free acid. The degree of esterification can be controlled within reasonable limits.

The polysaccharide acid esters participate

---

[1] F. C. McIntire, L. W. Roth and J. L. Shaw, *J. Biol. Chem.*, **170**, 537 (1947).

[2] H. A. Levy, *Ind. Eng. Chem.*, **12**, 743 (1920).

TABLE I

SODIUM ION BINDING CAPACITY AND DEGREE OF ESTERIFICATION OF TYPICAL POLYSACCHARIDE ACID ESTER PREPARATIONS

Acid ester	Sodium ion binding capacity, milliequivalents per gram	Available hydroxyls esterified, %
Cotton succinate	3.15	25
Cotton maleate	1.13	6.9
Cotton glutarate	0.80	4.8
Cotton phthalate	1.7	12.3
Starch succinate	4.9	52

rapidly in cation exchange reactions. Cations can be removed from them completely by washing with an equivalent (or slightly more) of dilute hydrochloric acid. For example: 5 ml. of a solution containing 0.4 mg. of histamine free base in 1.4×10^{-3} *M* trisodium phosphate (*p*H about 12) was filtered through 100 mg. of cotton acid succinate (sodium ion binding capacity 0.32 milliequivalent). The histamine was removed quantitatively from solution by the cotton acid succinate and then was removed completely from the cotton succinate by washing with 1 ml. of 0.4 *N* hydrochloric acid followed by 2 ml. of water.

The estimation of the acidic strength of the polysaccharide acid esters was approached in two ways:

(1) Measurements of *p*H were made on the aqueous phase at equilibrium (0.1 g. of polysaccharide acid ester in equilibrium with 10 ml. of water) after the polysaccharide acid ester had been half neutralized with sodium hydroxide. The *pKa* values so obtained are shown in Table II.

(2) The extent to which the polysaccharide acid esters would remove sodium ion from a sodium acetate solution was determined as follows: A quantity of each acid ester having 0.5 milliequivalent of free carboxyl group was suspended in 10 ml. of 0.05 *M* aqueous sodium acetate. One-half hour of shaking or mixing was allowed for the system to come to equilibrium. Duplicate 3-ml. samples of the aqueous phase were removed and the free acetic acid was determined by titration with 0.1 *N* sodium hydroxide. This titration may be considered a direct measure of the sodium ions removed from the sodium acetate solution by the polysaccharide acid ester. If it can be assumed that the acetate ion and the acid esters actually compete for sodium ion and that the distribution of sodium ion between the acetate ion and the polysaccharide acid esters will be dependent upon the strengths of the acids, these values should give an indication of the acidic strengths of the polysaccharide acid esters relative to acetic acid. In Table II the *pKa* values are shown along with the per cent. sodium ion bound by the polysaccharide acid esters at equilibrium, when the acid ester carboxyl, acetate ion, and sodium ion were present in equivalent amounts. That the polysaccharide acid esters are as weakly acidic as the *pKa* values indicate is difficult to believe. The data on competition with acetate ion are more in accord with expectations. The significance of the great quantitative differences between these two types of data is a matter for future consideration.

TABLE II

THE ACIDIC STRENGTH OF POLYSACCHARIDE ACID ESTERS

Acid ester	*pKa*	Na p. e.[a]/Total Na, %
Cotton glutarate	8.8	12
Cotton succinate	7.8	16.8
Starch succinate	7.5	18
Cotton maleate	5.7	40.4
Cotton phthalate	5.6	40.6

[a] Na p. e. = sodium bound by the polysaccharide acid ester.

The usefulness of the polysaccharide acid ester cation exchangers as compared to the ion exchange resins[3] is yet to be determined. Cations can be eluted with dilute solutions of strong acids much more readily from the acid esters than from the sulfonic acid exchange resins. A comparison with carboxy exchange resins has not been attempted. One attractive feature of the polysaccharide acid esters is the availability of exchangers of different acidic strengths. The acid esters have a high ion-binding capacity as compared to the carboxy resins available at present, and their mechanical properties are particularly suited for semi-micro or micro operations. It is likely that other polysaccharide acid esters may be produced which are either weaker or stronger acids than those reported here. The polysaccharide acid esters have one serious limitation to their use, *i. e.*, their ease of saponification. This fact prevents their extensive use in systems where an excess of strong bases may be encountered.

Summary

A series of new cation exchange media, the polysaccharide acid esters, have been reported. Their preparation and properties have been described.

NORTH CHICAGO, ILL.

RECEIVED OCTOBER 20, 1947

---

[3] Robert J. Myers, "Advances in Colloid Science," Interscience Publishers, Inc., New York, 1942, Vol. I, pp. 312–351.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

Spectrophotometric Studies on Complex Formation with Sulfosalicylic Acid. I. With Iron III

BY ROBERT T. FOLEY AND ROBBIN C. ANDERSON[1]

Sulfosalicylic acid has long been known as an analytical reagent for iron,[2] giving characteristic colors with iron(III) solutions, apparently because of complex formation. The color variations, shading from violet through deep red or rose in acid solutions to yellow in alkaline, suggest that more than one complex may be involved. The present investigations were undertaken to obtain information concerning the nature of the complex or complexes responsible for these effects.

Experimental

Materials.—Standard iron(III) perchlorate solution was prepared by dissolving primary standard iron wire in hydrochloric and nitric acids. Perchloric acid was then added and the solution boiled slowly to drive off the more volatile acids.

C. P. sulfosalicylic acid (Eastman Kodak Co.) was dissolved in water, with sufficient perchloric acid to adjust to the same *p*H as that of the iron(III) perchlorate solution. The solution was standardized by titration with sodium hydroxide.

Sodium hydroxide solution for use in adjusting the *p*H was prepared from Merck Reagent grade sodium hydroxide. It was standardized with potassium acid phthalate. All solutions were prepared in calibrated apparatus at 25°.

Apparatus.—*p*H measurements were made with a Beckmann *p*H meter, Model G, with an accuracy of ±0.02 *p*H unit.

Light absorption measurements were made with an Automatic Recording General Electric Spectrophotometer of the Hardy type[3] over a range of 400 to 700 mμ with slit adjustment to measure a 10 mμ band. Per cent. transmission values for solutions of equal concentration prepared independently varied not more than 0.3 per cent.

Procedure.—Calculated volumes of iron(III) perchlorate and sulfosalicylic acid were mixed. Sodium hydroxide was then added if needed to adjust the *p*H and the whole diluted to the proper volume and allowed to stand one hour. The transmittance curve was then recorded, the absorption cells being rinsed very carefully before filling with each sample.

Preliminary experiments showed that the solutions reached equilibrium within one hour and showed no measurable variation thereafter for periods of less than twenty-four hours.

The absorption cell was not thermostated, but all solutions were brought to constant temperature before measurements were made.

Results

The composition of the complex was studied using Job's method of continuous variations,[4] the ratio of iron(III) to sulfosalicylic acid being varied with the total molarity of the two kept constant. Several typical transmittance curves for solutions at a *p*H of 2.38 are shown in Fig. 1.

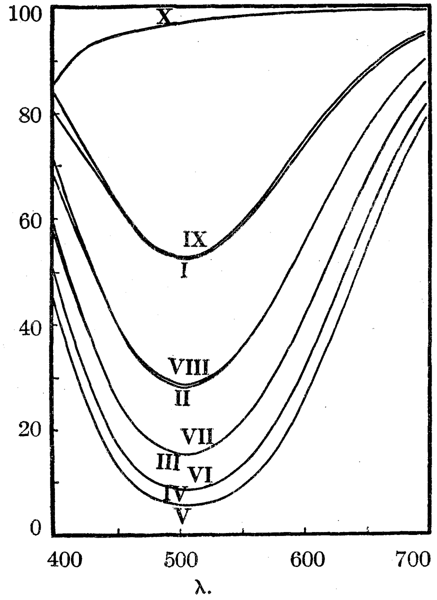


Fig. 1.—Method of continuous variations—absorption curves. The $[\mathrm{Fe^{III}}]/[\mathrm{Fe^{III}}]$ + [sulfosalicylic acid] ratio varied as I, 0.1; II, 0.2; III 0.3; IV, 0.4; V, 0.5; VI, 0.6; VII, 0.7; VIII, 0.8; IX, 0.9; X, 1.0.

From these curves values of the optical density ($D = \log_{10} 1/T$ where T = transmittance) for a particular wave length were calculated for each solution. Sulfosalicylic acid and perchloric acid show no absorption at the wave lengths used. The absorption for a system with no reaction is determined therefore by subtracting the optical density of iron(III) perchlorate determined from curve X of Fig. 1. Subtraction of this absorption for a particular wave length, from the optical density of the solution gives $\overline{D}$, a quantity which is proportional to the concentration of the complex and which passes through a maximum when the ratio of iron(III) to total sulfosalicylic acid in the solution is the same as that in which they react to form the complex.[4,5] $\overline{D}$ was plotted against the ratio

$$\frac{\text{concn. Fe(III) (moles/l.)}}{\text{concn. Fe(III)} + \text{concn. } \mathrm{HO_3SC_6H_3(OH)COOH}}$$

The results for wave lengths of 440, 500 and 540 mμ are shown in Fig. 2.

The occurrence of the maximum of $\overline{D}$ in the curves of Fig. 2 at a ratio of 0.5 indicates that un-

---

[1] Presented in part at Southwest Regional Meeting, American Chemical Society, Dallas, Texas, Dec. 12, 1946.

[2] Alten, Wieland and Hille, *Z. anorg. allgem. Chem.*, **215**, 81 (1933); Thiel and Peter, *Z. anal. Chem.*, **103**, 161 (1935); Kennard and Johnson, *Texas Acad. Sci. Proc. and Trans.*, **27**, 45 (1943).

[3] Hardy, *J. Opt. Soc. Am.*, **25**, 305 (1935); **28**, 360 (1938); U. S. Patent 1,987,441 (1935).

[4] Job, *Ann. chim.*, [10] **9**, 113 (1928); Vosburgh and Cooper, THIS JOURNAL, **63**, 437 (1941).

[5] Moore and Anderson, *ibid.*, **67**, 167 (1945).

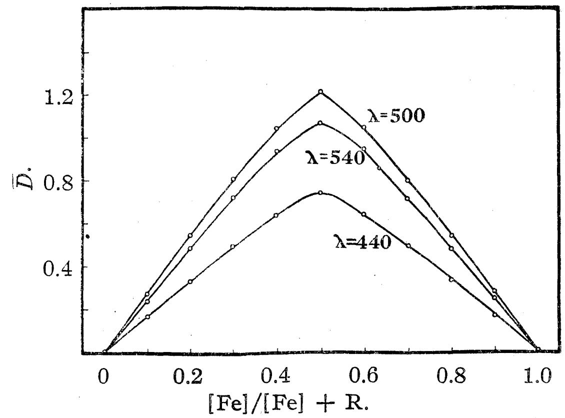


Fig. 2.—Method of continuous variations, *p*H 2.38.

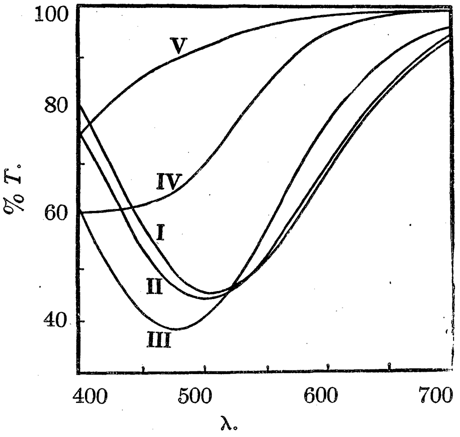
der these conditions the iron and sulfosalicylic acid react in a 1:1 ratio to form the complex.

It may be noted also that the absorption is essentially the same at the two extremes where the ratio of iron(III) to R (sulfosalicylate) is 9:1 and 1:9. Reasonable approximations for the extinction coefficients may be calculated by assuming that under such conditions essentially all of the reagent present in smaller proportion will react to form the complex. Correction can be made for absorption by excess iron(III). For the solution with ratio iron(III): R = 9:1, the value so obtained for the molar extinction coefficient of the complex was 753 at a wave length of 508 mμ. For solutions of ratios 1:9, 8:2, and 2:8, respectively, the corresponding values were 756, 761, 752. Thus there is no indication that in this *p*H range complex formation occurs with more than one iron (III) ion or R group. Similar agreement is obtained for absorption at other wave lengths.

With a change in *p*H, the results vary markedly. In more strongly acid solutions (*e. g.*, *p*H 0.9) $\bar{D}$ curves similar to those in Fig. 2 are obtained, except that the maximum tends to shift slightly to a concentration ratio of 0.46. Some variation is also apparent in solutions with excess sulfosalicylic acid as contrasted to excess iron; but, in general, solutions at *p*H values less than 2.5 show closely similar behavior.

From the curves of Fig. 1, values of the extinction coefficient may be calculated as indicated above. These can then be used to calculate the concentration of the complex in other solutions, *e. g.*, where equal concentrations of iron and sulfosalicylic acid are present. A better value for the extinction coefficient may then be calculated. By a series of successive approximations reasonably good values for the apparent dissociation constant (where R = sulfosalicylic acid concentration) K = [Fe(III)][R]/[FeR] may be determined. At *p*H 2.38 and ionic strength of 0.061 a value of 1.3 ($\pm$0.2) $\times 10^{-5}$ is obtained. At *p*H 0.9 and ionic strength 0.153 the value is 2.1 ($\pm$0.4) $\times 10^{-4}$.

Earlier workers[2] have referred to red or orange or yellow "complexes" in less acid solutions, but experiments at higher *p*H values in the present work indicate that information on such complexes based on ordinary color measurements alone is of doubtful significance. Typical results are shown in the curves of Fig. 3, for solutions of different *p*H and constant iron(III) and sulfosalicylic acid concentrations. The *position* of maximum absorption and thus the color of the solutions changes as well as the extent of absorption.



Effect of *p*H.

Fig. 3.—[Fe]^{III} = 1.791 $\times 10^{-4}$ mole/l. [sulfosalicylic acid] = 2.292 $\times 10^{-3}$ mole/l.: I, *p*H, 1.95; II, *p*H, 3.03; III, *p*H, 4.05; IV, *p*H 5.72; V, *p*H 9.38.

Graphs of $\bar{D}$ against concentration ratios show maxima shifted toward values less than 0.5. For *p*H 4.58, for example, the maximum $\bar{D}$ occurs at a concentration ratio of 0.25–0.30 and for *p*H 6.2 the maximum is between 0.1 and 0.2. These maxima might be taken as evidence of complexes with more R groups, but in some cases more than five sulfosalicylic acid molecules reacting per iron (III) ion would be indicated. It seems evident that other factors than complex formation are involved and that such maxima do not represent the compositions of real complexes.

It has been shown[6] that, even at *p*H 2.38, $FeOH^{++}$ is of major importance in iron(III) solutions; and, although dissociation constants for sulfosalicylic acid are not known exactly, experiments on buffers[7] have shown that the sulfonic acid group is highly ionized and that between *p*H 1 and *p*H 4 conversion in large measure to $^-O_3SCH_3(OH)COO^-$ should occur. These changes in ionic species might account in part for the effect of the hydrogen ion.

However, blank determinations show that in solutions of high *p*H, iron(III) perchlorate solutions absorb more strongly in the same regions as the iron(III)–sulfosalicylic acid mixtures, probably as a result of formation of hydrous iron(III) oxide sols. Where excess iron is present many of

[6] Rabinowitch and Stockmayer, THIS JOURNAL, **64**, 335 (1942); Bray and Hershey, *ibid.*, **56**, 1889 (1934).

[7] Private communication, U. S. Bur. Stds., Dr. R. G. Bates.

the mixtures form precipitates of hydrous iron (III) oxide on standing. The Job method may be applied successfully where other equilibria in solution are involved but any such sol formation makes uncertain the comparison and interpretation of absorption data for mixtures of varying concentrations.

Just recently, Babko's experiments on iron–salicylic acid systems, which might be expected to be closely analogous to the sulfosalicylic acid system, have been reported.[8] He found FeR^+ (violet) in acid solution, then FeR_2^- (red), and finally $FeR_3^{=}$ (yellow) at about *p*H 10, but abstracts available do not indicate what corrections were made for hydrolysis or dissociation.

Experiments are now under way to extend transmittance measurements on the iron–sulfosalicylate systems to the ultraviolet region in an attempt to determine concentrations of the various species, especially $FeOH^{++}$, so that their effects may be measured.

Effect of Temperature.—The instrument used is such that accurate control of temperature is not possible, but approximate measurement of the temperature effect showed that increased temperatures increase the extent of complex formation. The per cent. transmittance decreased about 7% on heating from 20 to 40°. A thermostated absorption cell has now been built so that the temperature effect may be measured more accurately in an attempt to determine the extent of dissociation of the complex.

The authors wish to express their appreciation to Mr. Leland L. Antes, Microscopy Specialist, Bureau Engineering Research, University of Texas, for his assistance in connection with use of the spectrophotometer.

Summary

1. Spectrophotometric studies of complex formation between iron(III) and sulfosalicylic acid were made over a *p*H range of 1 to 9.

2. In strongly acid solutions (to *p*H 2.4) iron (III) and sulfosalicylic acid react in a 1:1 ratio to form a violet complex. Stability of the complex is a function of the acidity.

3. Measurements at higher *p*H values indicate complexes of other mole ratios, but accurate formulas could not be determined from ordinary concentration measurements.

AUSTIN, TEXAS RECEIVED JUNE 30, 1947

---

[8] Babko, *J. Gen. Chem.* (*U. S. S. R.*), **15**, 745 (1945); *C. A.*, **40**, 7042 (1947).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

Some Reactions of Trisodium Monobismuthide in Liquid Ammonia[1,2]

BY GEORGE W. WATT AND THOMAS E. MOORE[3]

Although numerous intermetallic compounds of the alkali and alkaline earth metals have been prepared in liquid ammonia, the literature provides very little information concerning their reactions in this medium.[4] The present paper is concerned with the preparation of trisodium monobismuthide and the study of its properties as a reducing agent in liquid ammonia. Since there is no known method for the production of pure sodium bismuthate, it was of interest (particularly in view of the work of McCleary and Fernelius[5]) to determine whether trisodium monobismuthide could be oxidized to sodium bismuthate by treatment with molecular oxygen.

Trisodium monobismuthide was prepared by the reaction

$$BiI_3 + 6Na \longrightarrow Na_3Bi + 3NaI \tag{1}$$

Treatment of the purified monobismuthide with molecular oxygen leads not to sodium bismuthate but rather to an insoluble mixture of bismuth(II) oxide, sodium hydroxide and sodium peroxide

$$4Na_3Bi + 5O_2 + 6NH_3 \longrightarrow 4BiO + 6NaOH + 6NaNH_2 \tag{2a}$$

$$4Na_3Bi + 8O_2 \longrightarrow 4BiO + 6Na_2O_2 \tag{2b}$$

In addition, the following reactions of trisodium monobismuthide have been observed.

$$Na_3Bi + 2Bi \longrightarrow Na_3Bi_3 \tag{3}$$

$$2Na_3Bi + 6NH_4Br \longrightarrow 2Bi + 6NaBr + 6NH_3 + 3H_2 \tag{4}$$

$$Na_3Bi + 3AgI \longrightarrow Bi + 3Ag + 3NaI \tag{5}$$

$$Na_3Bi + BiI_3 \longrightarrow 2Bi + 3NaI \tag{6}$$

$$2Na_3Bi + Bi_2O_3 + 3NH_3 \longrightarrow 4Bi + 3NaOH + 3NaNH_2 \tag{7}$$

In the course of this work the conventional type of apparatus for the study of reactions in liquid ammonia at its boiling temperature has been modified extensively. The major improvements are concerned with techniques for filtration in a closed system.

Experimental

Apparatus.—With the exceptions noted below, the over-all details of construction and mode of operation of the equipment shown in Fig. 1 are similar to those described by Johnson and Fernelius.[6] Both reactors A

---

[1] This work was supported, in part, by grants from The University Research Institute, Project No. 25.

[2] Presented at the Second Southwestern Regional Meeting of the American Chemical Society, Dallas, Texas, Dec. 13, 1946.

[3] Present address: Department of Chemistry, The Oklahoma A. and M. College, Stillwater, Oklahoma.

[4] Johnson and Fernelius, *J. Chem. Education*, **7**, 981–999 (1930).

[5] McCleary and Fernelius, THIS JOURNAL, **56**, 803 (1934).

[6] Johnson and Fernelius, *J. Chem. Education*, **6**, 445 (1929).

and B are provided with tubes b into which solid reaction products are transferred for removal from the system. These tubes are sealed off, evacuated, and opened in an inert atmosphere in a "dry box." At the start of a run, dry ammonia gas is admitted through stopcocks s_1 and s_2 as well as through tubes a in order to remove air more completely. Liquids may be added from *g* by means of an ammonia gas pressure applied at m, while gases may be added (with or without dilution with gaseous ammonia) *via* stopcock s_3.

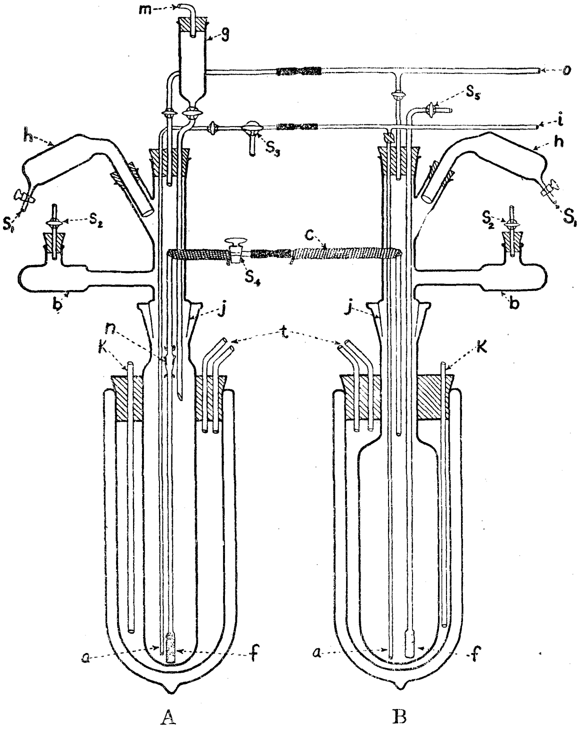


Fig. 1.

Reactor A is equipped with a fritted glass filter f attached by means of a ground glass joint n in order that change to filters of different porosity may be facilitated. The filter tube leads to reactor B through stopcock s_4 and a rubber connection tube.[7] The exposed connection tube between reactors A and B is wrapped with asbestos cord to provide the insulation necessary to prevent excessive "surging" during transfers. Filtration is accomplished by building up a gas pressure on the surface of the liquid in reactor A by admitting anhydrous ammonia gas through o (or less satisfactorily through stopcock s_1 or s_2) with stopcock s_4 open. Following filtration, solids remaining in reactor A may be washed by successive condensation of fresh portions of ammonia, followed by filtration. *Continuous washing* of a solid may be accomplished by balancing the rate of take-off through the filter with the rate of condensation of ammonia. This latter procedure is particularly advantageous when it is desired to extract an ammonia-soluble component of a mixture of solids in reactor A.

Reactor B may be made substantially identical with A although, as represented in Fig. 1, B does not include provision for addition of liquid reactants nor for interchangeable fritted glass filters. The filter tube shown for reactor B also differs in that it is supported through the rubber stopper at the top of the reactor rather than through a ring seal. This arrangement is shown for the reason that it is somewhat more flexible and less readily subject to breakage. For certain purposes, it is convenient to eliminate the fritted glass filter, f, in reactor B and to remove a slurry *via* the open tube through stopcock s_5 and into an external filter of the type shown in Fig. 2. This consists of a glass filter crucible r (having an extra fine porosity fritted glass filter plate) supported in a Dewar test tube w and connected to the tube bearing stopcock s_5 (Fig. 1) *via* a rubber connection e which carries a screw clamp d. With the screw clamp and stopcocks s and s_5 open and s′ closed, the pressure is lowered by a vacuum pump attached at x. After the insoluble material has been collected on the filter, washing is accomplished by means of successive fresh portions of liquid ammonia condensed in reactor B and subsequently drawn over into the external filter. Ammonia collected in the Dewar test tube is removed under reduced pressure *via* s or allowed to escape *via* the tube which bears stopcock s′ and which is connected to an ammonia absorber. Finally, s, s′, and d are closed, the entire assembly is detached and transferred to a "dry box" for removal of the solid on the filter and/or the residue in the Dewar test-tube.

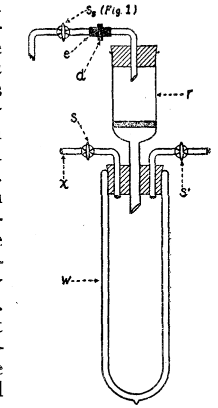


Fig. 2.

Numerous modifications of this equipment have been employed and are more or less obvious. Particular attention is called to the possibility of providing a third reactor which permits preparation, in separate vessels, of two liquid ammonia solutions that may then be brought together in the central unit.

Materials.—All apparatus and materials were thoroughly dried before use.

Bismuth(III) Iodide.—This material was prepared by the method of Birchenbach[8] and purified by three sublimations in an atmosphere of carbon dioxide.

Anal. Calcd. for BiI_3: Bi, 35.43. Found: Bi, 35.41.

Preparation of Trisodium Monobismuthide.—The black insoluble monobismuthide was prepared by reducing 1.5046 g. of bismuth(III) iodide in about 35 ml. of liquid ammonia with 0.3675 g. (6.26 equivalents) of sodium. The reaction was strongly exothermal and intermediate brown and violet colors characteristic of the ammonia-soluble tri and pentabismuthides[9] were observed. Analysis of the thoroughly washed precipitate showed that the Na/Bi ratio is 3.3.[10] Only traces of iodide ion and nitrogen were detected.

In order to show that bismuth is the *primary* product of reduction of the iodide, 1.4747 g. of bismuth(III) iodide was reduced with 0.1821 g. (3.17 equivalents) of sodium. The ammonia-insoluble product was found to contain 96.2% bismuth (pyrophoric) and 3.1% sodium hydroxide. When the bismuth was treated in liquid ammonia with an excess of ammonium bromide to remove sodium hydroxide, the final product contained 98.2% bismuth (non-pyrophoric) and 1.6% sodium hydroxide. This product gave X-ray diffraction patterns (Cu K_α radiation) that showed exactly and only the

---

(7) This and the other two rubber connections should be longer than shown in Fig. 1, in order to provide the flexibility necessary for tilting of the reactor during transfer of solid samples from the bottom of the reactor to tube b.

(8) Birchenbach, *Ber.*, **40**, 1404 (1907).

(9) Zintl, Goubeau and Dullenkopf, *Z. physik. Chem.*, **A154**, 1 (1931).

(10) This value corresponds exactly to that found by Kraus and Kurtz [THIS JOURNAL, **47**, 43 (1925)] in their study of the reduction of bismuth(III) chloride. Zintl, *et al.*,[9] however, found a ratio of 3.0 using a potentiometric titration method. If sodium in excess of that required by the formula Na_3Bi is assumed to be present as sodium hydroxide resulting from the ammonolysis of sodium monoxide [*cf.* Kraus and White, THIS JOURNAL, **48**, 1781 (1926)], formed by surface oxidation of the sodium used, the composition of the insoluble product is 97.0% Na_3Bi and 3.4% NaOH.

lattice spacings and relative intensities characteristic of bismuth.[11]

Preparation of Bismuth(II) Oxide.—Trisodium monobismuthide from the reduction of 1.7185 g. of bismuth (III) iodide by 0.4337 g. of sodium was washed, suspended in liquid ammonia and treated with oxygen[12] for three hours. Addition of 2.29 g. of ammonium bromide[13] resulted in the liberation of 4.4 cc. of oxygen[14] (0°, 760 mm.) and the color of the solid changed from gray to jet black. Several independent sets of analytical data showed that the final solid product had the following percentage composition: BiO (96.5); NH$_3$ (0.4); NaBr (1.8); NaOH (1.8).

Bismuth(II) oxide reacts with atmospheric oxygen at a negligible rate at room temperature but is converted to bismuth(III) oxide upon gentle ignition. The black product failed to form an amalgam when agitated with mercury and was unchanged when heated to 300° *in vacuo*. X-Ray diffraction patterns showed the presence of only a trace of bismuth and the absence of other oxides of bismuth.

Conversion of Trisodium Monobismuthide to Trisodium Tribismuthide.—The trisodium monobismuthide prepared from 1.0154 g. of bismuth(III) iodide by reaction (1) was agitated in 30 ml. of liquid ammonia for two hours with 0.4231 g. of bismuth prepared by reduction of bismuth(III) iodide with three equivalents of sodium. The violet colored ammonia solution[9] was transferred from reactor A to reactor B and found to contain 0.1323 g. of bismuth. This corresponds to the utilization [in accordance with equation (3)] of 21% of the elemental bismuth used.

Reduction of Ammonium Bromide with Trisodium Monobismuthide.—Trisodium monobismuthide from 1.5137 g. of bismuth(III) iodide and 6.23 equivalents of sodium was suspended in 30 ml. of liquid ammonia and treated with 1.5060 g. of ammonium bromide. The insoluble products were a black precipitate and hydrogen (found, 80.6 cc.; calcd., 86.2 cc.). The precipitate was washed ten times and found to contain 98.3% bismuth and only traces of sodium and ammonia.

Reduction of Silver(I) Iodide with Trisodium Monobismuthide.—To 0.7880 g. of silver(I) iodide dissolved in 30 ml. of liquid ammonia was added 0.3040 g. of trisodium monobismuthide. A rapid exothermal reaction led to the formation of a heterogeneous mixture of a gray and a black solid which was washed thoroughly.

Anal. Calcd. for a 1:1 mixture of Ag and Bi: Ag, 61.3; Bi, 38.7. Found: Ag, 59.6; Bi, 37.5; Na, 0.6; I, 1.5.

Reduction of Bismuth(III) Iodide with Trisodium Monobismuthide.—In a similar manner, 1.3375 g. of bismuth(III) iodide was treated with 0.6242 g. of trisodium monobismuthide. The rapid exothermal reaction resulted in a black precipitate which was washed free of iodide ion.

Anal. Found: Bi, 96.7; NaOH, 2.8; NH$_3$, 0.4.

Reduction of Bismuth(III) Oxide with Trisodium Monobismuthide.—Bismuth(III) oxide (0.4900 g.) was agitated vigorously with 0.5800 g. of trisodium monobismuthide in liquid ammonia for three hours. The yellow color of the oxide was progressively replaced by a gray-black mixture of insoluble solids. Unreacted bismuthide was determined by addition of an excess of ammonium bromide, whereupon 40.0 cc. of hydrogen was liberated (see equation 4). By difference, this corresponds to the reduction of 43% of the oxide used. X-Ray diffraction patterns showed all of the lines characteristic of bismuth and bismuth(III) oxide[11] and only these lines.

Substantially identical results were obtained when the oxide was added slowly to a suspension of the tribismuthide in liquid ammonia.

Discussion

The formation of bismuth(II) oxide by oxidation of bismuth in a lower oxidation state has not been reported previously. In the present work, both physical and chemical evidence showed that the black solid did not contain more than traces of elemental bismuth, that the compound contained oxygen and that no other known oxide of bismuth was present.

Bismuth(II) oxide has been reported as a product of the reduction of bismuth(III) oxide with tin(II) chloride,[15,16] hydrogen or carbon monoxide,[17] and the reduction of bismuth(III) dioxyoxalate with carbon monoxide.[18-20] Early work purportedly leading to the formation of bismuth(II) oxide has been criticized by Neusser[21] who contends that the product is probably a mixture of bismuth(III) oxide and elemental bismuth. In the present work, it is significant that the observed properties of bismuth(II) oxide are in generally good agreement with those reported by earlier workers, and that the X-ray diffraction studies rule out the possibility of a mixture of the type suggested by Neusser except for the remote possibility that both of the components of such a mixture might be produced in an amorphous condition.

Summary

1. Improved apparatus and procedures for use in the study of reactions in liquid ammonia at its boiling temperature are described.

2. The reduction of bismuth(III) iodide by three equivalents of sodium in liquid ammonia leads to the formation of elemental bismuth which is essentially unreactive toward molecular oxygen in the same medium.

3. Bismuth(III) iodide is reduced to trisodium monobismuthide by six equivalents of sodium, and the monobismuthide reacts with molecular oxygen to form bismuth(II) oxide and a mixture of oxides of sodium.

4. The reducing properties of trisodium monobismuthide are demonstrated by its use in the partial reduction of bismuth to tribismuthide ion and bismuth(III) oxide to bismuth, and

---

(11) Hanawalt, Rinn and Frevel, *Ind. Eng. Chem., Anal. Ed.*, **10**, 457 (1938).

(12) In related experiments it was found that, under similar conditions, bismuth [from the reduction of bismuth(III) iodide with three equivalents of sodium] is not oxidized upon treatment with oxygen over a period of four hours, either in the presence or absence of water.

(13) Preliminary experiments showed that in addition to bismuth (II) oxide, the gross solid product contained sodium hydroxide and sodium peroxide, both of which were dissolved upon addition of ammonium bromide.

(14) Considerable variation in the volume of oxygen liberated reflected the comparative extent of occurrence of reactions 2a and 2b. *Cf.* Kraus and Parmenter, This Journal, **56**, 2384 (1934).

(15) Schneider, *Pogg. Ann.*, **63**, 53 (1844); **68**, 49 (1846); **88**, **45** (1853).

(16) Muir, *J. Chem. Soc.*, **31**, 650 (1877).

(17) Muir, Hoffmeister and Robbs, *ibid.*, **39**, 21 (1881).

(18) Tanatar, *Z. anorg. Chem.*, **27**, 437 (1901).

(19) Hertz and Guthmann, *ibid.*, **53**, 63 (1907).

(20) Denham, This Journal, **43**, 2367 (1921).

(21) Neusser, *Z. anorg. Chem.*, **135**, 313 (1924); **138**, 180 (1924).

the complete reduction of ammonium ion to hydrogen, silver (I) iodide to silver, and bismuth(III) iodide to bismuth.

AUSTIN, TEXAS RECEIVED JULY 3, 1947

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

The Catalytic Reaction of Hydrogen and Oxygen on Plane Faces of a Single Crystal of Copper[1]

BY HENRY LEIDHEISER, JR., AND ALLAN T. GWATHMEY

Introduction

The determination of the positions of different activity on a catalyst surface is a question of primary importance. The two great difficulties in determining these positions are the preparation of a surface of known structure and the development of a method for following changes in the structure as the reaction takes place.

Most studies made in the past on the activity of a solid catalyst surface have consisted of measuring the amounts of materials consumed and produced by powdered metal catalysts. Such catalysts generally consist of many crystals randomly arranged and exposing faces, edges and corners of many kinds. Measurements made on such materials are composite quantities and give little direct information about the reactivity of the various types of structure exposed.

In an effort to obtain simple, reproducible surfaces of known structure, large single crystals with surfaces prepared parallel to special planes were selected. Furthermore, previous studies with large single crystals[2] have shown that the rate of many surface processes varies with the crystal face exposed at the surface. Therefore in order to determine the influence of crystal plane on catalytic activity and to extend our knowledge of metal surfaces in general, studies have been made of the reaction of hydrogen and oxygen on several plane faces of a large single crystal of copper.

In the study of the reaction of gases on the surface of metallic crystals, it has been found that the reactions may be divided into two classes, those which readily produce rearrangements in the surface and those which do not, at least on a microscopic scale. The reaction of hydrogen and oxygen on copper belongs to the first class. The nature of the rearrangements produced by the action of hydrogen and oxygen will first be described, and then the measurement of rates on several faces will be presented. An important feature of these studies is the correlation between catalytic activity and surface structure which can be observed.

Method of Experiment

Preparation of Surface of Catalyst.—There is a tendency in catalytic studies to underrate the importance of the preparation of the surface. Very fine measurements are often of limited value because they are made on surfaces, about the structure and composition of which little is known. Emphasis was placed in these studies on the preparation of the surface.

Single crystals of copper in the form of rods, $^5/_8$ in. in diameter and 4 in. long, were grown by the method previously described.[2,3] For use in the studies of rearrangements, spheres were machined from the $^5/_8$ in. rods and polished mechanically and electrolytically. For the rate measurements thin slices, about $^1/_8$ in. thick and parallel to the (100) and (111) planes were cut from a 1-inch crystal. In order to assure that there could be no difference in the chemical composition of the two crystal faces on which rates were measured, a sphere was machined from a 1-inch rod, and two flat faces, one parallel to the (100) face and one to the (111) face, were cut on the sphere. This was done by the same method used in cutting the slices. Photographs of the several specimens are shown in Figs. 2 and 14. The flat faces for rate measurements were polished as follows. The face was mechanically polished with metallographic polishing papers nos. 1 through 0000, and after each paper it was electrolytically etched in the polishing solution at a current density of about 0.02 amp./sq. cm. for a sufficient length of time to remove the strained layer produced by the last mechanical polishing. The time varied from about thirty minutes after the no. 1 paper to about ten minutes after the last paper. After the last etching the surface was slightly roughened on a microscopic scale but plane on a macroscopic scale and in a strain-free condition. The final step consisted of polishing mechanically on a felt wheel moistened with levigated alumina. In order to prevent subsequent recrystallization of the surface it was necessary to keep the cloth wet, to operate the wheel at a slow speed of about 150 r.p.m., and to press the specimen only lightly against the felt. After the first treatment with the reacting gases, it was only necessary to repolish with the 0000 paper and alumina, or with alumina alone. The surface was swabbed with a soft tissue under a stream of water in order to remove traces of alumina. Surfaces prepared by this method gave essentially the same results as those prepared by careful electrolytic polishing but the method described above was generally used because of the tendency of large surfaces to become pitted during electrolytic polishing. In order to reduce oxide and remove any distortion in the surface, all crystals were annealed in hydrogen at 550° for at least sixteen hours immediately prior to study of rearrangements or measurement of rates of reaction.

The Study of Rearrangements.—Since the surface of a monocrystalline sphere of copper exposes every crystal plane in at least six places, the (100) face appearing six times, most of the rearrangement studies were carried out on $^5/_8$ in. spheres. Also the symmetry of the patterns on a sphere make it easy to identify the location of the crystal faces. For the study of rearrangements the sphere was supported, generally with shaft downward, within the bulb of a glass apparatus connected with suitable inlet and exit tubes. The sphere was placed in the apparatus through a ground glass joint at the top and was suspended from the upper half of the joint by means of a no. 20 B. and S.

---

[1] This work was supported by a grant from the Research Corporation.

[2] See Leidheiser and Gwathmey, *Trans. Electrochem. Soc.*, **91**, (1947) [printed as Preprint 91-6, but not yet published] for a résumé of previous studies with massive single crystals.

[3] Gwathmey and Benton, *J. Phys. Chem.*, **44**, 35 (1940).

gage copper wire. When it was desired to protect the supporting wire from the action of the gases in order to prevent a change in concentration of the gases before they reached the crystal, the wire was enclosed in a glass tube and the shaft of the sphere, pointing upward, was inserted into the lower end of the tube. The appearance of the crystal as the reaction proceeded was observed through a glass window in the side of the furnace, the inside of which was illuminated by a small light at the top. Different crystal faces could be brought into view opposite the window by rotating the upper half of the ground glass joint to which the supporting wire was attached. It was found convenient, in identifying crystal regions during the early states of formation of the pattern, to have three adjacent (100) pole positions previously marked on the sphere by means of a deep pin prick. One great advantage of this method of study is that it is possible to follow changes in surface structure as the reaction proceeds.

The crystals were finally removed from the reaction chamber and examined under a microscope and in a darkened room with the aid of a flashlight. The methods of examining the patterns, identifying the planes and recording the results have been previously described.[2] The temperature of the reaction was assumed to be the temperature of the air just outside of the reaction vessel as measured by a mercury thermometer. The question of the exact temperature of the catalytic surface will be discussed later. In all reactions with the spheres the rate of flow of gas approximated 200 ml./minute.

Measurement of Rates of Reaction.—In order to determine rates on a surface prepared parallel to one particular crystal plane, it is necessary to prevent from exposure to the reacting gases other parts of the crystal, such as other faces, edges, and corners. Several different methods of accomplishing this were tried, but the simple apparatus shown in Fig. 1 was found to be satisfactory for the reaction under consideration. The surface of the crystal was ground flat and placed on top of the enclosed tube A, which had been flanged on the upper end and likewise ground exceedingly smooth. The crystal was placed in position and the outer glass cover tube was vacuum sealed to the base of the apparatus with the aid of a ground glass joint. The incoming gases consisting of purified tank hydrogen and electrolytic oxygen passed up the center tube, reacted on the surface of the crystal, passed down the middle tube, and out through a drying train of calcium chloride and Dehydrite where the water formed was absorbed. The rate of flow of the gases was measured with the aid of orifice meters and was 40 ml./min. unless stated otherwise. A furnace was placed over the top of the apparatus and extended down to within about 6 in. of the upper ground glass joint. The temperature was kept constant in the final experiments by means of a thermoregulator. In the experiments with thin slices an iron weight sealed in glass was placed on the slice to hold it in place. In experiments with the spheres on which the two faces had been cut, this was unnecessary. The failure of the polished surface to rearrange in the region of the crystal not exposed to the action of the flowing gases indicated that the amount of gas which leaked by the metal-flange joint was negligible. A photograph showing the difference in the appearance of the region exposed to the direct action of the gas and that of the region in the dead space surrounding the inner reaction chamber is given in Fig. 2. The apparent surface of the metal exposed to the action of the gases was always 2.69 sq. cm. Through the aid of this apparatus it is possible to measure the rates of reaction on surfaces prepared parallel to special crystal planes and containing always the same apparent area. At the completion of a run the surface of the crystal was examined under the microscope and in a darkened room with the aid of a flashlight. During preliminary studies, whenever inconsistent rate measurements were obtained because of such reasons as recrystallization of the surface or the presence of an accidental impurity, it was found that the final appearance of the surface was always abnormal.

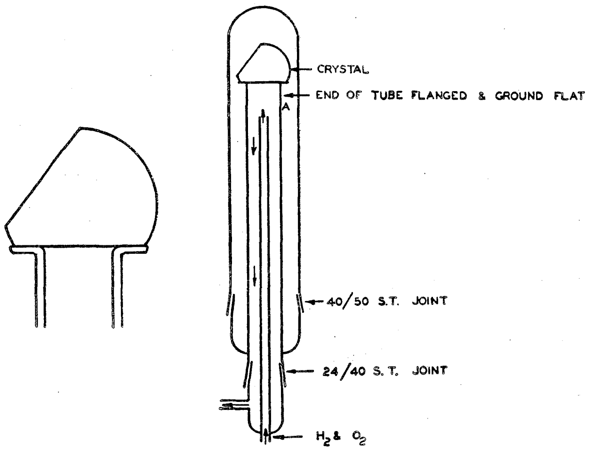


Fig. 1.—Apparatus for measuring rate of catalytic reaction of hydrogen and oxygen on plane faces of a metallic single crystal.

Results

Rearrangements of the Surface.—Rearrangements of the metallic surface under the action of reacting gases have been found to take place with a number of metals and gases. The nature and the intensity of the rearrangement depend on the metal, the gases, and the conditions of the experiment such as temperature and gas flow. Only rearrangements produced by the action of hydrogen and oxygen on copper will be described, although a photograph of the hydrogen–oxygen reaction on nickel is shown in Fig. 3 to illustrate the complicated fine structure of a pattern produced by another system. Brief mention has previously been made that such rearrangements take place on the surface of a copper crystal serving as a catalyst for the reaction of hydrogen and oxygen.[4]

Experiments were carried out over a temperature range of 360–440° and an oxygen concentration of 1–20%. The rearrangements which took place with 14% oxygen at a temperature of 400° will be described. Within a few seconds after oxygen was added to the stream of hydrogen in which the crystal was being heated, the surface of the crystal became slightly foggy in certain preferred crystal regions. After about fifteen minutes a definite pattern of light reflections from certain regions could be seen when a beam of light was directed through the window in the furnace wall, and after sixteen hours the striking pattern shown in Figs. 4 and 5 was obtained. Photomicrographs of the final surface structures on several different faces are shown in Figs. 6–10. The surface immediately at the (111) face remained quite smooth, while that at the (100) became very rough. Still another type of structure developed at the (110). Not only did the (111) face remain relatively smooth but (111) planes developed in large three-armed areas adjacent to each (111) pole as shown by the photograph in Fig. 5 taken when a beam of

---

(4) Gwathmey and Benton, *J. Chem. Phys.*, **8**, 569 (1940).

light was directed normally to the surface at the (111) pole. (110) planes were slightly developed in the (100) regions as shown by faint reflections obtained from these regions when a light beam was directed normally to the surface at the (110) pole. The facets developed parallel to these special planes as described above could also be identified by examination under the microscope. Figure 11 shows a microscopic view of a polycrystalline surface exposed to a hydrogen–oxygen mixture at 400°. Structures characteristic of the various surface regions on a monocrystalline sphere may be observed on the individual grains. The specimen shown in Fig. 11 was formed by recrystallization of a single crystal, although similar surface structures have been observed on many polycrystalline samples of copper.

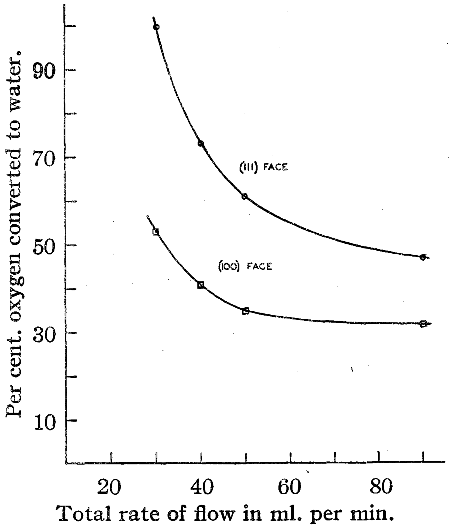


Fig. 12.—Curves showing change in rate of reaction with change in rate of flow: 400°, oxygen flow = 0.5 ml. per min., hydrogen flow varied.

Although many features of the patterns were the same over a temperature range of 360–440° and an oxygen concentration of 1–20%, there were some variations depending on the oxygen concentration and the time of reaction. With an oxygen concentration of 14% after sixteen hours, (111) planes were developed in large areas surrounding the (111) poles, but after about twenty-four days the development of (111) planes had decreased and (110) planes had developed in large areas surrounding the (110) poles. After seven days at this concentration a reddish-brown powder had formed over the entire surface. When this powder was wiped off with a tissue at the end of twenty-four days, the typical pattern with the exception noted above was observed. When the powder was removed, the contrast between the smooth (111) and the rough (100) areas was not as striking as it had been before the powder formed. The formation of this powder appears to be similar to the disintegration of copper tubes by heating in ammonia as observed by Beilby and Henderson.[5]

The presence of a small amount of a second metal, such as zinc or nickel, when electrodeposited on a copper sphere greatly influenced the pattern formed by the catalytic reaction of hydrogen and oxygen.

Measurement of Rates of Reaction.—Since the rate of reaction depends on the type and total area of surface exposed as a result of rearrangement, it is essential that the nature of the surface be known to some degree of approximation when the rates of reaction are measured. The change in the nature of the surface with the conditions of the experiment makes it difficult to present a complete picture of all events taking place in this reaction. A detailed study of each individual surface might reveal much additional information about its structure, but in the studies herein reported the structure was examined by the methods described, primarily for the purpose of showing the differences in structure of the various faces and the influence of these differences on the rates of the catalytic reaction.

No powder was ever observed on either face over a period of seven days with an oxygen concentration of 1.25% or less. Therefore experiments carried out within this range should give results which are dependent on the rearranged structure of the individual faces and are independent of the influence of the powder which forms at higher oxygen concentrations. As will be shown later, when a large amount of copper powder forms on the surface, the specific influence of the crystal face will be obscured.

With oxygen concentrations in the range of 0.6–2.5% and temperatures from 250–420°, the rate of reaction on the (111) face was approximately twice that on the (100) face, although the latter face had become much rougher and therefore exposed more surface area than the (111) face. All rates of reaction for both faces are referred to the same amount of apparent starting surface, 2.69 sq. cm. A plot of the rates of reaction on the (111) and (100) faces for various rates of flow of the reacting gases is shown in Fig. 12. The variations in the rates of reaction with temperature are shown in Fig. 13. The difference in the roughness of the (100) and (111) faces after reaction had taken place is shown in Fig. 14. The photograph was taken looking down on the sphere with the flat (100) face on the left side of the sphere and the (111) face on the right side, both faces making the same angle with the plane of the photograph. The crystal was illuminated from both sides, the beams of light pointing down and making an angle of about 45° with the plane of the photograph. The part of the (100) face on which the reaction took place appears as the light elliptical-shaped region in the center of the face on the left since the light was scattered upward by the rough surface. The part of the (111) face on which reaction took

(5) Beilby and Henderson, *J. Chem. Soc.*, **79**, 1245 (1901).

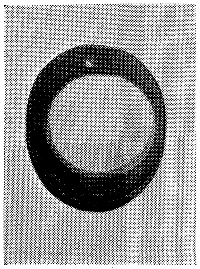


Fig. 2.—Typical appearance of a (100) slice exposed to a mixture of hydrogen and oxygen at 400° for forty-eight hours.

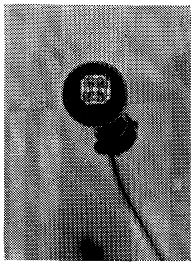


Fig. 3.—Action of a 7:1 mixture of hydrogen and oxygen on a nickel single crystal at 420° for three days. Normal to (100).

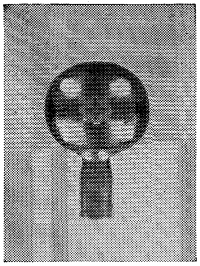


Fig. 4.—Action of a 7:1 mixture of hydrogen and oxygen on a copper single crystal at 400° for sixteen hours. Normal to (100). Four bright lights were focused on (110) areas.

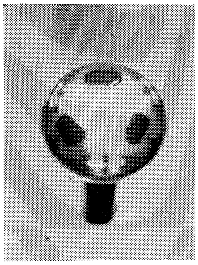


Fig. 5.—Action of a 7:1 mixture of hydrogen and oxygen on a copper single crystal at 400° for sixteen hours. Normal to (111). Note strong reflection from area around (111) pole.

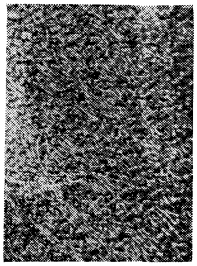


Fig. 6.—Action of a 7:1 mixture of hydrogen and oxygen on a copper single crystal at 400° for sixteen hours: at (100), ×600.

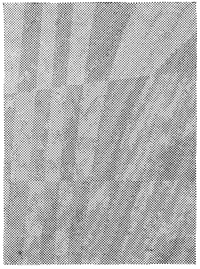


Fig. 7.—Action of a 7:1 mixture of hydrogen and oxygen on a copper single crystal at 400° for sixteen hours: at (111), ×600.

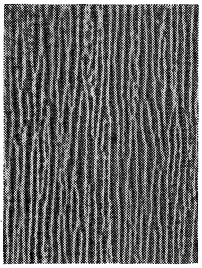


Fig. 8.—Action of a 7:1 mixture of hydrogen and oxygen on a copper single crystal at 400° for sixteen hours: at (110), ×600.

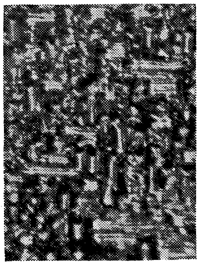


Fig. 9.—Action of a 7:1 mixture of hydrogen and oxygen on a copper single crystal at 400° for sixteen hours: near (100), ×600.

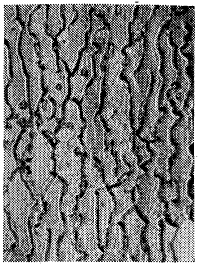


Fig. 10.—Action of a 7:1 mixture of hydrogen and oxygen on a copper single crystal at 400° for sixteen hours: near (111), ×600.

Fig. 11.—Polycrystalline copper surface exposed to a hydrogen–oxygen mixture at 400°, ×200, compare with Figs. 6–10.

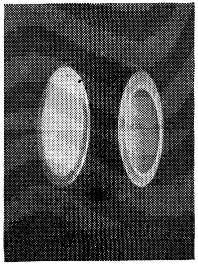


Fig. 14.—Photograph showing difference in roughness of (100) and (111) faces after independent exposure to a hydrogen–oxygen mixture containing 1.25% oxygen at 400° for forty-eight hours. (100) face on left, (111) face on right.

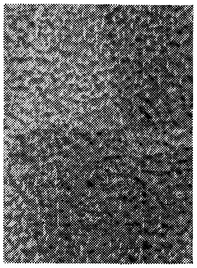


Fig. 15.—Microscopic view of (100) face shown in Fig. 14, ×650.

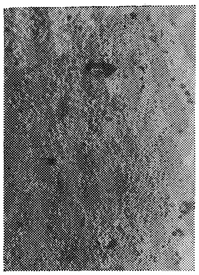


Fig. 16.—Microscopic view of (111) face shown in Fig. 14, ×650.

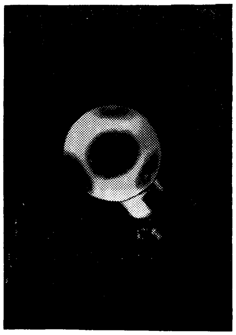


Fig. 1.—Selective deposition of carbon on the (111) face of a nickel crystal heated at 550° in carbon monoxide; view normal to (111) (see p. 1206).

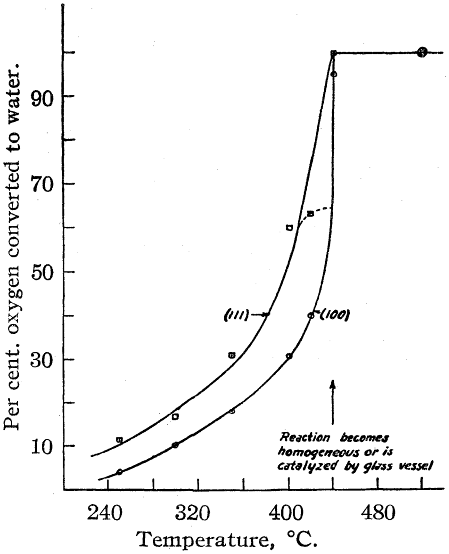
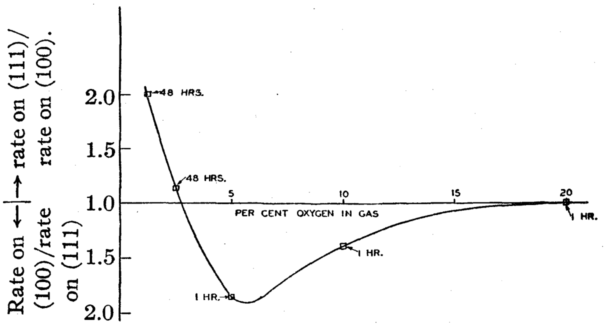


Fig. 13.—Curves showing change in rate of reaction with temperature: hydrogen–oxygen reaction on plane faces of a copper single crystal, total flow = 40 ml. per minute, O_2 concn. = 1.25%.

place appears as the dark elliptical-shaped region in the center of the face on the right since little light is reflected upward into the camera by the relatively smooth (111) surface. Microscopic views of the two faces are shown in Figs. 15 and 16.

Several experiments were carried out to determine the effect of the method of preparation of the starting surface on the rate of the reaction. It was found that within limits, as long as the base single crystal metal was exposed, the rates were independent of the exact surface preparation at the start. The reaction tended to form a surface characteristic of the face and reaction under consideration. For example, surfaces polished mechanically with alumina on felt, surfaces polished electrolytically, and surfaces roughened by etching electrolytically in a copper sulfate–sulfuric acid solution gave similar results after rearrangement. With an oxygen concentration of 1.25% and at a temperature of 400° the rate on the (111) face was twice that on the (100). In the case of the roughening of the surface by electrolytic etching, the area of the (111) face which had been exposed to the hydrogen and oxygen reaction for twenty-seven and one-half hours had become much smoother than the surrounding surface which had not been so exposed. The contrast between the two areas was very marked. In the case of the (100) face, since it is roughened by the catalytic reaction, the contrast between the two types of areas was not great, although a definite line of demarcation could be seen. When the (100) face was examined with a flashlight in a darkened room, brilliant reflections were visible from (110) facets in the reactive area but no reflections from (110) facets were obtained from the etched external area. Thus surfaces characteristic of the hydrogen and oxygen reaction were finally obtained regardless of the several different initial treatments given to the surface.

As the oxygen concentration was increased, the speed with which the rearrangement took place and the surface area exposed, especially on the (100) face, increased greatly. Figure 17 shows the ratio of the rates of reaction on the (111) and (100) faces with changes in oxygen concentration at 400°. As the oxygen concentration was increased below 5%, the rate on the (100) face relative to the (111) increased rapidly on account of the great increase in surface on the (100) face. No red powder formed within at least forty-eight hours. With oxygen concentrations of about 5% at which the powder began to form, the difference in rates between the two faces became increasingly less, until at 20% oxygen within one hour so much powder had formed on both faces that the inherent difference between the two faces was not detected. In order to obtain comparisons of the activity of the two faces as free as possible from powder, measurements were made at the higher oxygen concentrations after one hour of reaction. With an oxygen concentration of 20% the powder formed very rapidly at temperatures as low as 300°.



Hydrogen–oxygen reaction on plane faces of copper single crystal.

Fig. 17.—Ratio of rates of reaction on (100) and (111) faces with changes in oxygen concentration at 400°: total gas flow = 40 ml. per min.

Figure 18 shows the change in rates of reaction with time at 400° for two single crystal slices, for a single crystal slice which had been mechanically polished, and for an ordinary piece of polycrystalline copper which had been electrolytically polished. The increase in the rate of reaction on all samples corresponds to the visual observation of the formation of powder. As the reaction proceeded on the mechanically polished single crystal slice, the disturbed layer recrystallized to produce a polycrystalline surface which had a greatly increased rate.

A qualitative comparison of the degree of roughness on the (100) face at different oxygen concentrations was determined by the following procedure. The (100) face was exposed to definite mix-

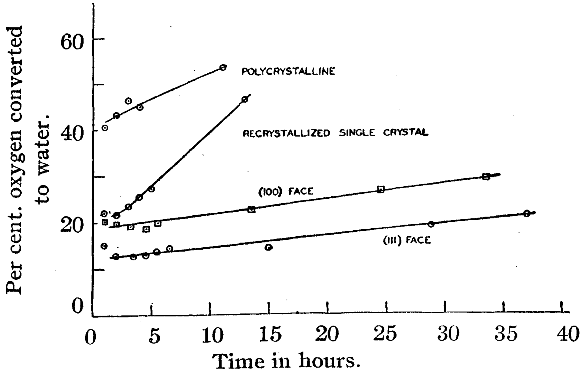


Fig. 18.—Change in rate of reaction with time at 400° and 10% oxygen concentration: gas flow = 40 ml. per min.

tures of hydrogen and oxygen for seven hours at 400°, and the surface was polished after each run with a suspension of levigated alumina on felt. The time necessary to polish away the roughened region was determined. Care was taken to insure equal conditions of polishing in each determination, and the results are shown in Table I.

TABLE I

% Oxygen in mixture	Time of polishing
1.25%	Less than 30 seconds
5.0	Approximately 50 seconds
10.0	Approximately 120 seconds
20.0	Greater than 240 seconds

In the case of the (111) face it took less than fifteen seconds to remove all traces of roughness under conditions at which no powder formed within seven hours.

Discussion

The discovery of a regular rearrangement of the catalyst surface under the influence of a gaseous reaction was made possible by the use of the catalyst in the form of a highly polished single crystal sphere exposing all possible crystal faces. The rearrangements showed themselves as highly complicated and symmetrical patterns which should be considered as records of the structure of the surface for a particular gas–metal reaction. On some faces definite facets parallel to one or more planes developed, on other faces a general roughening took place showing the development of no special planes, while other faces seemed to remain highly polished and apparently undisturbed. Although there were often similar features in the different patterns, in that the (100) face roughened greatly and the (111) remained relatively smooth, no two patterns for different gas–metal systems were found to be exactly the same.

In order to appreciate the significance of these regular surface rearrangements, it should be understood that they have been found with a number of reactions. The complications of these beautiful patterns and the differences between the patterns of different systems emphasize the complications of surface reactions and explain in part why they are so difficult to understand.

Not only does the pattern depend on the nature of the reactants, but for any one gas–metal system the pattern also depends on the conditions of experiment, such as temperature, concentration and rate of flow of the reacting gases, and time of reaction. As regards the latter, the planes developed in certain regions varied with time, emphasizing the importance of both rate and equilibrium factors in the rearrangement process. For example, with 14% oxygen at 400° (111) facets developed over a large region surrounding the (111) pole within twenty-four hours of reaction, but after a week of operation the size of the region containing the (111) facets had decreased considerably and the size of the region containing (110) facets had correspondingly increased. Also during the early period of the reaction a fine structure developed in many parts of the pattern, showing a variation in activity of many different faces, but after the reaction had proceeded for several days the complexity of the pattern was reduced and a fewer number of planes appeared. The crystal planes developed also depended on a certain critical angle between the plane in question and the surface of the metal specimen. In this connection it might be expected, if the rearrangement resulted simply from the heat evolved, that the most stable plane would be developed over the entire surface of the sphere, but facets parallel to a particular plane developed in one region, and, when the angle between the plane in question and the surface reached a certain value, facets parallel to another plane developed. In some regions several planes seemed to compete with each other for their existence.

It is surprising that these rearrangements, involving in some cases movement of the metal atoms over tremendous distances in terms of atomic dimensions, would take place so readily on massive metal at measured gas temperatures of only 400°, which is 680° below the melting point of the metal. The evaporation of considerable metal which deposited on the walls of the glass vessel suggested that the temperature of the metal surface was considerably higher than the measured gas temperature, but heating a crystal in hydrogen at 1000° failed to produce any rearrangement or evaporation. In fact a surface which has been roughened by this reaction may be "heat polished" by heating in hydrogen at such a high temperature. Therefore, high temperatures alone would not cause rearrangement or appreciable evaporation. Furthermore rearrangements have been obtained with an endothermic reaction. The evaporation of copper during the reduction of polycrystalline copper oxide has been attributed to the formation of steam between the grains and the expulsion of copper by the steam. In the copper single crystal surface used in these experiments there were no grain boundaries and no visible film of oxide. However, the (100) face which roughened greatly during the catalytic reaction is a face having a high rate of oxidation when heated in air.[6] The oxygen may possibly diffuse more rapidly down into the lattice of the (100) face and react to form steam which may then expel metal. Although the exact nature of such a catalyst surface was not known, these rearrangements indicated that the surface was in a state of great agitation, at least during the initial stages of rearrangement which lasted over a number of days for this particular reaction. These rearrangements which take place with catalytic reactions but not with adsorption indicate that the nature of the surface during such reactions may be quite different from that during adsorption. This fact in turn indicates that great care must be exercised in using adsorption measurements to interpret the nature of a catalytic surface of this kind.

One important experimental feature of these studies was that the reaction in effect prepared its own surface, and therefore reproducible surfaces exposing the structure of the base metal were obtained. In this method of study the use of light reflections, against a background of a single crystal sphere whose orientation was known, made it possible to identify the plane exposed right at the surface. The actual planes exposed at the surface cannot be determined by the diffraction of X-rays or electrons which penetrate the surface. The preparation of a catalyst surface with the aid of a gaseous reaction which produces a characteristic surface of a relatively well-known structure offers the possibility of standard surfaces for experimental studies.

One interesting effect of these rearrangements is that a surface originally prepared parallel to an unreactive plane may finally become a very active surface per unit starting area since both a greater total area and/or different facets may be finally produced. This suggests the possibility of preparing a surface parallel to one plane and then activating it by reaction with one set of gases for use with another set. In order to obtain appreciable adsorption on platinum Langmuir[7] found that it was necessary to activate the surface by means of the reaction of hydrogen and oxygen. Obviously this treatment increased the surface area, but it was not known whether special facets developed.

The alteration of the pattern on copper by the addition on the surface of small amounts of a second metal, such as zinc or nickel, indicates that the action of a promoter in some cases is to control the planes developed.

During the study of rates several different slices as well as the spherical specimen containing both faces were used. Similar results were obtained on all samples of the same face.

Since the structure of the surface continued to rearrange over a considerable length of time depending on the conditions of the experiment, the rate measurements must be considered in relation to these structural changes. There is no simple method of measuring the true surface area of small specimens, and it was elected to report the rate measurements, unless otherwise stated, in terms of the apparent starting area which in all cases was 2.69 sq. cm. This method of reporting rates enabled the more important facts to be arrived at and the minimum values for the relative rates on the two faces to be given. It is planned to measure surface areas, but this in itself is a major undertaking for these small specimens.

At low concentrations of oxygen in the neighborhood of 1%, where the rearrangements were relatively slight, the rate on the (111) face was approximately twice that on the (100) face. Since it can be seen in Figs. 14–16 that the surface on the (100) face was much rougher, and therefore had a much greater final surface than the (111), the actual rate on the (111) face per unit of final surface must have been considerably greater than twice the rate on the (100) face per same unit. It would appear that the surface on the (100) face was at least twice that on the (111) face at this concentration, and this estimate would make the rate on the (111) face per unit of final surface at least four times that on the (100). The rates on only two different faces were measured in these studies, and there may be others which have greater or lower rates.

As the concentration of oxygen was increased and the (100) face became much rougher than the (111), it would be expected that the rate on the (100) would become greater than that on the (111), although the rate per unit of final surface might still be greater on the (111) face. As the oxygen concentration was increased still higher and powder began to form, the surface of the powder was so much greater than that of the base metal that most of the reaction took place on the powder and the rates on the two faces became approximately equal as would be expected. The underlying pattern could still be seen when most of the powder was removed.

Summary

The catalytic reaction of hydrogen and oxygen on a single crystal of copper has been studied. Single crystals in the form of spheres exposing all possible faces and in the form of slices parallel to a particular face were used. The crystals were mechanically and electrolytically polished and annealed in hydrogen so that the surface of the base crystal was exposed to the action of the gases. With oxygen concentrations of 1–20% at 400° regular rearrangements were found to take place in the surface of the metal, exposing certain facets on some faces, roughening others without the development of particular planes, while other faces remained quite smooth and were apparently undisturbed. Rate measurements were made on

---

[6] Gwathmey and Benton, *J. Phys. Chem.*, **46**, 969 (1942).

[7] Langmuir, THIS JOURNAL, **40**, 1361 (1918).

(100) and (111) faces, and it was found that appreciable differences in rates existed between the two faces. These differences depended on both the differences in activity per unit of surface and on the differences in total surface area exposed on the two faces. The rate measurements were correlated with the structure of the surfaces as the surfaces rearranged under the action of the catalytic reaction.

UNIVERSITY, VIRGINIA RECEIVED AUGUST 18, 1947

The Selective Deposition of Carbon on the (111) Face of a Nickel Crystal in the Catalytic Decomposition of Carbon Monoxide[1]

BY HENRY LEIDHEISER, JR., AND ALLAN T. GWATHMEY

Previously reported results[2] have shown that the catalytic reaction of hydrogen and oxygen leads to rearrangement of a copper surface and proceeds at a rate dependent on the crystal face exposed to the reacting gases. Results reported herein give an example of a catalytic process which does not lead to visible rearrangement of the surface initially and which proceeds at a rate dependent on crystal face.

A monocrystalline sphere[3] of nickel, 0.5 in. in diameter, with a shaft, $^3/_{16}$ in. in diameter and $^3/_8$ in. long, on one side was mechanically polished and then electrolytically polished by the method of Hothersall and Hammond[4] in order to give a smooth and strain-free surface. It was heated to 550° in carbon monoxide at a pressure of one atmosphere in an electric furnace provided with a window for continuous observation. After ten hours the pattern shown in Fig. 1 (see insert facing page 1203) began to develop. Black deposits had formed in large areas around the (111) poles but not in areas at the (100) and (110) poles. As the reaction continued the diameter of the (111) areas increased until the deposit covered the entire surface with the exception of a small square at each (100) pole and a narrow band between neighboring (100) poles and running through (110) poles. The photograph shows in a striking manner that the decomposition of carbon monoxide to form carbon on nickel at 550° proceeds at widely different rates on the (100) and (111) faces. The black deposit was readily removable by rubbing with tissue within several hours after it was first observed. As the reaction continued, however, the deposit tenaciously adhered to the surface, and it could not be removed by rubbing.

Evidence summarized by Hofer[5] indicates that when nickel is treated with carbon monoxide above 500° the major product left on the surface is carbon, although the presence of an intermediate carbide is not excluded. In order to obtain a sufficient amount of deposit for analysis, a polycrystalline nickel foil of larger surface area was treated with carbon monoxide under identical conditions as the single crystal. The analysis of the product on the surface was as follows: carbon 88.52 wt. %, nickel 11.01 wt. %. This analysis corresponds to approximately 97.5 atom % carbon and 2.5 atom % nickel.

Results similar to those shown in Fig. 1 were obtained at 550° in mixtures of hydrogen and carbon monoxide when the carbon monoxide was in excess. When the carbon monoxide was present in low concentrations in the neighborhood of 10%, no carbon deposit was observed and rearrangement patterns resulted.

It is interesting that the crystal lattice of graphite may be superimposed on the (111) face of nickel with only slight distortion. No similar match is possible on the (100) or (110) faces of nickel. It should be pointed out, however, that even though the (111) face of copper would give almost as good a match, no carbon deposits were visible after forty-eight hours at 550°.

Information on the deposition of carbon is important in an understanding of the Fischer–Tropsch catalytic process, and the results herein reported indicate the importance of crystal face in reactions of this type.

SCHOOL OF CHEMISTRY
UNIVERSITY OF VIRGINIA
UNIVERSITY, VIRGINIA

RECEIVED OCTOBER 20, 1947

---

[1] This work was supported by a grant from the Research Corporation.

[2] Leidheiser and Gwathmey, THIS JOURNAL, **70**, 1200 (1948).

[3] See Gwathmey and Benton, *J. Phys. Chem.*, **44**, 35 (1940), for a description of the technique for growing and machining single crystals.

[4] Hothersall and Hammond, *J. Electrodepositors' Tech. Soc.*, **16**, 83 (1940).

[5] Hofer, U. S. Bur. Mines Rept. Investigations 3770, 39 pp. (1944).

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH AND DEVELOPMENT, TENNESSEE EASTMAN CORP., CLINTON ENGINEERING WORKS]

A Kinetic Study of the Oxidation of Uranium Tetrachloride

BY JOHN VAN WAZER AND GEORGE JOHN

A novel method for kinetic studies of solid–gas reactions in which the solid undergoes a color change has been used in this Laboratory for determining the activation energy for oxidation of uranium tetrachloride. The oxidation process consists of two independent steps which can be described by the equation

$$UCl_4\text{(green)} + O_2 \longrightarrow UO_2Cl_2\text{(yellow)} + Cl_2 \quad (1)$$
$$3UO_2Cl_2\text{(yellow)} + O_2 \longrightarrow U_3O_8\text{(black)} + 3Cl_2 \quad (2)$$

There is also a side reaction in which the uranium tetrachloride reacts with the chlorine evolved to form volatile uranium pentachloride.

Experimental

Working in a dry box a thin layer of uranium tetrachloride was dusted on the top of a rectangular copper bar which could be heated electrically at one end and cooled by a water coil at the other (see Fig. 1). The bar was then put into an air-tight glass envelope and purified helium was passed over it while the temperature of the hot end was raised to about 600°. The temperatures were measured by the thermocouples soldered to the bar at several points along its length. Then oxygen instead of helium was allowed to stream over the bar. This caused the green uranous chloride to change into yellow uranyl chloride at the hot end of the bar and a boundary separating the green from the yellow region was seen to move at an approximate velocity of 1 cm. in several seconds from the hot toward the cold end of the bar. This boundary was soon followed by another separating the yellow region from one of black uranium oxide. These boundaries were quite sharply defined and the kinetics of the reaction was studied by measuring the velocity at which the boundaries moved.

Interpretation of Results

The rate constant for either of the over-all reactions is inversely proportional to the time, *t*, required for the material to undergo a given color change at any particular temperature. Thus the rate constant in the Arrhenius equation can be replaced by B/t to give

$$t = (B/A)e^{E/RT} = Ke^{E/RT}$$

where E is the activation energy and A is the frequency factor. As the positions of the boundaries along the bar are determined as a function of time and each position corresponds to a definite temperature, values of time and temperature can be found which when substituted in the above equation will give the activation energy. Since time in these experiments was measured from the instant oxygen was allowed to flow into the system, the time origin was displaced from experiment to experiment and the data were best interpreted by plotting log t against $1/T$.

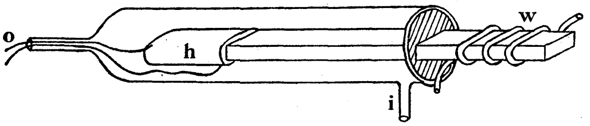


Fig. 1.—Reaction bar: w, water coil for cooling; i, gas inlet; h, heating element; o, gas outlet with wires to heating element.

In the oxidation of uranium tetrachloride to uranyl chloride the activation energy was found to be 12 (±2) kcal. and the lowest temperature for measurable reaction is 230 ± 5°. In the conversion of uranyl chloride to the black oxide the activation energy was 45 (±5) kcal. and the lowest temperature for observable reaction is 250 ± 10°. The mechanism of these reactions can be divided into three steps: (1) transport of oxygen to the reacting surface, (2) diffusion of oxygen into a uranium tetrachloride particle coated over with oxidation product, and (3) the rate at which oxidation will occur when the oxygen molecules reach the unreacted solid. From kinetic theory it can be shown that step (1) does not determine the rate. Also, since varying the rate of gas flow over the bar did not change the oxidation rate, diffusion of oxygen through a concentration gradient of chlorine near the surface does not affect the measured rate.

Diffusion of the oxygen through a thick surface layer is probably not the rate determining process either since the color of such a surface layer is used as the criterion of completion of the reaction. It also seems doubtful that a tight skin such as is found on passive metals can be formed over a salt. Thus it appears that step (3) is the rate determining process and that plenty of oxygen is available for the reaction.

Acknowledgment.—We wish to thank Dr. C. E. Larson for his permission to undertake this problem and his interest in it. This document is based on work performed under Contract No. W-7401-eng-23 for the Atomic Energy Project at the Tennessee Eastman Corporation, Oak Ridge, Tennessee.

Summary

A simple procedure for studying the kinetics of a heterogenous reaction involving color change of the solid phase has been applied to the investigation of uranium tetrachloride oxidation.

OAK RIDGE, TENN. RECEIVED SEPTEMBER 30, 1947

[CONTRIBUTION FROM AVERY LABORATORY OF CHEMISTRY, UNIVERSITY OF NEBRASKA]

The Thermal Decomposition of Benzoyl Peroxide

BY D. J. BROWN

In continuation of our studies[1] we investigated the effects of the temperature, of the solvent and of halide substitution on the benzene nucleus on the rate of decomposition of benzoyl peroxide.

The best procurable peroxides and solvents were further purified. *o*-Chlorobenzoyl peroxide alone was not obtained in the pure state; it appeared to contain some of the decomposition products. The purity of the peroxides was determined and the course of the decomposition was followed iodometrically.

In all cases, as previously observed[1], there was a preliminary period during which the rate of decomposition increased to a maximum. This was followed by two parallel reactions whose calculated order is n. The first order rate constant, k, as calculated from the observed molarity, $C - x$, the elapsed time and the initial observation, is included.

In Table I we have data representative of the results for the decomposition of benzene solutions of benzoyl peroxide in sealed bomb tubes at 90° ± 0.05.

TABLE I

DECOMPOSITION OF BENZOYL PEROXIDE IN BENZENE AT 90° ($n = 1.33$)

Time, min.	$(C - x)$ mole/l.	k min.$^{-1}$	$(C - x)$ mole/l.	k min.$^{-1}$
10	0.3260		0.1730	
20	.2902	0.0121	.1586	0.0087
30	.2624	.0111	.1479	.0078
40	.2307	.0107	.1302	.0094
60	.1935	.0105	.1107	.0089
80	.1563	.0106	.0921	.0090
120	.1070	.0102	.0670	.0085

When our values for the first order rate constants for tenth molar solutions in benzene at 80°, reported in the preceding paper,[1] and at 90° are included with those observed by Cohen[2] (starred in Table II), they extend his curve.

TABLE II

TEMPERATURE COEFFICIENT FOR THE DECOMPOSITION OF TENTH MOLAR BENZOYL PEROXIDE IN BENZENE

Temp., °C.	k, first order
*54°	1.83×10^{-6} sec.$^{-1}$
*64	5.84
*74	19.3
80	33.5
90	110

A number of series of observations were made for the thermal decomposition of benzoyl peroxide in nitrobenzene at 80 ± 0.05°. Representative data with the first order constants for two series are included in Table III.

TABLE III

DECOMPOSITION OF BENZOYL PEROXIDE IN NITROBENZENE AT 80°

Time, min.	$(C - x)$ mole/l.	k min.$^{-1}$	$(C - x)$ mole/l.	k min.$^{-1}$
30	0.1151		0.0358	
90	.0975	0.00277	.0311	0.00235
150	.0834	.00263	.0274	.00233
210	.0729	.00253	.0242	.00220
330	.0564	.00248	.0196	.00204

The calculated order of the reaction, n, for the range of concentrations in nitrobenzene which was studied, appear in Table IV. For each initial concentration of the series, $C - x_1$, the elapsed time for a third decomposition, Δt, is given.[1]

TABLE IV

ORDER OF REACTION OF THE DECOMPOSITION OF BENZOYL PEROXIDE IN NITROBENZENE AT 80°

$(C - x_1)$ mole/l.	Δt, min.	n
0.2835	120	
.1151	155	1.24
.0583	175	1.22
.0358	195	1.22
.0147	230	1.21

The first order rate constant for the decomposition of a tenth molar solution of benzoyl peroxide in the two solvents in relation to the dielectric constant, D, and the relative orders of reaction in these solvents are included in Table V.

TABLE V

RELATION OF RATE AND ORDER OF REACTION TO THE DIELECTRIC CONSTANT, 80°

Solvent	D	k min.$^{-1}$	n
Benzene	2.2	0.00201	1.29
Nitrobenzene	26.2	.00258	1.22

The rates of decomposition of several concentrations of three halogen substituted benzoyl peroxides in benzene as a solvent were observed at 80°. In Table VI we have included the ionization constant for each corresponding acid, K, the calculated rate constant for a tenth molar solution and the order of the reaction.

TABLE VI

DECOMPOSITION OF HALOBENZOYL PEROXIDES IN BENZENE, 80°

Solute, peroxide	K	k min.$^{-1}$	n
Benzoyl	6.6×10^{-5}	0.00201	1.29
p-Chloro	9.3	.00130	1.33
m-Bromo	13.7	.00156	1.18
o-Chloro	132	.0187	1.19

---

[1] Brown, THIS JOURNAL, **62**, 2657 (1940).

[2] Cohen, *ibid.*, **67**, 17 (1945).

Discussion

The results presented in the preceding article[1] indicated that benzoyl peroxide in benzene, following a "preliminary period," decomposed as if two parallel reactions were occurring, a first order and a second order. This decomposition was interpreted as an initial dissociation of the peroxide followed by the further dissociation of the hemimer and the parallel reaction of the hemimer as an oxidizer. The final products of the reaction were determined by the reactions of the hemimer. The almost constant order of reaction with changing environment (Tables I, IV and V) and with halogen substitution on the benzene nucleus (Table VI) indicate a uniform mechanism of decomposition.

If the initial dissociation were ionic, $(RO)_2 = RO^+ + RO^-$, we would expect a large solvent effect on the rate of reaction in relation to the dielectric constant.[3] The increase in the rate of decomposition for a twelve-fold increase in the dielectric constant of the solvent is relatively small (Table V). The temperature coefficient for a reaction involving an ionized substance is usually relatively low.[3] The large variation of the rate constant with temperature and the comparative insensitivity to changes in dielectric constant may be further evidence that the decomposition proceeds via an uncharged radical mechanism, as was previously advanced[4,1] and is now accepted by many workers in the field.

The degree of the initial dissociation may be determined in part by the relative "negativity" of the radicals R and R′ of the peroxide R–O–O–R′ exactly as found by Gomberg[5] for the formation of trivalent carbon. The rate of reaction of the peroxide is determined by the degree of the dissociation which precedes and thus controls the subsequent rate determining reactions. Of those studied *o*-chlorbenzoyl peroxide decomposes the most rapidly. The rate constants for the *o*- and *p*-chlorobenzoyl peroxides have approximately the same ratio as the ionization constants of the two chlorobenzoic acids (Table VI), but no such simple relationship is found among the corresponding constants in the unsubstituted, *p*-chloro and *m*-bromo derivatives.

The data are correlated by the postulate that the initial reaction is a simple dissociation of the peroxide with the formation of radicals which contain monovalent oxygen as a constituent followed by two parallel reactions. The products of the decomposition are determined by these parallel reactions.

Summary

The rates of decomposition of benzoyl peroxide in benzene and the order of reaction at two temperatures are reported.

A study of the relation of the rate of reaction and order of reaction to the dielectric constant of the solvent was made.

The effect of substitution on the benzene nucleus of the benzoyl peroxide was studied.

LINCOLN, NEBRASKA RECEIVED APRIL 15, 1946

---

[3] Walden, *Z. physik. Chem.*, **54**, 129 (1905), and later.

[4] Hey and Waters, *Chem. Rev.*, **21**, 169 (1937).

[5] Gomberg, *ibid.*, **1**, 91 (1924).

[CONTRIBUTION FROM THE LABORATORY OF C. A. WAMSER]

Hydrolysis of Fluoboric Acid in Aqueous Solution

BY CHRISTIAN A. WAMSER

Aqueous fluoboric acid, which is now commercially available in the form of a 40% concentrate, is prepared[1] by treating aqueous hydrofluoric acid with the calculated amount of boric acid according to the equation

$$4HF + H_3BO_3 = HBF_4 + 3H_2O$$

It has been well known that aqueous solutions of fluoboric acid are more or less strongly hydrolyzed depending on the dilution, temperature and length of time they have been standing after preparation. Such solutions always contain more H ion than can be accounted for by the fluoboric acid they are calculated to contain.

Any successful explanation of the net changes occurring on hydrolysis must be capable of accounting for the following experimentally observable facts:

(1) When four moles of hydrofluoric acid and one mole of boric acid are mixed in aqueous medium, an immediate sharp increase in conductance occurs and heat is evolved, yet the solution contains no fluoboric acid immediately after the preparation (no precipitate with nitron). The total titratable acidity (as measured by the volume of standard alkali consumed to the phenolphthalein end-point in the presence of mannitol) of such a mixture immediately after preparation corresponds to five equivalents of acid, the solution at the end-point containing only F^- and BO_2^- anions.

(2) After preparation, the fluoboric acid content gradually increases to a final (equilibrium) value, while the total acidity decreases to a definite value. The only anions present at the titration end-point are BF_4^-, F^- and BO_2^-.

(3) When a fluoboric acid concentrate (which is itself appreciably hydrolyzed) is diluted with water, the total acidity gradually increases to a final (equilibrium) value.

---

[1] F. Fischer and K. Thiele, *Z. anorg. Chem.*, **67**, 304 (1910).

According to Wilke-Dörfurt and Balz[2] the fluoborate ion hydrolyzes

$$BF_4^- + 3H_2O \rightleftarrows H_3BO_3 + 3H^+ + 4F^-$$

so that a hydrolyzed solution contains hydrofluoric and boric acids as well as fluoboric acid. Assuming this reaction, Ryss and Bakina[3] have determined the hydrolysis constant from *p*H data. It has been found, however, that except in the case of very dilute solutions, hydrolyzed aqueous fluoboric acid solutions probably do not contain any free boric acid because the addition of mannitol to such solutions does not result in any increase in conductance.

According to Travers and Malaprade[4] hydrofluoric acid and boric acid react immediately to form a fluoboric acid, not HBF_4, and the latter is only formed slowly at the expense of the first-formed complex until finally an equilibrium between the two acids is reached.

It will be shown herein that when 4HF and H_3BO_3 are mixed in aqueous solution an immediate reaction occurs and HBF_3OH is formed. This is followed by a slower reaction involving this first-formed complex and hydrofluoric acid and resulting in the formation of fluoboric acid

(1) $H_3BO_3 + 3HF \longrightarrow HBF_3OH + 2H_2O$ (very fast)
(2) $HBF_3OH + HF \rightleftarrows HBF_4 + H_2O$ (slower)

Reaction (2) continues until finally a state of equilibrium is reached.

The Reaction $H_3BO_3 + 3HF \rightarrow HBF_3OH + 2H_2O$.—If an aqueous solution of boric acid is titrated conductometrically with hydrofluoric acid, it will be found that the conductance increases sharply until the point representing the addition of between three and four moles of hydrofluoric acid per mole of boric acid has been reached; further additions of hydrofluoric acid cause a much more gradual increase. Figure 1 is a plot of such a titration and the data for it were obtained as follows:

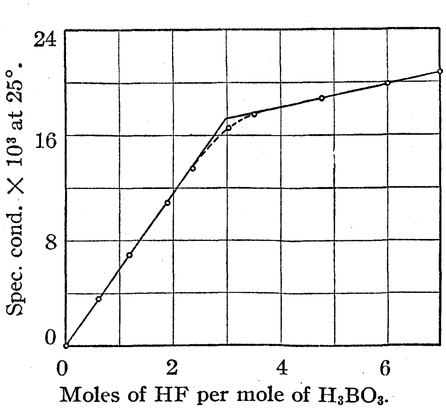


Fig. 1.—Conductance of H_3BO_3–HF mixtures immediately after preparation.

For each point on the curve a separate mixture was made up by treating a solution containing a fixed amount of recrystallized boric acid with a measured volume of a standard hydrofluoric acid solution in a calibrated polystyrene volumetric bottle at 25°. Immediately after preparation the mixture was transferred to a polystyrene conductance cell. The concentration of boric acid in each case was 0.0522 *M*.

Figure 1 is the plot of the conductance of the mixtures against the number of moles of hydrofluoric acid added per mole of boric acid. The well-defined break corresponds to a ratio of 3 to 1, and the reaction is probably

$$H_3BO_3 + 3HF \longrightarrow HBF_3OH + 2H_2O$$

Boric acid here behaves as a base analogous to aluminum hydroxide

$$Al\,(OH)_3 + 3HF \longrightarrow AlF_3 + 3H_2O$$

The acid HBF_3OH is known in the anhydrous state (Meerwein's acid, $BF_3 \cdot H_2O$)[5] and probably does not exist in aqueous solutions except in equilibrium with fluoboric acid. It is apparently able to form salts, for, as will be shown, KBF_3OH may be easily prepared.

The conductance plot of Fig. 1 indicates that HBF_3OH is a strong acid, although its specific conductance at this concentration (0.0522 *M*) is 17.3×10^{-3} at 25° compared with 20.3×10^{-3} for fluoboric acid at this same concentration (corrected for hydrolysis from data presented in a later section). HBF_3OH is hence somewhat weaker than fluoboric acid.

The reaction deduced from the previous data is probably oversimplified; it does not represent all the important changes that can take place, and the following may also occur

$$\begin{array}{lr} H_3BO_3 + HF \longrightarrow HBF(OH)_3 & \text{(rapid)} \\ HBF(OH)_3 + HF \longrightarrow HBF_2(OH)_2 + H_2O & \text{(rapid)} \\ HBF_2(OH)_2 + HF \longrightarrow HBF_3OH + H_2O & \text{(rapid)} \end{array}$$

If HBF_3OH were the only acid formed immediately after boric acid and hydrofluoric acid are mixed, it would be expected that the specific conductance of the mixture $H_3BO_3 + 3HF$ would be 17.3×10^{-3} (the intersection of the lines of Fig. 1). Actually about 3.3 moles of hydrofluoric acid per mole of boric acid are required to give this conductance and this seems to indicate that a weaker acid is in rapid reversible equilibrium with HBF_3OH, and present in appreciable amount. It is therefore possible that appreciable amounts of $HBF_2(OH_2)$ (probably a slightly weak acid) and $HBF(OH)_3$ (probably weak) exist in rapid reversible equilibrium with boric acid, hydrofluoric acid and HBF_3OH. The acid $HBF_2(OH)_2$ is in fact known in the anhydrous state (dihydroxyfluoboric acid[6]). The author has also prepared a salt from concentrated solutions of equimolar proportions of potassium bifluoride and boric acid which has a

---

(2) E. Wilke-Dörfurt and G. Balz, *Z. anorg. allgem. Chem.*, **159**, 197 (1926).

(3) J. G. Ryss and N. P. Bakina, *Compt. rend. l'acad. Sci. U. S. S. R.* (N. S.), **2**, 107 (1936).

(4) A. Travers and L. Malaprade, *Bull. soc. chim.*, **47**, 788 (1930).

(5) H. Meerwein, *Ber.*, **66B**, 411 (1933).

(6) F. J. Sowa, J. W. Kroeger and J. A. Nieuwland, THIS JOURNAL, **57**, 454 (1935).

ratio of K:B:F of 1:1:2 and the analysis of which corresponds closely to $KBF_2(OH)_2$. The salt further gives a well-defined X-ray diffraction pattern different from potassium fluoborate and KBF_3OH.

Preparation of Potassium Hydroxyfluoborate (KBF_3OH).—In their attempts to identify the first-formed complex acid in $4HF–H_3BO_3$ mixtures in aqueous solution, Travers and Malaprade[4] isolated a salt from cold, concentrated mixtures of potassium bifluoride and boric acid. Their chemical analyses of this salt indicated a ratio of K:B:F of 1:1:3 and they ascribed to it the formula $K_2B_2F_6 \cdot 1.5H_2O$. They found that the salt hydrolyzes readily and that the volume of standard alkali consumed by an aqueous solution of it up to the phenolphthalein end-point (in the presence of mannitol) corresponded closely to that calculated to decompose it to fluoride and metaborate.

This salt is, however, probably KBF_3OH, produced in accordance with the following equation, which also explains the increase in alkalinity that occurs when strong solutions of potassium bifluoride are treated with boric acid

$$2KHF_2 + H_3BO_3 \longrightarrow KBF_3OH + KF + 2H_2O$$

Travers and Malaprade[4] do not offer an equation to explain the formation of their salt, for no simple reaction (not involving an oxidation or reduction) presented itself.

Several samples of KBF_3OH were prepared as follows: 100 grams of potassium bifluoride was dissolved in 250 ml. of water in a polystyrene beaker. After standing for several hours at room temperature, the solution was freed from potassium fluosilicate and undissolved potassium bifluoride by filtering through paper in a polystyrene funnel. The solution, in polystyrene, was placed in an ice–water-bath and 40 g. of powdered boric acid added with continual stirring. The boric acid dissolved readily and within an hour, during which time the solution was occasionally stirred, small crystals deposited. These were filtered off on a sintered glass funnel (this liquor has a *p*H of about 6 and does not attack glass appreciably), washed sparingly with ice–water, then with larger amounts of 95% ethanol and acetone and dried at 120°. The analysis of two lots of crystals thus obtained is given in Table I.

TABLE I

ANALYSIS OF CRYSTALS OBTAINED FROM $2KHF_2 + H_3BO_3$

	Theoretical for KBF_3OH	Theoretical for $K_2B_2F_6 \cdot 1^1/_2 H_2O$	Lot 1	Lot 2
% K[a]	31.56	32.47	31.85	31.68
% B[b]	8.73	8.98	8.90	8.81
% F[c]	46.00	47.34	45.82	46.10
Milli-eq. weight[d]	0.0413	0.0401	0.0410	0.0411

[a] By repeated evaporation with sulfuric acid in platinum crucible and ignition to potassium sulfate. [b] By methyl alcohol distillation method of Chapin. [c] By lead chlorofluoride method. [d] Weight of a sample divided by the number of ml. of 1 *N* sodium hydroxide required to the phenolphthalein endpoint (in presence of mannitol).

The product obtained by the method described above and that obtained by following the directions of Travers and Malaprade[4] give identical X-ray diffraction patterns.

The salt KBF_3OH is distinguished from potassium fluoborate as follows: (1) The hydroxyfluoborate is much more soluble in water. (2) An aqueous solution of the hydroxyfluoborate gives no precipitate with nitron acetate. (3) An aqueous solution of the hydroxyfluoborate hydrolyzes readily in the presence of alkali, at room temperature: ($KBF_3OH + 3KOH \rightarrow 3KF + KBO_2 + 2H_2O$, while salts of fluoboric acid hydrolyze only very slowly in the presence of alkali (rapidly only at the boiling point and in the presence of excess calcium ions[7]).

The ease with which KBF_3OH decomposes in the presence of alkali explains why a mixture of $4HF + H_3BO_3$ immediately after preparation and though a reaction has taken place, requires five equivalents of alkali in a titration of total acidity and why the only anions present at the end-point are F^- and BO_2^-.

It was also found that KBF_3OH may be fused without suffering any decomposition or loss in weight, a property which would not be expected of a hydrate of the form assumed by Travers and Malaprade.[4]

Attempts to recrystallize the hydroxyfluoborate from aqueous solutions were unsuccessful, the product obtained being contaminated with fluoride and boric acid (extractable with ether–alcohol).

The Reaction $HBF_3OH + HF \rightarrow HBF_4 + H_2O$.—This reaction is slow enough, at concentrations of the order of 0.1 *M* at 25°, to permit of accurate estimation of the acids present based on total acidity, from which the amount of fluoboric acid formed can be easily calculated and the kinetics of the reaction studied. That the total acidity may be used for calculating the proportion of the three acids present has been proved over a wide range of concentration by the comparison of fluoboric acid concentrations thus calculated with direct gravimetric determinations of fluoboric acid as nitron fluoborate, as will be indicated in a later section.

For studying the kinetics of $HBF_3OH + HF \rightarrow HBF_4 + H_2O$, the reaction mixture is conveniently prepared from four moles of hydrofluoric acid and one mole of boric acid. Immediately after preparation, *i. e.*, at time $t = 0$, the total acidity is equal to five times that theoretically equivalent to the (stoichiometrically possible) fluoboric acid. If this latter calculates to T_1 and the observed titration at any time t is T_2, then the fraction of the possible fluoboric acid which is actually present at that time is $(5T_1 - T_2)/4T_1$.

The kinetics of this reaction was investigated at 25° at a concentration of 0.1105 *M* by mixing a solution of 3.805 g. of pure boric acid and one con-

---

(7) A. Gonard, *Bull. soc. chim.*, **9**, 917 (1942).

taining 4.922 g. of hydrogen fluoride in a calibrated polystyrene bottle (volume at mark 556.8 ml.) which was allowed to remain suspended in a thermostat bath. At recorded intervals of time, aliquots of the mixture were removed and quickly titrated for total acidity. Table II contains the data for this reaction. T_1 is here 2.62 ml. and the final (equilibrium) value of T_2 = 4.07 ml. indicates that at this concentration there is present, at equilibrium, 86.2% of the stoichiometrically possible fluoboric acid (or that the solution is hydrolyzed to the extent of 13.8% when the reaction is considered in the reverse direction). When the mixture had come to equilibrium, an aliquot was analyzed directly for fluoboric acid by precipitation with nitron acetate, using essentially the procedure described by Lange[8] except that the precipitate was filtered off within five minutes. There was obtained, from 25 ml. of the mixture, 0.9515 g. of $C_{20}H_{16}N_4 \cdot HBF_4$, corresponding to 86.1% of the total possible fluoboric acid.

TABLE II

KINETICS OF $HBF_3OH + HF \rightarrow HBF_4 + H_2O$ AT 25°

t = time in minutes. T_1 = 2.62 (ml. 1.054 N NaOH) per 25 ml. aliquot. T_2 = observed titration (ml. 1.054 N NaOH ≎ total acidity). a = initial concn. of HBF_3OH (and HF) in moles/liter = 0.1105. x = concn. of HBF_3OH (or HF) reacting in time t.

t	T_2	%HBF_4 formed = $(5T_1 - T_2)/4T_1$ × 100	$K_1 = \frac{1}{t}\frac{x}{a(a-x)}$
0	(13.10)	(0)	
8.5	10.32	26.5	0.382
16.5	8.72	41.8	.394
24	7.75	51.0	.392
32	6.98	58.4	.397
41	6.38	64.1	.394
52	5.85	69.2	.390
72	5.26	74.8	.372
103	4.77	79.5	.340
163	4.36	83.4	.280
218	4.19	85.0	.236
equil.	4.07	86.2	

The last column of Table II lists values of a specific reaction rate calculated on the basis of the reaction being of second order. The average value of K_1 obtained from the earlier part of the reaction is 0.392 liters moles^{-1} min.$^{-1}$ at 25°.

The Reaction $HBF_4 + H_2O \rightarrow HBF_3OH + HF$.—This reaction represents the hydrolysis of fluoboric acid in aqueous solution, and its kinetics were investigated at the same concentration (0.1105 M) as the reverse reaction considered in the previous section. The reaction mixture was prepared from equivalent quantities of barium fluoborate dihydrate and sulfuric acid: $Ba(BF_4)_2 + H_2SO_4 \rightarrow 2HBF_4 + BaSO_4$. This device was used by Travers and Malaprade[4] in their studies of solutions containing fluoboric acid free from its hydrolysis products.

Pure barium fluoborate dihydrate was prepared by the method of Funk and Binder[9] and analyzed as follows: Calcd. for $Ba(BF_4)_2 \cdot 2H_2O$: Ba, 39.59; BF_4, 50.04. Found: Ba, 39.65; BF_4, 49.66 (BF_4 by nitron method). The kinetics of this hydrolysis reaction was investigated as follows:

A solution of 10.675 g. of $Ba(BF_4)_2 \cdot 2H_2O$ in water was mixed with a solution containing 59.27 ml. of 1.038 N H_2SO_4 in the polystyrene bottle mentioned previously. The mixture was maintained at 25° in a thermostat bath and aliquots were withdrawn at recorded intervals of time. Total acidity was determined by titration in the usual manner. The precipitated barium sulfate was not removed since it is inert with respect to the hydrolysis reaction and to the titrations. The degree of hydrolysis at any time t will be $(T_2 - T_1)/4T_1$, the symbols having the same significance as in the case of the reverse reaction. Here T_1 is 4.87 ml. and the final (equilibrium) value of T_2 = 7.53 ml. indicates a degree of hydrolysis of 13.7% which is in good agreement with the result obtained from the measurements of the equilibrium approached from the opposite direction.

Table III contains the data obtained and the last column lists a specific rate calculated on the basis of the reaction being of first order. The average value of K_2 obtained from the earlier part of the reaction is 0.00090 min.$^{-1}$ at 25°.

The ratio $K_2/K_1 = 2.3 \times 10^{-3}$ thus represents the equilibrium constant for the hydrolysis of fluoboric acid: $HBF_4 + H_2O \rightleftarrows HBF_3OH + HF$ at 25°.

TABLE III

KINETICS OF $HBF_4 + H_2O \rightarrow HBF_3OH + HF$ AT 25°

t = time in minutes. T_1 = 4.87 (ml. 0.5680 N NaOH) per 25 ml. aliquot. T_2 = observed titration (ml. 0.5680 N NaOH ≎ total acidity). a = initial concn. of HBF_4 in moles/liter = 0.1105. x = concn. of HBF_4 reacting in time t.

t	T_2	%Hydrolysis = $(T_2 - T_1)/4T_1$ × 100	$K_2 = \frac{1}{t}\ln\frac{a}{a-x}$
0	(4.87)	(0)	
8	5.01	0.72	0.00090
13	5.10	1.18	.00091
20	5.22	1.80	.00091
31	5.40	2.72	.00089
43	5.59	3.70	.00088
60	5.85	5.02	.00087
94	6.28	7.23	.00080
147	6.87	10.27	.00074
206	7.23	12.1	.00063
equil.	7.53	13.7	

TABLE IV

EFFECT OF CONCENTRATION ON THE RATE CONSTANTS K_1 AND K_2

Concn. in moles/liter	K_1 at 25°	K_2 at 25°	K_2/K_1
0.0130	0.0823	0.00019	2.31×10^{-3}
.0561	.244	.00055	2.25×10^{-3}
.1105	.392	.00090	2.30×10^{-3}

---

[8] W. Lange, *Ber.*, **59B**, 2107 (1926).

[9] H. Funk and F. Binder, *Z. anorg. allgem. Chem.*, **155**, 327 (1926).

TABLE V

DEGREE OF HYDROLYSIS OF AQUEOUS FLUOBORIC ACID SOLUTIONS AT EQUILIBRIUM; TEMP. 25°

A = from 38.04% HBF_4 concentrate and water. B = from 4HF and H_3BO_3. C = from $Ba(BF_4)_2$ and H_2SO_4.

Concn. in moles/liter	Method of prep.	Sample taken, ml. or g.	Titration, ml. std. NaOH or grams $C_{20}H_{16}N_4 \cdot HBF_4$	Hydrolysis %	$\frac{[HBF_3OH][HF]}{[HBF_4]}$
0.001018	A	50 ml.	9.90 of 0.0211 *N*	77.7	2.75×10^{-3}
.00509	A	50	6.88 of 0.1054 *N*	46.3	2.04×10^{-3}
.01018	A	50	4.67 of 0.2634 *N*	35.5	1.98×10^{-3}
.01296	B	25	3.53 of 0.2108 *N*	32.5	2.02×10^{-3}
.02036	A	50	7.97 of 0.2634 *N*	26.6	1.95×10^{-3}
.02036	A	100	0.6003 g.	26.3	1.90×10^{-3}
.0504	A	50	4.19 of 1.054 *N*	18.8	2.20×10^{-3}
.0504	A	50	0.8212 g.	18.6	2.15×01^{-3}
.0527	B	50	4.32 of 1.054 *N*	18.2	2.14×10^{-3}
.0561	A	50	4.50 of 1.054 *N*	17.3	2.02×10^{-3}
.1018	A	50	7.54 of 1.054 *N*	14.1	$2.35 = 10^{-3}$
.1018	A	25	0.8758 g.	14.1	2.35×10^{-3}
.1105	B	25	4.07 of 1.054 *N*	13.8	2.42×10^{-3}
.1105	C	25	7.53 of 0.5680 *N*	13.7	2.38×10^{-3}
.2850	A	50	10.43 of 0.9577 *N*	10.0	3.15×10^{-3}
.2850	A	10	1.0238 g.	10.1	3.23×10^{-3}
.557	A	50	13.95 of 2.634 *N*	8.01	3.95×10^{-3}
.557	A	5	1.0265 g.	7.95	3.76×10^{-3}
5.41	(concentrate)	4.123 g.	8.28 of 2.634 *N*	5.53	17.6×10^{-3}
5.41	(concentrate)	0.5881	0.9636 g.	5.47	17.6×10^{-3}

The specific reaction rates K_1 and K_2 have also been determined at other concentrations using the experimental methods previously described.

The variation of K_1 and K_2 with concentration may be in part an ionic strength effect and in part a result of the hydrogen ion concentration change which simultaneously takes place.

It has been observed that an increase in hydrogen ion concentration (such as occurs for example if hydrochloric acid be added to the reaction mixture $HBF_3OH + HF$) results in an increase in the specific rate K_1. This explains why KBF_4 is rapidly precipitated from the reaction mixture $[2KHF_2 + H_3BO_3 \rightarrow KBF_3OH + KF + 2H_2O]$ on acidification with, say, hydrochloric acid.

Degree of Hydrolysis of Aqueous Fluoboric Acid Solutions.—The degree of hydrolysis of aqueous fluoboric acid solutions (at equilibrium) was determined over the concentration range 0.001 *M* to 5.41 *M* at 25° by diluting weighed amounts of a fluoboric acid concentrate with water. These solutions were stored in sealed polyethylene bottles for three months (a 0.001 *M* solution requires about two months to come to equilibrium), and then suspended in a thermostat bath at 25° for a day. Appropriate aliquots were withdrawn and titrated with standard alkali for total acidity. In those cases where a blank on the mannitol used was significant, it was carefully determined and deducted.

Table V lists the concentration of the solution (always with respect to stoichiometrically possible fluoboric acid), the method of preparation, and the analytical data on which the degree of hydrolysis is based.

Equilibrium constants calculated from the degree of hydrolysis are listed in the final column of Table V. The assumption is here made that the HBF_3OH is itself not appreciably hydrolyzed and therefore $[HF] = [HBF_3OH]$. An examination of these values shows that only that calculated for the most dilute solution measured is appreciably different from the average of the next nine (2.04×10^{-3}). This figure is in good agreement with the constant derived from rate data. At the higher concentrations, the values in the final column increase rapidly, due probably to the increasing difference between activity and concentration as the latter increases.

If the hydrolysis of HBF_3OH proceeds according to $HBF_3OH + H_2O \rightleftarrows HBF_2(OH)_2 + HF$, and the constant is of the same order of magnitude as that for the hydrolysis of fluoboric acid, the amount of $HBF_2(OH)_2$ will be significant only in very dilute solutions. The equilibrium constant would have to be modified from

$$\frac{A \times A}{HBF_4} = \frac{A^2}{HBF_4}$$

where $A = [HF] = [HBF_3OH]$ to

$$\frac{(A + X)(A - X)}{HBF_4} = \frac{A^2 - X^2}{HBF_4}$$

where X = the decrease of $[HBF_3OH]$ due to its hydrolysis = the increase of [HF]. The effect of ignoring the hydrolysis of HBF_3OH is to neglect the X^2 term, and since X is probably of the order of 10^{-3}, the value of the constants as previously calculated will not be appreciably affected until A is of the order of 3×10^{-3}.

Conductometric and *p*H Titrations of Hydrolyzed Fluoboric Acid Solutions.—Several hydrolyzed fluoboric acid solutions were titrated conductometrically and potentiometrically, and in the case of the former method, comparison was made with (a) unhydrolyzed fluoboric acid solution and (b) a solution prepared from salts of the three acids involved.

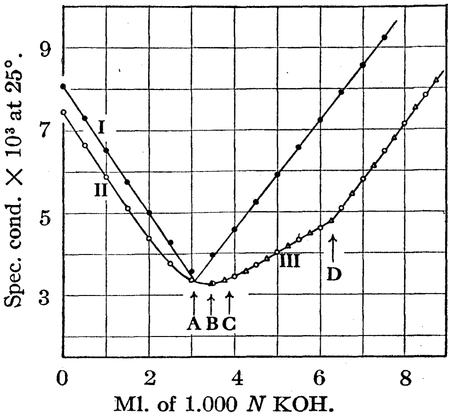


Fig. 2.—Conductometric titrations of aqueous fluoboric acid solutions: I, ●, unhydrolyzed HBF_4 solution; II, O, hydrolyzed HBF_4 solution; III, △, solution of KBF_4 + KBF_3OH + KHF_2.

Figure 2 summarizes graphically the results of three conductometric titrations: I. The titration of 150 ml. of 0.02036 *M* fluoboric acid (prepared from barium fluoborate and sulfuric acid and titrated immediately after preparation) with 1.000 *N* potassium hydroxide. II. The titration of 150 ml. of 0.02036 *M* fluoboric acid solution at equilibrium, with 1.000 *N* potassium hydroxide. This curve shows the effect of the hydrolysis products on the titratable acidity, the end-point having been displaced from 3.08 to 6.30 ml. This titration (point D on curve II of Fig. 2) corresponds to 26.6% hydrolysis. The point *A* = 3.06 ml. corresponds to the neutralization of the strong acids fluoboric acid and HBF_3OH and very nearly coincides with the end-point of titration I, indicating that the conductance of potassium fluoborate is not appreciably changed by the replacement of a large part of it with an equivalent amount of KBF_3OH (neglecting the conductance of the relatively weak hydrofluoric acid which is present at the point A). It was also found that in this case and in the case of other titrations of fluoboric acid solutions (at equilibrium) at various concentrations, the point of minimum conductance corresponds very closely to the stage of the titration at which KBF_4, KBF_3OH and KHF_2 are present in solution, *i. e.*, point B on curve II. The segment CD = 2.43 ml. which represents the decomposition of KBF_3OH, was found to be a straight line at various concentrations.

III. It was found that the last part of curve II (BD) could be exactly reproduced by titrating a solution containing 0.283 of KBF_4, 0.100 g. of KBF_3OH, and 0.0312 g. of KHF_2 dissolved in water and diluted to the volume of the solution corresponding to this point (B) on curve II (*i. e.*, 153.5 ml.). This is evidence of the correctness of the assumed hydrolysis reaction.

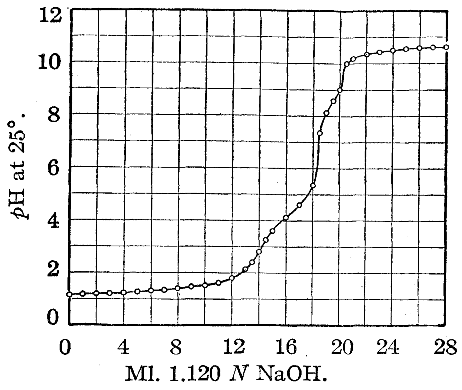


Fig. 3.—*p*H titration of 100 ml. of 0.1512 *M* fluoboric acid at equilibrium.

Figure 3 represents a *p*H titration of 100 ml. of 0.1512 *M* fluoboric acid at equilibrium (hydrolysis 12.4%) with 1.120 *N* sodium hydroxide at 25°. The first inflection corresponds closely to the neutralization of HBF_4 + HBF_3OH, the second to the stage of the titration corresponding to the decomposition of the $NaBF_3OH$ to sodium fluoride and boric acid, and the final inflection to the total acidity. It is interesting to note here that when a hydrolyzed fluoboric acid solution is treated with iodate–iodide mixture as in the standard iodimetric determination of acidity, the iodine liberated is equivalent to the second inflection in the *p*H curve.

This *p*H titration was performed in a polystyrene beaker using glass and calomel electrodes and although this cell combination may not be well suited to such a titration, it enables the measurements to be extended over the desired range.

Effect of Excess Boric Acid or Hydrofluoric Acid on the Hydrolysis Equilibrium.—A series of solutions containing the same concentration of fluoboric acid concentrate but various amounts of added excess boric or hydrofluoric acid were allowed to come to equilibrium at 25° in sealed polyethylene bottles. Total acidity was determined on appropriate aliquots and after correcting for the known added amount of either acid, the remaining titration was considered as due to fluoboric acid and its hydrolysis products and the degree of hydrolysis so calculated. Some of the solutions were also analyzed directly, by the nitron method, for fluoboric acid.

Figure 4 is a plot of the degree of hydrolysis of a 0.0527 *M* HBF_4 solution against the indicated concentrations of added boric or hydrofluoric acid. Excess hydrofluoric acid markedly decreases the hydrolysis while boric acid increases the equilibrium ratio of HBF_3OH to fluoboric acid.

Conductance of Aqueous Fluoboric Acid Solutions.—The conductances at 25° of aqueous solutions of fluoboric acid were measured in polystyrene cells over the concentration range 0.005 to 0.1 *M*. The curves of Fig. 5 were plotted from measurements made on the following

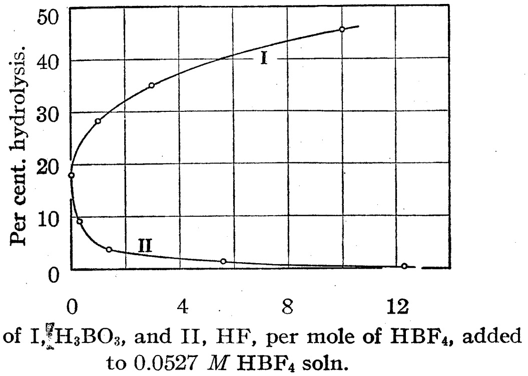


Fig. 4.—Influence of added excess H_3BO_3 and HF on the degree of hydrolysis (at equilibrium) at 25°.

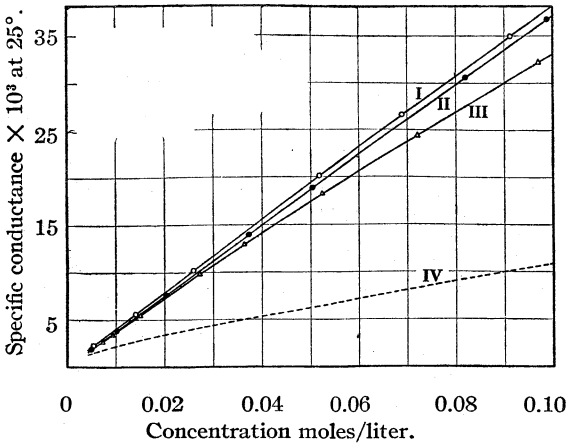


Fig. 5.—Conductance of aqueous fluoboric acid solutions: I, O, no hydrolysis; II, ●, equilibrium hydrolysis; III, △, complete hydrolysis; IV, ----, 4 HF.

solutions: I. Mixtures of equivalent amounts of barium fluoborate and sulfuric acid immediately after preparation. II. Aqueous fluoboric acid solutions at equilibrium. III. Mixtures of four moles of hydrofluoric acid and one mole of boric acid immediately after preparation. A curve of the conductance of 4HF has been included for comparison (IV).

The measurements from which curve I was obtained are uncorrected for the barium sulfate contained or for any adsorption or other possible effects caused by its presence in the solutions.

It was found that the addition of pure recrystallized mannitol did not appreciably alter the conductance of any of the solutions, indicating that no appreciable amount of free boric acid was present.

Acknowledgment.—The author acknowledges his indebtedness to Thomas L. Allen of the California Institute of Technology for helpful suggestions.

Summary

Conductance measurements show that when four moles of hydrofluoric acid and one mole of boric acid are mixed in aqueous solution, three moles of the hydrofluoric acid react immediately with the boric acid to form HBF_3OH.

HBF_3OH then reacts more slowly with hydrofluoric acid to form fluoboric acid until an equilibrium is reached.

The kinetics of the reaction $HBF_3OH + HF \rightleftarrows HBF_4 + H_2O$ was measured (1) from left to right (second order), and (2) from right to left (first order).

The equilibrium constant at 25° for the hydrolysis of fluoboric acid in aqueous solution is about 2.3×10^{-3}.

The salt KBF_3OH was prepared from $2KHF_2$ and boric acid and is the same as that reported by Travers and Malaprade[4] as $K_2B_2F_6 \cdot 1^1/_2H_2O$.

The degree of hydrolysis of aqueous fluoboric acid solutions at equilibrium at 25° has been determined over the range 0.001 to 5.41 *M*.

The conductance of aqueous fluoboric acid solutions at 25° has been determined over the range 0.005 to 0.1 *M* for the cases (1) no hydrolysis, (2) equilibrium hydrolysis and (3) complete hydrolysis.

FLUSHING, N. Y. RECEIVED APRIL 28, 1947

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

The Interaction of Manganic Ion and Oxalate. Rates, Equilibria and Mechanism

BY HENRY TAUBE

Recent observations[1] on the manganic ion catalysed reaction of chlorine and oxalic acid were shown to be consistent with a mechanism in which the slow step is the oxidation of oxalic acid by manganic ion. Accepting this assumption, the rate data fixed the rate law for this reaction and its specific rate in solutions at high hydrogen ion concentration. In the present work, the interpretation of the catalytic data has been checked by direct measurements of the rate of the manganic ion–oxalic acid reaction

$$2\mathrm{Mn(III)} + \mathrm{H_2C_2O_4} = 2\mathrm{Mn(II)} + 2\mathrm{H^+} + 2\mathrm{CO_2}$$

Measurements of the rate of this reaction in solutions at low hydrogen ion concentration have been reported.[2,3,4] However, since there are important differences in the conclusions reached by some of the observers,[2,3] and since in no case did the conditions sufficiently approach those obtaining in the catalytic work, unambiguous comparisons of rate could not be made. While the present measurements do not extend to solutions as acidic as those employed in the catalytic work—the rate of reduction of manganic ion at high hydrogen ion concentration being so rapid as to make direct measurement difficult—a comparison is still possible since the rate law established in the catalytic work predicts the variation of reaction rate with hydrogen ion concentration for conditions under which the assumed mechanism operates. The measurements reported here have been extended also to solutions at low hydrogen ion, and conclusions about the mechanisms operative over the whole hydrogen ion concentration range are offered.

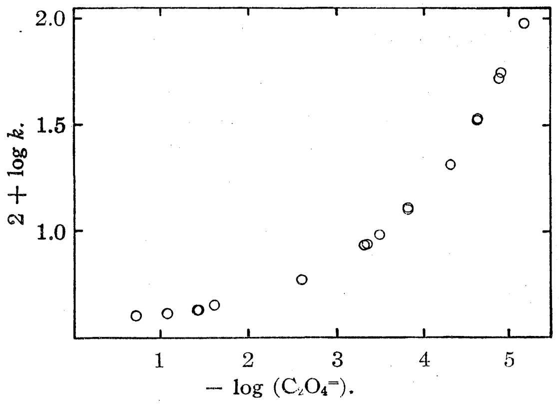


Fig. 1.—The variation of specific rate with oxalate ion concentration. Data are from Table I, experiments 1 to 17.

Method

To the solution containing oxalate, hydrochloric acid and manganous ion, a small volume of a solution of potassium permanganate was added. After sufficient time (*ca.* 1 min.) had elapsed to ensure complete reduction by the excess manganous ion of permanganate ion to Mn(III), a sample was withdrawn and quenched by discharging it into a solution of potassium iodide. Other samples were withdrawn at measured intervals of time and quenched in like manner, and the Mn(III) content determined by titrating the liberated iodine. The initial concentration of Mn(III) was of the order of 3.0×10^{-3} *M* in most cases, much less than the concentration of added oxalate, and, during the course of the run, the concentration fell to one-third to one-sixth of the original value. The first order specific rates calculated from the several samples, usually four, measured at intervals agreed within 1 to 2% of the mean, and in no case showed a significant drift. Over the concentration range covered, 3.0×10^{-3} *M* down to about 0.5×10^{-3} *M*, the reaction is strictly first order with respect to the concentration of Mn(III).

To remove oxygen, carbon dioxide was swept through the more acidic solutions, and nitrogen, from which residual oxygen had been scrubbed, through those in the range of low acid concentration. Except where otherwise noted, the reactions were carried out at 25.2°. The ionic strength was maintained at 2 in the majority of experiments by the addition of potassium chloride.

Results and Discussion

The Rate Determining Steps.—In Table I are recorded the results of a series of experiments, 1–17, in which the concentration of total oxalate and of acid have been varied, the ionic strength and temperature being constant. Each specific rate tabulated in column 6 is the mean of the several which were obtained during a single run. The specific rate is defined by the equation

$$k = \frac{2.303}{t} \log \frac{(\mathrm{Mn(III)})_0}{(\mathrm{Mn(III)})_t}$$

The time being expressed in minutes. The data show that at high acid concentration (low oxalate ion concentration) the specific rate increases rapidly as the acid concentration is raised, approaching variation with the second power, and that the specific rate at high oxalate ion concentration reaches a limiting value, which is independent of the oxalate ion or acid concentration. The important features are more strikingly portrayed in Fig. 1, in which log *k* for experiments 1–17 is plotted against log $1/(\mathrm{C_2O_4^=})$. The specific rate is observed to be fixed by the oxalate ion concentration, and does not depend directly on the hydrogen ion, oxalic acid or binoxalate ion concentrations.

These observations can be interpreted quantitatively by the simple mechanism in which each of the ions $\mathrm{MnC_2O_4^+}$, $\mathrm{Mn(C_2O_4)_2^-}$, $\mathrm{Mn(C_2O_4)_3^{\equiv}}$ known to be in rapid equilibrium,[1,5] undergoes

---

[1] THIS JOURNAL, **69**, 1418 (1947).

[2] Launer, *ibid.*, **54**, 2597 (1932).

[3] Lidwell and Bell, *J. Chem. Soc.*, 1303 (1935).

[4] Bradley and van Praagh, *ibid.*, 1624 (1938).

[5] Cartledge and Ericks, THIS JOURNAL, **58**, 2065 (1936).

TABLE I

KINETICS OF THE REACTION AT 25.2°

Columns 2, 3 and 4 express the compositions of the solutions in terms of the reagents initially added; column 5 presents the equilibrium concentration of oxalate ion at the time of withdrawing the first sample. All concentrations are expressed in moles per liter. [$MnCl_2$] was 0.01 *M* except in experiment 18, [$KMnO_4$] *ca.* 7×10^{-4} *M*, $(Mn(III))_0$ from 2×10^{-3} to 3×10^{-3} *M*. The ionic strength was 2 (maintained by KCl) except in experiment 19. The content of columns 7, 8, 9 and 10 is described in the text.

No.	$[HCl]_0$	$[H_2C_2O_4]$	$[K_2C_2O_4]$	$(C_2O_4^=)_0$	k	Fraction[c] of Mn(III) as $Mn(C_2O_4)_3^=$	Contribution to k by $MnC_2O_4^+$ path	Contribution to k by $Mn(C_2O_4)_2^-$ path	k calcd.
1	0.436	0.150		6.42×10^{-6}	0.95	0.004	0.877	0.088	0.965
2	.292	.150		1.22×10^{-5}	.558	.009	.466	.089	.555
3	.194	.150		2.27×10^{-5}	.342	.016	.252	.0895	.342
4	.194	.150		2.27×10^{-5}	.335	.016	.252	.0895	.342
5	.194	.0795		1.27×10^{-5}	.525	.009	.449	.089	.538
6	.0971	.150		4.85×10^{-5}	.208	.033	.116	.088	.205
7		.150		1.50×10^{-4}	.130	.0965	.0353	.083	.122
8		.150		1.50×10^{-4}	.128	.0965	.0353	.083	.122
9		.100	0.0200	3.20×10^{-4}	.0970	.186	.0147	.0748	.0966
10		.0900	.0284	4.52×10^{-4}	.0870	.244	.0097	.0693	.0890
11		.0743	.0249	4.67×10^{-4}	.0867	.250	.094	.0688	.0884
12		.0776	.0583	2.50×10^{-3}	.0596	.640	.0008	.0330	.0600
13		.0485	.0728	2.47×10^{-2}	.0448	.947		.0049	.0437
14		.0440	.0824	3.73×10^{-2}	.0429	.964		.0033	.0428
15		.0097	.0533	3.88×10^{-2}	.0429	.966		.0031	.0427
16		.0194	.1065	8.40×10^{-2}	.0416	.984		.0015	.0418
17		.0194	.214	1.92×10^{-1}	.0410	.994		.0007	.0413
18[a]		.0194	.214	1.92×10^{-1}	.0432				
19[b]		.0194	.214	1.92×10^{-1}	.0361				

[a] [$MnCl_2$] = 0.05 *M*. [b] No added KCl; ionic strength = 0.65. [c] Solutions in experiments 1–6 are a deep straw color; a reddish tint appears in experiments 7 and 8; at high oxalate ion concentration, the solutions are a wine red color.

decomposition. Thus to cover the whole oxalate ion concentration range, the three independent paths below are assumed

$$MnC_2O_4^+ \xrightarrow{k_1'}$$

$$Mn(C_2O_4)_2^- \xrightarrow{k_1''}$$

$$Mn(C_2O_4)_3^= \xrightarrow{k_1'''}$$

The contribution by each path depends on the concentration of the ion in question and on its specific rate of decomposition.

$$-\mathrm{d}\,Mn(III)/\mathrm{d}t = k(Mn(III)) = 2k_1(MnC_2O_4^+) + 2k_1'(Mn(C_2O_4)_2^-) + 2k_1''(Mn(C_2O_4)_3^=)$$

The factor 2 is introduced into the equation above since it may reasonably be supposed, as in fact the comparison of the results at high acid with those of the catalytic experiments show, that the reducing intermediate formed in the rate determining step rapidly reacts with a second manganic ion, as for example

$$C_2O_4^- + Mn(III) = 2CO_2 + Mn(II)$$

This mechanism has been tested by assigning values to the specific rates k_1, k_1' and k_1'' and to the equilibrium quotients governing the distribution of Mn (III) among the three manganic species, and from these parameters, knowing the compositions of the solutions, calculating the values of k for each of the experiments 1–17 of Table I. The values of the above mentioned parameters which give close agreement between the experimental and calculated values for k were chosen as follows: k_1 has been measured[6] in the catalytic work as 11.8 min.$^{-1}$; k_1' has been selected as 0.046 min.$^{-1}$ to fit the present data; k_1'' is fixed by the present data at high oxalate ion concentration as 0.0205 min.$^{-1}$; K_b, the quotient governing the equilibrium

$$MnC_2O_4^+ + H_2C_2O_4 = Mn(C_2O_4)_2^- + 2H^+$$

was determined in the catalytic work as 42; $1/K_c$, governing the equilibrium

$$Mn(C_2O_4)_3^= = Mn(C_2O_4)_2^- + C_2O_4^=$$

has been selected[7] to fit the present data as 1.4×10^{-3}. Values for the first and second dissociation constants of oxalic acid (K_1 and K_2) are also required, these in order to calculate the equilibrium concentrations of $H_2C_2O_4$, $HC_2O_4^-$, $C_2O_4^=$ and H^+ in each experiment; these constants are reported by Dawson[8] as 6.3×10^{-2} and 1.66×10^{-4} for a medium 2*M* in potassium chloride.

In making the calculations, allowance has been made for the changes produced in oxalate and acid by the net reduction of MnO_4^- to Mn (II)

---

(6) The data on the catalysis of the oxalic acid–chlorine reaction gave for k_1 and K_b values of 11.4 min.$^{-1}$ and 44, respectively; more recent data on bromine and oxalic acid catalyzed by manganic ion give for k_1 and K_b values of 11.9 min.$^{-1}$ and 41. Weighted means were chosen for the comparisons with the present results. Results obtained in the bromine–oxalic acid work furthermore show that there is no interference by chloride ion in the Mn(III)–oxalic acid reaction, if the oxalate ion concentration is as high as that used in the present work.

(7) The value of Cartledge and Ericks for 0° and lower ionic strength is 3.8×10^{-3}.

(8) Dawson, *J. Chem. Soc.*, 1889 and 2534 (1929).

and to the mangani–oxalate complexes. No corrections were applied for the oxalate consumed by association with Mn (II) since the pertinent equilibrium constants are not known; in any case, the effects due to this cause are small since the concentration of manganous ion is low in comparison to the total oxalate.

Data for a typical experiment are present below, and the calculation of the equilibrium oxalate ion concentration and of the specific rate outline to illustrate the factors which have been considered.

Experiment 9, Table I.—Square brackets denote stoichiometric, round brackets equilibrium concentrations.

$$[H_2C_2O_4] = 0.100\ M$$
$$[K_2C_2O_4] = 0.02\ M$$
$$[KMnO_4] = 6.9 \times 10^{-4}\ M$$

Since the concentration of oxalate ion in the solution will be low, it is convenient to express the concentrations in terms of $H_2C_2O_4$ and KHC_2O_4; thus: $[H_2C_2O_4] = 0.080\ M$ and $[KHC_2O_4] = 0.040\ M$

Time in minutes	0.00	3.33	7.00	11.12	15.38
$(Mn(III)) \times 10^3$	2.350	1.710	1.195	0.800	0.525
k		0.0963	0.0968	0.970	0.974

The concentrations of oxalic acid and potassium oxalate are altered by the oxidation of Mn^{++} to Mn(III), and of oxalic acid to carbon dioxide (from one-quarter to one-half of the added total oxidizing power is lost by the time of the first sampling). Allowing for these changes, $[H_2C_2O_4]_{t=0}$ and $[KHC_2O_4]_{t=0}$ become 0.0797 M and 0.0352 M, respectively; allowing then for the dissociation of oxalic acid, the stoichiometry and equilibrium constants are satisfied by: $(H^+) = 0.0374\ M$, $(H_2C_2O_4) = 0.0426\ M$, $(HC_2O_4^-) = 0.0720\ M$ and $(C_2O_4^=) = 3.20 \times 10^{-4}\ M$.

The specific rate is calculated making use of the equation

$$k_{\text{calcd.}} = 2k_1 \frac{1}{1 + b + c} + 2k_1' \frac{b}{1 + b + c} + 2k_1'' \frac{c}{1 + b + c} \qquad \text{I}$$

where

$$b = \frac{K_b}{K_1K_2}(C_2O_4^=) = 4.02 \times 10^6(C_2O_4^=)$$

and

$$c = \frac{K_bK_c}{K_1^2K_2^2}(C_2O_4^=)^2 = 2.87 \times 10^9(C_2O_4^=)^2$$

In deriving the equation, the principal manganic ion species are considered to be the complexes with oxalate ion; even for the solution at lowest oxalate ion concentrations used in the present study, it is a sufficiently close approximation to neglect the species Mn_{Cl}^{+++}. The quotients in the three terms on the right-hand side of the equation I represent the fractions of the total manganic ion present as $MnC_2O_4^+$, $Mn(C_2O_4)_2^-$ and $Mn(C_2O_4)_3^{\equiv}$, respectively. The fraction present as $MnC_2O_4^+$ is in every case small, being 0.04 in the maximum case of experiment 1. The fraction present as $Mn(C_2O_4)_3^{\equiv}$ has been entered in column 7 of Table I. The three terms of equation I give the contributions to the total specific rate by the decompositions of $MnC_2O_4^+$, $Mn(C_2O_4)_2^-$ and $Mn(C_2O_4)_3^{\equiv}$, respectively, and were calculated by substituting the value of $(C_2O_4^=)$ appropriate for each experiment into the terms of equation 1. The values of the first and second terms are recorded in columns 8 and 9 of Table I, and the sum of the three terms, representing the calculated values k to be compared to the experimental values, in the final column.

Some features of the data may require special emphasis. In the more acidic solutions, most of the reaction proceeds by decomposition of $MnC_2O_4^+$, which was the only path exposed by the catalytic data in the highly acid solutions there studied. Since the calculated values of k in experiments 1–5 are not very sensitive to the values assumed for k_1', k_1'' and K_c the quantitative agreement of the experimental and calculated values of specific rate in these experiments confirms the earlier cited conclusions about the character of the rate determining step in the catalytic work. The results also show definitely that at high oxalate ion concentration the rate becomes independent of this variable. This conclusion agrees with that reached by Lidwell and Bell,[3] but is at variance with that reached by Launer.[2] Not much emphasis can be placed on the agreement of the experimental and calculated values of k for intermediate ranges of oxalate ion concentration since both k_1' and K_c are adjustable parameters, and the limits of error on these constants are judged to be about 10 and 30%, respectively.

An additional feature of the manganic ion-oxalic acid reaction which was exposed by the catalytic work[1,6] has been checked by observations (qualitative only) on the direct reaction. Where the principal manganic species in solution is $Mn(C_2O_4)_2^-$, the rate of reaction is expected, and is observed, to rise rapidly as the oxalate ion concentration is reduced. If, however, the oxalate ion is reduced to such low values, that the dissociation of $MnC_2O_4^+$ to Mn^{+++} and $H_2C_2O_4$ takes place, the rate of reaction will *diminish* as the concentration of oxalate ion (proportional to oxalic acid) is decreased, and in the limit will be first order with respect to oxalic acid. These effects were observed in the manganic catalyzed chlorine–oxalic and bromine–oxalic reactions. In the present work it was shown that in a solution about $10^{-3}\ M$ in oxalic acid and 7 M in perchloric acid, the half-life of manganic ion is about fifteen seconds; if all the manganic ion were present as $MnC_2O_4^+$, a half-life of about three seconds would be expected. Furthermore, the half-life of manganic ion was observed to increase as the concentration of oxalic acid diminished.

Experiment 18 in comparison with 17 shows that a moderate change in Mn (II) concentration has only a minor effect on the rate of decomposition of $Mn(C_2O_4)_3^{\equiv}$; the slight increase observed when the prevailing manganous concentration is increased about eight-fold may however be real. A 20% reduction in rate of $Mn(C_2O_4)_3^{\equiv}$ decomposition is produced by changing the ionic strength from 2 to 0.65. The limiting Brönsted equation predicts no variation of specific rate with ionic strength for a reaction of this type. Since however the act of decomposition involves a separation of charged particles, it would not be surprising if the activity coefficients of the original ion and the activated, deformed ion are differently affected by media of high ionic strength.

Calculations of the type made above were applied also to the data of Lidwell and Bell[3] and of Bradley and van Praagh.[4] The calculated values of specific rate in typical cases, experiment 7, reference 3, and experiment 105, reference 4, for example, exceed by a factor of about 3 those observed by Lidwell and Bell. Part of the difference may be due to the differences in ionic strength and part to differences in temperature. No mention of removal of oxygen was made in the papers mentioned, and if this precaution was not taken, part of the difference may also be attributed to this cause.[9]

Temperature Coefficients of the Mangani-oxalate Decomposition.—The temperature coefficient of the rate of decomposition of $MnC_2O_4^+$ has already been measured[1]; in the present work new data for $Mn(C_2O_4)_3^{\equiv}$ are presented. These are recorded in Table II.

TABLE II

VARIATION OF THE RATE OF DECOMPOSITION OF $Mn(C_2O_4)_3^{\equiv}$ WITH TEMPERATURE

Initial Mn(II) = 0.01 *M*; E_3 is defined by $k_1'' = ae^{-E_3/RT}$

No.	$(C_2O_4^{=})$	Temp., °C.	$2k_1''$	E_3
1	0.120	17.9	0.0163	
2	.192	25.2	.0410	21,900
3	.180	35.6	.1455	22,200
4	.095	36.3	.156	22,500
			Mean	22,200 ± 500

Only the decomposition of $Mn(C_2O_4)_3^{\equiv}$ contributes appreciably to the reaction at the concentrations of oxalate ion used in the experiments above, and the activation energy measured may therefore be ascribed to this reaction.

The data on the specific rates, activation energies and frequency factors (*a* in the equation above Table II) for the mangani–oxalate decompositions are presented below.

	$MnC_2O_4^+$	$Mn(C_2O_4)_2^-$	$Mn(C_2O_4)_3^{\equiv}$
k_1 at 25.2°, min.$^{-1}$	11.8 ± 0.5	0.046 ± 0.005	0.0205 ± 0.001
E	18,300 ± 500		22,200 ± 500
a	2×10^{14}		3×10^{14}

An interpretation of the decrease in the rate of decomposition of the complexes as the number of associated oxalate ions increases, has been advanced elsewhere.[1] This interpretation attributes the decrease primarily to an effect on the activation energies and thus is supported by the data recorded in the table above. It may be noted that the interpretation is also consistent with the observation that a greater decrease in specific rate occurs for the first stage of the stepwise addition of oxalate ion than for the second.

The Products Formed in the Rate Determining Step.—It was observed in the catalytic work[1,10] that the reducing intermediate formed on decomposition of $MnC_2O_4^+$ reacts with Mn(III), Fe(III), Cl_2 and Br_2. Launer[9] has shown that the reducing intermediate reacts also with oxygen, and that it thereby induces the reaction

$$H_2C_2O_4 + O_2 = H_2O_2 + 2CO_2$$

This observation has been checked in the present work for more acidic solutions; in a solution 0.15 *M* in oxalic acid and 0.45 *M* in hydrochloric acid, with initial manganic ion sufficiently low, as many as twenty equivalents of hydrogen peroxide are produced for each equivalent of manganic ion consumed when oxygen is present. None of these observations, however, distinguish between the alternatives[1]

$$MnC_2O_4^+ = Mn^{++} + C_2O_4^- \text{ (or } CO_2 + CO_2^-\text{)} \quad (1)$$

$$MnC_2O_4^+ = Mn^+ + 2CO_2 \quad (2)$$

Evidence is offered below that part at least of the reaction must proceed to produce an organic radical, step 1, but some participation also by step 2 is not excluded by the new results.

It has been found that hydrogen peroxide is produced even in the absence of oxygen for solutions over a limited range of acidity (*ca.* 0.4 *M*–1 *M* hydrochloric acid). This was shown by experiments in which oxygen was removed by a current of carbon dioxide, and more rigorously by experiments in which the solutions were degassed by repeated freezing and evacuation, the solutions being mixed to initiate reaction after the system was sealed off. The amounts of hydrogen peroxide which appear, while not great, are great enough to make precise[11] determination of the rate of the mangani-oxalate decomposition difficult in the critical acid range. In the optimum case observed, a solution 0.45 *M* in hydrochloric acid with the initial manganic ion 1.2×10^{-3} *M*, about one-eighth of the oxidizing capacity appeared as hydrogen peroxide after the complex ion had decomposed. The residual oxidizing agent was identified as hydrogen peroxide by comparing its specific rate of reaction with iodide ion with that observed for hydrogen peroxide when this was added to the same iodide solution.

---

(9) Launer, THIS JOURNAL, **55**, 865 (1933).

(10) Publication of the data on Br_2—$H_2C_2O_4$ reaction catalyzed by manganic ion will be forthcoming.

(11) In experiment (1), Table I, the samples were quenched by using a solution low in iodide concentration cooled to 0°. The oxidation of iodide by the peroxide within the time of titration was small. Residual peroxide was determined and a correction applied for the fact that not each molecule of reducing intermediate accounted for a second molecule of mangani-oxalate ion.

There appears to be no chemically reasonable way of explaining the appearance of hydrogen peroxide if only Mn^+ is formed as the reducing intermediate. With the first alternative however, the observation can readily be understood. Two radicals $C_2O_4^-(HC_2O_4)$ or $CO_2^-(HCO_2)$ may be expected to form a peroxide on association. In the acid solutions the perdioxalic acid or perdiformic acid would hydrolyze to form hydrogen peroxide and regenerate the organic acid. Hydrogen peroxide is not produced in very acidic solutions presumably because the reducing intermediate reacts rapidly with $MnC_2O_4^+$, and the concentration of this ion increases with increasing acid concentration. At low acid, where the rate of decomposition of the mangani–oxalate complexes is low, the stationary concentration of the organic radicals will be similarly low, and the reaction of the radicals with Mn(III), being first order with respect to the radical concentration, will be favored over the association of the radicals. The decrease in peroxide production as the acidity is decreased however seems too sharp to be completely explained in this way, and it seems possible that effects due to an equilibrium

$$HC_2O_4 = H^+ + C_2O_4^-$$

become important when the hydrogen ion concentration is about 0.5 *M*. This would attribute to HC_2O_4 a dissociation constant about 0.5, and this value seems not unreasonable in comparison with 1.7×10^{-4} for $HC_2O_4^-$.

Summary

Kinetic data on the oxidation of oxalate by manganic ion over the range 6×10^{-6} *M* oxalate ion to 0.19 *M* oxalate ion are presented. These data are interpreted if it is assumed that the first order decomposition of each of the ions $MnC_2O_4^+$, $Mn(C_2O_4)_2^-$, $Mn(C_2O_4)_3^{=}$ contributes to the reaction. Values for the specific rates of decomposition of these ions, for the activation energy of the decomposition of $MnC_2O_4^+$ and $Mn(C_2O_4)_3^{=}$, and for the equilibrium quotients relating the complexes, are presented.

The rate of decomposition of $MnC_2O_4^+$ deduced from experiments on catalysis by manganic ion agrees quantitatively with that directly observed in the present work.

When the oxalate ion concentration is sufficiently great, *ca.* 0.1 *M*, the rate of reaction is independent of this variable.

Hydrogen peroxide is produced in the oxidation of oxalic acid by manganic ion within a limited acid concentration range, and conclusions about the detailed mechanism of reaction based on this observation are offered.

RECEIVED MAY 12, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Phenyl Silicon Isothiocyanates

BY HERBERT H. ANDERSON

Five monoisothiocyanates remain the sole stable members of the corresponding ternary series. They are: $(CH_3O)_3Si(NCS)$,[1] $SiCl_3(NCS)$,[1] $PCl_2(NCS)$,[1] $POCl_2(NCS)$[1] and $PF_2(NCS)$.[1]

Introduction of the small, neutral methyl group allowed isolation of the first complete ternary series—$(CH_3)_3Si(NCS)$, $(CH_3)_2Si(NCS)_2$ and $(CH_3)Si(NCS)_3$.[2] Apparently the normal boiling point of the compound was not an important factor in determining stabilities; the "acidity" of the other group seemed to be the criterion.

To test this further, the author has now synthesized a complete series of phenyl silicon isothiocyanates, in which the phenyl groups are definitely more acidic than the neutral methyl groups of the only previously known complete series, and less acidic than methoxyl and the halogens. Moreover, phenyl is a group of rather large molar volume, approximately double that of isothiocyanate.

Steric effects may be encountered in proposed future syntheses of isopropyl and tertiarybutyl silicon isothiocyanates; the planar phenyl ring was no steric hindrance to introduction of isothiocyanate groups.

Preparation of New Compounds.—Dr. E. G. Rochow of the General Electric Company, Schenectady, N. Y., kindly furnished samples of phenyltrichlorosilane and diphenyldichlorosilane, which were used after distillation at 200–202.5° and 301–303°, respectively. Triphenylchlorosilane, prepared from the diphenyl analog, was distilled at 189° under 3 mm. pressure.

Silver isothiocyanate in 30% excess converted each of the three phenylchlorosilanes, in benzene solution, into the corresponding isothiocyanate; after an hour at 80–90°,[3] the suspended silver salts were filtered and washed with benzene. After distillation of benzene at atmospheric pressure, each compound was distilled at 3 mm. pressure through a plain column 4 mm. i. d. and 300 mm. long. Middle fractions used in physical measurements and analyses were collected at the following temperatures: phenyl silicon triisothiocyanate, 153.5–154.5°; diphenyl silicon diisothiocyanate, 173–174°; triphenyl silicon isothiocyanate, 188.5–189.5°. Yields varied from 72 to 90%.

Analyses.—A weighed sample of each compound was decomposed in methanol; after addition of water, thiocyanate was determined by titration with silver nitrate solution in the presence of ferric iron. The slow rate of solution of triphenyl silicon isothiocyanate in methanol

---

[1] Anderson, THIS JOURNAL, **67**, 223, 2176 (1945); **69**, 2495 (1947).

[2] Anderson, *ibid.*, **69**, 3049 (1947).

[3] Forbes and Anderson, *ibid.*, **62**, 761 (1940).

TABLE I

DATA ON PHENYL SILICON ISOTHIOCYANATES

Compound	$(C_6H_5)_4Si$	$(C_6H_5)_3Si(NCS)$	$(C_6H_5)_2Si(NCS)_2$	$(C_6H_5)Si(NCS)_3$	$Si(NCS)_4$
Boiling point, °C.	428[6]	396 ± 1.5	376 ± 1.5	339.6 ± 1	314.2[7]
B. p. calcd.,[8] °C.	..	399.5	371	342.5	....
M. p., °C.	233[6]	76 ± 1	46 ± 1	52 ± 1	143.2[7]
Density at (T)° C., in solution	..	....	1.188 (30)	1.291 (31)	1.41 (20)
Log $P = A - B/T$ A	..	8.2182	8.9132	8.7676	8.4484[2]
B	..	3572	3913	3607	3276
ΔH calcd., kcal./mole	..	16.3	17.9	16.5	13.9[2]
Trouton constant	..	24.4	27.6	26.9	23.7[2]
Rate of hydrolysis in pure water	Inert	Practically inert	Moderate	Moderate	Rather rapid

was a hindrance. In two cases silica was obtained, with some difficulties, by hydrolysis, oxidation with nitric or sulfuric acids, and ignition. One compound was burned in oxygen in a tube containing lead chromate and silver wire, and hydrogen estimated thereby. Molecular weights, obtained through lowering of the freezing point of camphor, confirmed monomeric formulas. Calcd. for $(C_6H_5)Si(NCS)_3$: NCS, 62.4; Si, 10.0; mol. wt., 279.4. Found: NCS, 62.0, 61.5; Si, 10.0; mol. wt. 318. Calcd. for $(C_6H_5)_2Si(NCS)_2$: NCS, 38.9; Si, 9.4; mol. wt., 298.4. Found: NCS, 38.7; Si, 9.5; mol. wt., 307. Calcd. for $(C_6H_5)_3Si(NCS)$: NCS, 18.3; H, 4.8; mol. wt. 317.4. Found: NCS, 18.2, 18.1; H, 4.9; mol. wt., 296.

Physical Properties (see Table I).—Dynamic vapor pressure measurements were made on the day of final purification, with calibrated mercury thermometers, and according to the method described by Mack and France.[4] Heats of vaporization and Trouton constants were calculated from the data.

Supercooling, apparently characteristic of compounds of this general type, occurred to the following extents: monophenyl, 52°; diphenyl, 46°; triphenyl, 20°. After formation of crystals during vigorous stirring, the samples showed rather sharp freezing points and melting points.

All the purified compounds were colorless. A solution of diphenyl silicon diisothiocyanate in phenyl silicon triisocyanate[5] furnished, upon application of the law of mixtures, a molar refraction (n^2 formula) of 90.1 ml., compared with 90.0 ml. calculated for $(C_6H_5)_2Si(NCS)_2$ and 85.5 ml. calculated for $(C_6H_5)_2Si(SCN)_2$. Assumptions made previously[2] were followed in these estimations of molar refractions.

Chemical Properties.—Tetraphenylsilane was inert to pure water; triphenylsilicon isothiocyanate was practically inert, since a sample stood for a week in open air during the summer without discoloration; the diisothiocyanate, triisothiocyanate and tetraisothiocyanate hydrolyzed with progressively increasing ease in water.

Benzene and carbon tetrachloride were good solvents for these isothiocyanates. Ethanol dissolved readily all save the triphenyl compound, which dissolved slowly even in methanol. Decomposition occurred, of course.

Discussion

1. A provisional conclusion from the existing information is that the stability of mixed isothiocyanates is associated with the "acidity" of the other group attached to the central atom rather than with the molar volume of that group, or the normal boiling point of the compound. Neutral methyl and the slightly acidic phenyl permit complete series, whereas acidic methoxyl, chloride and fluoride allow only monoisothiocyano derivatives. (The investigation of possible steric effects is planned.) At this time the existence of certain new related isothiocyanates is known: benzyl silicon triisothiocyanate, *n*-butyl silicon triisothiocyanate and triethoxy silicon isothiocyanate, of boiling points 349°, 300° and 206°, respectively. The stability of the last three compounds is consistent with the interpretation made in this paragraph.

2. Supercooling is encountered in the phenyl silicon isothiocyanates, while the analogous methyl silicon isothiocyanates do not do this.[2]

3. Triphenyl silicon isothiocyanate resists hydrolysis almost as markedly as does the inert tetraphenylsilane.

The author thanks Professor George S. Forbes of this Laboratory for sustained interest in these investigations.

Summary

1. Phenyl silicon isothiocyanates were formed through reaction of silver (iso)thiocyanate with phenylchlorosilanes. All three possible ternary compounds were isolated: phenyl silicon triisothiocyanate, $(C_6H_5)Si(NCS)_3$, melting at 52° and boiling at 340°; diphenyl silicon diisothiocyanate, $(C_6H_5)_2Si(NCS)_2$, melting at 46° and boiling at 376°; triphenyl silicon isothiocyanate, $(C_6H_5)_3Si(NCS)$, melting at 76° and boiling at 396°.

2. Measurements of physical properties included vapor pressures, and two densities and one molar refraction obtained in solution. The resistance of triphenyl silicon isothiocyanate to hydrolysis was striking.

3. All the evidence available at present indicates that the non-existence of certain diisothio-

---

(4) Mack and France, "Laboratory Manual of Physical Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1934, p. 47.

(5) Forbes and Anderson, THIS JOURNAL, **70**, (1948).

(6) Lewis and Newkirk, *ibid.*, **69**, 701 (1947).

(7) Reynolds, *J. Chem. Soc.*, **89**, 397 (1906).

(8) Swarts rule, Swarts, *Bull. soc. chim.*, **35**, 1557 (1924).

cyano and triisothiocyano compounds is associated with the electrical configuration (acidity) of the other group attached to the central atom rather than with either the molar volume of the group or the boiling point of the compound itself.

CAMBRIDGE, MASSACHUSETTS RECEIVED OCTOBER 1, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Methyl Silicon Isocyanates and *n*-Butyl Silicon Triisocyanate

BY GEORGE S. FORBES AND HERBERT H. ANDERSON

This paper on the methyl silicon isocyanates describes the first isolation of organosilicon pseudo halides; the introduction of methyl groups into silicon tetraisocyanate was first attempted, unsuccessfully, using methylmagnesium iodide, and also dimethylmercury. All three methyl silicon isocyanates and also *n*-butyl silicon triisocyanate were then prepared through reaction of silver isocyanate with the appropriate alkylchlorosilanes, with yields of at least eighty per cent.

Preparation of Alkyl Silicon Isocyanates.—The homogeneity of their reaction products indicated that the methylchlorosilanes, obtained from the Dow Corning Corporation of Midland, Michigan, had been carefully purified. A thirty-gram sample of each methylchlorosilane was treated with a 25% excess of silver isocyanate, added in three portions; benzene was the solvent used in preparation of the monomethyl and dimethyl compounds, while isopropylbenzene proved more suitable for the trimethyl derivative. After the usual half-hour at 90°,[1] the suspension of silver salts was filtered and washed. After distilling off the benzene, the triisocyanate and diisocyanate were recovered; the monoisocyanate was distilled directly from the higher-boiling isopropylbenzene. Each individual compound was distilled at least twice in a plain column, 4 mm. i. d. and 500 mm. long, and final fractions were taken at the following (uncorrected) temperatures: $(CH_3)Si(NCO)_3$, 169.2–169.6° at 755 mm.; $(CH_3)_2Si(NCO)_2$, 138.3–138.5° at 760 mm.; $(CH_3)_3Si(NCO)$, 90.5–90.8° at 760 mm.

n-Butyltrichlorosilane, prepared from tetrachlorosilane and the alkylmagnesium bromide and boiling at 148.7–149.3°, was gradually added to an excess of silver isocyanate suspended in benzene, in a reaction of moderate vigor. The middle fraction, boiling at 134.6–135.4° under 59 mm., was used for all measurements.

Chemical Properties.—The monoisocyanate floats on water and hydrolyzes slowly at the interface; the diisocyanate hydrolyzes slowly at first and finally at a moderate rate. *n*-Butyl silicon triisocyanate hydrolyzes at a moderately fast rate; when shaken with an equal volume of water, the temperature rise is only about 20°—much less than in the vigorous hydrolysis of silicon tetraisocyanate.

These four new liquids are easily soluble in petroleum ether (30–60°), carbon disulfide, carbon tetrachloride, benzene and isopropylbenzene.

TABLE I

DATA ON ALKYL SILICON ISOCYANATES

Compound		$(CH_3)_4Si$[2]	$(CH_3)_3Si(NCO)$	$(CH_3)_2Si(NCO)_2$	$(CH_3)Si(NCO)_3$	$Si(NCO)_4$[1]	$(nC_4H_9)Si(NCO)_3$
B. p., °C.		26.5	91.0 ± 0.3	139.2 ± 0.3	170.8 ± 0.3	185.6 ± 0.5	215.5 ± 0.5
M. p., °C.		....	−49.0 ± 3	−31.2 ± 3	2.7 ± 0.5	26	−37 ± 3[b]
Refractive index at 20° (Abbe) ± 0.0010		1.3591	1.3960	1.4221	1.4430	1.4610	1.4479
d^{20}_4, found		0.6464	0.867	1.076	1.267	1.442[a]	1.141
Molar refraction, ml.	Found	30.02	31.92	33.60	35.39	37.29	48.53
	Calcd.	(30.02)	31.84	33.66	35.47	(37.29)	49.34
Log P = $A - B/T$	A	....	7.8446	8.1540	8.4150	9.0198	8.4830
	B		1807	2174	2457	2816	2737
ΔH vap. (calcd.), kcal.		....	8.3	10.0	11.2	12.9	12.5
Trouton constant		....	22.7	24.1	25.3	26.5	25.6
Molecular wt. (Dumas)	Found	....	117.5	146.5	176	204	225
	Calcd.	....	115.2	142.2	169.1	196	211.2
Carbon, %[3]	Found	....	41.6	33.7	28.1	..	..
	Calcd.	....	41.7	33.8	28.4	..	..
Hydrogen, %[3]	Found	....	8.1	4.4	1.6	..	4.0
	Calcd.	....	7.9	4.3	1.8		4.3
Nitrogen, % (Dumas)	Found	....	12.0	19.5	25.0	..	20.3
	Calcd.		12.2	19.7	24.8		20.0

[a] Calculated from D^{25}_4 of 1.434. [b] Forms glass persistently; difficult to convert glass to crystalline solid.

Physical Properties (See Table I).—All four compounds were colorless liquids. The vapor of trimethyl silicon isocyanate was nauseating and also very easily inflammable. Dynamic

---

(1) Forbes and Anderson, THIS JOURNAL, **62**, 761 (1940).

(2) Bygden, *Z. physik. Chem.*, **90**, 243 (1915). Index and density at 18.7°.

(3) Combustions in oxygen with lead chromate and silver wire in tube. See Elving and McElroy, *Ind. Eng. Chem., Anal. Ed.*, **13**, 660 (1941).

vapor pressure measurements, following a standard method,[4] always made on the day of final purification, employed mercury thermometers which had been calibrated in the same apparatus with boiling water, bromobenzene or aniline; the apparatus was of Pyrex glass, and included stopcocks and ground joints in non-critical positions. Errors in temperatures could not have exceeded 0.3°; the four vapor pressure equations predicted the observed points with an average error of approximately three mm. All three methyl silicon isocyanates showed sharp melting points, and freezing points without perceptible supercooling; on the other hand, *n*-butyl silicon tended to supercool and form a glass to such an extent that the use of liquid nitrogen and vigorous stirring were necessary to obtain a crystalline solid of fairly sharp melting point. Due to incomplete drainage and other uncertainties, the readings of the toluene thermometer used in obtaining some of the melting points appeared subject to errors possibly as great as three degrees. Densities were obtained using a special 2-ml. micropycnometer.

Discussion

Swarts' rule of linear progression in boiling points[5] does not fit the new methyl compounds satisfactorily. Calculations based on the "increment method," by adding 32.0° to the boiling point of the corresponding chloride[6] for each replacement of one chlorine by isocyanate, predicted the following boiling points: monoisocyanate, 89.7° (57.7 + 32.0); diisocyanate, 134.0° (70.0 + 64.0); triisocyanate, 161.7° (65.7 + 96.0).

After this isolation of the complete series of methyl silicon isocyanates, and of *n*-butyl silicon triisocyanate, the stable existence of at least a part of the ethyl and *n*-propyl series can be inferred.

Summary

1. Certain alkylchlorosilanes yielded the corresponding (new) isocyanates upon treatment with silver isocyanate.

The complete methyl series consisted of trimethyl silicon isocyanate, $(CH_3)_3Si(NCO)$, boiling at 91.0°, dimethyl silicon diisocyanate, $(CH_3)_2Si(NCO)_2$, boiling at 139.2°, and methyl silicon triisocyanate, $(CH_3)Si(NCO)_3$, boiling at 170.8°.

n-Butyl silicon triisocyanate, $(n\text{-}C_4H_9)Si(NCO)_3$, boiling at 215.5°, showed a marked tendency to supercool.

2. Physical data included vapor pressure equations, melting points, refractive indices, densities and molar refractions. The heat of hydrolysis seems to decrease as the number of alkyl groups increases.

---

(4) See for instance: Mack and France, "Laboratory Manual of Physical Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1934, p. 47.

(5) Swarts, *Bull. soc. chim.*, **35**, 1557 (1924).

(6) Anderson, THIS JOURNAL, **64**, 1757 (1942).

CAMBRIDGE, MASSACHUSETTS

RECEIVED OCTOBER 14, 1947

[CONTRIBUTION FROM RESEARCH LABORATORIES, THE UPJOHN COMPANY]

Actidione, an Antibiotic from Streptomyces Griseus[1]

BY JARED H. FORD AND BYRON E. LEACH

It has been found in this Laboratory that the beers from streptomycin-producing strains of *Streptomyces griseus* contain another antibiotic which we have named actidione. In contrast to streptomycin, actidione is very effective against many yeasts but has little or no activity against bacteria.

Simultaneous bio-assays for actidione and streptomycin on a series of production beers demonstrated a wide variation in the ratio of concentrations of the two antibiotics. In a few cases the actidione content was as high as 200-250 mg. per l. but the average was about 80–100 mg. per l. A number of strains of *S. griseus* which produce actidione but little or no streptomycin and vice versa have been obtained by irradiating the conidia with X-rays.[2]

The crude product was isolated from the filtered beer by extracting with chloroform either directly or after a preliminary concentration step which involved adsorption on activated carbon, elution with 80% acetone and removal of acetone from the eluates by distillation. The chloroform extracts were orange-brown or an intense green, depending on the culture medium employed, but most of the color was removed by treatment with carbon. After removing the chloroform by distillation *in vacuo*, the resulting crude products were orange-brown sticky oils having a moldy odor. Bio-assays indicated a purity of 30–60% based on crystalline actidione as the standard.[3]

---

(1) An outline of this work was reported in a preliminary communication: Leach, Ford and Whiffen, THIS JOURNAL, **69**, 474 (1947).

(4) Observations of Drs. George M. Savage and Alma J. Whiffen of these Laboratories.

(3) The assay method was developed by Dr. Alma J. Whiffen. It is a modification of the paper-disc plate method for streptomycin[4] and employs *Saccharomyces pastorianus* ATCC 2366 as the test organism. The medium consists of 10 g. of glucose, 2.5 g. of Difco yeast extract, 1.0 g. of potassium dihydrogen phosphate and 20 g. of agar made up to 1.0 l. with distilled water and adjusted to *p*H 6.0. The inoculation was at the rate of 1.8 × 10^5 yeast cells per ml. of medium. The *p*H of the aqueous test solutions is not critical and the samples may also be assayed in methanol, ethanol or acetone.

(4) Loo, Skell, Thornberry, Ehrlich, McGuire, Savage and Sylvester, *J. Bact.*, **52**, 610 (1945).

TABLE I

ANALYTICAL DATA

Compound	Formula	Calculated for C_{15} Formula C	H	N	Calculated for C_{27} Formula C	H	N	Found[c] C	H	N
Actidione	$C_{15}H_{23}NO_4$ or $C_{27}H_{42}N_2O_7$	64.02	8.24	4.98	64.01	8.36	5.53	64.16	8.17	5.13
Acetate	$C_{17}H_{25}NO_5$ or $C_{31}H_{46}N_2O_9$	63.14	7.79	4.33	63.03	7.85	4.74	63.13	7.53	4.47
Oxime	$C_{15}H_{24}N_2O_4$ or $C_{27}H_{44}N_4O_7$	60.79	8.16	9.46	60.42	8.27	10.44	60.66[b]	8.29[b]	9.62
Semicarbazone hydrate[a]	$C_{16}H_{28}N_4O_5$ or $C_{27}H_{52}N_8O_9$	53.92	7.92	15.72	53.03	7.98	17.06	53.73[b]	8.16[b]	16.19[b]

[a] Calculated as a monohydrate for the C_{15} formula and as a dihydrate for the C_{27} formula. [b] Analysis by Oakwold Laboratories. Other analyses by our Analytical Department under the supervision of Mr. Harold Emerson. [c] Averages of two or more determinations. Individual results given in Experimental.

These crude products proved to be highly irritating to the skin.

Crystalline material was first obtained by counter-current distribution[5] between benzene and water, using separatory funnels. A comparison of the experimental curve with the theoretical curve (Fig. 1) would indicate that the central band was composed, in the main part, of one material. Since the activity was also located in this band, it can be concluded that the material in this band is primarily actidione. The emulsions that were encountered by this method proved to be troublesome. For the isolation of larger amounts of crystalline material carbon chromatography was found to be more convenient. The crude product was put on the column in 20% acetone, developed with 20% acetone and eluted from the column with 60–100% acetone. The peak eluate fractions gave solids that could be crystallized readily by adding amyl acetate and seeding. Several recrystallizations from amyl acetate gave a constant melting point of 115–116.5°. Further recrystallization from water or 30% methanol gave a melting point of 115–117°. The specific rotation is −3.0° in methanol (c = 10) and +6.8° in water (c = 2). The crystalline product is very soluble in all the common organic solvents with the exception of the saturated hydrocarbons. At 2° the solubility is 2.1 g. per 100 ml. in water and 7 g. per 100 ml. in amyl acetate.

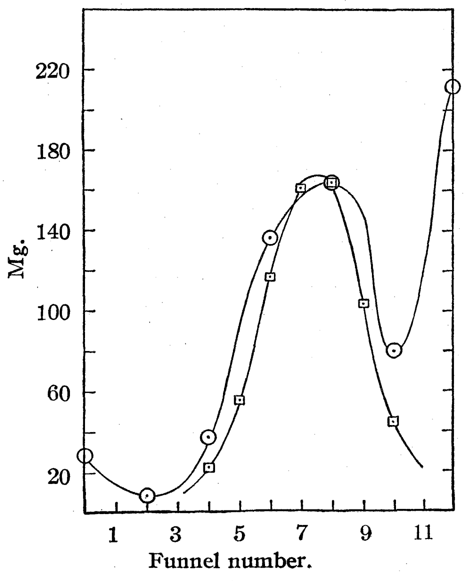


Fig. 1.—⊙, experimental; ⊡, theoretical.

Treatment of the compound with acetic anhydride and pyridine at room temperature produced a biologically inactive acetate, m.p. 148–149°. The oxime, m.p. 203–204°, was also inactive but the semicarbazone, m.p. 182–183°, was found to be about one-twentieth as active as actidione. The melting points of the acetate and semicarbazone are somewhat higher than those reported previously.[1]

Analytical data for carbon, hydrogen and nitrogen on actidione and its derivatives are listed in Table I. It will be noted that the majority of the data is in better agreement with a $C_{15}H_{23}NO_4$ formula for actidione[6] than for our previously suggested $C_{27}H_{42}N_2O_7$ formula. The only values which differ greatly enough to be of much use in distinguishing between the two formulas are the carbon percentages of the semicarbazones and nitrogen contents of the oximes and semicarbazones.

Our previous cryoscopic molecular weight data, using benzene as the solvent, were inconclusive, apparently because of association. The values ranged from 420 to 875, depending upon the concentration. We have now obtained satisfactory molecular weight determinations on actidione and its oxime by the Rast method and on the acetate by a cryoscopic determination in benzophenone (the acetate decomposed at the melting point of camphor). The results (listed in Table II) are in good agreement with the C_{15} formula and appear to exclude any C_{27} or C_{30} formula.

TABLE II

CRYOSCOPIC MOLECULAR WEIGHT DETERMINATIONS

Compound	Formula	Solvent	Molecular weight Calculated	Found
Actidione	$C_{15}H_{23}NO_4$	Camphor	281	254
Acetate	$C_{17}H_{25}NO_5$	Benzophenone	323	334
Oxime	$C_{15}H_{24}N_2O_4$	Camphor	296	291

---

(5) Craig, Golumbic, Mighton and Titus, *J. Biol. Chem.*, **161**, 321 (1945).

(6) This formula was first suggested by Dr. Reuben G. Jones of the Lilly Research Laboratories, Indianapolis, Indiana.

Degradation studies on actidione are being carried out by Drs. Reuben G. Jones and Edmund C. Kornfeld of The Lilly Research Laboratories.

The acute toxicity of actidione has been found to vary widely with the species of test animals employed. In addition to our previously reported value of 150 mg. per kg. for the LD_{50}, intravenously in mice, the following results have been obtained: subcutaneously in guinea pigs, 60 mg. per kg.; intravenously in rabbits, 17 mg. per kg.; intraperitoneally in cats, 4 mg. per kg.; subcutaneously in rats, 2.7 mg. per kg.; intravenously in rats, 2.5 mg. per kg.

Acknowledgments.—The authors wish to express thanks to Dr. W. G. Jackson for helpful suggestions concerning the chromatography, to Mr. George C. Prescott and Mrs. Alice Sterk for technical assistance, to Dr. Alma J. Whiffen for bioassays, to Messrs. William DeVries, Malcolm Bergy and Russell Heald for isolation of the crude products, and to Dr. M. J. Vander Brook for the toxicity studies.

Experimental

Isolation of Crude Actidione.—Eleven hundred liters of seventy-two hour *S. griseus* beer which assayed 110 mg. of actidione per liter was acidified[7] with sulfuric acid to *p*H 2 and stirred with a mixture of 2 kg. of carbon (Nuchar C-190NU) and 5 kg. of Celite #545[8] and then filtered. The press cake was eluted successively with 40 l. of acetone, three 30-l. volumes of acetone and 20 l. of water. The combined eluates were concentrated *in vacuo* to 38 l. and extracted with 5 l. of chloroform followed by three extractions with 3 l. volumes of chloroform. The combined extracts were decolorized with 300 g. of carbon (Nuchar C-190NU), concentrated *in vacuo* to a sirup, and warmed to 30° under 200–500 μ pressure overnight to remove chloroform. The resulting very thick sirup weighed 97.5 g.; purity, as indicated by bioassay, 59%; 48% yield of activity from beer to crude product.

Counter-Current Distribution Studies on Crude Actidione.—Preliminary tests indicated that crude actidione could be distributed between benzene and water with a partition coefficient of approximately 0.70. Nine-hundred and eighty milligrams of crude actidione was dissolved in 40 ml. of benzene and equilibrated with an equal volume of water in separatory funnels. Twelve such transfers were carried out using the aqueous layer as the traveling phase according to the method described by Craig, Golumbic, Mighton and Titus.[4] The emulsions that were encountered during these transfers were broken by centrifugation. Figure 1 shows the weight curve obtained from this 12-transfer distribution. The biologically active fractions very closely approximated the peak fractions (nos. 6, 7, 8 and 9) and these were combined and dried. One hundred and twenty-seven milligrams of this dried product was dissolved in 4 ml. of anhydrous ethyl ether and poured into 150 ml. of low boiling petroleum ether. The milky suspension crystallized slowly after vigorous scratching with a glass rod. After standing overnight in the refrigerator the crystals were collected and dried; weight 43 mg. Recrystallization from ether–petroleum ether gave crystals melting at 112–115°.

Carbon Chromatography.—Ten grams of crude actidione (bio-assay, 53% actidione) was dissolved in sufficient acetone to give 80 ml. of solution. The acetone solution was diluted with 320 ml. of water and poured into a 4-foot length of 2-inch Pyrex pipe containing a mixture of 100 g. of Darco G-60 and 100 g. of Celite that had been slurried with 20% acetone and packed under pressure. Using a flow rate[9] of 12 ml. per minute the column was developed with 1500 ml. of 20% acetone followed by 500 ml. of 60% acetone, 500 ml. of 80% acetone, 500 ml. of 90% acetone and 500 ml. of 100% acetone. The eluates were collected in 100-ml. volumes. The first 2000 ml. contained a total of 0.92 g. of light yellow gummy solids, none of which yielded crystals when treated with amyl acetate (2 ml. per g.) and seeded. The next three 100-ml. eluates yielded 1.28 g., 1.31 g. and 0.88 g. of white fluffy solids which crystallized readily when treated with amyl acetate. The next six 100-ml. eluates also gave solids which could be crystallized but were rather gummy in appearance. The total recovery of solids was 9.33 g., of which 7.53 g. was in fractions that could be crystallized. The combined weight of crystals was 4.05 g.; m. p. 113–115°.

Preparation of Pure Actidione.—Two recrystallizations from amyl acetate (2 ml. per g.) raised the melting point of the above-described product to 115–116.5° but subsequent recrystallizations from this solvent caused no change. The analytical sample was recrystallized twice from 30% methanol; m. p. 115.5–117°; $[\alpha]^{25}_{D}$ −3.0° (*c* 10, methanol); +6.8° (*c* 2, water).

Anal. Calcd. for $C_{15}H_{23}NO_4$: C, 64.02; H, 8.24; N, 4.98. Found: C, 64.17, 64.02, 64.23, 64.24; H, 8.00, 8.53, 8.25, 7.91; N, 5.17, 5.10.

Actidione Acetate.—One gram of actidione was dissolved in 5 ml. of acetic anhydride by warming on the steam-bath. After the solution had cooled to room temperature 5 ml. of dry pyridine was added. After standing eighteen hours at room temperature the volatile products were removed *in vacuo*. The residue crystallized upon standing. When recrystallized from 99% isopropanol the yield was 0.83 g.; m. p. 143–149°. Two recrystallizations from hot water gave glistening plates; m. p. 148–149°; $[\alpha]^{25}_{D}$ +22° (*c* 2.3, methanol).

Anal. Calcd. for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.04, 63.22; H, 7.45, 7.61; N, 4.50, 4.45.

Actidione Oxime.—A solution of 1.0 g. of actidione in 2.5 ml. of methanol was added to a solution of 1.4 g. of hydroxylamine hydrochloride and 2.4 g. of anhydrous sodium acetate in 10 ml. of water. Upon standing overnight at room temperature 0.80 g. of white crystals was obtained; m. p. 194–196° (dec.). The analytical sample was recrystallized from methanol; m. p. 203–204° (dec.).

Anal. Calcd. for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16; N, 9.46. Found: C, 60.79, 60.52; H, 8.26, 8.32; N, 9.65, 9.59.

Actidione Semicarbazone.—A solution of 1.0 g. of actidione in 5 ml. of methanol was added to a solution of 1.0 g. of semicarbazide hydrochloride and 1.3 g. of anhydrous sodium acetate in 5 ml. of water. Upon standing overnight at room temperature 1.13 g. of white crystals was obtained; m. p. 175–178°. Recrystallization from methanol raised the melting point to 182–183°.

Anal. Calcd. for $C_{16}H_{26}N_4O_4 \cdot H_2O$: C, 53.92; H, 7.92; N, 15.72; H_2O, 5.05. Found: C, 53.72, 53.74; H, 7.95, 8.37; N, 16.08, 16.30; H_2O (by drying to constant weight at 60–80° in high vacuum), 5.09.

Summary

1. Actidione appears to have the formula $C_{15}H_{23}NO_4$ rather than $C_{27}H_{42}N_2O_7$ as previously suggested.

2. Methods for its isolation and purification are described.

3. Acute toxicities vary greatly with the species of test animals employed.

KALAMAZOO, MICHIGAN RECEIVED SEPTEMBER 27, 1947

---

[7] The acidification aids the subsequent filtration of the carbon-mycelium cake. It is unnecessary for adsorption of the actidione.

[8] A filter aid composed of diatomaceous earth.

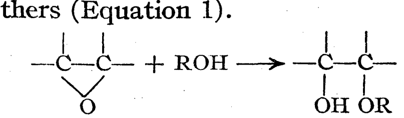
[9] The rate of flow was regulated by adjustment of the pressure at the top of the column.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Chemistry of Epoxy Compounds. V.[2] Preparation of Some Hydroxy-ethers from 9,10-Epoxystearic Acid and 9,10-Epoxyoctadecanol

BY DANIEL SWERN, GERALDINE N. BILLEN AND JOHN T. SCANLAN

The reaction of oxirane compounds with compounds containing a hydroxyl group offers a convenient way of preparing many types of hydroxy-ethers (Equation 1).



$$\underbrace{-\overset{|}{C}-\overset{|}{C}-}_{O} + ROH \longrightarrow -\underset{OH}{\overset{|}{\underset{|}{C}}}-\underset{OR}{\overset{|}{\underset{|}{C}}}- \quad \text{(Equation 1)}$$

Acidic or alkaline materials are usually employed to catalyze this reaction, although for the more reactive oxirane compounds, a catalyst is not necessary. The reaction is generally applicable, and numerous hydroxy-ethers which contain a variety of functional groups can be readily prepared. Most of the published work has described the reaction of short-chain oxirane compounds with saturated aliphatic alcohols, and little information is available on the reaction of long-chain oxirane compounds with hydroxyl compounds. In this paper, the preparation of some hydroxy-ethers by the reaction of 9,10-epoxystearic acid and 9,10-epoxyoctadecanol with methyl, ethyl, *n*-propyl, *n*-butyl, *iso*-butyl, *n*-octadecyl, allyl, and β-chloroallyl alcohol and phenol, respectively, is reported. (Mixtures of products are obtained, since it is equally probable that the oxirane ring is opened between the oxygen atom and C_9 or C_{10}.)

The reaction of 9,10-epoxystearic acid (prepared from oleic acid by hypochlorination followed by dehydrohalogenation) with a large excess of ethyl, *n*-propyl and *n*-butyl alcohol, respectively, in the presence of catalytic quantities of sulfuric acid, has been reported by Nicolet and Poulter.[3] The reaction products which they obtained were saponified with aqueous alkali, and the three compounds isolated were mixtures of the 9- and 10-monoalkyl ethers of 9,10-dihydroxystearic acid. Yields were not reported. The oxirane ring of 9,10-epoxystearic acid can best be opened by heating the acid with a large molar excess of the alcohol and catalytic quantities of sulfuric acid, and under these conditions the carboxyl group is quantitatively esterified. By omitting the saponification step we obtained the hydroxy-ethers shown in Table I, in which the alkyl radicals in the ester and ether groups are identical. These products were isolated by vacuum distillation of the reaction products. We also treated 9,10-epoxystearic acid with *n*-octadecyl alcohol, phenol and β-chloroallyl alcohol under the conditions described above in an attempt to prepare *n*-octadecyl 9,10(10,9)-octadecoxyhydroxystearate, 9,10(10,9)-phenoxyhydroxystearic acid, and β-chloroally-9,10(10,9)-chloroalloxyhydroxystearate, respectively, but we were unable to purify the products completely. The analytical data which we obtained indicated, however, that in the main the reaction had proceeded in the expected manner.

We were unable to find any literature references to the reaction of 9,10-epoxyoctadecanol with hydroxyl compounds. We prepared the compounds shown in Table II in 25 to 65% yields, by heating 9,10-epoxyoctadecanol with a large molar excess of the appropriate alcohol in the presence of sulfuric acid as catalyst, and subsequently distilling the reaction products. We were unable to isolate pure 9,10(10,9)-*n*-octadecoxyhydroxyoctadecanol, 9,10(10,9)-phenoxyhydroxyoctadecanol and 9,10(10,9)-β-chloroalloxyhydroxyoctadecanol, although as mentioned earlier, the reactions proceeded in the expected manner.

The purified hydroxy-ethers are colorless, odorless, high-boiling liquids, soluble in all the common organic solvents and insoluble in water. They do not solidify when stored at 0° for long periods of time. Yields and characteristics of the products are shown in Tables I and II. Their high boiling points, insolubility in water, and stability suggest their possible use as plasticizers.

Allyl 9,10(10,9)-alloxyhydroxystearate (Table I) was co-polymerized in various proportions (from 1 to 40% by weight of total monomers) with vinyl acetate, according to the procedure of Guile and Huston.[4] Over the entire percentage range, insoluble, infusible products were obtained which ranged in physical appearance from hard, glass-like resins to soft, rubbery gels, thereby indicating that cross-linking probably had occurred and that both allyl groups must have reacted. That the fatty derivative was probably completely chemically bound was demonstrated by the fact that no oil was extruded when the co-polymers were squeezed in thin layers between sheets of absorbent paper.

In the reactions of 9,10-epoxystearic acid with hydroxyl compounds, small quantities of by-products, tentatively identified as esters of 9,10-dihydroxystearic acid,[5] were formed, and in the re-

---

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

[2] For previous papers, see THIS JOURNAL, **66**, 1925 (1944); **67**, 412, 1786 (1945); **68**, 1504 (1946).

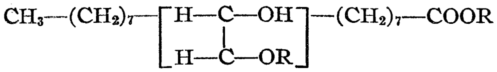
[3] Nicolet and Poulter, *ibid.*, **52**, 1186 (1930). These workers gave 53.8° as the melting point of the 9,10-epoxystearic acid which they employed. It has been shown by Ellis, *Biochem. J.*, **30**, 753 (1936), and confirmed in our laboratory, that the correct melting point of 9,10-epoxystearic acid prepared from oleic acid by hypochlorination followed by dehydrohalogenation is 59.5°.

[4] Guile and Huston, "A Revised Laboratory Manual of Synthetic Plastics and Resinous Materials," Michigan State College, 1944, p. 99.

[5] Swern and Jordan, THIS JOURNAL, **67**, 902 (1945); Swern, Jordan and Knight, *ibid.*, **68**, 1673 (1946).

TABLE I

9,10(10,9)-HYDROXY-ALKOXY ESTERS OF THE TYPE



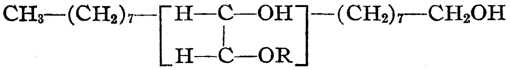
$$\mathrm{CH_3{-}(CH_2)_7{-}\left[\begin{array}{c} H{-}C{-}OH \\ | \\ H{-}C{-}OR \end{array}\right]{-}(CH_2)_7{-}COOR}$$

R	Formula	Yield, %[a]	Boiling range °C.	Boiling range Mm.	Saponification equivalent Calcd.	Saponification equivalent Found	Hydroxyl, % Calcd.	Hydroxyl, % Found	Carbon, %[b] Calcd.	Carbon, %[b] Found	Hydrogen, %[b] Calcd.	Hydrogen, %[b] Found	n^{30}_D	d^{30}_4	Molecular refraction Calcd.	Molecular refraction Found
Methyl	$C_{20}H_{40}O_4$	85	186–189	0.7–1.1	344.5	344.7	4.94	4.95	69.7	69.9	11.7	11.8	1.4500	0.9306	99.4	99.5
Ethyl	$C_{22}H_{44}O_4$	50	160–190	.02–0.2	372.6	368.2	4.56	4.57	71.0	70.7	11.9	12.0	1.4479	.9154	108.6	108.9
n-Propyl	$C_{24}H_{48}O_4$	45	180–184	.02–0.04	400.7	399.5	4.25	4.20	72.0	72.1	12.1	12.0	1.4490	.9099	117.9	118.1
n-Butyl	$C_{26}H_{52}O_4$	45	185–190	.01	428.7	425.2	3.97	3.95	72.9	72.6	12.2	12.2	1.4498	.9051	127.1	127.1
iso-Butyl	$C_{26}H_{52}O_4$	40	172–180	.02–0.04	428.7	427.2	3.97	3.76	72.9	73.2	12.2	12.4	1.4471	.8989	127.1	127.5
Allyl[c]	$C_{24}H_{44}O_4$	60	196–202	.35–0.5	396.6	387.5	4.59	4.71	72.7	72.2	11.2	11.2	1.4589	.9266	116.9	117.1

[a] Purified products, after at least two distillations. [b] Analyses by Mary J. Welsh of this Laboratory. [c] Iodine number: calcd., 128.0; found, 126.0.

TABLE II

9,10(10,9)-HYDROXY-ETHERS OF THE TYPE



$$\mathrm{CH_3{-}(CH_2)_7{-}\left[\begin{array}{c} H{-}C{-}OH \\ | \\ H{-}C{-}OR \end{array}\right]{-}(CH_2)_7{-}CH_2OH}$$

R	Formula	Yield, %[a]	Boiling range °C.	Boiling range Mm.	Hydroxyl, % Calcd.	Hydroxyl, % Found	Carbon, %[b] Calcd.	Carbon, %[b] Found	Hydrogen, %[b] Calcd.	Hydrogen, %[b] Found	n^{30}_D	d^{30}_4	Molecular refraction Calcd.	Molecular refraction Found
Methyl	$C_{19}H_{40}O_3$	65	158–161	0.007–0.008	10.7	10.8	72.1	71.5	12.7	12.6	1.4584	0.9151	94.6	94.5
Ethyl	$C_{20}H_{42}O_3$	60	179–185	.005–0.01	10.3	9.82	72.7	73.0	12.8	12.5	1.4565	.9078	99.3	99.7
n-Propyl	$C_{21}H_{44}O_3$	30	156–168	.005–0.01	9.87	9.32	73.2	73.1	12.9	12.7	1.4559	.9040	103.9	103.6
n-Butyl	$C_{22}H_{46}O_3$	50	170–175	.007	9.49	9.42	73.7	73.5	12.9	13.1	1.4562	.9002	108.5	108.3
iso-Butyl	$C_{22}H_{46}O_3$	25	163–170	.007–0.02	9.49	9.29	73.7	73.8	12.9	13.0	1.4550	.8980	108.5	108.3
Allyl[c]	$C_{21}H_{42}O_3$	40	171–188	.02–0.03	9.93	9.83	73.6	73.4	12.4	12.3	1.4627	.9166	103.4	102.9

[a] Purified products, after at least two distillations. [b] Analyses by Mary J. Welsh of this Laboratory. [c] Iodine number: calcd. 74.1; found, 73.3.

actions of 9,10-epoxyoctadecanol, the by-product was 9,10-dihydroxyoctadecanol. These side-reaction products were separated from the hydroxy-ethers by crystallization from acetone.

Experimental

Starting Materials.—9,10-Epoxystearic acid, m. p. 59.5°, and 9,10-epoxyoctadecanol, m. p. 54°, were prepared by epoxidation of pure oleic acid and oleyl alcohol, respectively.[2] The short-chain aliphatic alcohols were the purest commercial grades, and they were distilled through an efficient fractionating column (40 to 50 theoretical plates) before use. The *n*-octadecyl alcohol, m. p. 57–58°, was the Eastman Kodak purest grade. The phenol was the U. S. P. grade.

Preparation of Hydroxy-ethers from 9,10-Epoxystearic Acid.—A typical reaction procedure suitable for the short-chain alcohols is given: 9,10-Epoxystearic acid (29.9 g., 0.1 mole) was dissolved in the freshly distilled anhydrous alcohol (4 ml. per gram), with gentle heating. The solution was cooled below 30°, and 0.3 g. of 95% sulfuric acid was added dropwise while the reaction mixture was shaken by hand. A temperature rise of several degrees was always observed during the addition of the catalyst. The solution was heated on the steam-bath for two hours, and a quantity of sodium bicarbonate equivalent to the sulfuric acid was then added. The reaction mixture was fractionally distilled, first at atmospheric pressure to recover unreacted alcohol and then under high vacuum to isolate the hydroxy-ether. A short Vigreux column was employed during the vacuum distillation, which was carried out as rapidly as possible, otherwise some dehydration of the product occurred. The hydroxy-ether was dissolved in acetone (2 to 3 ml. per gram), and the solution was cooled to −20° to precipitate the ester of 9,10-dihydroxystearic acid, which was always obtained as a by-product. This was separated by filtration and rejected. The acetone was evaporated from the filtrate, and the residual oil consisted of almost pure hydroxy-ether without further treatment (yield 60 to 95%). This residue was rapidly redistilled, and fractions having the same refractive index were combined for analysis. The results are summarized in Table I.

Preparation of Hydroxy-Ethers from 9,10-Epoxyoctadecanol.—These were prepared and isolated as described under the preparation of hydroxy-ethers from 9,10-epoxystearic acid. The results are summarized in Table II.

Benzoyl Peroxide-Catalyzed Co-polymerization of Allyl 9,10(10,9)-Alloxyhydroxystearate with Vinyl Acetate.—This was conducted as recommended by Guile and Huston,[4] a maximum content of allyl 9,10(10,9)-alloxyhydroxystearate of 40% by weight of the total monomers and 0.5% by weight of benzoyl peroxide being used. Solubility tests on the co-polymers were conducted in acetone at the boiling point and in acetic acid and amyl acetate at 100°. When thin layers of the co-polymers were squeezed between sheets of absorbent paper, no extrusion of oil was observed.

Summary

Twelve hydroxy-ethers have been prepared from 9,10-epoxystearic acid and 9,10-epoxyoctadecanol by reaction with methyl, ethyl, *n*-propyl, *n*-butyl, isobutyl and allyl alcohol, respectively. The high boiling points of the products, their insolubility in water and their stability suggest their possible use as plasticizers.

The benzoyl peroxide-catalyzed co-polymerization of allyl 9,10(10,9)-alloxyhydroxystearate (prepared from 9,10-epoxystearic acid and allyl alcohol) with vinyl acetate has been studied. Over the entire percentage range investigated (allyl 9,10(10,9)-alloxyhydroxystearate content from 1 to 40% by weight of total monomers), insoluble and infusible co-polymers which ranged from hard, glass-like resins to rubbery gels were obtained, thereby indicating that cross-linking probably occurred and that both allyl groups take part in the co-polymerization reaction.

The reaction of 9,10-epoxystearic acid and 9,10-epoxyoctadecanol with *n*-octadecyl alcohol,

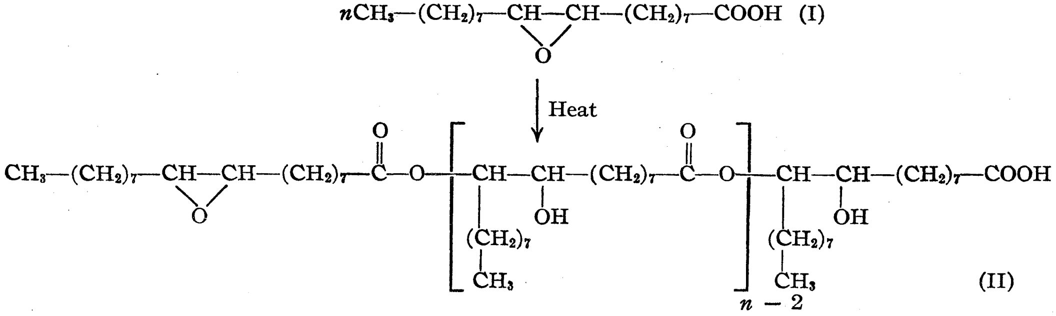
phenol and β-chloroallyl alcohol was also investigated. Although pure hydroxy-ethers were not obtained, analytical data indicated that the reaction proceeded mainly in the expected manner.

PHILADELPHIA 18, PA. RECEIVED JULY 10, 1947

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Chemistry of Epoxy Compounds. VI.[2] Thermal Polymerization of the Isomeric 9,10-Epoxystearic Acids[1a]

BY DANIEL SWERN, GERALDINE N. BILLEN AND C. ROLAND EDDY



(I)

(II)

The isomeric 9,10-epoxystearic acids[3,4] (I), m. p. 59.5° and 55.5°, contain two very reactive functional groups, and theoretically they should yield linear polyesters of structure II on thermal polymerization at relatively low temperatures. (Mixtures of isomers would be obtained, since it is equally probable that the oxirane ring would be opened between the oxygen atom and C_9 or C_{10}). Since no product of reaction would be eliminated in their formation and since the molecular formula of the recurring unit would be identical with that of the monomer, they would resemble addition polymers, but on hydrolysis they would yield a monomer whose molecular formula is not identical with that of the recurring unit, and in this respect they would resemble condensation polymers.[5] This interesting point, coupled with the fact that convenient methods for the laboratory preparation of the isomeric 9,10-epoxystearic acids in a high degree of purity were available,[3,4] prompted us to study the quantitative thermal polymerization of these compounds.

A limited amount of work on the thermal polymerization of the 9,10-epoxystearic acids has been published,[6] but the starting materials were apparently impure and, in general, higher temperatures than necessary were employed, thereby encouraging side reactions.

Experimental

Starting Materials.—The isomeric 9,10-epoxystearic acids, m. p. 59.5° and 55.5°, were prepared from pure oleic and elaidic acids, respectively, by epoxidation with peracetic or perbenzoic acids.[3,4] *Anal.* Calcd. for $C_{18}H_{34}O_3$: neutralization equivalent, 298.5; oxirane oxygen,[6,7] 5.36. Found: neutralization equivalent, 297.5–299.5; oxirane oxygen, 5.32–5.37.

Polymerization Procedures.—Approximately 5-g. portions of the 9,10-epoxystearic acids were weighed into a series of test-tubes. The tubes were flushed with nitrogen, tightly stoppered and immersed in a constant temperature oil-bath which maintained the desired temperature to ±0.2°. Fifteen minutes was allowed for the establishment of temperature equilibrium before polymerization times were counted. At selected time intervals, a tube was removed from the oil-bath and rapidly cooled to room temperature. The required analytical information was usually obtained within twenty-four hours.

Analytical Procedures.—Acid numbers were determined by means of 0.1 *N* aqueous sodium hydroxide on 0.15–0.30 g. of sample dissolved in neutralized 95% ethanol, phenolphthalein being employed as indicator. Oxirane oxygen was determined by the modified method of Nicolet and Poulter.[6,7] Carbonyl oxygen analyses were conducted by the method described by Leithe,[8] except that a *p*H meter was employed to determine the end-point.

Discussion

The course of the polymerization of 9,10-epoxystearic acid, m. p. 59.5°, at 65°, 75° and 85° is shown in Tables I, II and III, and that of its isomer, m. p. 55.5°, at 75°, 100° and 120° is shown in Tables IV, V and VI. The rate of disappearance of the oxirane and carboxyl groups is plotted in

---

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

[1a] This paper was presented at the meeting-in-miniature of the Philadelphia section of the American Chemical Society held in Philadelphia, Pa., Jan. 22, 1948.

[2] For the previous paper in this series, see THIS JOURNAL, **70**, 1226 (1948).

[3] Swern, Findley and Scanlan, *ibid.*, **66**, 1925 (1944).

[4] Findley, Swern and Scanlan, *ibid.*, **67**, 412 (1945).

[5] Carothers, *ibid.*, **51**, 2548 (1929).

[6] Nicolet and Poulter *ibid.*, **52**, 1186 (1930).

[7] Swern, Findley, Billen and Scanlan, *Anal. Chem.*, **19**, 414 (1947).

[8] Leithe, *Fette u. Seifen*, **45**, 615 (1938).

TABLE I

THERMAL POLYMERIZATION AT 65° OF 9,10-EPOXYSTEARIC ACID, M. P. 59.5°

Time, hours	n^{60}_{D} (Abbe)	Acid no.	% Decrease in acid no.	% Oxirane oxygen	% Decrease in oxirane oxygen	Moles of carboxyl group per 100 g. of monomer[a]	Moles of oxirane group per 100 g. of monomer[b]	Physical appearance
0	1.4450	188.0	0	5.36	0	0.335	0.335	White solid
2	1.4459	181.5	3.46	5.10	4.85	.324	.319	White solid
4	1.4465	177.0	5.86	4.87	9.14	.316	.304	White solid
7	1.4474	170.2	9.46	4.57	14.7	.303	.286	White solid
24	1.4519	145.2	22.8	3.65	31.9	.259	.228	Partially solid
30	1.4530	137.0	27.1	3.51	34.5	.244	.219	Viscous oil
48	1.4555	122.2	35.0	2.75	48.7	.218	.172	Viscous oil
96	1.4590	97.0	48.4	2.06	61.6	.173	.129	Viscous oil
144	1.4610	82.0	56.4	1.52	71.7	.146	.095	Viscous oil
226	1.4629	70.5	62.5	0.89	83.4	.126	.056	Viscous oil
344	1.4639	59.8	68.2	0.47	91.2	.107	.029	Viscous oil
576	1.4650	51.2	72.8	0.10	98.2	.091	.006	Viscous oil

[a] Moles of carboxyl group per 100 g. of monomer = acid number/561.0. [b] Moles of oxirane group per 100 g. of monomer = % oxirane oxygen/16.

TABLE II

THERMAL POLYMERIZATION AT 75° OF 9,10-EPOXYSTEARIC ACID, M. P. 59.5°

Time, hours	n^{60}_{D} (Abbe)	Acid no.	% Decrease in acid no.	% Oxirane oxygen	% Decrease in oxirane oxygen	Moles of carboxyl group per 100 g. of monomer	Moles of oxirane group per 100 g. of monomer	Physical appearance
0	1.4450	188.0	0	5.37	0	0.335	0.336	White solid
2	1.4470	177.7	5.48	4.89	8.94	.317	.306	White solid
4	1.4480	168.4	10.4	4.55	15.3	.300	.284	White solid
8	1.4508	152.9	18.7	3.98	25.9	.273	.249	Partially solid
18	1.4549	128.5	31.7	3.09	42.5	.229	.193	Viscous oil
32	1.4576	103.9	44.7	2.25	58.1	.185	.141	Viscous oil
56	1.4601	84.7	54.8	1.63	69.6	.151	.102	Viscous oil
101	1.4625	66.6	64.6	1.04	80.8	.119	.065	Viscous oil
200	1.4651	52.3	72.2	0.65	87.9	.093	.041	Viscous oil
312	1.4660	46.1	75.6	0.22	95.9	.082	.014	Viscous oil
392	1.4662	...	..	..	..	...	...	Viscous oil[a]
504	....	...	..	..	..	...	...	Gel

[a] Viscous oil only partially soluble in ethyl alcohol, isopropyl alcohol and acetone.

TABLE III

THERMAL POLYMERIZATION AT 85° OF 9,10-EPOXYSTEARIC ACID, M. P. 59.5°

Time, hours	n^{60}_{D} (Abbe)	Acid no.	% Decrease in acid no.	% Oxirane oxygen	% Decrease in oxirane oxygen	Moles of carboxyl group per 100 g. of monomer	Moles of oxirane group per 100 g. of monomer	Physical appearance
0	1.4450	188.0	0	5.36	0	0.335	0.335	White solid
2	1.4491	163.6	13.0	4.48	16.4	.292	.280	White solid
4	1.4518	148.1	21.2	3.88	27.6	.264	.242	Partially solid
8	1.4543	128.4	31.7	3.18	40.6	.229	.199	Partially solid
16	1.4580	106.3	43.5	2.56	52.2	.190	.160	Viscous oil
32	1.4611	75.2	60.0	1.24	76.8	.134	.077	Viscous oil
64	1.4639	59.3	68.5	0.72	86.6	.105	.045	Viscous oil
128	1.4655	50.1	73.4	0.37	93.2	.089	.023	Viscous oil
256	....	...	..	..	..	...	...	Gel

Figs. 1 and 2 for the high-melting isomer and in Figs. 3 and 4 for the low-melting isomer.

Examination of the tables and figures reveals several significant points. First, both epoxy-acids may be polymerized to form gels. Second, in the polymerization of the high-melting isomer, m. p. 59.5°, the oxirane group disappears more rapidly than the carboxyl group throughout the reaction. In fact at the gel point more than 90% of the oxirane group has been consumed, whereas only about 73–76% of the carboxyl group has disappeared. Third, in the polymerization of the low-melting isomer, m. p. 55.5°, the rates of disappearance of both the oxirane and carboxyl groups are almost the same over the entire period investigated. This is best observed when Figs. 3

TABLE IV

THERMAL POLYMERIZATION AT 75° OF 9,10-EPOXYSTEARIC ACID, M. P. 55.5°

Time, hours	$n^{60}\text{D}$ (Abbe)	Acid no.	% Decrease in acid no.	% Oxirane oxygen	% Decrease in oxirane oxygen	Moles of carboxyl group per 100 g. of monomer	Moles of oxirane group per 100 g. of monomer	Physical appearance
0	1.4419	189.0	0	5.35	0	0.337	0.334	White solid
4	1.4421	185.6	1.80	5.28	1.31	.331	.330	White solid
8	1.4422	182.8	3.28	5.19	2.99	.326	.324	White solid
16	1.4428	179.8	4.87	5.10	4.67	.321	.319	White solid
32	1.4434	173.6	8.14	4.92	8.04	.310	.307	White solid
64	1.4448	161.6	14.8	4.58	14.4	.287	.286	White solid
128	1.4488	139.5	26.2	3.84	28.2	.249	.244	White solid
256	1.4527	110.0	41.8	3.21	40.0	.196	.201	White solid
512	1.4569	74.9	60.4	2.29	59.2	.134	.143	Partially solid

TABLE V

THERMAL POLYMERIZATION AT 100° OF 9,10-EPOXYSTEARIC ACID, M. P. 55.5°

Time, hours	$n^{60}\text{D}$ (Abbe)	Acid no.	% Decrease in acid no.	% Oxirane oxygen	% Decrease in oxirane oxygen	Moles of carboxyl group per 100 g. of monomer	Moles of oxirane group per 100 g. of monomer	Physical appearance
0	1.4419	187.3	0	5.32	0	0.334	0.332	White solid
4	1.4442	175.3	6.41	5.04	5.26	.313	.315	White solid
8	1.4458	165.0	11.9	4.76	10.5	.294	.297	Partially solid
16	1.4478	151.5	19.1	4.39	17.5	.270	.274	Partially solid
32	1.4510	123.9	33.9	3.33	37.4	.221	.208	Partially solid
64	1.4549	90.4	51.8	2.78	48.9	.161	.174	Viscous oil
128	1.4582	61.3	67.2	1.96	63.2	.109	.122	Viscous oil
256	1.4609	36.5	80.6	1.35	74.6	.065	.084	Viscous oil
512	1.4624	19.6	89.6	0.98	81.6	.035	.061	Viscous oil

TABLE VI

THERMAL POLYMERIZATION AT 120° OF 9,10-EPOXYSTEARIC ACID, M. P. 55.5°

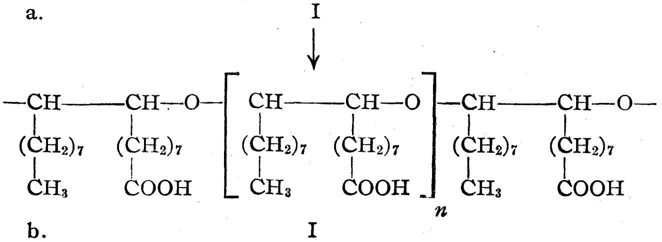
Time, hours	$n^{60}\text{D}$ (Abbe)	Acid no.	% Decrease in acid no.	% Oxirane oxygen	% Decrease in oxirane oxygen	Moles of carboxyl group per 100 g. of monomer	Moles of oxirane group per 100 g. of monomer	Physical appearance
0	1.4419	187.3	0	5.32	0	0.334	0.332	White solid
4	1.4480	149.4	20.2	4.33	18.6	.266	.271	Partially solid
8	1.4510	126.5	32.5	3.77	29.1	.226	.236	Partially solid
16	1.4545	95.8	48.9	2.87	46.1	.171	.179	Partially solid
32	1.4584	65.4	65.1	2.10	60.6	.117	.131	Viscous oil
64	1.4609	41.9	77.6	1.48	72.2	.075	.093	Viscous oil
128	1.4624	27.1	85.6	1.04	80.4	.048	.065	Viscous oil
256	1.4638	16.3	91.2	0.80	85.0	.029	.050	Viscous oil
512	....	...	..	..	..	...	...	Gel

and 4 are superimposed, although it is fairly evident from Tables IV, V and VI. Fourth, the polymerization of the high-melting isomer proceeds at a more rapid rate than that of the low-melting isomer.

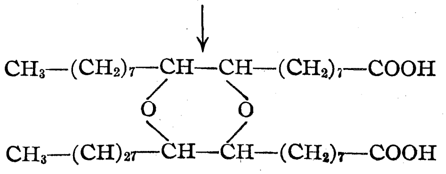
The fact that both epoxy-acids may be polymerized to gels indicates that these compounds have a higher functionality than two. Consideration of the possible addition and condensation reactions which may occur makes this point evident. These reactions are listed below:

1. Reaction between the oxirane and carboxyl groups (addition reaction).
2. Reaction between the hydroxyl groups, formed as a result of reaction 1, and carboxyl groups, with the elimination of water (condensation reaction).

a.



b.



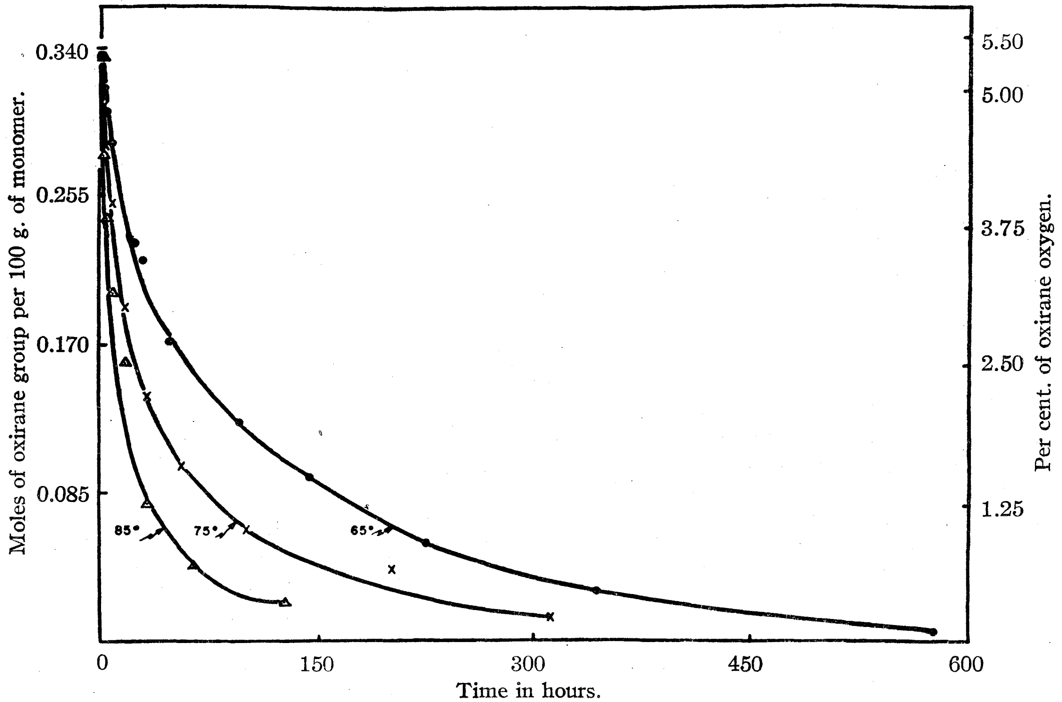


Fig. 1.—Thermal polymerization of 9,10-epoxystearic acid, m. p. 59.5°.

3. Reaction between the hydroxyl groups, formed as a result of reaction 1, and oxirane groups (addition reaction).

4. Reaction between oxirane groups (addition reactions).

5. Reaction between the hydroxyl groups, formed as a result of reaction 1, with the elimination of water (condensation reaction).

Reaction 1 is undoubtedly the main polymerization reaction, since carboxyl groups react readily with oxirane groups at moderate temperatures without catalysts, but such a reaction cannot ac-

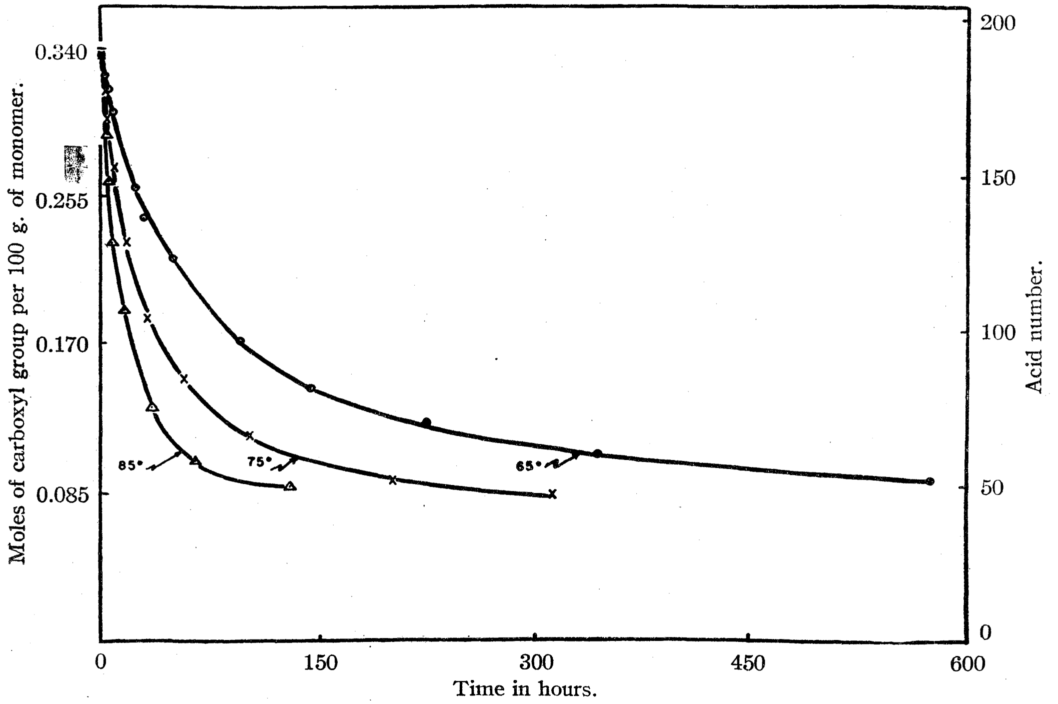


Fig. 2.—Thermal polymerization of 9,10-epoxystearic acid, m. p. 59.5°.

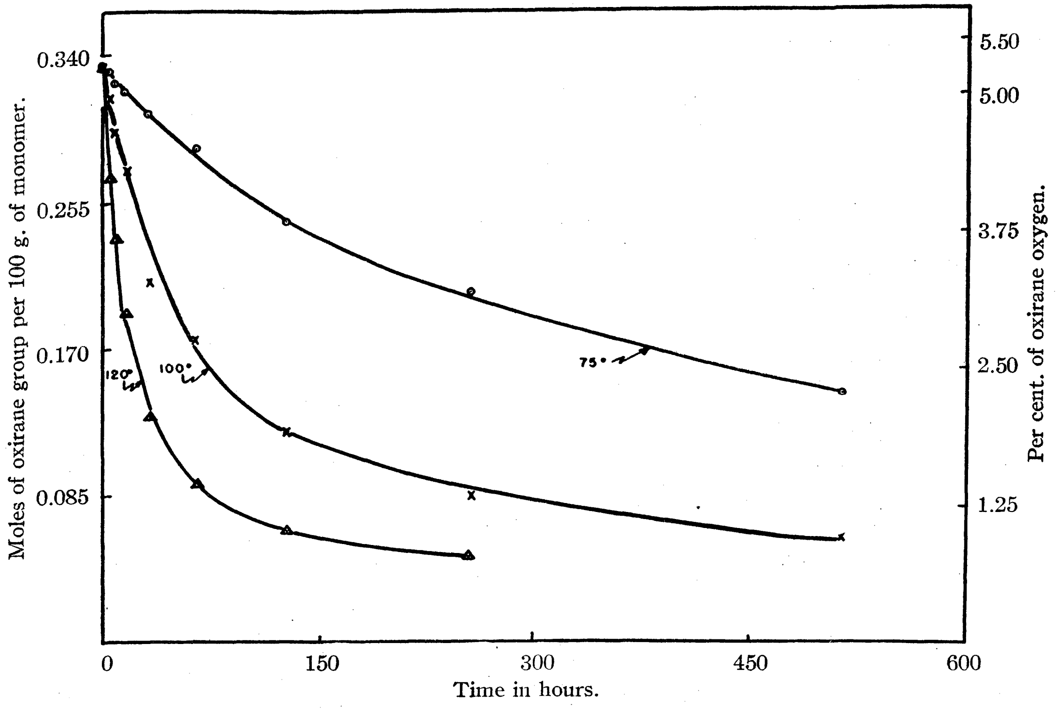


Fig. 3.—Thermal polymerization of 9,10-epoxystearic acid, m. p. 55.5°.

count for gel formation, since it yields only linear polyesters. Likewise, reaction 4b, which yields a difunctional dimer, cannot account for gel formation. The concept that reaction 4b may account for the oxirane group's disappearance at a more rapid rate than the carboxyl group's in the high-melting isomer, is not tenable because such a reaction requires high temperatures and acid catalysts. Reactions 2, 3 and 5, however, are cross-linking reactions, and reaction 4a yields a polyfunctional product capable of cross-linking. Reactions 4a and 5, however, in common with reac-

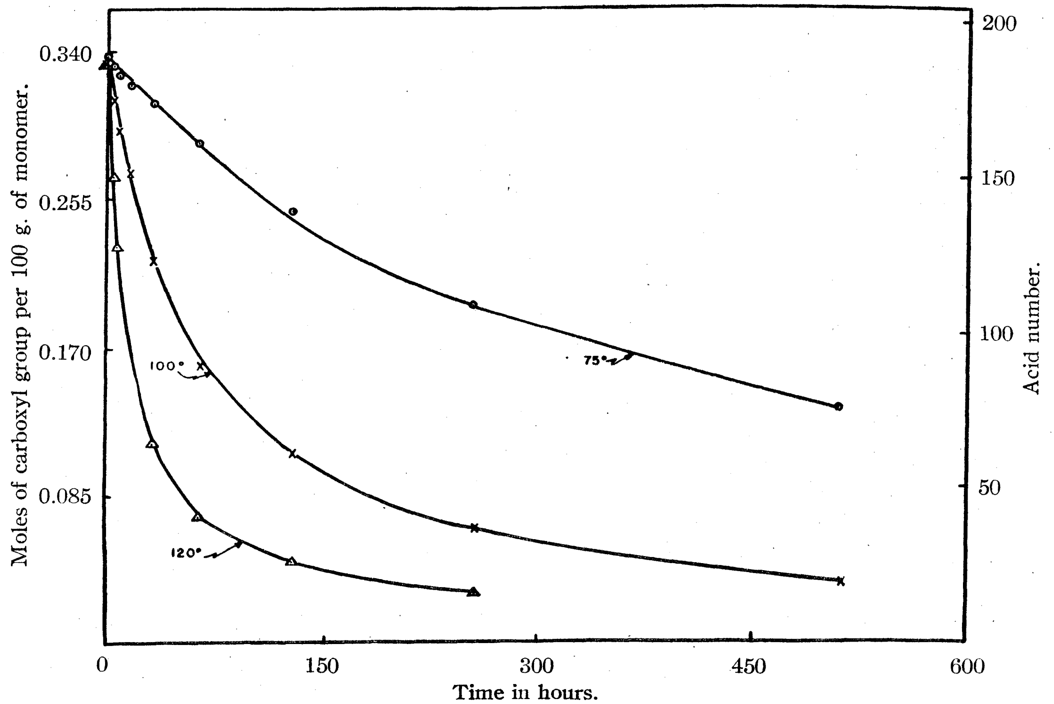


Fig. 4.—Thermal polymerization of 9,10-epoxystearic acid, m. p. 55.5°.

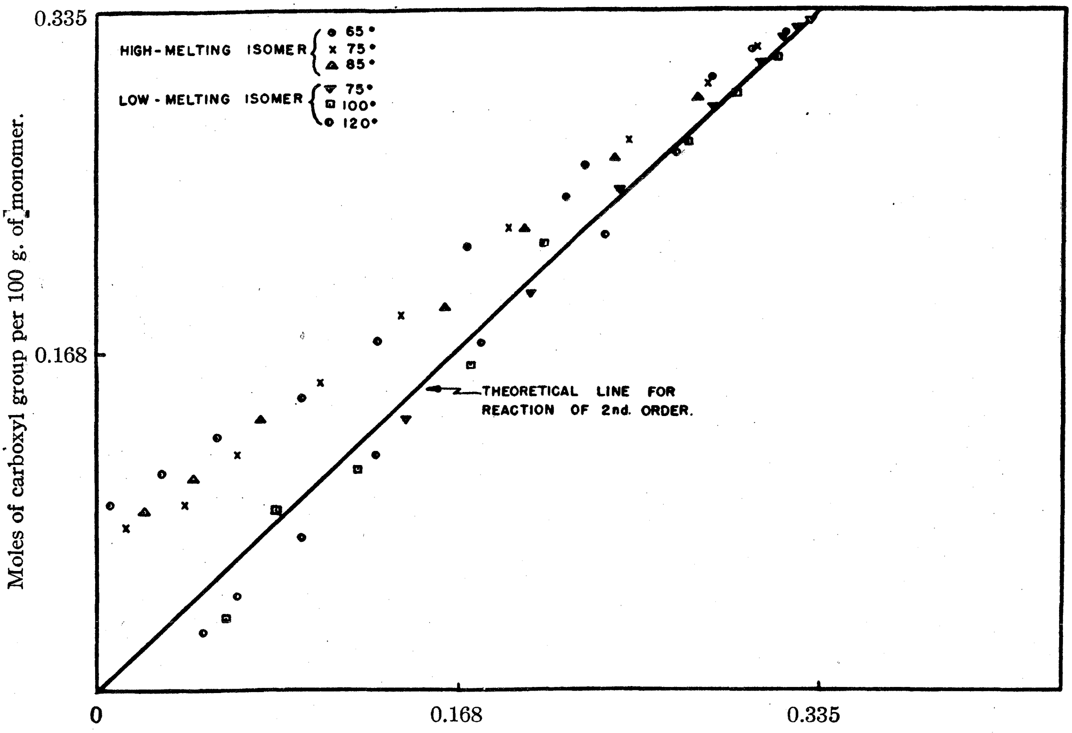


Fig. 5.—Thermal polymerization of the 9,10-epoxystearic acids, m. p. 59.5° and 55.5°.

tion 4b, require catalysts and high temperatures and probably do not account for cross-linking in either isomer or for the oxirane group's disappearance at a greater rate than the carboxyl group's in the high-melting isomer. Although we cannot state positively which of the remaining cross-linking reactions predominate, in the high-melting isomer it is probably reaction 3, and in the low-melting isomer it is probably reaction 2. These reactions can account not only for gelation, but reaction 3 also accounts for the oxirane group's disappearance at a more rapid rate than the carboxyl group's in the high-melting isomer, and reaction 2 accounts for the carboxyl group's disappearance at a slightly more rapid rate than the oxirane group's in the low-melting isomer, noticeable toward the end of the reaction. The assumption that reaction 3 accounts for gelation in the high-melting isomer is consistent with the fact that the oxirane group in this isomer reacts considerably faster with various simple secondary alcohols than the oxirane group in the low-melting isomer.

It was thought that the disappearance of the oxirane group at a more rapid rate than the disappearance of the carboxyl group in the high-melting isomer might be explained on the assumption that this group was isomerizing to the carbonyl group. Carbonyl oxygen analyses,[8] however, carried out on the polymers just prior to the gel point indicated that this reaction would account for only about one-third of the oxirane groups which had disappeared in excess of the carboxyl groups. In the low-melting isomer, carbonyl oxygen values were negligible, as would be expected from the data already discussed.

Cross-linking reactions must occur to only a limited extent in the low-melting 9,10-epoxystearic acid, since the disappearance of the carboxyl and oxirane groups proceeds at nearly the same rate throughout the entire polymerization and gelation does not occur until about 85% of the oxirane groups have disappeared. The parallel disappearance of these two functional groups suggested that the polymerization of this isomer might be a simple second order reaction. In Fig. 5, the concentration of carboxyl group is plotted against the concentration of oxirane group both for this isomer and the high-melting one. If the only process is a second order reaction between oxirane and carboxyl groups, a straight line which makes an angle of 45° with the co-ordinate axes, should be obtained. In the low-melting isomer, the points fall almost exactly on this line during the early stages of the polymerization, and diverge slightly toward the later stages. The best straight line drawn through these points makes an angle of 47° with the abscissa. It was fairly obvious from an inspection of the data in Tables I, II and III and by superimposition of Figs. 1 and 2, that a simple second order reaction was not the sole process occurring in the high-melting isomer, but this fact was strikingly illustrated when the points for this isomer, m. p. 59.5°, were also plotted in Fig. 5.

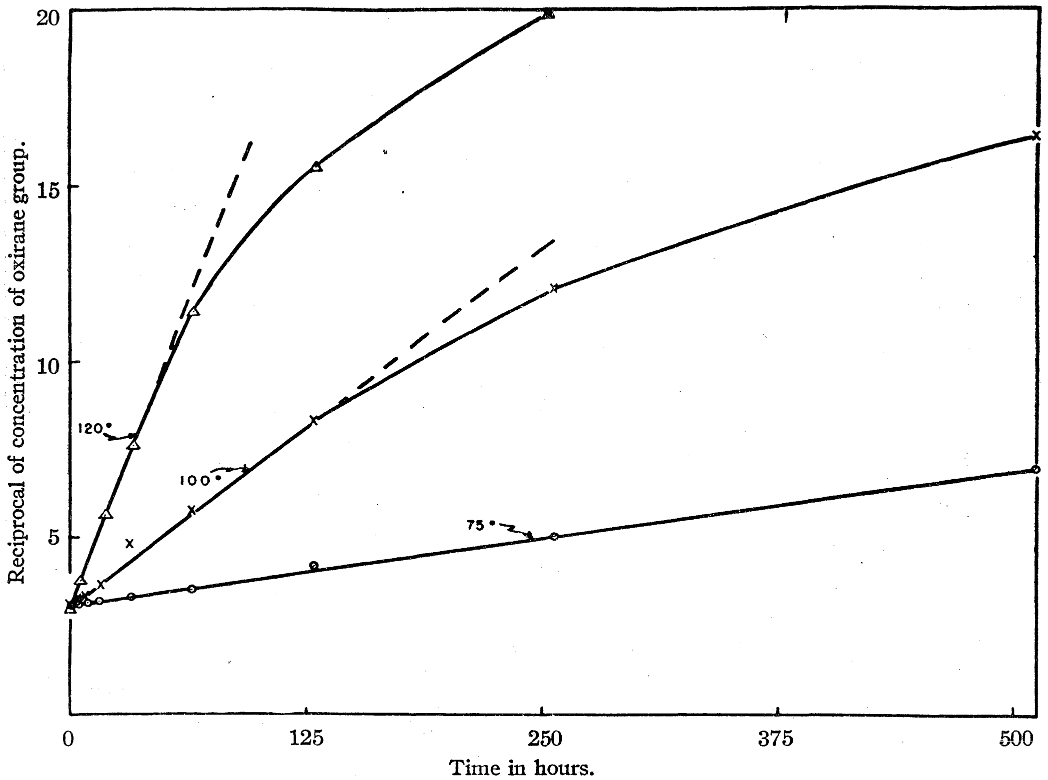


Fig. 6.—Thermal polymerization of 9,10-epoxystearic acid, m. p. 55.5°.

These points diverge from the line for equimolar disappearance of the oxirane and carboxyl groups even during the early stages of the reaction, and the best straight line drawn through these points makes an angle of about 36° with the abscissa.

Furthermore, if the second order reaction between oxirane and carboxyl groups is the only process occurring, plotting the reciprocal of the concentration of either the oxirane or carboxyl group against time should give a straight line, since both groups are initially present in equimolar amounts, and the slope of the line is the reaction rate constant, k. This is shown in Fig. 6 for the low-melting isomer only. At 75°, an almost perfect straight line is obtained over the entire range investigated, whereas at 100° and 120°, the first seven and five points, respectively, appear to fall on straight lines. These early points were replotted on larger graph paper, and the broken lines in Fig. 6 represent the extensions of the best straight lines for these points, as obtained from the plots on the larger graph paper. The rate constants at 75, 100 and 120° for the low-melting isomer are 0.00781, 0.0412 and 0.161, respectively (time in hours, concentration in moles per 100 g.). The energy of activation was calculated from the slope of the line in Fig. 7, in which log k is plotted against $1/T$. The value of E thus obtained is 18,600 calories per mole. The equation for correlating k with T is shown below

$$\log k = -4081/T + 9.59$$

Just prior to the gel point, the polymers are highly viscous, colorless oils, which are soluble in ethanol, diethyl ether, butanol, acetone, xylene, ethylene dichloride and ethyl acetate, and insoluble in water and in aliphatic hydrocarbons. At the gel stage, the polymers are insoluble in all these solvents at their boiling points.

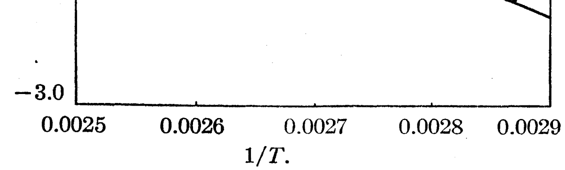


Fig. 7.—Thermal polymerization of 9,10-epoxystearic acid, m. p. 55.5°.

Acknowledgment.—We are indebted to Rudolph Speiser, Thomas W. Findley and John T. Scanlan for valuable discussions in connection with this problem.

Summary

The thermal polymerization of the isomeric 9,10-epoxystearic acids, m. p. 59.5° and 55.5°, derivable from oleic and elaidic acids, respectively, has been quantitatively studied. Both isomers can be polymerized to the gel stage, the high-melting isomer yielding a gel when about 75% of the carboxyl groups and 95% of the oxirane groups have disappeared, the low-melting isomer when about 85% of the oxirane groups and 90% of the carboxyl groups have disappeared. The main process appears to be the formation of linear polyesters by the reaction of the oxirane with the carboxyl group.

In the high-melting isomer, side reactions, which take place from the beginning of the reaction, cause the oxirane group to disappear at a more rapid rate than the carboxyl group, thereby preventing a kinetic analysis of the polymerization. In the low-melting isomer, the approximately parallel disappearance of both functional groups permits calculation of reaction rate constants as well as activation energy. This latter value is 18,600 cal. per mole. For both isomers, the reaction rate approximately doubles for each ten-degree rise in temperature.

The polymers just prior to the gel stage are highly viscous, colorless oils, soluble in many common organic solvents, and insoluble in water and in aliphatic hydrocarbons. At the gel stage they are insoluble at the boiling point in all the solvents tested.

PHILADELPHIA 18, PA. RECEIVED JULY 10, 1947

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Chemistry of Epoxy Compounds. VII.[2] Stereochemical Relationships between the 9,10-Epoxy-, Chlorohydroxy- and Dihydroxystearic Acids

BY DANIEL SWERN

The stereochemical relationships involved in the conversion of oleic and elaidic acids (*cis*- and *trans*-9-octadecenoic acids, respectively) to the 9,10-dihydroxystearic acids by way of the intermediate oxirane and chlorohydroxy compounds have been studied by King[3] and also by Atherton and Hilditch.[4] These investigators have proposed reaction schemes which not only differ on several fundamental points but which are at variance with accepted thinking on the Walden inversion[5] and double bond addition reactions[5] in some important respects.

A satisfactory reaction scheme must be in agreement with the following experimentally determined facts: (1) The 9,10-epoxystearic acid obtained from oleic acid by epoxidation with organic per-acids and that obtained by hypohalogenation and subsequent dehydrohalogenation are identical, and therefore have the same configuration; (2) the 9,10-epoxystearic acid obtained from elaidic acid by epoxidation and that obtained by hypohalogenation and dehydrohalogenation are also identical, and differ from the 9,10-epoxystearic acid described under (1) above; (3) the 9,10-dihydroxystearic acid obtained from oleic acid by oxidation with potassium permanganate and that obtained from elaidic acid by epoxidation and subsequent hydrolysis are identical; (4) the 9,10-dihydroxystearic acid obtained from elaidic acid by oxidation with potassium permanganate and that obtained from oleic acid by epoxidation and hydrolysis are also identical and differ from the 9,10-dihydroxystearic acid described under (3) above; (5) the chlorohydroxystearic acids obtained from oleic acid by reaction with hypochlorous acid and those obtained by epoxidation of oleic acid and subsequent treatment of the 9,10-epoxystearic acid with hydrochloric acid are identical; (6) the chlorohydroxystearic acids obtained from elaidic acid by reaction with hypochlorous acid and those obtained by epoxidation of elaidic acid and treatment of the 9,10-epoxystearic acid with hydrochloric acid are also identical and differ from the chlorohydroxystearic acids described under (5) above; and (7) treatment of either 9,10-dihydroxystearic acid with hydrochloric acid, followed by dehydrohalogenation and hydrolysis, yields the other isomer.

For some time we have been studying the reactions discussed above, and in this paper we are suggesting a scheme which correlates configurational relationships involved, in harmony with accepted theories of the Walden inversion and double bond addition reactions. This reaction scheme is shown in Fig. 1 (the + and − signs do not refer to optical rotations but are employed to correlate configurational relationships and to demonstrate the inversions more clearly).

Although it is generally agreed that opening and closing of the oxirane ring is accompanied by inversion,[6,7,8,9] and this rule has been followed in re-

---

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

[2] For paper VI of this series, see THIS JOURNAL, **70**, 1228 (1948).

[3] King, *J. Chem. Soc.*, 387 (1942).

[4] Atherton and Hilditch, *ibid.*, 204 (1943).

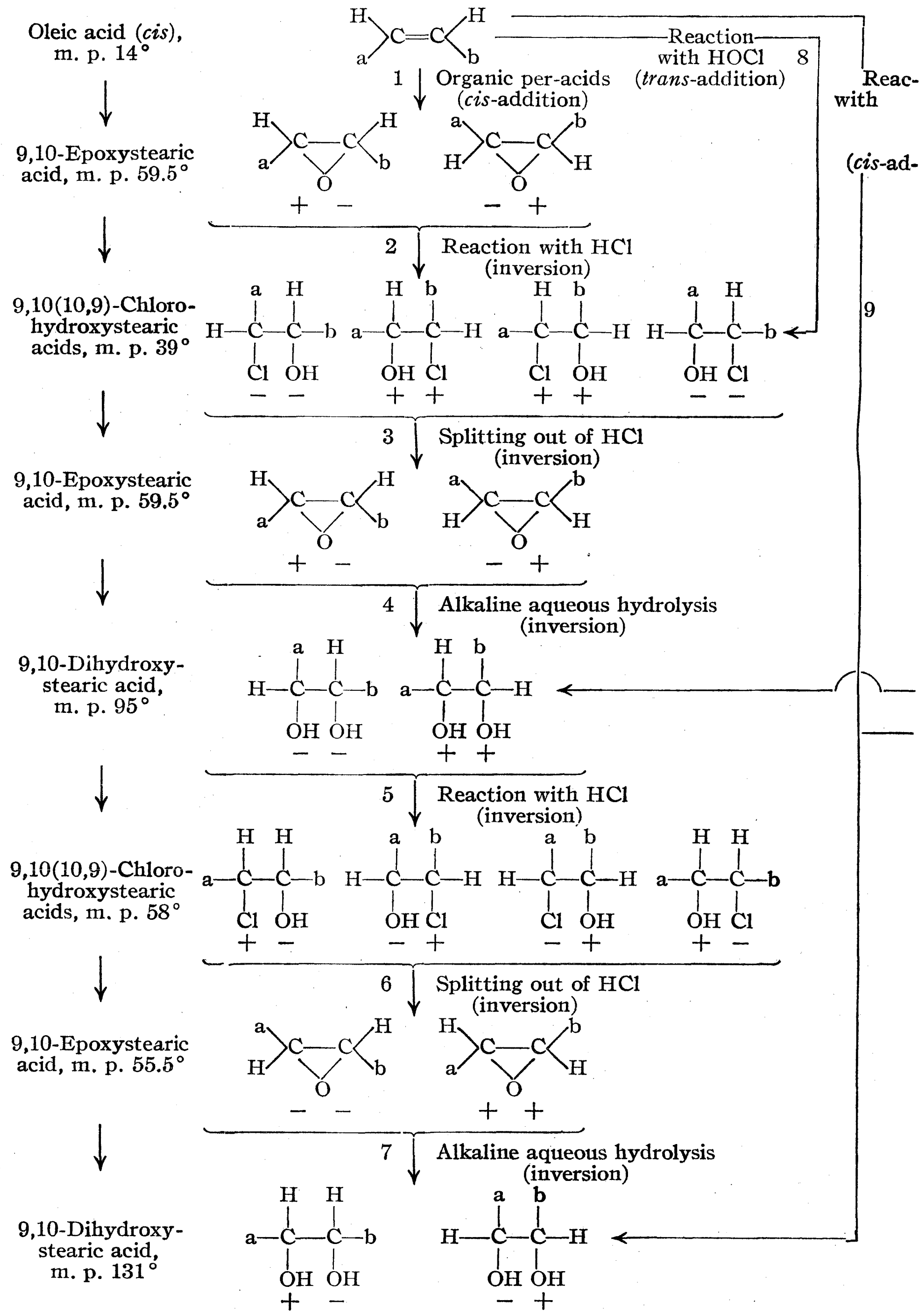
[5] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940; Remick, "Electronic Interpretations of Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1943.

[6] Kuhn and Ebel, *Ber.*, **58**, 919 (1925).

[7] Böeseken and co-workers, *Rec. trav. chim.*, **47**, 683 (1928). Consult this paper for previous contributions.

[8] Esafov, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 1403 (1937).

[9] Wilson and Lucas, THIS JOURNAL, **58**, 2396 (1936); Winstein and Lucas, *ibid.*, **61**, 1576, 1581 (1939); Lucas, Schlatter and Jones, *ibid.*, **63**, 22 (1941); Wilson and Gould, *ibid.*, **63**, 2541 (1941).



a = CH$_3$—(CH$_2$)$_7$—;

Fig. 1.

actions 2, 3, 4, 6 and 7 of Fig. 1, Atherton and Hilditch[4] have suggested that inversion may not occur when the oxirane ring of 9,10-epoxystearic acid is hydrated. One of the reasons offered to explain this is the fact that hydrolysis of the oxirane ring by alkaline or by acidic hydrolytic agents yields the same isomeric form of dihydroxystearic acid, although the mechanisms of hydrolysis differ. Thus, in acid hydrolysis the oxirane compound is converted to the glycol by a two-step process in which a hydroxy-ester is an intermediate, whereas in alkaline hydrolysis the glycol is obtained directly in one step. We believe that the formation of the same 9,10-dihydroxystearic acid can be adequately accounted for on the assumption that in both types of hydrolysis only *one* inversion occurs, namely, at the time that the oxirane ring is opened. This is shown in Fig. 2, in which the conversion of 9,10-epoxystearic acid, m. p. 59.5°, to 9,10-dihydroxystearic acid, m. p. 95°, is em-

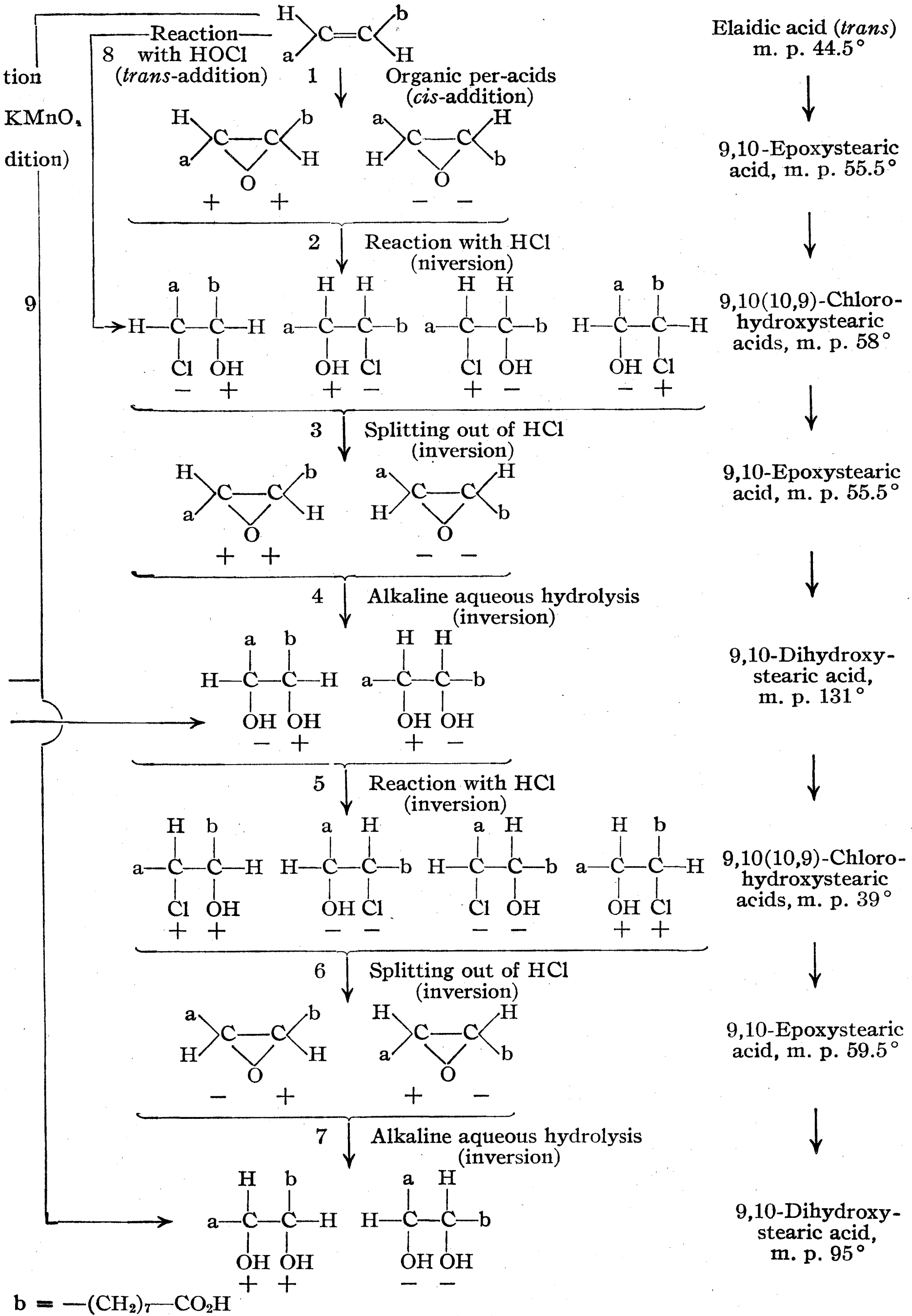


Fig. 1.

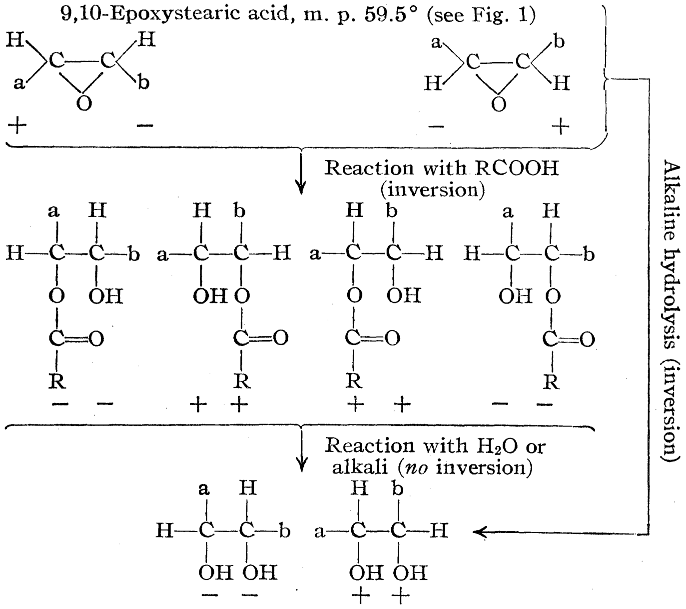
ployed as the example, although the same reasoning applies to the conversion of its isomer, m. p. 55.5°, to 9,10-dihydroxystearic acid, m. p. 131°. It is important to note that inversion cannot occur in the hydrolysis of the intermediate hydroxyester obtained by treatment of the oxirane compound with acid because the carbon–oxygen bond of the alcoholic component, in this case 9,10-dihydroxystearic acid, is not ruptured.[5] Identical results are obtained when sulfuric acid is employed instead of organic acids, or when concentrated or dilute alkali is used.

As further evidence that the oxirane ring may be hydrated without inversion, Atherton and Hilditch[4] have referred to the work of Abderhalden and Eichwald,[10] but we believe that this work is inapplicable to the present problem. Thus, inversions may not occur during the opening or closing of an oxirane ring which is attached to a

---

[10] Abderhalden and Eichwald, *Ber.*, **48**, 1847 (1915).

Fig. 2



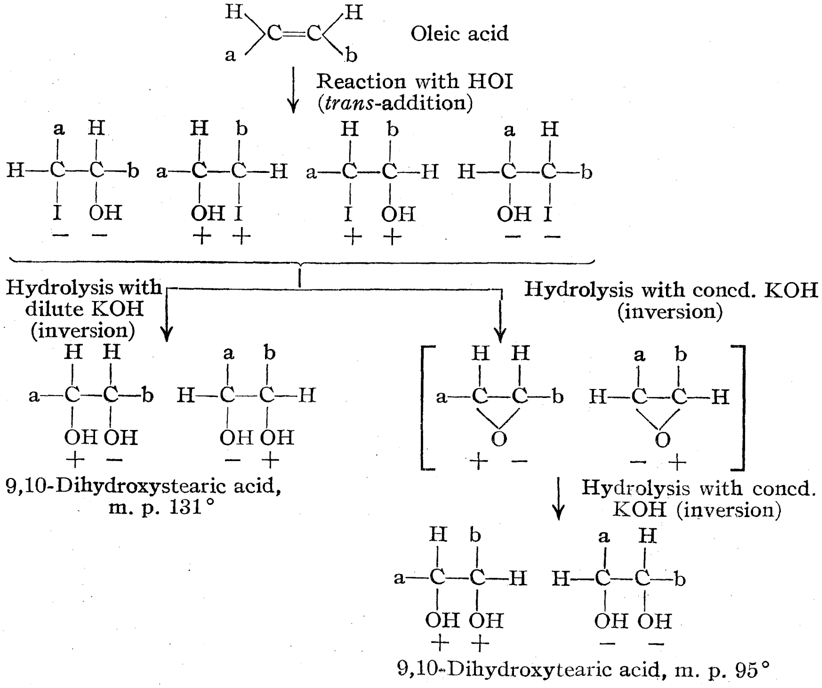
9,10-Dihydroxystearic acid, m. p. 95°

terminal, non-asymmetric carbon atom,[11] as is the case in the three-carbon systems studied by Abderhalden and Eichwald, but inversions occur during ring opening and closure when the oxirane group is attached to a pair of asymmetric carbon atoms[6,9] as is the case in the isomeric 9,10-epoxystearic acids.

Halohydrins of the same configuration (see later discussion) may be prepared either by treating the oxirane compound with hydrogen chloride, hydrogen bromide or hydrogen iodide (reaction 2), or by treating the appropriate unsaturated acid with a hypohalous acid (reaction 8). The form of dihydroxystearic acid obtained by alkaline hydrolysis of these halohydrins is determined by the concentration of the alkali used, since oxirane compounds may be formed as intermediates when the concentration of alkali exceeds a certain value. Thus, Esafov[8] has shown that iodohydroxystearic acid, prepared from oleic acid, yields 9,10-dihydroxystearic acid, m. p. 131°, on hydrolysis with dilute potassium hydroxide, whereas the isomeric 9,10-dihydroxystearic acid, m. p. 95°, is obtained when concentrated potassium hydroxide is employed. According to the scheme proposed in this paper, when dilute alkali is employed, the iodine atom is replaced directly by the hydroxyl group, with inversion,[5] and the 9,10-dihydroxystearic acid, m. p. 131°, is obtained. With concentrated alkali, the oxirane compound is formed as an intermediate, accompanied by inversion,[9] and this on hydrolysis also accompanied by inversion,[9] yields 9,10-dihydroxystearic acid, m. p. 95°. Thus, in the latter case two inversions must occur, whereas in the former only one takes place. This is shown in Fig. 3.

The chlorohydroxystearic acids obtained directly from the unsaturated acids by reaction with hypochlorous acid (reaction 8) and those obtained by treatment of the oxirane compounds with hydrogen chloride (reaction 2) have the same configuration, since they (the chlorohydrins) yield the same oxirane compound on ring closure. Since opening of the oxirane ring is accompanied by inversion,[6,7,8,9] it follows that hypohalogenation of the unsaturated acids must take place by *trans*-addition, as would be expected,[5] and epoxidation (reaction 1), therefore, must occur by *cis*-addition. That epoxidation occurs by *cis*-addition was also concluded by Braun[12] from a study of the perbenzoic acid oxidation of crotonic and isocrotonic acids.

Fig. 3



Furthermore, hydroxylation with potassium

---

[11] Sowden and Fischer, THIS JOURNAL, **64**, 1291 (1942).

[12] Braun, *ibid.*, **51**, 228 (1929).

permanganate (reaction 9) must also occur by *cis*-addition, which is in accord with accepted views on such oxidations,[6,7,13] and photochemical addition of hydrogen peroxide to the double bond, as well as the catalytic hydroxylation of the double bond with *t*-butyl hydroperoxide, must also take place by *cis*-addition.[14] The hydroxylation of maleic and fumaric acids to meso and racemic tartaric acids, respectively, by these reactions is excellent proof that a *cis*-addition mechanism is operative.

The interconversion of the 9,10-dihydroxystearic acids[3,4] (reactions 5, 6 and 7) must proceed, therefore, as shown in Fig. 1. The postulation of an inversion when a hydroxyl group is replaced by a halogen atom, or when the reverse change occurs, is substantiated by extensive experimental evidence.[5]

Experimental

Preparation of the Isomeric 9,10-Epoxystearic Acids.—The high-melting isomer, m. p. 59.5–59.8°, was prepared in good yield by the epoxidation of pure oleic acid[15] with perbenzoic[16] or peracetic acids.[17] It can also be prepared by treating oleic acid with hypochlorous acid followed by dehydrohalogenation with alkali,[4,18] although the yields are poor.

The low-melting isomer, m. p. 55.5°, was similarly prepared[4,16,17,18] from pure elaidic acid.[19]

Preparation of the Isomeric 9,10-Dihydroxystearic Acids.—The high-melting isomer, m. p. 131°, was prepared in excellent yield from oleic acid by oxidation with alkaline potassium permanganate[20] or from elaidic acid by epoxidation,[16,17] yielding 9,10-epoxystearic acid, m. p. 55.5°, as an intermediate product, followed by alkaline aqueous hydrolysis.[18] It was also prepared in more than 95% yield by heating 5 g. of 9,10-epoxystearic acid, m. p. 55.5°, for several hours at 100° with 100 ml. of glacial acetic acid, removing the solvent by vacuum distillation and treating the residual hydroxyacetoxystearic acids with an excess of 1 to 6 *N* aqueous sodium hydroxide for one hour at 100° (or overnight at room temperature), followed by acidification with dilute hydrochloric acid. The high-melting isomer was also prepared under milder reaction conditions by allowing 9,10-epoxystearic acid, m. p. 55.5°, to stand overnight at room temperature in anhydrous formic acid solution or in glacial acetic acid solution containing 1 to 5% of 95% sulfuric acid, or by allowing it to stand for several weeks at room temperature in glacial acetic acid solution, followed by removal of the solvent and aqueous hydrolysis. The best over-all procedure for preparing the high-melting isomer, which does not require isolation of the intermediate oxirane compound, involves oxidation of elaidic acid with 25 to 30% hydrogen peroxide in formic or acetic acid solution.[21] Yields are over 95%.

The low-melting isomer, m. p. 95°, was prepared in excellent yields from elaidic acid by oxidation with alkaline potassium permanganate,[20] from oleic acid by epoxidation[16,17] and hydrolysis,[18] from 9,10-epoxystearic acid, m. p. 59.5°, as described above, or from oleic acid by oxidation with 30% hydrogen peroxide in formic or acetic acid solution.[21]

Preparation of the Isomeric 9,10(10,9)-Chlorohydroxystearic Acids.—Although the 9,10(10,9)-chlorohydroxystearic acids can be prepared from oleic and elaidic acids by reaction with hypochlorous acid (prepared from gaseous chlorine and sodium hydroxide and utilized *in situ*,[4,18,22]) in our experience the yields may be low and the products are usually contaminated with polychlorinated materials. The best procedure for their preparation is to dissolve 2.98 g. (0.01 mole) of 9,10-epoxystearic acid (either isomer) in 100 ml. of a 0.2 *N* solution of anhydrous hydrogen chloride in absolute ether[22,23] contained in a 250-ml. separatory funnel, and allow the solution to stand at room temperature for three hours. The ether solution is washed with cold water until acid-free, dried over anhydrous calcium sulfate and filtered. Distillation of the ether yields 3.30 to 3.35 g. (99 to 100% yield) of 9,10(10,9)-chlorohydroxystearic acids as a non-volatile residue. Neutralization equivalent, calcd., 334.5; found, 334 to 335. 9,10-Epoxystearic acid, m. p. 59.5°, yields 9,10(10,9)-chlorohydroxystearic acids, m. p. 39–40° (lit.[22] 35°), which are reconverted to 9,10-epoxystearic acid, m. p. 59.5°, on treatment with concentrated alkali.[4,18] The chlorohydroxystearic acids, m. p. 39–40°, are identical with those obtained by the hypochlorination of oleic acid, since they both yield 9,10-epoxystearic acid, m. p. 59.5°, on dehydrohalogenation.[4] 9,10-Epoxystearic acid, m. p. 55.5°, yields 9,10(10,9)-chlorohydroxystearic acids, m. p. 58.0–58.8° (lit.[4] 58°), which are reconverted to 9,10-epoxystearic acid, m. p. 55.5°, on treatment with concentrated alkali.[4] The chlorohydroxystearic acids, m. p. 58–58.8°, are identical with those obtained by the hypochlorination of elaidic acid, since they both yield 9,10-epoxystearic acid, m. p. 55.5°, on dehydrohalogenation.[4]

Acknowledgment.—The author wishes to thank Thomas W. Findley and John T. Scanlan for thought-provoking discussions which helped to clarify some of the ideas presented in this paper.

Summary[24,25]

A reaction scheme is described which correlates the configurational relationships in the conversion of oleic and elaidic acids (*cis*- and *trans*-9-octadecenoic acids, respectively) to 9,10-dihydroxystearic acids by way of the intermediate oxirane

---

(13) Böeseken and Cohen, *Rec. trav. chim.*, **47**, 839 (1928); King, *J. Chem. Soc.*, 37 (1943).

(14) Milas, Kurz and Anslow, Jr., THIS JOURNAL, **59**, 543 (1937); Milas and Sussman *ibid.*, **58**, 1302 (1936); Milas, *ibid.*, **59**, 2342 (1937); Milas, Sussman and Mason, *ibid.*, **61**, 1844 (1939).

(15) Brown and Shinowara, *ibid.*, **59**, 6 (1937); Wheeler and Riemenschneider, *Oil and Soap*, **16**, 207 (1939).

(16) Swern, Findley and Scanlan, THIS JOURNAL, **66**, 1925 (1944).

(17) Findley, Swern and Scanlan, *ibid.*, **67**, 412 (1945).

(18) Ellis, *Biochem. J.*, **30**, 753 (1936).

(19) Bertram, *Chem. Weekblad*, **33**, 3 (1936).

(20) Lapworth and Mottram, *J. Chem. Soc.*, **127**, 1628 (1925).

(21) Swern, Billen, Findley and Scanlan. THIS JOURNAL, **67**, 1786 (1945).

(22) Nicolet and Poulter, *ibid.*, **52**, 1186 (1930).

(23) Swern, Findley, Billen and Scanlan, *Anal. Chem.*, **19**, 414 (1947).

(24) NOTE ADDED IN PROOF: In the recent paper by McKay and Bader, *J. Org. Chem.*, **13**, 75 (1948), it was assumed that oxidation of oleic and elaidic acids with alkaline potassium permanganate proceeds by a *trans* hydroxylation mechanism. This was based on infrared absorption studies of the isomeric methyl 9,10-dihydroxystearates, Davies, *J. Chem. Phys.*, **8**, 577 (1940), and on the difference between the rates of reaction of the 9,10-dihydroxystearic acids with lead tetraacetate, Hilditch and Jasperson, *Nature*, **147**, 327 (1944). In these papers no conclusions regarding the absolute configuration of the dihydroxystearic acids and their relationship to oleic and elaidic acids were made. It is our belief, based upon the information presented in our paper and also in literature references 3, 6 and 13 cited therein, that the conclusions drawn by McKay and Bader regarding the configurations of the dihydroxy and tetrahydroxystearic acids are unjustified [see also Wittcoff and Miller, THIS JOURNAL, **69**, 3138 (1947)]. Furthermore, the terms *cis* and *trans*, employed by McKay and Bader and some earlier investigators, should not be applied to the hydroxy acids since these compounds are diastereoisomers and not geometric isomers, for which the terms are intended.

(25) This paper was presented at the meeting of the American Chemical Society held in New York, N. Y., on Sept. 15–19, 1947.

and chlorohydroxy compounds. This scheme is self-consistent and is in harmony with accepted theories of the Walden inversion and double bond addition reactions.

According to this scheme, epoxidation of the unsaturated acids with organic per-acids, or oxidation with alkaline potassium permanganate, takes place by *cis*-addition, whereas reaction with hypochlorous acid proceeds by *trans*-addition. Furthermore, it is postulated that opening (either in alkaline or acidic media) and re-forming of the oxirane ring, as well as replacement of a hydroxyl group of 9,10-dihydroxystearic acid by halogen, are each accompanied by an inversion. An inversion is also postulated when halogen is replaced by hydroxyl in the 9,10(10,9)-halohydroxystearic acids, and an explanation is offered for the formation of high- or low-melting 9,10-dihydroxystearic acid when 9,10(10,9)-iodohydroxystearic acids (from oleic acid) are treated with dilute or concentrated alkali, respectively.

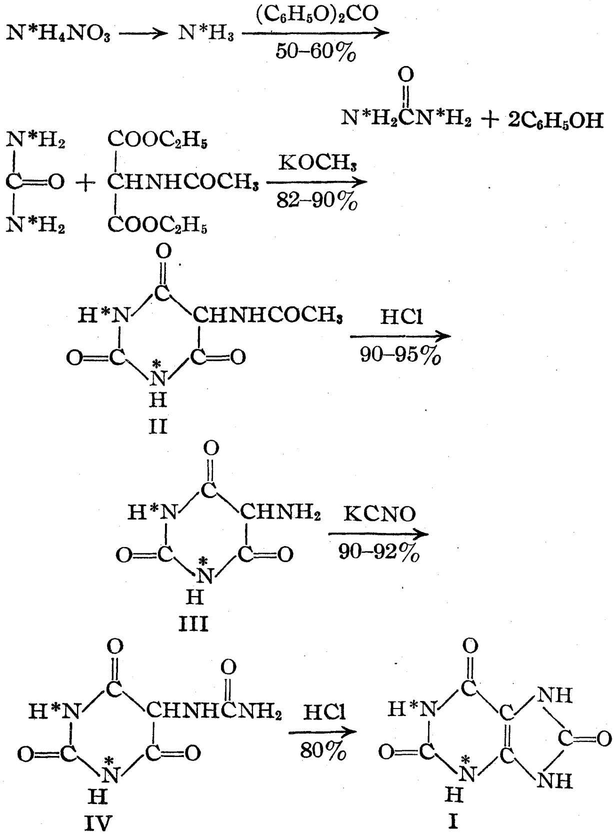
PHILADELPHIA 18, PA. RECEIVED JULY 10, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

The Synthesis of Uric Acid Containing Isotopic Nitrogen

BY LIEBE F. CAVALIERI, VIRGINIA E. BLAIR AND GEORGE BOSWORTH BROWN

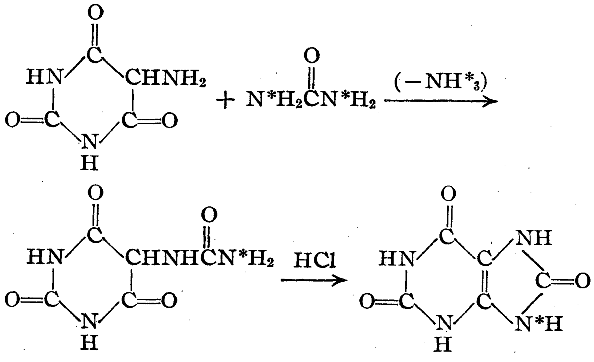
The existing procedures[1,2,3,4,5,6] for the synthesis of uric acid involve many steps and the over-all yields are low, based upon the urea used. For the introduction of isotopic nitrogen a modified synthesis has been developed in order to insure optimum utilization of the isotope. This synthesis introduces N^{15} in the pyrimidine ring (positions 1 and 3) (I) as shown in the following equations:



IV I

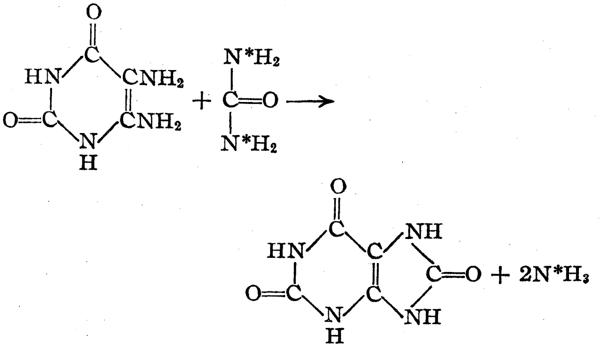
The over-all yield in this synthesis was 55%, based upon the urea used. The yields afforded by the older procedures can be estimated to be about 27%.

A second synthesis of uric acid (V) incorporating N^{15} presumably in position 9 was carried out according to the method of Grimaux.[2]



V

It will be noted that one amino group of the urea molecule was eliminated in the initial reaction. Cyclization with hydrochloric acid produced uric acid (V) containing about 1 atom of isotopic nitrogen. Since in the analogous reaction of 2,6-dioxy-4,5-diaminopyrimidine with urea[7] both of the amino groups of the urea were eliminated and no isotopic nitrogen was introduced into the uric



---

[1] Baeyer, *Ann.*, **127**, 1 (1863).

[2] Grimaux, *Bull. soc. chim.*, [2] **31**, 535 (1879).

[3] Fischer, *Ber.*, **30**, 559 (1897).

[4] Horbaczewski, *Monatsh.*, **8**, 201 (1887).

[5] Behrend and Roosen, *Ann.*, **251**, 235 (1889).

[6] Behrend, *ibid.*, **441**, 215 (1925).

[7] Levene and Senior, *J. Biol. Chem.*, **25**, 618 (1916).

acid it may be presumed that in the uric acid (V) formed from urea and uramil the isotopic nitrogen was introduced chiefly in position 9.

Experimental

Urea.—The preparation of urea from diphenyl carbonate and ammonia was reported by Hentschel.[8] Bloch and Schoenheimer[9] introduced the use of copper powder as the catalyst. The preparation is described here since the technique used was more reproducible, in our hands, than that of Bloch and Schoenheimer.

A three-necked flask was equipped with a reflux condenser, dropping funnel and an inlet tube for nitrogen. A potassium hydroxide drying tower was placed on top of the condenser and a wide-mouth tube from this was led into a glass bomb tube, 15 cm. above the bottom of the bomb. An outlet tube from the bomb tube was passed through an acid trap containing a known quantity of standard acid. A flask of liquid nitrogen was placed around the bomb tube to condense and freeze the isotopic ammonia.

A solution of 4.088 g. (0.0511 mole) of $N^{15}H_4NO_3$ (32.0 atom % excess N^{15}) in 25 cc. of water was introduced into the three-necked flask. The bomb tube was charged with an intimate mixture of 4.95 g. (0.0231 mole) of diphenyl carbonate and 130 mg. of copper powder. Before the ammonia was liberated from the ammonium nitrate, the apparatus was swept with nitrogen for ten minutes. The bomb tube was then immersed in the liquid nitrogen. While continuing the slow stream of nitrogen, an excess of sodium hydroxide was slowly introduced from the funnel and the generating flask was heated to boiling. Care must be exercised not to allow the ammonia to be liberated too rapidly since the inlet tube in the bomb may become clogged with crystalline ammonia. The generating flask was heated for three hours and about 5% of uncondensed ammonia was collected in the acid trap. The bomb tube was transferred to a solid carbon dioxide-bath and sealed. It was then heated in a water-bath at 90–100° for four hours. The contents of the tube were dissolved in a minimal amount (about 50-cc.) of warm water and the copper powder was removed by filtration. The filtrate was extracted with six 50-cc. portions of chloroform. The aqueous layer was decolorized and evaporated to dryness on a water-bath. The yield of crude urea was 0.977 g. Recrystallization from acetone gave 0.830 g. of urea (57%, based upon the ammonia condensed); m. p. 133.5–135° (stage).

Acetyluramil (Potassium Salt).—A three-necked flask was equipped with a Hershberg stirrer, reflux condenser and glass stopper. The apparatus was dried and potassium methylate was prepared by adding absolute methanol (dried over Drierite) to 0.9 g. (0.23 mole) of clean potassium under benzene. The solvents were removed under reduced pressure and to the dry residue was added 1.180 g. (0.0197 mole) of urea in 4 cc. of absolute methanol. Ethyl acetamidomalonate[10] (4.3 g., 0.02 mole) was dissolved in 8 cc. of methanol and added in one portion to the urea solution. The mixture was refluxed and stirred for four hours. The white precipitate of potassium acetyluramil was collected by filtration; yield 3.74 g. (85%). An analytical sample of acetyluramil was prepared as follows: potassium acetyluramil (500 mg.) was dissolved in 15 cc. of concentrated hydrochloric acid at room temperature. The solution was added to 100 cc. of ethanol and cooled overnight. The precipitate which formed weighed 400 mg.

Anal. Calcd. for $C_6H_7O_4N_3$: N, 22.70. Found: N, 22.50.[11]

Uramil.—The potassium acetyluramil (3.61 g., 0.0161 mole) was hydrolyzed to uramil in 30 cc. of concentrated hydrochloric acid. The mixture was heated to boiling for about five minutes at which time all the solid had gone into solution. The uramil was precipitated by diluting with 70 cc. of water; yield 2.16 g. (94%). An analytical sample was prepared by dissolving 100 mg. of uramil in dilute sodium hydroxide and reprecipitating with hydrochloric acid; recovery 72 mg.

Anal. Calcd. for $C_4H_5O_3N_3$: C, 33.57; H, 3.52. Found: C, 33.01; H, 3.60.

Pseudouric Acid (Potassium Salt).—Potassium pseudourate was prepared by a modification of the procedure of Baeyer.[1] Uramil (2.16 g., 0.0151 mole) was added in one portion to a boiling solution of 55 g. of potassium cyanate in 260 cc. of water. The uramil dissolved producing a clear pink solution and potassium pseudourate precipitated almost immediately. The solution was refluxed for one-half hour while stirring. Upon cooling, 3.14 g. (92%) was obtained.

Uric Acid.—Potassium pseudourate was converted to uric acid according to the procedure of Fischer.[3] Yields of 72 to 80% were obtained, after two recrystallizations.

Anal. Calcd. for $C_5H_4O_3N_4$: C, 35.71; H, 2.39; N, 33.33. Found: C, 35.81; H, 2.50; N, 33.25.

The isotopic preparation contained 34.05% total nitrogen (calcd. 33.52% with allowance for the N^{15} present), and 16.1 atom % excess N^{15} (expected 16.0%).[12]

Absorption Spectra of Uric Acid.—The ultraviolet absorption spectrum of synthetic samples prepared by either method (determined upon a solution of 0.013 mg. per cc. at *p*H 7.0; 0.1 *M* phosphate buffer) showed maxima of ϵ 12,700 at 292 mμ and of ϵ 10,100 at 235 mμ. A commercial sample of uric acid,[13] purified in the same manner as the synthetic sample, exhibited slightly lower maxima (ϵ = 11,500 and 8,820) at the same wave lengths. The data on the commercial sample agree with the values previously reported.[14,15]

Uric Acid from Urea and Uramil (Isotopic Nitrogen in the 9 Position).—Urea (550 mg., 0.0092 mole, 0.97 atom % excess N^{15}) was fused with 500 mg. (0.0035 mole) of uramil[16] at 150–170° for forty-five minutes. The cooled melt was extracted with 20 cc. of boiling water and the insoluble material was removed by filtration. The filtrate was decolorized and evaporated to about 6 cc. Upon cooling, 355 mg. (50%) of ammonium pseudourate precipitated. This was dissolved in aqueous sodium hydroxide and pseudouric acid was precipitated by acidification with hydrochloric acid; yield, 200 mg. (35%). This pseudouric acid contained 0.28 atom % excess N^{15}. This was converted to uric acid (calcd. N, 33.34; found 33.18) which also contained 0.28 atom % excess N^{15}. This is slightly more than the theoretical of 0.24 atom % N^{15} excess for the introduction of one nitrogen atom from the urea used.

Uric Acid from 2,6-Dioxy-4,5-diaminopyrimidine.—Urea (700 mg., 0.0117 mole, 0.97 atom % excess N^{15}) was fused with 468 mg. (0.0011 mole) of 2,6-dioxy-4,5-diaminopyrimidine sulfate[9] for one hour at 150–170°. The cooled melt was washed with 10 cc. of water and filtered. The residue was dissolved in dilute sodium hydroxide, decolorized with charcoal and precipitated by the addition of acetic acid. It was dissolved again in alkali and precipitated by the addition of hydrochloric acid. The product was then recrystallized from water and the 163 mg. of uric acid obtained was shown to contain no excess isotopic nitrogen.

Summary

An improved synthesis of uric acid, suitable for

---

[8] Hentschel, *Ber.*, **17**, 1284 (1884).

[9] Bloch and Schoenheimer, *J. Biol. Chem.*, **138**, 176 (1941).

[10] Snyder and Smith, THIS JOURNAL, **66**, 350 (1944).

[11] We are indebted to Dr. Elek of the Rockefeller Institute for Medical Research for the analyses.

[12] We are indebted to the M. W. Kellogg Co. for the mass spectrometer determinations of isotopic nitrogen.

[13] Eastman Kodak Co.

[14] Fromherz and Hartmann, *Ber.*, **69**, 2420 (1936).

[15] Stimson and Reuter, THIS JOURNAL, **65**, 153 (1943).

[16] "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, 1943, p. 617.

the incorporation of isotopic nitrogen in positions 1 and 3 is described. The formation of uric acid from the reaction of isotopic urea with uramil or with 2,6-dioxy-4,5-diaminopyrimidine has been studied.

NEW YORK, NEW YORK RECEIVED MAY 19, 1947

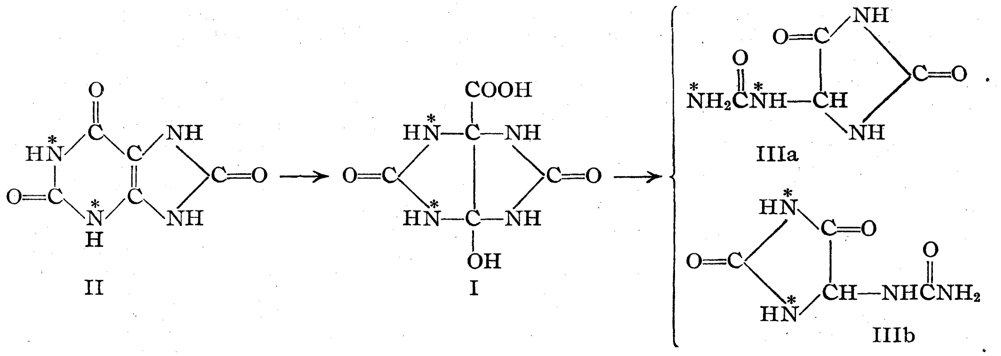
[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

The Mechanism of the Oxidation of Uric Acid Studied with Isotopic Nitrogen as a Tracer[1]

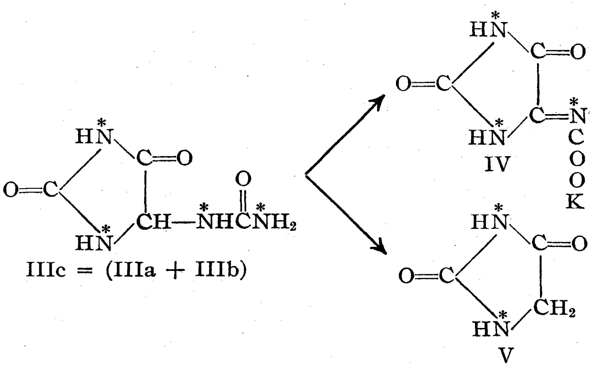
BY LIEBE F. CAVALIERI AND GEORGE BOSWORTH BROWN

The oxidation of uric acid with potassium permanganate in alkaline solution results in the formation of allantoin,[2,3,4] while oxidation with nitric acid or chlorine produces alloxan.[5,6] In the alkaline permanganate oxidation it has been suggested[3] that the reaction proceeds *via* the symmetrical intermediate I. In support of this hypothesis, Fischer and Ach[7] have shown that both 1- and 7-methyluric acids yield upon oxidation 3-methylallantoin and that both 3- and 9-methyluric acids yield 1-methylallantoin. Schuler and Reindel[8] isolated the silver salt of an intermediate compound to which they assigned the symmetrical structure (I) originally postulated by Behrend. Klemperer[9] has also obtained what is believed to be this compound by the action of uricase on uric acid.

We have studied the oxidation of uric acid (II) containing an excess of isotopic nitrogen in positions 1 and 3. II was oxidized to allantoin with alkaline permanganate. If the symmetrical intermediate I is formed, the N^{15} will be present in only one pair of the nitrogen atoms of the molecule. The cleavage of either ring of this molecule will result in the formation of allantoin. The result in one case will be the introduction of the isotopic nitrogen into the urea moiety of the allantoin (IIIa) and in the other case into the ring of the allantoin (IIIb).[10] The allantoin isolated will contain the same number of molecules of each of IIIa and IIIb. Statistically, therefore, the allantoin will have the isotopic nitrogen distributed uniformly among all four nitrogens of the molecule.



A sample of the allantoin obtained (IIIc) was oxidized to potassium oxonate (IV) with potassium permanganate, while a second portion was converted by reduction with hydriodic acid to hydantoin (V). Isotope analyses showed that the nitrogen of the potassium oxonate and that of the hydantoin contained the same atom per cent. excess of N^{15} as the allantoin. The isotopic nitro-



---

(1) The authors gratefully acknowledge the use of funds from The Office of Naval Research and The Barker Welfare Foundation.

(2) Biltz and Schauder, *J. prakt. Chem.*, [2] **106**, 114 (1923).

(3) Behrend, *Ann.*, **333**, 146 (1904).

(4) Hartman, Moffett and Dickey, "Organic Syntheses," Coll. Vol. II, 21 (1943).

(5) Liebig and Wöhler, *Ann.*, **26**, 256 (1838).

(6) Biltz and Hehn, *ibid.*, **413**, 60 (1916).

(7) Fischer and Ach, *Ber.*, **32**, 2723 (1899).

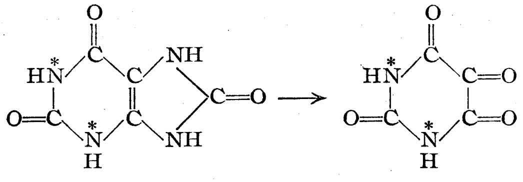
(8) Schuler and Reindel, *Z. physiol. Chem.*, **208**, 248 (1932).

(9) Klemperer, *J. Biol. Chem.*, **160**, 111 (1945).

(10) In the work of Fischer and Ach[7] only the substituted allantoins with the methyl group on the hydantoin ring were isolated. This may have been due to failure to isolate an accompanying allantoin with the methyl substituent on the urea moiety, or it may be that no such allantoin is formed because of a preferential cleavage of the unsubstituted ring of a methylated I.

gen originally present in the 1 and 3 positions of the uric acid was thus proven to have become distributed equally between the imidazolone and the urea moieties of the allantoin and the isotope in the urea moiety was shown to be equally distributed between its two nitrogens. This evidence furnishes direct proof of the formation of a symmetrical intermediate in this oxidation of uric acid to allantoin.

When the uric acid, labelled with isotopic nitrogen in the 1 and 3 positions, was oxidized either with nitric acid or with chlorine, the atom per cent. excess of N^{15} in the alloxan (VI) formed was twice that of the uric acid from which it was derived.



II VI

This demonstrates that the nitrogen atoms of the alloxan were derived solely from the 1 and 3 nitrogens of the uric acid. Thus the oxidation in acid media is a direct cleavage of the imidazolone ring with the formation of the alloxan from the pyrimidine ring alone.

Experimental

Uric Acid.—Two samples of uric acid containing N^{15} in the 1 and 3 positions, synthesized according to the directions given in another communication,[11] were shown to contain, respectively, 0.43 and 0.34 atom per cent. excess N^{15}.[12]

Allantoin.—Uric acid (1.20 g., 0.43 atom per cent. excess N^{15}) yielded 866 mg. of allantoin when oxidized according to the procedure of Hartman, Moffett and Dickey.[4] Recrystallization from water yielded 647 mg., (57%); 0.41 atom per cent. excess N^{15}.

Anal. Calcd. for $C_4H_6O_3N_4$: N, 35.4. Found: N, 35.3.[13]

Potassium Oxonate.—Allantoin was oxidized to potassium oxonate according to Biltz and Giesler.[14] Allantoin (100 mg.) yielded 85 mg. of potassium oxonate. Recrystallization from water gave 50 mg., (40%); 0.41 atom per cent. excess N^{15}.

Anal. Calcd. for $C_4H_2O_4N_3K$: N, 21.5. Found: N, 21.8.

Hydantoin.—The procedure of Baeyer[15] for the reduction of allantoin to hydantoin was simplified as follows. Allantoin (200 mg.) was refluxed with 2 cc. of hydriodic acid, containing a trace of hypophosphite, for eight minutes. The mixture was then evaporated to dryness with a stream of air. Three cc. of acetone was added to the dry residue and the solution was placed in an ice-box for one-half hour. The hydantoin (70 mg.) was collected by filtration and washed with fresh acetone and then recrystallized from ethyl alcohol. Yield was 57 mg. (45%); 0.43 atom per cent. excess N^{15}.

Anal. Calcd. for $C_3H_4O_2N_2$: N, 28.0. Found: N, 28.6.

Alloxan (a) Nitric Acid Oxidation.—The procedure for the oxidation of uric acid was similar to that of Nightingale[16] for the oxidation of alloxantin to alloxan. Uric acid (400 mg., 0.34 atom per cent. excess N^{15}) yielded 50 mg. of alloxan, 0.67 atom per cent. excess N^{15}.

Anal. Calcd. for $C_4H_2O_4N_2 \cdot 4H_2O$: N, 13.1. Found: N, 13.2.

(b) **Chlorine Oxidation.**—Uric acid (400 mg., 0.34 per cent. excess N^{15}) was treated with 107 mg. of potassium chlorate, 0.67 cc. of concentrated hydrochloric acid and 1.1 cc. of water.[17] After all the solid had gone into solution, the mixture was evaporated with a stream of air to about one-half the volume. After standing in the ice-box overnight, 100 mg. of alloxan crystallized, 0.69 atom per cent. excess N^{15}.

Anal. Calcd. for $C_4H_2O_4N_2 \cdot 4H_2O$: N, 13.1. Found: N, 13.5.

Summary

By the use of isotopic nitrogen as a tracer, it has been demonstrated that the oxidation of uric acid to allantoin with alkaline potassium permanganate proceeds through a symmetrical intermediate. Oxidation with either nitric acid or chlorine results in a direct cleavage of the imidazolone ring to produce alloxan.

NEW YORK, N. Y. RECEIVED JULY 31, 1947

---

(11) Cavalieri, Blair and Brown, THIS JOURNAL, **70**, 1241 (1948).

(12) We are indebted to Mr. Stephen Friedland of this Laboratory for the isotope analyses.

(13) We are indebted to Miss Alice Angelos for the nitrogen determinations.

(14) Biltz and Giesler, *Ber.*, **46**, 3413 (1913).

(15) Bayer, *Ann.*, **130**, 158 (1864).

(16) Nightingale, "Organic Syntheses," **23**, 5 (1946).

(17) Nightingale, *ibid.*, **23**, 6 (1946).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEVADA]

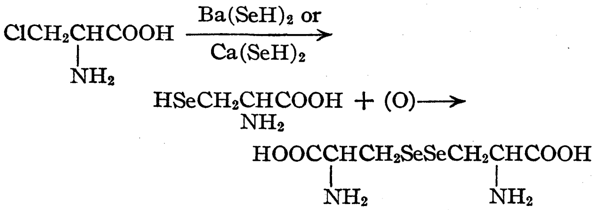
Syntheses of the Selenium Analog of *dl*-Cystine

BY LORING R. WILLIAMS AND ABRAHAM RAVVE

Several methods for the synthesis of the selenium analog of cystine have been previously described. Fredga[1] prepared a seleno-cystine by treating the methyl ester of α-amino-β-chloropropionic acid hydrochloride with potassium diselenide in an aqueous solution. A yellow, crystalline compound was obtained, m. p. 215° with decomposition. A 30% yield was reported. Painter[2] reported several methods for preparing the compound. Methods were sought which would avoid the prolonged use of diselenides in aqueous alkali as they are generally unstable. In these syntheses the methyl ester of α-amino-β-chloropropionic acid hydrochloride was used as the starting compound. The best yields were obtained by the use of the following method: The amino acid, β-(benzylseleno)-alanine was prepared by treating the ester with sodium benzyl selenide. The acid was reduced with sodium in liquid ammonia and the product formed by the cleavage of the benzyl group was oxidized to give the selenium analog of *dl*-cystine. Small plates (some hexagonal, some rectangular) were obtained, m. p. 222° with decomposition.

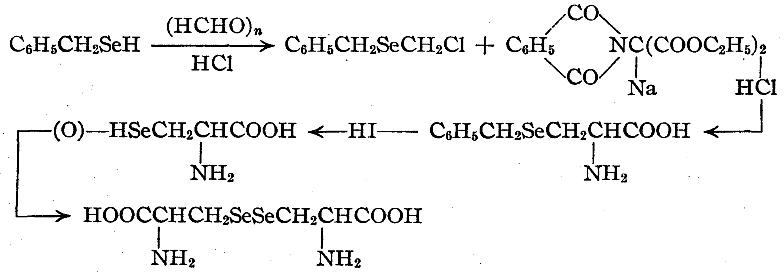
In the present investigation the selenium analog of cystine was prepared by substituting selenium analogs for the sulfur compounds used in the methods of preparation described by Abderhalden[3] and Wood and du Vigneaud[4] for the preparation of *dl*-cystine. The modifications may be summarized as follows:

(I) Abderhalden Modification.—α-Amino-β-chloropropionic acid reacted with barium hydrogen selenide or calcium hydrogen selenide and the product was oxidized.



$$Cl\underset{NH_2}{CH_2CH}COOH \xrightarrow[Ca(SeH)_2]{Ba(SeH)_2\text{ or}} HSeCH_2\underset{NH_2}{CH}COOH + (O) \longrightarrow HOOC\underset{NH_2}{C}HCH_2SeSeCH_2\underset{NH_2}{C}HCOOH$$

(II) Wood and du Vigneaud Modification.—Benzyl selenol was condensed with polyoxymethylene and hydrogen chloride according to a reaction carried out by Böhme[5] in the synthesis of the ethyl homolog. Benzyl chloromethyl selenide was obtained which was condensed with sodium phthalimidomalonic ester. The resulting compound was hydrolyzed to give β-(benzylseleno)-alanine. After the benzyl group was cleaved with hydriodic acid the resulting seleno-acid was oxidized and the β,β'-diselenodialanine was separated by the procedure described by Fredga.[1]



$$C_6H_5CH_2SeH \xrightarrow[HCl]{(HCHO)_n} C_6H_5CH_2SeCH_2Cl + C_6H_5\langle(CO)_2\rangle N\underset{Na}{C}(COOC_2H_5)_2 \xrightarrow{HCl} C_6H_5CH_2SeCH_2\underset{NH_2}{C}HCOOH \xrightarrow{HI} HSeCH_2\underset{NH_2}{C}HCOOH \xrightarrow{(O)} HOOC\underset{NH_2}{C}HCH_2SeSeCH_2\underset{NH_2}{C}HCOOH$$

Experimental

Method (I).—**Barium Hydrogen Selenide.**—Barium hydrogen selenide and calcium hydrogen selenide were both prepared by saturating a solution of the hydroxides with hydrogen selenide. The solutions that were formed were used as no attempts were made to isolate the compounds.

Serine.—Prepared by the method of Wood and du Vigneaud.[6]

Methyl Ester of Serine Hydrochloride.[7]—Fifteen grams of pulverized serine was suspended in 450 g. of absolute methyl alcohol and dry hydrogen chloride added until saturated. The alcohol was removed *in vacuo* and the ester remained as a white crystalline mass, m. p. 133°; yield 8.7 g., 58%.

α-Amino-β-chloropropionic Acid.—The methyl ester of α-amino-β-chloropropionic acid hydrochloride was prepared by the method of Fischer and Raske[8] and was subsequently hydrolyzed in sodium hydroxide solution. The resulting salt was carefully neutralized with hydrochloric acid to produce α-amino-β-chloropropionic acid, m. p. 160°.

β,β'-Diselenodialanine.—One gram of α-amino-β-chloropropionic acid was digested with a water solution of barium hydrogen selenide at the boiling point for two hours. The solution was filtered and just neutralized (litmus) with ammonium hydroxide. A yellow, crystalline precipitate was formed after thirty-six hours in the refrigerator, which was filtered, washed with water, alcohol and ether. The crystals were thin, yellow, hexagonal plates which turned gray upon heating to 175–180°. The crystals melted with decomposition at 213–215°; yield, 0.55 g., 20%.

The same results were obtained when calcium hydrogen selenide was used instead of barium hydrogen selenide.

Anal. Calcd. for $C_6H_{12}O_4N_2Se_2$: Se, 47.27. Found[9]: Se, 47.09.

Method (II).—**Benzyl Chloromethyl Selenide.**—Seventy-three grams of benzyl selenol[2] was placed in a flask with 25 g. of polyoxymethylene. The mixture was

---

[1] Fredga, *Svensk Kem. Tids.*, **48**, 160 (1936); **49**, 124 and 139 (1937).

[2] E. P. Painter, THIS JOURNAL, **69**, 229 (1947).

[3] E. Abderhalden, "Biochemisches Handlexicon," Vol. IV, 649.

[4] J. L. Wood and V. du Vigneaud, *J. Biol. Chem.*, **131**, 267 (1939).

[5] H. Böhme, *Ber.*, **69**, 1610 (1936).

[6] J. L. Wood and V. du Vigneaud, *J. Biol. Chem.*, **134**, 413 (1940).

[7] E. Fischer and W. A. Jacobs, *Ber.*, **39**, 2949 (1906).

[8] E. Fischer and K. Raske, *ibid.*, **40**, 3717 (1907).

[9] W. O. Robinson, H. C. Dudley, K. T. Williams and H. G. Byers, *Ind. Eng. Chem., Anal. Ed.*, **6**, 274 (1934).

cooled in an ice-bath and saturated with dry hydrogen chloride. To this, 30 g. of calcium chloride was added, the mixture was allowed to stand at room temperature for twenty-four hours and the solid material was removed by filtration. The liquid was a yellow oil with a very unpleasant odor. The compound was unstable at high temperatures, boiling at 158–160°, 16 mm.

β-(Benzylseleno)-alanine.—Ten grams of benzyl chloromethyl selenide was refluxed for four hours with 15 g. of sodium phthalimidomalonic ester in the presence of toluene. The toluene was removed *in vacuo*, the compound recrystallized and the white crystals were collected. The compound was unstable at high temperatures and a melting point could not be determined. Fifteen grams of the compound was suspended in 100 ml. of an ethyl alcohol and water mixture (1:1) and 10 ml. of dioxane added. Two drops of phenolphthalein solution was added and the mixture was heated to 50°. Fifteen ml. of 5 N sodium hydroxide solution was added dropwise with stirring at a rate to maintain a temperature of 55–60°. When all of the alkali had been added the temperature of the solution was brought up to 70°. The solution was stirred constantly while the temperature was allowed to drop to room temperature. Hydrochloric acid was added until the solution was acid to phenolphthalein and the solution was distilled to half volume *in vacuo*. Water was added to make a total volume of 150 ml. and 20 ml. of concentrated hydrochloric acid was added with the evolution of carbon dioxide. The solution was heated for one and one-half hours, more hydrochloric acid added and heating continued for two more hours. The solution was taken to dryness, the residue dissolved in water and ammonium hydroxide was added until a neutral reaction was obtained with congo red. The precipitate which consisted of β-(benzylseleno)-alanine and phthalic acid was removed by filtering, suspended in boiling ethyl alcohol and again filtered. This was repeated until all of the phthalic acid had been removed leaving the β-(benzylseleno)-alanine as a white, crystalline residue, m. p. 185°; yield, 59%.

Anal. Calcd. for $C_{10}H_{13}O_2NSe$: Se, 30.52; C, 47.0; H, 5.07; N, 5.41. Found: Se,[9] 30.03; C, 47.0; H, 5.5; N,[10] 5.42.

β,β'-Diselenodialanine.—Three and one-half grams of β-(benzylseleno)-alanine was cleaved with concentrated hydriodic acid after digesting for forty-eight hours while air was bubbled through the mixture. Yellow hexagonal plates were obtained, m. p. 215° with decomposition; yield, 0.32 g.

Anal. Calcd. for $C_6H_{12}O_4N_2Se_2$: Se, 47.27. Found: Se, 47.10.

Summary

Two syntheses of the selenium analog of cystine are described which furnish additional evidence that selenium analogs may be substituted for the sulfur compounds used in published methods for the preparation of *dl*-cystine. In the first method α-amino-β-chloropropionic acid was treated with barium hydrogen selenide or calcium hydrogen selenide and the product was oxidized to produce the selenium analog of cystine. In the second method, the Gabriel synthesis of amino acids was used to produce the selenium analog from benzyl chloromethyl selenide and sodium phthalimidomalonic ester.

(10) J. K. Parnas and R. Wagner, *Biochem. Z.*, **125**, 253 (1931).

RENO, NEVADA RECEIVED OCTOBER 27, 1947

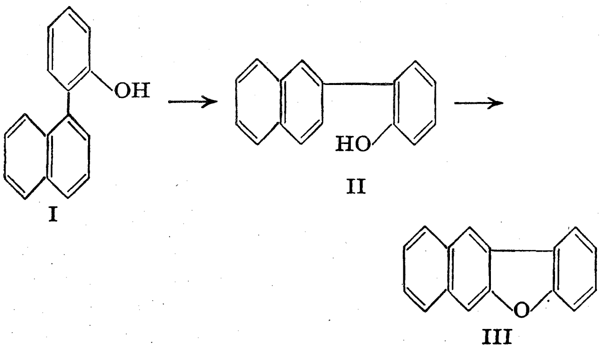
[CONTRIBUTION FROM THE U. S. BUREAU OF MINES, CENTRAL EXPERIMENT STATION]

Aromatic Cyclodehydrogenation. VII. Rearrangements in the Phenylnaphthalene Series[1]

BY MILTON ORCHIN[2] AND LESLIE REGGEL[2]

It was shown previously[3] that liquid-phase treatment of 2′-hydroxy-1-phenylnaphthalene, I, with a palladium-on-charcoal catalyst resulted in cyclodehydrogenation to 1,9-benzoxanthene. It was of interest to study the behavior of I under the vapor-phase conditions used in earlier cyclodehydrogenation studies.

Treatment of I with a chromia–alumina catalyst at 490° gave a mixture of conversion products. The first compound to be isolated from this mixture had properties and composition consistent with its formulation as the hitherto unknown 2′-hydroxy-2-phenylnaphthalene, II. It had a higher melting point than I and on treatment with diazotized p-nitroaniline gave a color identical with that observed for I under the same conditions. The ultraviolet absorption spectrum of II differed from that of I in the same manner as the spectrum of 2-phenylnaphthalene differed from that of 1-phenylnaphthalene.[4] Although none of this evidence fixes the position of the hydroxyl group, the isolation of compound III supports its placement in the *ortho* position, as shown in II.



A second compound isolated from the reaction mixture had properties identical with those reported[5] for benzo[b]naphtho[2,3-*d*]furan, III

---

[1] Published by permission of the Director, U. S. Bureau of Mines.

[2] Organic Chemist, Central Experiment Station, U. S. Bureau of Mines, Pittsburgh, Pennsylvania.

[3] Orchin, THIS JOURNAL, in press.

[4] Friedel, Orchin and Reggel, *ibid.*, **70**, 199 (1948).

[5] Robinson and Mosettig, *ibid.*, **61**, 1148 (1939).

(brazan); direct comparison with a sample of brazan kindly furnished by Dr. E. Mosettig confirmed the identity. The formation of III from I can be explained by the rearrangement of I to II followed by the intramolecular loss of hydrogen between the hydroxyl group and the naphthalene nucleus.[3] The ultraviolet absorption spectrum of brazan is shown in Fig. 1.[6]

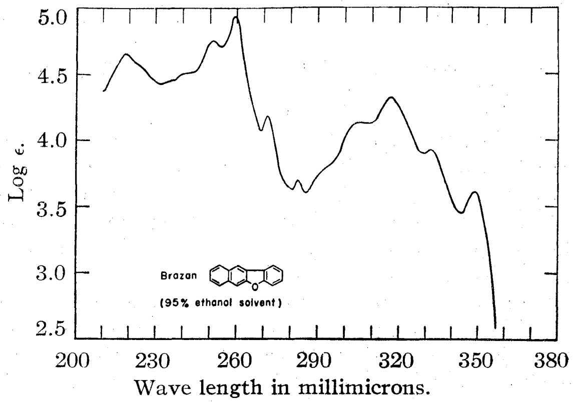
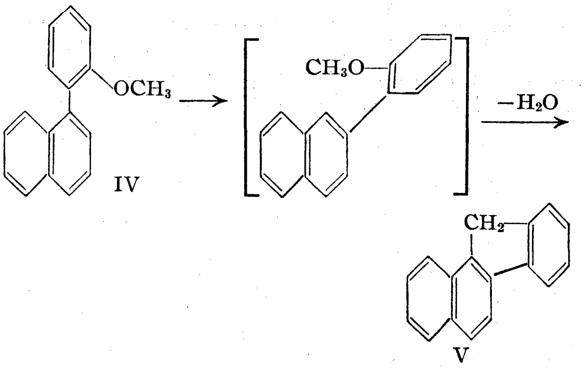


Fig. 1.—Ultraviolet absorption spectrum of brazan.

2-Phenylnaphthalene was also isolated from the reaction products.

Treatment of 1-*o*-anisylnaphthalene, IV, with a chromia–alumina catalyst at 510–520° gave a mixture of products from which it was exceedingly difficult to separate pure compounds. The hydrocarbon fraction of the products appeared to be a mixture of 1,2- and 2,3-benzfluorene (ultraviolet absorption spectra) and indeed one fraction, on oxidation, gave a ketone the color and melting point of which were identical with that reported[7] for authentic 1,2-benzfluorenone. The transformation of IV to 1,2-benzfluorene, V, may be explained by assuming the shift of the anisyl group in IV to the *beta* position to give the indicated intermediate, followed by a most unusual intramolecular loss of water (cyclodehydration) to V. The presence of 2,3-benzfluorene can be accounted for by assuming cyclodehydration of the intermediate into the beta position of the naphthalene nucleus.



Although the various fractions from IV were examined intensively by ultraviolet spectra, no evidence was found for the presence of fluoranthene or a substituted fluoranthene. We have previously shown[8] that 1-phenylnaphthalene undergoes cyclodehydrogenation to fluoranthene in good yield, and that there is only slight migration of the phenyl group to give 2-phenylnaphthalene. The present work makes it appear probable that in some cases migration of a group from the 1- to the 2-position of the naphthalene nucleus takes precedence over cyclodehydrogenation involving the 8-position.

Experimental[9]

Apparatus and Catalysts.—The apparatus used was similar to that employed in earlier experiments.[10] The catalyst tube was vertical and was heated by means of a standard combustion furnace. A detailed drawing and photograph of the apparatus will be found in a Bureau of Mines publication.[11] The catalyst, designated as Cr-181, was purchased from the Harshaw Chemical Company, Cleveland, Ohio.[8]

Conversion of 2′-Hydroxy-1-phenylnaphthalene, I.—During the course of two hours, 7.1 g. of molten I[3] was passed over 76 g. of catalyst at 490°. The partly crystalline material in the receiver weighed 6.18 g. This material was refluxed for a short time with a small volume of petroleum ether and the insoluble material filtered to give 1.4 g., melting point 78–91°. Three recrystallizations gave 0.47 g. of colorless crystals, m. p. 96.2–96.8°. *Anal.* Calcd. for $C_{16}H_{12}O$: C, 87.2; H, 5.5. Found: C, 87.7; H, 5.7. When this compound was tested with diazotized *p*-nitroaniline,[12] it produced a deep color identical with that obtained when I was similarly treated. The infrared absorption spectrum of the compound showed a strong band in the 2.8 micron region, indicating the presence of a hydroxyl group. The compound is regarded as 2′-hydroxy-2-phenylnaphthalene, II. The ultraviolet absorption spectrum of this compound has been reported.[4] Ferric chloride tests in aqueous and alcoholic solutions were negative with both 2′-hydroxy-1-phenyl- and 2′-hydroxy-2-phenylnaphthalene.

All mother liquors were combined and chromatographed on alumina–celite. Two percolate fractions were collected, the column extruded, and arbitrarily cut into four fractions. The first percolate fraction on evaporation gave a small (unweighed) quantity of material with the odor and appearance of naphthalene; it was discarded. Evaporation of the second percolate fraction gave 0.7 g. of material which after one crystallization from methanol was obtained as colorless crystals, m. p. 99.4–102.2°; mixed melting point with authentic 2-phenylnaphthalene[4] showed no depression. The fractions on the chromatographic column were called 3, 4, 5, and 6 in order of increasing strength of adsorption. Fraction 3 on elution gave 0.22 g. of an obvious mixture which was not investigated. Fraction 5 (0.10 g.) was also not investigated. Fraction 6 consisted of 4.57 g. of a very viscous liquid which was probably a mixture of I and II. Frac-

---

(6) We wish to thank Mrs. Lois Harnack and Mrs. Lois Pierce for the spectra measurements. It is a pleasure to acknowledge the very valuable assistance of Dr. Robert A. Friedel in the interpretation of the data.

(7) Cook and Hewett, *J. Chem. Soc.*, 365 (1934); Kruber, *Ber.*, **70B**, 1556 (1937).

(8) Orchin and Reggel, THIS JOURNAL, **69**, 505 (1947).

(9) All melting points corrected. All analyses were microanalyses performed by G. L. Stragand, University of Pittsburgh.

(10) Orchin, *Ind. Eng. Chem., Anal. Ed.*, **17**, 673 (1945).

(11) Orchin, Reggel, Friedel and Woolfolk, Bureau of Mines Technical Paper, in press.

(12) Fieser, "Experiments in Organic Chemistry," D. C. Heath & Co., Boston, Mass., 2nd edition, 1941, p. 259.

tion 4 gave 0.12 g. of material, which, after two recrystallizations from ethanol, was obtained as colorless plates, m. p. 209.2–209.8°. *Anal.* Calcd. for $C_{16}H_{10}O$: C, 88.1; H, 4.6. Found: C, 88.3; H, 5.1. This material was identical (melting point, mixed melting point, ultraviolet absorption spectrum) with a sample of brazan obtained from Dr. E. Mosettig (secured from the Gesellschaft fur Teerverwertung).[13] It has been reported[5] that brazan does not form a picrate. We have found that the *s*-trinitrobenzene complex of brazan is very unstable, but that it readily forms a complex with 2,4,7-trinitrofluorenone[14] in the usual manner. The complex crystallized from benzene–alcohol in orange needles, m. p. 215.2–216.0°. *Anal.* Calcd. for $C_{29}H_{15}N_3O_8$: C, 65.3; H, 2.8. Found: C, 66.5; H, 3.0.

Conversion of 1-*o*-Anisylnaphthalene, IV.—During two and one-half hours, 11.25 g. of molten IV[3] was passed over 98 g. of catalyst at 510–520°. The partly crystalline product weighed 6.4 g. Four recrystallizations gave 0.22 g. of material which still had not reached a constant melting point. The material was converted to the trinitrofluorenone[14] complex, the orange needles recrystallized twice, and then decomposed by chromatography on alumina. The recovered hydrocarbon portion, melting point 203.0–205.2°, was still impure and was shown by ultraviolet absorption spectra (Fig. 2) to be a mixture of 1,2-benzfluorene and 2,3-benzfluorene.[15] About 0.08 g. of the impure material was refluxed with 0.20 g. of sodium dichromate dihydrate in 5 cc. of acetic acid for fifteen minutes, the mixture poured into water, and extracted with benzene. The benzene solution was extracted with sodium carbonate and the neutral portion chromatographed on alumina. Two bands were observed, separated, and eluted. The bottom orange colored band consisted of 29 mg.; recrystallization gave orange crystals, m. p. 129.4–132.4°. *Anal.* Calcd. for $C_{17}H_{10}O$: C, 88.7; H, 4.4. Found: C, 88.4; H, 4.3. The analysis, melting point, and appearance of this compound are consistent with that of 1,2-benzfluorenone.[7] The upper yellow band from the chromatography of the oxidation products consisted of 27 mg. and could not be recrystallized. The ultraviolet absorption spectrum was very similar to that of authentic 2,3-benzfluorenone.

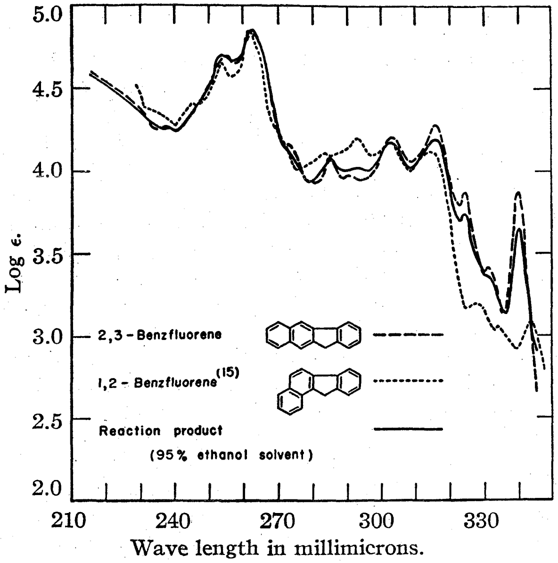


Fig. 2.—Ultraviolet absorption spectra.

The mother liquor containing 6.3 g. of the conversion product was evaporated to dryness. A methoxyl determination indicated that only a very small amount (2%) of this mixture could be unchanged starting material. All the product was dissolved in benzene and extracted with Claisen alkali. The alkali-soluble fraction weighed 2.5 g.; ultraviolet absorption spectrum indicated it was principally 2′-hydroxy-1-phenylnaphthalene, I. Chromatography of the neutral fraction (4.0 g.) gave 0.02 g. of naphthalene, 0.06 g. of 2-phenylnaphthalene, a third fluorescent fraction of 2.7 g. and a fourth fraction of 0.3 g. The ultraviolet absorption spectrum of fraction 4 indicated that it was a mixture of 1,2- and 2,3-benzfluorenes. The ultraviolet absorption spectrum of fraction 3 indicated principally a mixture of 1,2- and 2,3-benzfluorenes with some 1,9-benzoxanthene, but no pure compounds could be isolated by crystallization of the mixture, of the T. N. F. complexes, chromatography, or crystallization of the T. N. B. complexes.

Summary

Vapor phase treatment of 2′-hydroxy-1-phenylnaphthalene over a chromia–alumina catalyst gave a mixture of products from which a compound of the probable structure of 2′-hydroxy-2-phenylnaphthalene was isolated. There was also obtained benzo[b]naphtho[2,3-*d*]furan (brazan).

Vapor phase treatment of 1-*o*-anisylnaphthalene gave a mixture of products among which 1,2- and 2,3-benzfluorene were shown to be present. These compounds were probably formed by the migration of the anisyl group to the *beta* position followed by an unusual type of cyclodehydration between the methoxyl group and the aromatic nucleus.

PITTSBURGH, PENNSYLVANIA RECEIVED OCTOBER 14, 1947

---

(13) A strictly unambiguous proof of structure of brazan is still lacking since, as Robinson and Mosettig have indicated, their synthesis gave two isomers, one of which was identical with the German commercial sample and to which they therefore assigned the structure of benzo[b]naphtho[2,3-*d*]furan (brazan).

(14) Orchin and Woolfolk, THIS JOURNAL, **68**, 1727 (1946).

(15) The ultraviolet absorption spectrum of 2,3-benzfluorene was obtained from a carefully purified authentic sample in our possession. The spectrum of 1,2-benzfluorene was obtained from the work of Mayneord and Roe, *Proc. Roy. Soc.* (*London*), **A158**, 634 (1937). Since the latter spectrum was determined in chloroform solution, we determined the spectrum of 2,3-benzfluorene in both alcohol and chloroform; band shifts were of the order of 1–3 mμ, and extinction coefficients were practically identical. On this basis the small band shifts could be safely applied to the corresponding bands in 1,2-benzfluorene, to produce a reliable spectrum of this compound in alcohol for comparison purposes. The spectra of the two benzfluorenes are very similar; the chief differences are not found in the location of band maxima, but in the extinction coefficients. The coefficients of our sample are intermediate between those of the two benzfluorenes.

[CONTRIBUTION FROM THE ARMOUR LABORATORIES]

Preparation of New Derivatives of Diethylstilbestrol and Hexestrol. II. Extension of the Claisen Rearrangement

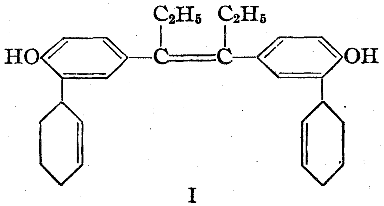
BY EMIL KAISER, A. L. ANDERSEN, JR., AND J. J. SVARZ

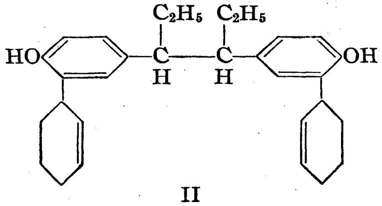
Rearrangement of the diallyl ethers of diethylstilbestrol and hexestrol to the corresponding 3,3'-disubstituted derivatives has been reported.[1]

These investigations were extended to the study of the behavior of the di-2-cyclohexene-1-yl ethers of synthetic estrogens. Heretofore only one other application of the Claisen rearrangement to 2-cyclohexene-1-yl phenol ethers has been described.[2] The 2-cyclohexene-1-yl ether of phenol was pyrolyzed at 215° yielding 5% of *o*-cyclohexene-2-phenol.

The di-2-cyclohexene-1-yl ether of diethylstilbestrol was prepared by two different methods: Method I, the reaction between 1-bromocyclohexene-2, diethylstilbestrol and potassium carbonate in methyl ethyl ketone; Method II, the reaction between 1,2-dibromocyclohexane and diethylstilbestrol in the presence of sodium alcoholate. Method I yielded 12% of the theoretical amount of di-2-cyclohexene-1-yl ether of diethylstilbestrol. Method II, an adaptation of the procedure of Solonina,[3] yielded 25 to 35% of the same compound. Method II was therefore used to prepare the dicyclohexene ether of hexestrol.

The di-2-cyclohexene-1-yl ethers were rearranged to the 3,3'-disubstituted derivatives by refluxing in diethylaniline in an atmosphere of nitrogen. 3,3'-Di-(2-cyclohexene-1-yl)-diethylstilbestrol (I) was isolated in a 25% yield and 3,3'-di-(2-cyclohexene-1-yl)-hexestrol (II) in a 38% yield.


I


II

A better yield of rearrangement products averaging 65 to 67% was obtained by the use of benzoic anhydride in the reaction mixture. The dibenzoates of the 3,3'-disubstituted products were formed in this reaction. Saponification of the dibenzoates yielded 3,3'-di-(2-cyclohexene-1-yl)-diethylstilbestrol and 3,3'-di-(2-cyclohexene-1-yl)-hexestrol, respectively. These compounds were identical to those formed by the rearrangements of the di-2-cyclohexene-1-yl ethers without the use of benzoic anhydride.

Experimental[4]

Di-2-cyclohexene-1-yl Ether of Diethylstilbestrol. Method I.—Diethylstilbestrol and 1-bromocyclohexene-2 were treated in the same manner as described for allyl phenyl ether.[5]

The di-2-cyclohexene-1-yl ether of diethylstilbestrol was crystallized from methanol, m. p. 118–119°, yield 12.1%.

Method II.—Twenty grams of 1,2-dibromocyclohexane was added to a solution prepared by dissolving 4 g. of sodium and 10.72 g. of diethylstilbestrol in 100 ml. of absolute ethanol and the mixture refluxed for twenty-four hours. The solution was then concentrated under reduced pressure and treated with a solution of 10 g. of sodium hydroxide in 100 ml. of water. The alkaline solution was extracted with ethyl ether and the ether layer washed with 100 ml. of 10% aqueous sodium hydroxide and water. The ether was removed by distillation and the residue crystallized twice from 100-ml. portions of 95% ethanol; m. p. 117–119°; yield 4.43 g. (25.3%).

Anal. Calcd. for $C_{30}H_{36}O_2$: C, 84.08; H, 8.46. Found: C, 84.08; H, 8.57.[6]

Preparation of 3,3'-Di-(2-cyclohexene-1-yl)-diethylstilbestrol.—Two grams of the di-2-cyclohexene-1-yl ether of diethylstilbestrol was dissolved in 15 ml. of diethylaniline and the solution refluxed for seven hours in an atmosphere of nitrogen. The diethylaniline was removed and the product crystallized from an ethyl ether–petroleum ether mixture as described for 3,3'-diallyldiethylstilbestrol.[1] The substance was recrystallized by dissolving in 10 ml. of ethanol and adding 10% of water to the hot solution; yield 0.5 g. (25%), m. p. 154–156°.

Anal. Calcd. for $C_{30}H_{36}O_2$: C, 84.08; H, 8.46. Found: C, 83.62; H, 8.86.[7]

Preparation of the 3,3'-Di-(2-cyclohexene-1-yl)-diethylstilbestrol Dibenzoate.—One and a half grams of the di-(2-cyclohexene-1-yl)-diethylstilbestrol and 3 g. of benzoic anhydride were dissolved in 15 ml. of diethylaniline and refluxed for six hours in an atmosphere of nitrogen. After cooling 100 ml. of 2 *N* hydrochloric acid was added and the mixture extracted with ether. The ether layer was washed with 2 *N* acid, water, and dried over sodium sulfate. It was then concentrated to about 15 ml. and 30 ml. of methanol added. The dibenzoate crystallized in the cold. It was recrystallized by dissolving in 15 ml. of carbon tetrachloride and adding 30 ml. of methanol; yield 1.5 g., m. p. 188–199°.

---

[1] Kaiser and Svarz, THIS JOURNAL, **68**, 636 (1946).

[2] Cornforth, Hughes and Lions, *J. Proc. Roy. Soc., N. S. Wales*, **71**, 323 (1938).

[3] W. Solonina, *J. Chem. Soc.*, **76**, I, 681 (1899).

[4] All melting points uncorrected.

[5] Claisen, *Ann.*, **418**, 69 (1919).

[6] Analysis made at the California Institute of Technology, Pasadena, California.

[7] Figures obtained for the percentage of carbon were consequently lower than the calculated values, regardless whether the compound was obtained by rearrangement of the ether or by saponification of the dibenzoate. The carbon values of the dibenzoate checked well with the calculated values. Such irregularities have been reported previously for 4,4'-dioxy-2,2-methyl-α,β-diphenylbutane by Bretschneider, de Ionze Bretschneider and Ajtai, *Ber.*, **74**, 571 (1941).

Anal. Calcd. for $C_{44}H_{44}O_4$: C, 82.98; H, 6.97. Found: C, 82.96; H, 7.15.[6]

Saponification of 3,3′-Di-(2-cyclohexene-1-yl)-diethylstilbestrol Dibenzoate.—One-half gram of 3,3′-di-(2-cyclohexene-1-yl)-diethylstilbestrol dibenzoate was refluxed for two hours in an atmosphere of nitrogen with 10 ml. of a 10% potassium hydroxide–isopropanol solution. After cooling the mixture was diluted with 30 ml. of water and acidified with *N* hydrochloric acid. An oil precipitated which solidified on standing at room temperature. This was filtered, washed with water and dissolved in 10 ml. of ethanol. The solution was clarified with a small amount of charcoal. After filtration 10% of water was added and the solution cooled. Crystals were obtained which melted at 153–156° and were identical to the 3,3′-di-(2-cyclohexene-1-yl)-diethylstilbestrol obtained by rearrangement of the ether; yield 0.15 g.

Anal. Calcd. for $C_{30}H_{36}O_2$: C, 84.08; H, 8.46. Found: C, 83.25; H, 8.56.[8]

Di-2-cyclohexene-1-yl Ether of Hexestrol.—Ten and eight-tenths grams of hexestrol was treated in the same manner as described in Method II for the preparation of the di-2-cyclohexene-1-yl ether of diethylstilbestrol. The product obtained after treatment with alkali was crystallized twice from 95% ethanol; m. p. 123–124°, yield 5.86 g. (34.1%).

Anal. Calcd. for $C_{30}H_{38}O_2$: C, 83.66; H, 8.89. Found: C, 83.57; H, 8.68.[6]

3,3′-Di-(2-cyclohexene-1-yl)-hexestrol.—This compound was prepared in the manner described for 3,3′-di-(2-cyclohexene-1-yl)-diethylstilbestrol. One and a half grams of the di-2-cyclohexene-1-yl ether of hexestrol yielded 0.58 g. of rearranged product; m. p. 169–171°.

Anal. Calcd. for $C_{30}H_{38}O_2$: C, 83.66; H, 8.89. Found: C, 83.4; H, 9.06.[6]

3,3′-Di-(2-cyclohexene-1-yl)-hexestrol Dibenzoate.—This compound was prepared in the manner described for 3,3′-di-(2-cyclohexene-1-yl)-diethylstilbestrol dibenzoate. One gram of the di-2-cyclohexene-1-yl ether of hexestrol when treated with 2 g. of benzoic anhydride in diethylaniline and crystallized from a carbon tetrachloride–methanol mixture yielded 0.98 g. of a product melting at 198–201°. Repeated analysis showed the existence of one mole of methanol of crystallization.

Anal. Calcd. for $C_{44}H_{46}O_4 \cdot CH_3OH$: C, 80.56; H, 7.51. Found: C, 80.64,[6] 80.51,[8] 80.80[9]; H, 7.06,[6] 7.25,[8] 6.95.[9]

The methanol of crystallization was removed by drying in high vacuum.

Anal. Calcd. for $C_{44}H_{46}O_4$: C, 82.72; H, 7.29. Found: C, 82.04; H, 7.47.[9]

3,3′-Di-(2-cyclohexene-1-yl)-hexestrol Dipropionate.—Twenty-seven hundreths of a gram of 3,3′-di-(2-cyclohexene-1-yl)-hexestrol was refluxed with 10 ml. of propionic anhydride for two and one-half hours. The product obtained after hydrolysis of the mixture with water was crystallized twice from 95% ethanol; yield 0.15 g., m. p. 133.5–135°.

Anal. Calcd. for $C_{36}H_{46}O_4$: C, 79.66; H, 8.54. Found: C, 79.5; H, 8.46.[8]

Summary

The di-2-cyclohexene-1-yl ethers of diethylstilbestrol and hexestrol have been prepared by two methods. Application of the Claisen rearrangement to these compounds produced the corresponding 3,3′-disubstituted derivatives. Use of benzoic anhydride in the rearrangement of the ethers increased the yield considerably.

---

(8) Analysis made by Dr. Charles W. Beazley, Skokie, Illinois.

(9) Analysis made by Dr. Joseph F. Alicino, Metuchen, New Jersey.

CHICAGO 9, ILLINOIS RECEIVED AUGUST 22, 1947

[CONTRIBUTION FROM THE WILLIAM G. KERCKHOFF LABORATORIES OF THE BIOLOGICAL SCIENCES, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Structure Determination and Synthesis of a Plant Growth Inhibitor, 3-Acetyl-6-methoxybenzaldehyde, Found in the Leaves of *Encelia Farinosa*

BY REED GRAY AND JAMES BONNER

Introduction

In a recent publication[1] it was demonstrated that the leaves of *Encelia farinosa* when applied to tomato and to other plants exert a marked inhibition of growth. The toxic principle was removed by extracting the dry *Encelia* leaves with purified ether. Water and ether extracts of the *Encelia* leaves, when fed to tomato seedlings in solution culture, caused death of the plants within one day. Fractionation of the leaf extracts led to the isolation of a pure crystalline compound which was toxic when fed to tomato seedlings in solution culture. It was suggested that the presence of the growth inhibitor in the leaves may be responsible for the fact that only few individuals of desert annuals are found growing in close relationship with the *Encelia* shrub on the desert.

The present work is concerned with the characterization and synthesis of this new toxic compound which was isolated from the *Encelia* leaves.

Experimental

Physical and Chemical Properties.—The toxic material crystallizes in colorless needles from ether or alcohol, m. p. 144°. Sublimation causes no change in melting point. The compound has no odor but when the crystals are heated a pleasant perfume-like odor is detected. It burns with a smoky flame leaving no residue after ignition. A sodium fusion showed the absence of nitrogen, sulfur and halogens. Evidently the compound is composed only of the elements carbon, hydrogen and oxygen. The compound is soluble in hot water, warm ether, alcohol, acetone, benzene and chloroform. It is insoluble in cold water, 5% hydrochloric acid, 5% sodium hydroxide, petroleum ether and carbon tetrachloride. It dissolves in

---

(1) Gray and Bonner, *Am. J. Bot.*, Jan. (1948).

concentrated sulfuric, hydrochloric, and hydrobromic acids producing orange-colored solutions.

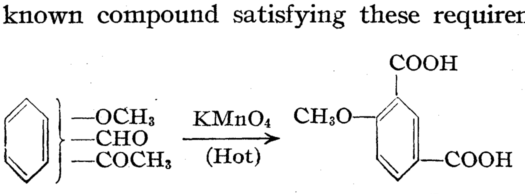
Classification tests[2] carried out on the toxic compound gave the following results: A red color with anhydrous aluminum chloride and chloroform, a substitution reaction with bromine in chloroform, a brown precipitate with cold permanganate solution, a precipitate with 2,4-dinitrophenylhydrazine reagent, a green color with Fehling solution, a black precipitate with Tollens reagent, a violet color with Schiff reagent, a positive test for methyl ketones with both sodium nitroprusside[3] and *o*-nitrobenzaldehyde,[3] no color with ferric chloride, or with the hydroxamic acid test[4] for esters. When heated in alkaline solution a new compound is formed as a result of condensation, m. p. 260–265° with decomposition. These tests show that an aldehyde and a methyl ketone group may be present in the toxic compound which also contains a benzene ring.

2,4-Dinitrophenylhydrazine Derivative.—A cold saturated solution of 2,4-dinitrophenylhydrazine in 95% ethyl alcohol was added to 5 mg. of the compound dissolved in 1 cc. of alcohol. After adding a drop of conc. hydrochloric acid, an orange precipitate formed immediately. The derivative was filtered off, washed twice with alcohol and dried, m. p. 258–261°. The derivative was insoluble in most organic solvents, and could be recrystallized only from nitrobenzene.

Quantitative Analysis.—A micro analysis[5] of the pure compound gave results agreeing closely with the empirical formula $C_{10}H_{10}O_3$. Calcd. for $C_{10}H_{10}O_3$: C, 67.14; H, 5.82; mol. wt., 178. Found: C, 67.41; H, 5.62; mol. wt. (Rast), 192; $-OCH_3$, 17.98.

A calculation of the molecular weight assuming one methoxyl group per molecule gives 172. A quantitative precipitation with 2,4-dinitrophenylhydrazine using the method described above shows that two moles of the reagent combine with one mole of the toxic compound giving 184 for the molecular weight. A Zerewitinoff determination showed the absence of active hydrogen.

The results indicate that the toxic compound is a benzene derivative containing an aldehyde, methyl ketone, and a methoxyl group, and having a molecular weight in the range 172–192. Considering the molecular formula ($C_{10}H_{10}O_3$) to be correct, no other groups could be present. A search in the chemical literature revealed no known compound satisfying these requirements, therefore, degradation to simpler known compounds was undertaken.



I II (1)

Oxidation with Hot Permanganate.—A 20-mg. sample of the toxic compound was mixed with 2 cc. of saturated potassium permanganate solution in a small reflux tube. The tube was sealed and heated on a steam-bath until the color of the permanganate had disappeared; this took two and one-half hours. The tube was cooled, opened, and the contents emptied into a centrifuge tube. After centrifuging, the clear supernatant was drawn off. Upon acidifying with dilute hydrochloric acid, a white precipitate formed. The precipitate was filtered off, recrystallized from hot water, dried and sublimed, m. p. 264–267°.

Examination of the carboxylic acid derivatives of anisole found in the literature gave the following possibilities for the oxidation product of the toxic compound: 5-methoxyisophthalic acid, m. p. 265,[6] 270°,[7] 4-methoxyisophthalic acid, m. p. 245,[8] 261,[9] 275°[10]; 2-methoxyterephthalic acid, m. p. 274–276, 277–279°, 281°.[11] The melting points of these acids vary considerably as determined by different investigators. Therefore, the acids were synthesized in order that mixed melting points with the oxidative product of the toxic compound could be taken.

5-Methoxyisophthalic Acid.—This compound was prepared by methylating 5-hydroxy-1,3-dimethylbenzene with dimethyl sulfate and oxidizing the side chains with permanganate as described above. After recrystallizing from hot water and subliming it melted at 269–270°. A mixed melting point with the oxidation product of the toxic compound gave a considerable depression.

4-Methoxyisophthalic Acid (II). (a) Prepared from *p*-Cresol.—An aldehyde group was substituted in the position ortho to the phenolic group of *p*-cresol using chloroform and alkali (Reimer–Tiemann reaction). The resulting 3-methyl-6-hydroxybenzaldehyde was methylated with dimethyl sulfate and then the side chains were oxidized to acids with permanganate. The product was recrystallized from hot water, dried and sublimed, m. p. 264–267°. A mixed melting point determination with the oxidation product of the natural toxic compound gave no depression in melting point.

(b) Prepared from 2,4-Dimethylphenol.—By methylating 5 g. of this compound with dimethyl sulfate in strong alkali, the methyl ether was obtained, b. p. 192°. To 2.72 g. of the ether in a round-bottomed flask fitted with a reflux condenser was added 200 cc. of water containing 12.64 g. of potassium permanganate. The mixture was heated on a steam-bath until the color of the permanganate had all disappeared (eight hours). The manganese dioxide was filtered off and the filtrate acidified with hydrochloric acid. The white crystals which separated were filtered off, recrystallized from hot water, and dried in an oven, m. p. 273–275°, yield 1 g., 25% of theoretical. After subliming the melting point was lowered to 264–267°.

The above reaction tentatively establishes the identity of the oxidative product of the toxic compound with 4-methoxyisophthalic acid (II). This indicates that the toxic compound which contains an aldehyde and a methyl ketone group must be either 3-acetyl-6-methoxybenzaldehyde,

---

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

(3) Feigl, "Qualitative Analysis by Spot Tests," Nordemann, 1939, p. 288.

(4) Davidson, *J. Chem. Ed.*, **17**, 81 (1940).

(5) Micro analyses, by G. Oppenheimer and G. Swinehart.

(6) *Chem. Abs.*, **29**, 137 (1935).

(7) Kruber and Schmitt, *Ber.*, **64**, 2276 (1931).

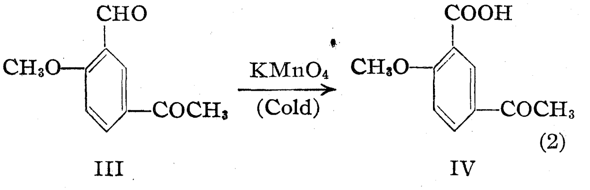
(8) Jacobson, *ibid.*, **11**, 899 (1878).

(9) Schall, *ibid.*, **12**, 828 (1879); Stoerner and Behn, *ibid.*, **34**, 2458 (1901).

(10) Chattaway and Calvet, *J. Chem. Soc.*, **131**, 2916 (1928).

(11) Beilstein, Band X, 505, 1927.

or 3-acetyl-4-methoxybenzaldehyde. The question as to which isomer is the correct one was answered by a selective oxidation of the aldehyde group with cold potassium permanganate solution.[2]



(2)

Selective Oxidation of the Aldehyde Group.—A sample of 30 mg. of the toxic compound was mixed in a small test-tube with 1 cc. of saturated potassium permanganate solution. The mixture was shaken for forty-five minutes, centrifuged and the supernatant drawn off. A few drops of ethyl alcohol were added to reduce the excess permanganate. A drop of 5 *N* sodium hydroxide solution hastened the reaction. After the violet color had disappeared the solution was heated to 60° on a water-bath and centrifuged. The clear supernatant was drawn off and concentrated to 0.33 cc. by bubbling air through the solution while heating on a water-bath. The solution was acidified with dilute hydrochloric acid. After standing for a few minutes, crystals began to separate and after two hours the crystals were filtered off and recrystallized from hot water. The yield was approx. 10 mg., m. p., 150–151°. This product gave a positive test for methyl ketones but gave a negative test for aldehydes.

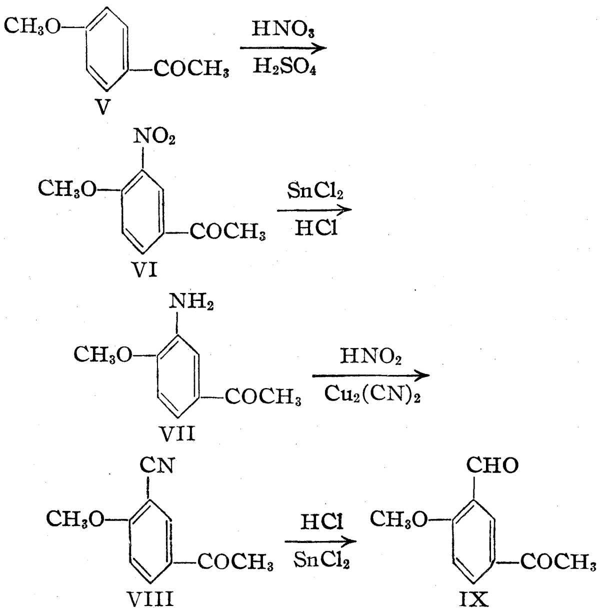
The identity of this cold permanganate oxidative product was established by its synthesis. The literature[12] reports 152° as the melting point of 3-acetyl-6-methoxybenzoic acid. (IV) This compound was synthesized and a mixed melting point determination made with the cold permanganate oxidative product of the toxic compound.

3-Acetyl-6-methoxybenzoic Acid (IV).—The corresponding phenol was prepared according to the directions of Bialobrzeski and Menki[13] and methylated as described by Krannichfeldt.[12] The product after recrystallization from hot water melted at 150–151°, and a mixed melting point with a cold permanganate oxidative product of the toxic compound showed no depression.

This determination shows that the aldehyde group is ortho to the methoxyl group and that the methyl ketone group must be in the para position. Therefore the structure of the toxic compound isolated from the *Encelia* leaves is established as 3-acetyl-6-methoxybenzaldehyde (III). This compound has not been reported in the chemical literature.

Synthesis

Since more of the toxic compound was needed for physiological testing, and since it had not been prepared before, synthesis of the compound was undertaken. A number of methods for synthesis of aromatic aldehydes and ketones were tried without success. A method was found by which the compound could be prepared, however, starting with *p*-methoxyacetophenone, according to the scheme



4-Methoxy-3-nitroacetophenone (VI).—The preparation of this compound was accomplished by nitration of 50 g. of *p*-methoxyacetophenone (V) according to the procedure of Bogert and Curtin[14]; yield 61.6 g., 95%; m. p. 96–98°.

3-Amino-4-methoxyacetophenone (VII).—The preparation of the amino compound from the corresponding nitro compound using tin and hydrochloric acid has been mentioned by Bogert and Curtin.[14] Directions were not given. In the present work poor yields and a colored product were obtained using tin and hydrochloric acid. It was found that stannous chloride in hydrochloric acid gave better yields and a colorless product.

Powdered stannous chloride dihydrate (180 g.) was dissolved in 180 cc. of concd. hydrochloric acid contained in a 1-liter Erlenmeyer flask. The solution was cooled to 0° in an ice–salt-bath and 40 g. of 4-methoxy-3-nitroacetophenone was added all at once with stirring. The ice-bath was removed, and the nitro compound dissolved as the reaction proceeded. When the heat of the reaction had raised the temperature to 95°, the flask and contents were cooled to 85° in the ice-bath and then the ice-bath was removed.

Light yellow crystals of the double salt of the hydrochloride of the amine and stannic chloride started to separate immediately. The mixture was stirred and allowed to cool slowly to room temperature. The mixture was cooled in the ice-bath and the double salt was filtered off. The amine was released by adding 50 cc. of water to the salt and then adding an excess of 40% sodium hydroxide solution. The amine was filtered off by suction, washed with cold water, and recrystallized from alcohol. Small colorless platelets were obtained which melted at 100–101°; yield, 25.7 g., 76% of theoretical.

3-Acetyl-6-methoxybenzonitrile (VII).—The nitrile was also prepared by Bogert and Curtin[14] using the Sandmeyer method, but no details were given. Borsche and Barthenheier[15] prepared this compound from *o*-methoxybenzonitrile using the Friedel–Crafts synthesis. The original Sandmeyer method with some modification was found to give a reasonably good yield.

To 20 g. of cuprous chloride suspended in 80 cc. of water was added a solution containing 30 g. of sodium cyanide dissolved in 50 cc. of water. Heat was evolved and after cooling, the solution was filtered. An additional 160 cc. of water was added and the solution cooled to 0°

---

(12) Krannichfeldt, *Ber.*, **47**, 158 (1914).

(13) Bialobrzeski and Menki, *ibid.*, **30**, 1776 (1879).

(14) Bogert and Curtin, THIS JOURNAL, **45**, 2161–2167 (1923).

(15) Borsche and Barthenheier, *Ann.*, **553**, 250 (1942).

in an ice–salt-bath. Meanwhile, 18 g. of 3-amino-4-methoxyacetophenone was mixed with 100 cc. of water. To this mixture was added 20 cc. of concentrated hydrochloric acid. The amine dissolved and 18 cc. more of concd. hydrochloric acid was added. The solution was cooled to 0° in an ice–salt-bath with stirring. Fine crystals of the amine hydrochloride separated. The cold solution was diazotized by adding from a dropping funnel a cold solution of 11 g. of sodium nitrite dissolved in 50 cc. of water, until an excess was indicated by starch iodide paper. The temperature was kept at 0° during the reaction. The diazonium solution was poured slowly with vigorous shaking into the cold cuprous cyanide solution contained in a 2-liter Erlenmeyer flask. A yellow-brown precipitate formed. Both solutions were kept at 0° until the addition was complete. The mixture was stirred for two hours longer while allowing the contents to reach room temperature. The mixture was then heated on a water-bath for thirty minutes and finally heated to boiling over a burner. The reaction was carried out under a hood, as hydrogen cyanide is given off. The mixture was cooled, filtered, and the residue dried in the room. The residue was extracted with hot benzene. A white copper salt remained behind. From the hot benzene solution light yellow needles of 3-acetyl-6-methoxybenzonitrile (VIII) crystallized, m. p. 157–158°; yield, 13.1 g., 68.5% of theoretical. Bogert and Curtin[14] report the m. p. 159.5°, while Borsche and Barthenheier[15] report 155° for the melting point of the nitrile.

3-Acetyl-6-methoxybenzaldehyde (IX).—This compound has not been reported previously. The aldehyde was prepared from the corresponding nitrile using Stephen's reaction. After a number of experiments it was found that the following conditions gave the best yield.

To 20 g. of anhydrous stannous chloride (prepared by the action of acetic anhydride on stannous chloride dihydrate) contained in a 3-necked flask fitted with a reflux condenser, a mercury sealed stirrer, and an inlet tube reaching nearly to the bottom of the flask, was added 200 cc. of absolute ether. Dry hydrogen chloride was passed in through the inlet tube while stirring the mixture. After four hours a clear lower layer separated, and the inlet tube was replaced by a dropping funnel. A solution of 12.7 g. of 3-acetyl-6-methoxybenzonitrile dissolved in 80 cc. of warm chloroform was added in a small stream from the dropping funnel while stirring vigorously. After a few minutes crystals of the aldimine-stannichloride began to separate. Dry hydrogen chloride was again passed into the solution for one and one-half hours. Stirring was continued one-half hour longer and the flask and contents were allowed to stand overnight. The yellow precipitate of the aldimine-stannichloride was filtered off and washed with 50 cc. of dry ether. The salt was heated with 100 cc. of water and filtered. The residue and filtrate were both extracted with benzene. The aldehyde was removed from the benzene by extracting with 20% sodium bisulfite solution. The aldehyde was released upon acidifying and heating the bisulfite solution. After cooling, the 3-acetyl-6-methoxybenzaldehyde (IX) was filtered off and dried. It was recrystallized from alcohol, m. p. 141–143°, yield, 5.05 g., 39% of theoretical. After recrystallizing from ether the melting point was 143–144°. This compound gave an aldehyde test with Schiff reagent and a positive test for methyl ketones with sodium nitroprusside reagent.[3] A mixed melting point with the natural toxic compound isolated from *Encelia* leaves showed no depression in melting point.

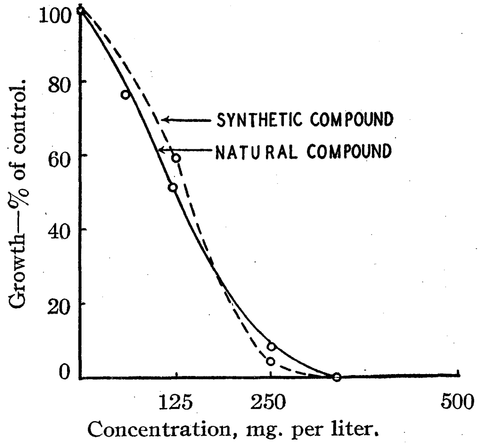


Fig. 1.—Effect of varying concentrations of synthetic and natural 3-acetyl-6-methoxybenzaldehyde on the growth of tomato seedlings in solution culture.

Thus the identity of the toxic compound has been confirmed by its synthesis. This method provides a way by which other aromatic compounds containing an aldehyde and a ketone group on the same ring may be synthesized.

Inhibitory Effect of Synthetic and Natural Compound and Activity of Related Compounds.—The inhibitory effect of the synthetic compound was compared to that of the natural compound. Both compounds were tested in the same concentrations using the toxic assay test described earlier,[1] in which the compounds to be tested are supplied to young tomato seedlings in solution cultures. The results are shown in Fig. 1. It may be seen that the inhibitory effect of the synthetic aldehyde is essentially the same as that of the natural aldehyde. Concentrations of 250 mg. per liter caused death of most of the plants and concentrations of about 125 mg. per liter caused 50% inhibition of growth of the tomato seedlings in both cases.

Substances related to the toxic compound which was isolated from *Encelia* leaves were tested to determine which group or combination of groups is responsible for the toxic effect. The pure compounds were weighed out and dissolved in a known volume of distilled water, the difficultly soluble solid compounds being taken up in hot water. These solutions were mixed with an equal volume of Hoagland's nutrient solution and fed to tomato seedlings contained in vials. The plants were measured at the time of transplanting and again after growing in the greenhouse at a constant temperature of 80° F. for one week. Four or five dilutions of each substance (1000, 500, 250, 125, and 0 mg. per liter) were tested using ten plants for each dilution. Concentration of inhibitor was plotted against growth in height as percentage of control for each substance as in Fig. 1, and the values for 50% inhibition determined by interpolation. The results are shown in Table I.

It may be seen from the table that benzene itself is not toxic and that substitution of a methyl ether group in the ring does not increase the toxicity. Introduction of an aldehyde group greatly increases the inhibitory activity, whereas a methyl ketone (acetyl) group is much less inhibitory than the aldehyde group. Combination of a methyl ketone group with a methoxyl group is more inhibitory than the combination of aldehyde and methoxyl groups. The toxic compound isolated

TABLE I

INHIBITORY ACTIVITY OF PURE COMPOUNDS ON GROWTH OF TOMATO SEEDLINGS

Substance	Concn. needed for 50% inhibition in height growth (mg./l.)	No. of plants dead after 1 week 500 mg./l.	250 mg./l.
Benzene	>1000	0	0
Anisole	>1000	0	0
Benzaldehyde	165	7	3
Acetophenone	365	1	0
p-Methoxyacetophenone	145	10	0
o-Methoxybenzaldehyde	170	6	4
m-Acetylbenzaldehyde	140	7	4
3-Acetyl-6-methoxybenzaldehyde	127	10	8
3-Acetyl-6-methoxybenzonitrile	90	10	10
3-Amino-4-methoxyacetophenone	40	10	10
4-Methoxy-3-nitroacetophenone	45	10	10
3-Acetyl-6-methoxybenzoic acid	237	7	2
4-Methoxyisophthalic acid	270	1	0
2-Methoxy-5-methylbenzaldehyde	125	10	5
Phenol	225	2	0
Salicylaldehyde	125	9	0
p-Hydroxyacetophenone	130	10	3
o-Hydroxyacetophenone	325	0	0
o-Methoxyacetophenone	175	8	0
3-Acetyl-4-hydroxyacetophenone	60	10	0
Aniline	155	0	0
Nitrobenzene	100	0	0
Benzoic acid	150	10	3

(3-acetyl-6-methoxybenzaldehyde) which contains all three groups is more toxic than combinations of any two of the other groups. The substitution of a cyano, nitro, or amino group for the aldehyde group causes increased inhibition, the amino group having the most toxic effect. The last two columns in the table show that most of these compounds do not cause death of the plants even though they may cause more inhibition in height growth than the naturally occurring inhibitor. Only the nitro, cyano, and amino substituted analogs brought about as high a mortality as the natural substance itself.

Acknowledgment.—The authors wish to express their appreciation to Dr. E. R. Buchman and to Dr. David R. Howton, Gates and Crellin Laboratories of Chemistry, California Institute of Technology, for their advice, assistance and encouragement in the prosecution of this work.

Summary

1. The structure determination and synthesis of a new compound, 3-acetyl-6-methoxybenzaldehyde, which was isolated from the leaves of *Encelia farinosa* is given.

2. The inhibitory activity of the toxic compound and other related compounds on the growth of tomato seedlings in solution culture is demonstrated.

PASADENA, CALIF. RECEIVED NOVEMBER 15, 1947

[CONTRIBUTION FROM THE UPJOHN RESEARCH LABORATORIES]

Crystalline Vitamin A Methyl Ether[1a]

BY A. R. HANZE, T. W. CONGER, E. C. WISE* AND D. I. WEISBLAT

The increased interest in vitamin A syntheses has placed vitamin A methyl ether in a position of considerable prominence, since its synthesis should be less difficult than that of the alcohol or its esters. The synthesis of vitamin A ethers recently has been the subject of numerous papers and patents.

Kipping and Wild[1] were the first to outline a possible synthesis of vitamin A methyl ether but no further work has appeared giving the results of this proposed synthesis. Oroshnik[2] reported a synthesis of vitamin A methyl ether which gave two fractions whose absorption maxima differed from that of vitamin A by 10 and 13 $m\mu$. No methoxyl analysis or biological assay of these fractions has been published. Milas[3] has published the synthesis of a product having a reproducible activity of 1.5 to 3.0% that of vitamin A. Cornwell[4] reported a synthesis of an ether of vitamin A, identifying the product by spectrophotometric data only. Isler, *et al.*,[5] reported the synthesis of a product having a potency greater than that of β-carotene.

In spite of the large amount of work done on vitamin A methyl ether, no one had reported the preparation of a product of sufficient purity for the property determination of its properties. For this reason we undertook the synthesis of pure vitamin A methyl ether and in a preliminary report have given[6] its physical properties and biological potency. The complete experimental details as to its preparation as well as the behavior of vitamin a methyl ether under various experimental conditions are given here.

---

* Deceased December 7, 1947.

(1) Kipping and Wild, *Chem. and Ind.*, **58**, 802 (1939).

(1a) Presented before the Division of Organic Chemistry, 112th A. C. S. Meeting, New York, N. Y., September 17, 1947.

(2) Oroshnik, THIS JOURNAL, **67**, 1627 (1945).

(3) Milas, *Science*, **103**, 581 (1946); this article contains references to the author's numerous patents in this field.

(4) Bishop C. Cornwell, U. S. Patent 2,414,722 (January 21, 1947).

(5) Isler, *et al.*, *Experientia*, **2**, 31 (1946); Jubilee Vol. Emil Barell, 31–44 (1946).

(6) Hanze, Conger, Wise and Weisblat, THIS JOURNAL, **68**, 1389 (1946).

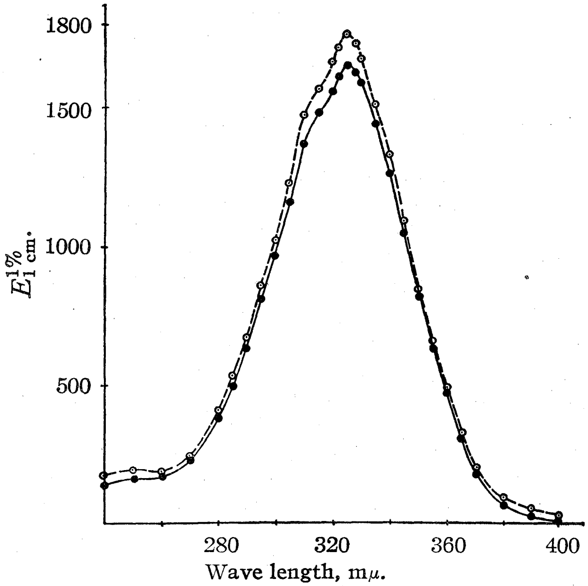


Fig. 1.—Spectrophotometric curves of vitamin A methyl ether, ●, and of vitamin A alcohol, ⊙, in isopropanol.

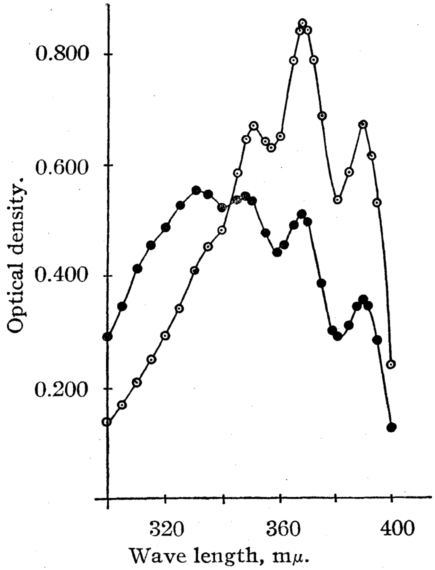


Fig. 2.—Spectrophotometric curves in isopropanol of vitamin A methyl ether, ●, and of vitamin A alcohol, ⊙, after treatment with 0.033 N hydrogen chloride in ethanol.

Subsequent to our initial publication[6] Cawley[7] reported the preparation of a vitamin A methyl ether for which he records a melting point of 33–33.5°, an extinction coefficient $E^{1\%}_{1\,\text{cm.}}$ at 328 mμ of 1800 and a biological potency of 4,800,000 units per gram.

Vitamin A methyl ether was prepared by the action of dimethyl sulfate on the lithium derivative of the vitamin. The lithium derivative was prepared by the reaction of *n*-butyl lithium[8] with crystalline vitamin A alcohol.[9] Attempts were made to form a metallic vitaminate using triphenylmethyl sodium, a Grignard reagent or potassium metal. The former possesses the disadvantage of giving triphenylmethane which is extremely difficult to separate from the desired product, while the latter two destroy the vitamin A molecule, the Grignard reagent with the formation of a product with absorption maxima at 333, 348 and 366 mμ and the metallic potassium generating hydrogen which probably reduces the molecule. Milas[10] has reported the preparation of metallic salts of vitamin A, using sodium amide, triphenylmethyl sodium and potassium *t*-butoxide.

The methyl ether obtained by the action of dimethyl sulfate on the lithium salt was purified by chromatography on activated alumina[11] and was obtained as an orange oil which crystallized from methanol at −70°. The spectrophotometric curve (Fig. 1) of vitamin A methyl ether is identical in all respects with that of vitamin A alcohol, both having absorption maxima at 326 mμ on the Beckman spectrophotometer (model DU). The extinction coefficient ($E^{1\%}_{1\,\text{cm.}}$) in isopropanol is 1660, which corresponds to an equivalent extinction coefficient of 1742 for vitamin A alcohol. We found an extinction coefficient of 1769 for crystalline vitamin A alcohol. Crystalline vitamin A methyl ether was found to have a provisional biological potency of 3,500,000 U.S.P. XII units per gram. This value was obtained as the average of three biological assays (a total of 30 rats used) made by Miss Elizabeth Musser of these Laboratories. Baxter and Robeson[12] reported 4,300,000 U. S. P. XI units per gram for crystalline vitamin A alcohol. A value of 3,500,000 for vitamin A alcohol is obtained consistently in our Laboratories.

Since the final step in most of the reported vitamin A ether syntheses involves dehydration, the stability of the ether under these conditions is of particular interest. Although vitamin A methyl ether was found to be more stable than the alcohol toward alcoholic hydrogen chloride by the method of Shantz, *et al.*,[13] absorption spectra studies (Fig. 2) showed that some anhydro vitamin A is formed. Similarly the ether possesses a greater stability than the alcohol toward the action of *p*-toluenesulfonic acid in boiling benzene. For example, at a molar ratio of one part of *p*-toluenesulfonic acid to 218 parts of vitamin A alcohol or its methyl ether, the ether is unaffected, whereas anhydro formation is observed with the alcohol (Fig. 3). However, at a molar ratio of 1:92 anhydro formation is observed with the vitamin A ether, whereas vitamin A acetate is little affected (Fig. 4).

The biological utilization of vitamin A methyl

---

(7) Cawley, British Patent 578,449 (August 2, 1946).

(8) Gilman, Langham and Moore, THIS JOURNAL, **62**, 2327 (1940).

(9) Distillation Products, Inc., Rochester, New York.

(10) Milas, U. S. Patent 2,296,291 (September 22, 1942).

(11) Grade F20, 80–200 mesh, Aluminum Ore Co., East St. Louis, Illinois.

(12) Baxter and Robeson, THIS JOURNAL, **64**, 2411 (1942).

(13) Shantz, Cawley and Embree, *ibid.*, **65**, 901 (1943).

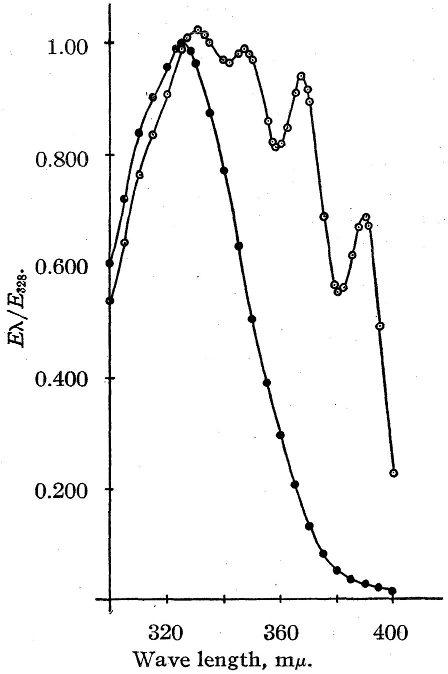


Fig. 3.—Spectrophotometric curves in isopropanol of vitamin A methyl ether, ●, and of vitamin A alcohol, ⊙, after treatment with 0.0046 mole of *p*-toluenesulfonic acid.

ether in the rat is now being investigated and will be reported at a later date.

Experimental

Crystalline Vitamin A Methyl Ether[14]

Crystalline vitamin A alcohol (500 mg., 1.75 millimoles) was dissolved in 60 cc. of dry benzene and the solution further dried by distillation of 10 cc. of benzene. To the solution, at room temperature, was added 6.0 cc. of 0.38 *N* *n*-butyllithium (2.28 millimoles)[8] in low boiling petroleum ether (30–40°). A sharp color change from yellow to deep cherry red occurred immediately. The solution was shaken and allowed to stand at room temperature for five minutes. Then dimethyl sulfate (560 mg., 4.52 millimoles) in 20 cc. of dry benzene was added, followed by a return of the yellow color. The solution was heated at 70° for one hour, cooled in ice, transferred to an amber separatory funnel where it was washed successively with cold solutions of 0.5 *N* sulfuric acid, 1 *N* ammonium hydroxide (twice) and water (three times). The solution was dried over anhydrous sodium sulfate, filtered and concentrated at 40° under reduced pressure to give an orange oil. The last traces of benzene were removed from the residual oil by the repeated addition of purified Skelly Solve B[15] followed by its removal under reduced pressure. An antimony trichloride blue color assay on the above oil showed a 92.5% recovery.

The orange oil was dissolved in 25 cc. of purified Skelly Solve B and put on a 15 × 5 cm. activated alumina column.[11] All reaction products were absorbed at the top of the column. After washing well with Skelly Solve B, the yellow vitamin A methyl ether was eluted with 1% acetone in Skelly Solve B. This gave a sharp separation from an orange pigment which remained at the top of the column. An antimony trichloride blue color assay on the ether fraction showed an over-all yield of 90%.

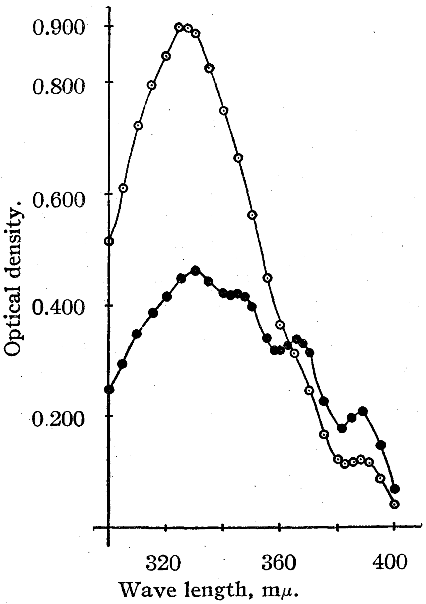


Fig. 4.—Spectrophotometric curves in isopropanol of vitamin A methyl ether, ●, and of vitamin A acetate, ⊙, after treatment with 0.011 mole of *p*-toluenesulfonic acid.

The oil, obtained on removal of the solvent at 40° under reduced pressure, crystallized from methanol after standing several months at −70°; m. p. 31–33°. Three recrystallizations from methanol and two from Skelly Solve B gave yellow crystals of vitamin A methyl ether; m. p. 33–34°. The yield of crystalline ether from 1 g. of alcohol was 660 mg. (62.7%).

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.95; H, 10.74; OCH_3, 10.34. Found: C, 83.96, 83.76; H, 11.16, 11.07; OCH_3, 10.00, 9.94. The antimony trichloride blue color assay was 100% of the expected value.

Crystalline vitamin A methyl ether is soluble in the common organic solvents such as alcohol, ether, benzene, etc., and is insoluble in water. It has been successfully crystallized from methyl alcohol, ethyl formate and Skelly Solve B, the former being the preferred solvent. For best crystallization results the oil obtained upon chromatography of a 1-g. run is dissolved in 5 cc. of absolute methanol, the solution cooled in ice, seeded, and allowed to stand in a refrigerator overnight, whereupon large crystals are formed. The mixture is then cooled in an ice–salt mixture for four hours, and then at about −70° (solid carbon dioxide) twenty hours. The crystals are filtered on a sintered glass funnel which has been cooled with Dry Ice. Recrystallizations are carried out in the same manner.

Behavior of Vitamin A Methyl Ether in $^1/_{30}$ *N* Dry Hydrogen Chloride in Alcohol (Fig. 2).—Crystalline vitamin A methyl ether (11.5 mg.) was dissolved in 0.75 cc. of absolute alcohol, after which 0.25 cc. of 0.132 *N* dry hydrogen chloride in absolute ethanol was added. The solution was shaken and allowed to stand at room temperature for fifteen minutes. Water (5 cc.) was added and the mixture extracted twice with 10-cc. portions of benzene. The combined benzene solutions were washed once with cold saturated sodium bicarbonate solution and three times with cold water, dried over anhydrous sodium sulfate, filtered and the solvent removed at 40° under reduced pressure to give an oil. The last traces of benzene were removed by repeatedly adding isopropanol followed by its removal under reduced pressure. The spectrophotometric curve was determined on this oil in isopropanol.

---

(14) All experiments were carried out in an atmosphere of dry nitrogen in subdued light.

(15) Purified by treatment with concentrated sulfuric acid, neutralization and distillation.

Vitamin A alcohol (10.5 mg.) was treated in exactly the same manner.

Behavior of Vitamin A Methyl Ether with *p*-Toluenesulfonic acid

1. In a Molar Ratio of 218 to 1 (Fig. 3).—A solution of 26 micrograms of *p*-toluenesulfonic acid monohydrate in 20 cc. of benzene was dried by distillation of 10 cc. of benzene. To this solution crystalline vitamin A methyl ether (8.9 mg.) was added and the solution refluxed for thirty minutes after which it was cooled in ice, and then poured onto cold saturated sodium bicarbonate contained in a separatory funnel. The benzene solution was washed well with the bicarbonate solution and then three times with cold water, dried over anhydrous sodium sulfate, filtered and concentrated. After the last traces of benzene were removed as above, an ultraviolet absorption curve was run on the residual oil.

Crystalline vitamin A alcohol (8.5 mg.) was run under identical conditions.

2. In a Molar Ratio of 92 to 1 (Fig. 4).—Vitamin A methyl ether (9.4 mg.) was treated with 65 micrograms of *p*-toluenesulfonic acid monohydrate exactly as in (1) above. Definite anhydro formation is indicated in the spectrophotometric curve.

Vitamin A acetate (10.6 mg.) under identical conditions was little affected.

Summary

1. Crystalline vitamin A methyl ether has been prepared by the action of dimethyl sulfate on the lithium salt of the alcohol.

2. Crystalline vitamin A methyl ether has a provisional biological potency of 3,500,000 U. S. P. XII units per gram.

3. The behavior of vitamin A methyl ether under dehydration conditions has been studied and a comparison is made between the stability of the vitamin A alcohol, ether and acetate under these conditions.

KALAMAZOO 99, MICHIGAN RECEIVED JUNE 23, 1947

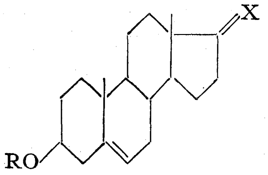
[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF SYNTEX S. A.]

Mercaptols of 17-Keto Steroids

BY L. NORYMBERSKA, J. NORYMBERSKI AND A. OLALDE

In a recent paper by Hauptmann[1] the reaction of estrone acetate with ethanedithiol was reported. Since the reactions of 17-keto steroids with mercaptans have been the object of investigation in our laboratory for a considerable period of time, we wish to communicate some of the results obtained.[2]

By condensation of dehydroisoandrosterone acetate (II) with benzyl and ethyl mercaptan in the presence of fused zinc chloride and anhydrous sodium sulfate, we were able to prepare the respective mercaptols III and V.



I. $R = H, X = O$
II. $R = CH_3CO, X = O$
III. $R = CH_3CO, X = (C_6H_5CH_2S)_2$
IV. $R = H, X = (C_6H_5CH_2S)_2$
V. $R = CH_3CO, X = (C_2H_5S)_2$
VI. $R = H, X = (C_2H_5S)_2$
VII. $R = CH_3CO, X = H_2$
VIII. $R = H, X = H_2$

Acid hydrolysis of dehydroisoandrosterone acetate dibenzylmercaptol (III) led to the formation of dehydroisoandrosterone (I); alkaline hydrolysis to dehydroisoandrosterone dibenzylmercaptol (IV); boiling with cadmium carbonate and mercuric chloride in acetone or acetic acid solution to dehydroisoandrosterone acetate (II); hydrogenolysis with Raney nickel to desoxo-dehydroisoandrosterone acetate (VII).

The last-mentioned reaction is of some special interest: Butenandt and Surányi[3] and recently Heard and McKay[4] described the Wolff–Kishner reduction of dehydroisoandrosterone semicarbazone and the product obtained has been proved to consist of a hard to separate mixture of desoxo-dehydroisoandrosterone, etiocholan-3(α)-ol and androstan-3(β)-ol. On the other hand, by hydrogenolysis of the dibenzylmercaptol, as well as of the diethylmercaptol of dehydroisoandrosterone acetate (III and V, respectively) with Raney nickel, we have obtained the pure desoxo-dehydroisoandrosterone acetate (VII) in excellent yield and by its saponification the desoxo-dehydroisoandrosterone (VIII).

Acknowledgment.—The microanalyses have been carried out by L. N. at the microanalytical laboratory of the Escuela Nacional de Ciencias Biológicas, Instituto Politecnico Nacional, with the kind permission of Dr. P. Hope, to whom we wish to express our thanks for his obligingness. Dr. G. Rosenkranz of our laboratory we thank for his kind interest in this work.

Experimental

Dibenzylmercaptol of Dehydroisoandrosterone Acetate (III).—A mixture of 15 g. of dehydroisoandrosterone acetate, 15 cc. of benzylmercaptan, 10 cc. of dioxane and 15 g. of anhydrous sodium sulfate is ice-cooled and 15 g. of freshly fused and pulverized zinc chloride is added.

---

(1) Hauptmann, THIS JOURNAL, **69**, 562 (1947).

(2) Further communications on this subject will be reported soon.

(3) Butenandt and Surányi, *Ber.*, **75**, 591 (1942).

(4) Heard and McKay, *J. Biol. Chem.*, **165**, 677 (1946).

The mixture solidifies in few minutes and is kept at room temperature overnight. The reaction product is extracted with chloroform, the chloroform solution washed with water, dried over sodium sulfate and evaporated. The residue crystallizes from a mixture of chloroform and methanol in the form of prismatic plates, m. p. 148–149°, yield 20 g. (78.5%).

Anal. Calcd. for $C_{35}H_{44}O_2S_2$: C, 74.95; H, 7.91. Found: C, 74.81; H, 7.95.

Diethylmercaptol of Dehydroisoandrosterone Acetate (V).—The preparation proceeds in the manner described above for dibenzylmercaptol. The crude product crystallizes from acetone, m. p. 147–149°.

Anal. Calcd. for $C_{25}H_{40}O_2S_2$: C, 68.76; H, 9.23. Found: C, 69.00; H, 9.33.

Acid Hydrolysis of the Dibenzylmercaptol Acetate (III).—One hundred milligrams of the compound (III) is refluxed for one hour with 5 cc. of dioxane, 5 cc. of methanol and 0.4 cc. of concentrated hydrochloric acid. The warm solution is diluted with water and the precipitated needles are filtered off, m. p. 138–140°. The product gives no depression with dehydroisoandrosterone.

Alkaline Hydrolysis of the Dibenzylmercaptol Acetate (III).—One and one-tenth grams of the compound (III) is dissolved in 10 cc. of dioxane and a solution of 0.5 g. of sodium hydroxide in 20 cc. of methanol is added. The dibenzylmercaptol of dehydroisoandrosterone is precipitated by dilution with water and recrystallized from acetone; prismatic needles, m. p. 185–186°.

Anal. Calcd. for $C_{33}H_{42}OS_2$: C, 76.40; H, 8.16. Found: C, 76.48; H, 8.31.

Acetylation of the compound with acetic anhydride in pyridine at room temperature gives the original acetate.

Reaction of the Dibenzylmercaptol Acetate (III) with Mercuric Chloride and Cadmium Carbonate.—Two-hundred-fifty milligrams of the compound (III), 300 mg. of mercuric chloride and 400 mg. of cadmium carbonate are refluxed in 10 cc. of acetone and 1 cc. of water for eight hours. The inorganic salts are filtered off, the crude reaction product purified by adsorption on activated alumina, the benzene fraction yielding crystals of dehydroisoandrosterone acetate of the melting point 165–166°. The resulting dehydroisoandrosterone acetate may be isolated from the crude product by recrystallization from methanol if the reaction is carried out in acetic acid instead of acetone.

Desoxo-dehydroisoandrosterone Acetate (VII).—To a suspension of 40 g. of Raney nickel[5] in 120 cc. of methanol is added a solution of 4 g. of dibenzylmercaptol of dehydroisoandrosterone acetate in 120 cc. of acetone and the mixture is refluxed for two hours. The nickel is filtered off, washed with methanol, the filtrate evaporated and the residue (2 g., m. p. 86–91°) recrystallized from methanol, yielding leaflets of constant melting point, 96–97°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.56; H, 10.03.

Hydrogenolysis of the diethylmercaptol (V) is carried out in the same manner and gives an identical product.

Desoxo-dehydroisoandrosterone (VIII).—Nine-tenths gram of the acetate (VII) is refluxed with 1 g. of potassium hydroxide in 20 cc. of methanol for one hour. The hot solution is diluted with water until the first crystals appear and the mixture is cooled to complete the precipitation; long needles, m. p. 136–137°. Repeated recrystallization from aqueous methanol or from hexane does not change the melting point.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.16; H, 11.16; $[\alpha]_D$ $-75.8°$ (in dioxane).

Summary

1. The dibenzylmercaptol and the diethylmercaptol of dehydroisoandrosterone acetate have been prepared; conditions are described under which the selective hydrolysis of either the acetyl or mercaptol group may be carried out.

2. Desoxo-dehydroisoandrosterone and its acetate have been prepared by the hydrogenolysis of the mercaptols of dehydroisoandrosterone acetate with Raney nickel and the advantages of this method over the Wolff–Kishner reduction for this particular case have been shown.

---

[5] The Raney nickel was prepared according to Mozingo, *et al.*, THIS JOURNAL, **65**, 1477 (1943).

MEXICO CITY, MEXICO RECEIVED JULY 31, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MEAD JOHNSON AND COMPANY]

Pyrazine Chemistry. III. Derivatives of 3-Amino-5,6-dimethylpyrazinoic Acid

BY RUDOLPH C. ELLINGSON AND ROBERT L. HENRY

3-Amino-5,6-dimethylpyrazinoic acid[1] can be obtained in excellent yield by the alkaline hydrolysis of 6,7-dimethyllumazine. The decarboxylation of this acid according to a modification of the described method[1] gives 2-amino-5,6-dimethylpyrazine (I) in good yield.

Bromination of I gives 2-amino-3-bromo-5,6-dimethylpyrazine (II). The structure of II was established by amination to the hitherto unknown diamine (III) followed by conversion of the diamine by reaction with glyoxal into the unknown 2,3-dimethylpyrazinopyrazine (IV). The structure of IV was established by its synthesis from diacetyl and the known 2,3-diaminopyrazine.[2] This series of reactions proves that in II the bromine atom is in position 3.

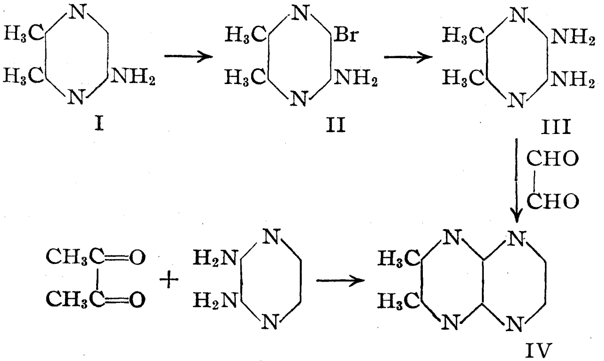


CHART 1

Condensation of III with diacetyl gave tetramethylpyrazinopyrazine. 2,3-Dimethylpyrazinopyrazine and tetramethylpyrazinopyrazine are

---

(1) Weijlard, Tishler and Erickson, THIS JOURNAL, **67**, 802 (1945).

(2) McDonald and Ellingson, *ibid.*, **69**, 1034 (1947).

members of a little known class of heterocyclic compounds, the basic ring structure of which is pyrazinopyrazine. The only compound found in the literature which might be considered to belong to this class is quinoxalo[2,3-b]quinoxaline.[3]

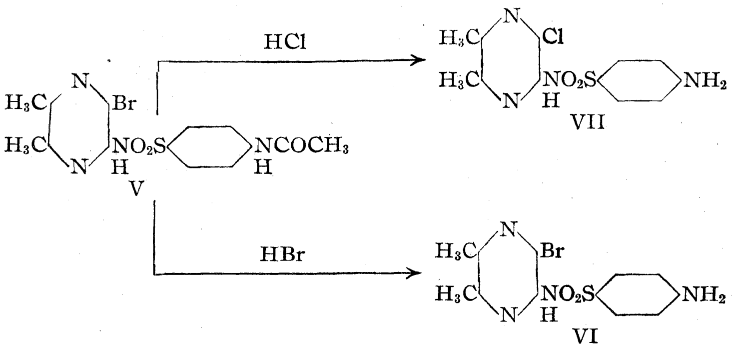


CHART 2

2-Amino-3-bromo-5,6-dimethylpyrazine (II) on reaction with acetylsulfanilyl chloride gave 2-(N^4-acetylsulfanilamido)-3-bromo-5,6-dimethylpyrazine (V). Deacetylation of V with hydrobromic acid gave the expected 2-sulfanilamido-3-bromo-5,6-dimethylpyrazine (VI), but deacetylation with hydrochloric acid gave the unexpected 2-sulfanilamido-3-chloro-5,6-dimethylpyrazine (VII). Even compound II is converted into 2-amino-3-chloro-5,6-dimethylpyrazine (VIII) when treated under similar conditions with a solution of ethanol and hydrochloric acid.

The replacement of carbon-linked halogen atoms in aliphatic and aromatic compounds by ionic halogen is not to our knowledge a frequently occurring phenomenon. Hepp[4] recorded the rapid conversion of chlorotrinitrobenzene into the iodo compound by treatment with a hot alcoholic solution of potassium iodide. Bennett and Vernon[5] reported the conversion of chloro-2,4-dinitrobenzene into the iodo compound by boiling it in a solution of sodium iodide in ethylene glycol. In compounds II, V and VI we have found that the bromine atom is readily replaced by chlorine on being treated with a solution of ethanol and hydrochloric acid.

Reaction between 2-amino-3-chloro-5,6-dimethylpyrazine (VIII) and acetylsulfanilyl chloride gives a mixture of the mono- and di-coupled compounds, the greater portion of which is the mono-coupled compound. Note that in the reaction[2] between 2-amino-3-chloropyrazine and acetylsulfanilyl chloride largely di-coupling occurred.

When III reacts mole for mole with acetylsulfanilyl chloride, the major portion of the product is the di-coupled compound from which 2,3-disulfanilamido-5,6-dimethylpyrazine (IX) may be obtained by deacetylation. Its solubility in dilute aqueous alkali indicates the 2,3-disulfanilamido structure. For an analogous case of 2,3-disulfanilamido substitution refer to paper II[2] of this series. A more soluble fraction which consists of a mixture of III and the mono-coupled compound, 2-(N^4-acetylsulfanilamido)-3-amino-5,6-dimethylpyrazine (X), was obtained by concentration of the mother liquors after removal of the di-coupled compound. X was separated from III by virtue of its greater solubility in aqueous alkali. This method, however, is unsatisfactory for preparing 2-sulfanilamido-3-amino-5,6-dimethylpyrazine (XI). XI is more readily obtained from VI by replacement of the bromine atom with the amino group.

The value of compounds VI, VII, IX and XI as anti-bacterial agents has been investigated by others and will be reported elsewhere. In preliminary studies 2-sulfanilamido-3-chloro-5,6-dimethylpyrazine (VII) proved to be the most interesting.

Experimental

3-Amino-5,6-dimethylpyrazinoic Acid.—This acid was prepared from 6,7-dimethyllumazine as described by Weijlard, *et al.*[1] The conversion of this acid into the methyl ester and amide was done by essentially the same procedure as was used for making 2-amino-3-carbomethoxypyrazine and 3-aminopyrazinamide.[6] The yield of crude ester was 51%. For analysis[7] the product was crystallized from water and came out as light yellow needles; m. p. 170–171° (cor.).

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.06, 52.78; H, 6.28, 6.24; N, 23.80, 23.66.

The yield of crude amide was low, 19.3%. The product was purified by crystallization from 85 parts of a 16% dioxane–water solution (v/v). The yellow, finely granular solid melted at 243–245° (dec.).

Anal. Calcd. for $C_7H_{10}N_4O$: C, 50.59; H, 6.07; N, 33.72. Found: C, 50.51, 50.41; H, 6.33, 6.22; N, 34.75, 34.57.

2-Amino-5,6-dimethylpyrazine (I).—This amine was prepared by Weijlard, *et al.*,[1] by decarboxylation of 3-amino-5,6-dimethylpyrazinoic acid in sulfuric acid. We made I by decarboxylation of the acid in carbitol acetate in much the same manner as the above-mentioned authors prepared aminopyrazine from 3-aminopyrazinoic acid. Pure 2-amino-5,6-dimethylpyrazine (I) exists as slightly yellow, brittle plates; m. p. 151° (cor.).

2-Amino-3-bromo-5,6-dimethylpyrazine (II).—One mole (123 g.) of crude 2-amino-5,6-dimethylpyrazine (I) was dissolved in 400 cc. of warm glacial acetic acid. After complete solution 54 cc. of bromine (5% excess) was added dropwise with stirring over a period of one hour. After five hours 1200 cc. of ethyl ether was added and the orange precipitate was collected. Without drying it was dissolved in 1600 cc. of hot water and the solution was decolorized with Norite. After filtration, the filtrate was made weakly alkaline by the addition of about 325 cc. of a 20% sodium hydroxide solution. The yellow granular solid was collected and air-dried. The yield was 154–163 g. (70.2–80.7%); m. p. 111–114°. For analysis a sample was crystallized three times from a 1 to 3 mixture

---

(3) Hinsberg and Pollak, *Ber.*, **29**, 785 (1896).

(4) Hepp, *Ann.*, **215**, 344 (1882).

(5) Bennett and Vernon, *J. Chem. Soc.*, 1783 (1938).

(6) Ellingson, Henry and McDonald, THIS JOURNAL, **67**, 1711 (1945).

(7) Dr. Carl Tiedcke, Laboratory of Microchemistry, New York, N. Y., performed the analyses recorded in this paper.

of ethanol and water. This compound crystallized as light yellow cubes; m. p. 114.7° (cor.). The compound sublimes readily in vacuum.

Anal. Calcd. for $C_6H_8BrN_3$: C, 35.66; H, 3.99; Br, 39.55; N, 20.80. Found: C, 35.65, 35.57; H, 3.84, 3.91; Br, 39.58, 39.84; N, 20.39, 20.31.

2,3-Diamino-5,6-dimethylpyrazine (III).—In each of four Carius tubes were placed 8.08 g. (0.04 mole) of crude 2-amino-3-bromo-5,6-dimethylpyrazine (II), 24 cc. of concentrated ammonium hydroxide and a trace of copper powder and the tubes were heated at 128° for twenty-four hours. After cooling, each tube was rinsed out with 75 cc. of water and the suspensions were combined and heated to dissolve all the crystalline solid. The hot solution was decolorized and filtered. After refrigeration the yellow needles were collected; they weighed 17.1 g. (77.4%); m. p. 211–214°. On repeated crystallizations of this diamine from water almost colorless needles were obtained; m. p. 216° (cor.).

Anal. Calcd. for $C_6H_{10}N_4$: C, 52.15; H, 7.29; N, 40.55. Found: C, 52.30, 52.08; H, 7.48, 7.38; N, 41.11, 40.90.

2,3-Dimethylpyrazinopyrazine (IV). A. (From glyoxal and 2,3-diamine-5,6-dimethylpyrazine).—A mixture of 4.14 g. (0.03 mole) of 2,3-diamino-5,6-dimethylpyrazine (III), 10 g. of glyoxal di-sodium bisulfite and 75 cc. of water was boiled under reflux for one hour. After cooling to room temperature, 20 cc. of concentrated ammonium hydroxide was added. On refrigeration long yellow needles separated; they weighed 1.83 g. (38.1%); m. p. 212–216° (dec.). On crystallization from 95% ethanol small, light yellow needles were obtained, m. p. 219° (dec.).

Anal. Calcd. for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.97, 59.90; H, 4.87, 4.89; N, 36.14, 36.02.

B. (From diacetyl and 2,3-diaminopyrazine).—In 25 cc. of hot water were dissolved 0.75 g. of 2,3-diaminopyrazine[2] and 1.0 cc. of diacetyl. The solution was boiled under reflux for thirty minutes. On refrigeration yellow crystals separated; they weighed 0.5 g. (45.9%); m. p. 215–217° (dec.). On crystallization from ethanol, light yellow needles were obtained; m. p. 216–218° (dec.). There was no depression of the melting point on mixed melting of this compound with that obtained in A.

Anal. Calcd. for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.23; H, 5.01; N, 36.24.

Tetramethylpyrazinopyrazine.—To a warm solution of 4.0 g. (0.028 mole) of 2,3-diamino-5,6-dimethylpyrazine (III) in 400 cc. of water was added 4.0 cc. of diacetyl. The solution was boiled under reflux for twenty-five minutes. As the clear orange solution cooled, long needles separated; they weighed 1.1 g.; m. p. 261–262°. By concentration of the mother liquors a second crop weighing 1.8 g. and melting at 260° was obtained. The total yield was 2.9 g. (55%). On two crystallizations from water, bright yellow needles were obtained; m. p. 261° (cor.).

Anal. Calcd. for $C_{10}H_{12}N_4$: C, 63.80; H, 6.43; N, 29.77. Found: C, 63.20, 63.51; H, 6.31, 6.19; N, 30.30, 30.16.

2-(N^4-Acetylsulfanilamido)-3-bromo-5,6-dimethylpyrazine (V).—A suspension of 156 g. (0.773 mole) of crude 2-amino-3-bromo-5,6-dimethylpyrazine (II) (dried over phosphorus pentoxide) in 980 cc. of dry pyridine was cooled to about 5° in an ice-bath. With constant stirring of the chilled suspension 190 g. (5.4% excess) of crystalline acetylsulfanilyl chloride was added over a period of forty-five minutes. After holding the reaction mixture at about 5° for five hours, it was allowed to come to room temperature and to stand overnight. The red-brown reaction mixture was poured into water and the pyridine removed by steam distillation in vacuum. After thorough cooling at 0°, the solid was collected and dried. The yield was 210 g. (68.2%) of a tan, light-weight powder; m. p. 204–206° (dec.). After one crystallization from a mixture of dioxane and water the melting point rose to 216° (dec.). For analysis the compound was crystallized from a mixture of ethanol and water; it came out in fluffy clusters of almost colorless small needles; m. p. 218° (dec.).

Anal. Calcd. for $C_{14}H_{15}BrN_4O_3S$: C, 42.11; H, 3.79; Br, 20.02; N, 14.03; S, 8.03. Found: C, 42.16, 42.13; H, 3.64, 3.71; Br, 19.76, 19.91; N, 14.90, 14.97; S, 8.00, 8.02.

2-Sulfanilamido-3-bromo-5,6-dimethylpyrazine (VI).—A mixture of 10 g. (0.025 mole) of 2-(N^4-acetylsulfanilamido)-3-bromo-5,6-dimethylpyrazine (V), 20 cc. of 40% hydrobromic acid and 60 cc. of 95% ethanol was boiled under reflux for thirty minutes. To the solution 200 cc. of water and 25 cc. of concentrated ammonium hydroxide then Darco-G60 were added. After filtration the filtrate was made weakly acid by the addition of hydrobromic acid. After thorough cooling the yellow granular solid was collected and dried. It weighed 7.7 g. (86%); m. p. 183–185°. After two crystallizations from 95% ethanol, the sulfonamide existed as small, light yellow crystals; m. p. 185° (cor.).

Anal. Calcd. for $C_{12}H_{13}BrN_4O_2S$: C, 40.34; H, 3.67; Br, 22.37; N, 15.68; S, 8.97. Found: C, 40.22, 40.13; H, 3.78, 3.79; Br, 22.70, 22.53; N, 16.67, 16.70; S, 8.40, 8.83.

2-Sulfanilamido-3-chloro-5,6-dimethylpyrazine (VII).—A. A mixture of 179 g. (0.449 mole) of 2-(N^4-acetylsulfanilamido)-3-bromo-5,6-dimethylpyrazine (V), 1000 cc. of 95% ethanol and 360 cc. of concentrated hydrochloric acid was boiled under reflux for forty-five minutes. Then Norite was added and the solution boiled five minutes longer. After filtration the hot solution was diluted with five liters of water and enough concentrated ammonium hydroxide was added to bring the *p*H to about 4. After thorough cooling the yellow granular solid was collected and dried. It weighed 119 g. (84.8%); m. p. 182–184°. After two crystallizations from 95% ethanol, large yellow crystals were obtained; m. p. 185° (cor.).

Anal. Calcd. for $C_{12}H_{13}ClN_4O_2S$: C, 46.08; H, 4.19; Cl, 11.34; N, 17.91; S, 10.25. Found: C, 45.82; H, 4.50; Cl, 11.70, 11.52; N, 17.90; S, 10.12.

B. To 50 cc. of pyridine at 55–60° a mixture of 6.0 g. (0.038 mole) of crystalline 2-amino-3-chloro-5,6-dimethylpyrazine (VIII) and 9.2 g. (5.0% excess) of acetylsulfanilyl chloride was added over a period of thirty minutes. The reaction mixture was held at that temperature for a total of four and one-half hours; then it was allowed to stand overnight at room temperature. The pyridine was removed by steam distillation in vacuum and after thorough cooling of the solution, the solid was collected and dried. The light yellow, fluffy product weighed 6.35 g. and melted at 195–207° (dec.). It was dissolved in 100 cc. of dioxane; the solution was filtered and the filtrate was diluted with 100 cc. of boiling water. The undissolved solid weighed 0.85 g. and melted at about 240° (dec.). As the filtrate cooled to room temperature a small quantity of solid separated; this was collected and dried; 0.7 g. melting at about 250° (dec.). The filtrate was then chilled in an ice-bath for several hours whereupon an almost colorless precipitate filled the solution. It weighed 4.4 g.; m. p. 208–210° (dec.).

The two portions of high melting material (0.85 g. and 0.7 g.) were combined and crystallized from 440 cc. of a 1 to 1 mixture of dioxane and water. After a second crystallization the small colorless crystals were analyzed; m. p. 269–270° (dec.). The analytical data show that some di-coupling has occurred; this compound is probably 2-di-(N^4-acetylsulfanilyl)-amino-3-chloro-5,6-dimethylpyrazine.

Anal. Calcd. for $C_{22}H_{22}ClN_5O_6S_2$: C, 47.87; H, 4.02; Cl, 6.42; N, 12.69; S, 11.60. Found: C, 47.70; H, 4.16; Cl, 6.20; N, 13.51; S, 11.54.

The 4.4-g. fraction was crystallized from a mixture of 150 cc. of dioxane and 300 cc. of water; 3.4 g. of slightly yellow granules was obtained; m. p. 210–212° (dec.). On another crystallization from a 2 to 1 mixture of water and ethanol the compound came out as light yellow, glistening plates; the melting point remained unaltered. Analysis shows it to be 2-(N^4-acetylsulfanilamido)-3-chloro-5,6-dimethylpyrazine.

Anal. Calcd. for $C_{14}H_{15}ClN_4O_3S$: C, 47.39; H, 4.26; Cl, 9.99; N, 15.79; S, 9.04. Found: C, 47.18, 47.01; H, 4.22, 4.40; Cl, 10.02, 9.96; N, 16.66, 16.42; S, 8.88, 9.03.

Deacetylation of this compound gave a slightly yellow crystalline substance which melted at 185° and showed no depression on mixed melting with 2-sulfanilamido-3-chloro-5,6-dimethylpyrazine (VII) obtained in A.

2-Amino-3-chloro-5,6-dimethylpyrazine (VIII).—A mixture of 10 g. (0.0495 mole) of crude 2-amino-3-bromo-5,6-dimethylpyrazine (II), 60 cc. of 95% ethanol and 20 cc. of concentrated hydrochloric acid was boiled to effect solution. The solution was then diluted with 250 cc. of water and made weakly alkaline by the addition of ammonium hydroxide. After cooling the colorless granules were collected and dried; they weighed 3.5 g. (45%); m. p. 97–100°. The compound crystallizes from water in long colorless prisms; m. p. 98° (cor.).

Anal. Calcd. for $C_6H_8ClN_3$: C, 45.72; H, 5.12; Cl, 22.50; N, 26.66. Found: C, 45.60, 45.84; H, 5.22, 5.06; Cl, 22.63, 22.40; N, 27.40, 27.15.

2,3-Disulfanilamido-5,6-dimethylpyrazine (IX).—The reaction between 13.8 g. (0.1 mole) of 2,3-diamino-5,6-dimethylpyrazine (III) and 48 g. (0.206 mole) of crystalline acetylsulfanilyl chloride was carried out in pyridine under essentially the same conditions as those used for the preparation of V. The yield of crude 2,3-di-(N^4-acetylsulfanilamido)-5,6-dimethylpyrazine was 40.9 g. (76.8%) of yellow granules; m. p. 253–257° (dec.). Before analysis the compound was crystallized three times from a 2 to 1 mixture of water and ethanol (v/v). Small yellow crystals were obtained; m. p. 264° (dec.).

Anal. Calcd. for $C_{22}H_{24}N_6O_6S_2$: C, 49.61; H, 4.54; N, 15.78; S, 12.04. Found: C, 49.53, 49.40; H, 4.46, 4.35; N, 16.53, 16.32; S, 11.92, 11.90.

The deacetylation was carried out in an alcoholic solution of hydrochloric acid as described for the deacetylation of V. The yield was 90% of a yellow granular product melting at 257° (dec.). 2,3-Disulfanilamido-5,6-dimethylpyrazine (IX) was purified by solution in 31 parts of a 4 to 1 mixture of dioxane and water and, after decolorization and filtration, dilution with an equal volume of hot water; light yellow granular crystals were obtained. IX is insoluble in ethanol and in water and only slightly soluble in dioxane. It dissolves both in weakly acidic or basic aqueous solutions.

Anal. Calcd. for $C_{18}H_{20}N_6O_4S_2$: C, 48.20; H, 4.49; N, 18.74; S, 14.30. Found: C, 48.90, 48.80; H, 4.55, 4.58; N, 18.67, 18.73; S, 14.11, 13.99.

2-Sulfanilamido-3-amino-5,6-dimethylpyrazine (XI).—**A.** In a Carius tube were sealed 5.35 g. (0.015 mole) of 2-sulfanilamido-3-bromo-5,6-dimethylpyrazine (VI), 25 cc. of concentrated ammonium hydroxide and a trace of copper powder. The tube was heated at 105° for eight hours. The contents of the tube were diluted with 40 cc. of water and filtered. The filtrate was chilled and then neutralized by the gradual addition of dilute hydrochloric acid.[8] A yellow solid separated; it weighed 3.6 g. (84.7%); m. p. 204–207°. It was crystallized from a 10 to 1 mixture of ethanol and water. After three crystallizations large, slightly yellow crystals which melted at 207° (cor.) were obtained.

Anal. Calcd. for $C_{12}H_{15}N_5O_2S$: C, 49.13; H, 5.15; N, 23.88; S, 10.93. Found: C, 48.90, 48.71; H, 5.30, 5.27; N, 24.01, 24.04; S, 10.80, 10.98.

More drastic reaction conditions such as higher temperatures and/or longer reaction times lowered the yield of the desired compound. Since 2,3-diamino-5,6-dimethylpyrazine was then also isolated, the more drastic conditions cause cleavage of either the starting sulfonamide, VI, or the product, XI.

B. To a mechanically stirred suspension of 6.9 g. (0.05 mole) of 2,3-diamino-5,6-dimethylpyrazine (III) in 100 cc. of dry pyridine cooled to about 2° was added gradually over a period of thirty minutes 12 g. (0.051 mole) of crystalline acetylsulfanilyl chloride. One hour after the addition had been completed a solution of 2 g. of sodium hydroxide in 100 cc. of water was added and the pyridine was removed by steam distillation in vacuum. The aqueous solution, freed from pyridine, was diluted with water to a volume of 1.5 liters and then cooled to room temperature. The light yellow, granular solid was collected and dried. It weighed 4.5 g. and melted at 258–260° (dec.). It is 2,3-di-(N^4-acetylsulfanilamido)-5,6-dimethylpyrazine as there was no depression of the melting point on mixed melting of it with an authentic sample of 2,3-di-(N^4-acetylsulfanilamido)-5,6-dimethylpyrazine.

The filtrate was concentrated in vacuum to a volume of about 500 cc. and then cooled overnight in the refrigerator. The tan, partially crystalline solid (9.8 g.) melted at 205–230° and evidently was a mixture.

The 9.8 g. of mixture was suspended in 100 cc. of a 2.5 per cent. aqueous sodium hydroxide solution; 2.3 g. of solid remained undissolved. It melted at 215–217° and gave no depression of the melting point on mixed melting with an authentic sample of 2,3-diamino-5,6-dimethylpyrazine (III). Evidently it is unreacted diaminodimethylpyrazine, III.

The clear yellow filtrate was carefully neutralized with dilute hydrochloric acid. On scratching the solution, a yellow solid separated. It weighed 2.7 g.; m. p. 225–231°. Crystallization from 150 cc. of a 2 to 1 ethanol–water solution (v/v) gave 2 g. of slightly pink crystals; m. p. 235–236°. This substance we believed to be 2-(N^4-acetylsulfanilamido)-3-amino-5,6-dimethylpyrazine (X). To confirm this belief we deacetylated the material in aqueous alcoholic hydrochloric acid and obtained 1.15 g. of colorless granules melting at 203–205°. There was no depression of the melting point on mixed melting of this compound with an authentic sample of 2-sulfanilamido-3-amino-5,6-dimethylpyrazine (XI) prepared from 2-sulfanilamido-3-bromo-5,6-dimethylpyrazine (VI). Obviously the way to prepare XI is by reaction of VI with ammonium hydroxide in the presence of copper rather than from III and acetylsulfanilyl chloride.

Summary

1. The preparation of five new simple pyrazine derivatives, namely, methyl-3-amino-5,6-dimethylpyrazinoate, 3-amino-5,6-dimethylpyrazinamide, 2-amino-3-bromo-5,6-dimethylpyrazine, 2-amino-3-chloro-5,6-dimethylpyrazine and 2,3-diamino-5,6-dimethylpyrazine, is described.

2. The chemical structures of 2-amino-3-bromo-5,6-dimethylpyrazine and 2,3-diamino-5,6-dimethylpyrazine have been established.

3. Two new members, 2,3-dimethylpyrazinopyrazine and tetramethylpyrazinopyrazine, of a little known class of heterocyclic compounds have been prepared and characterized.

4. Four new derivatives of sulfapyrazine have been synthesized, namely, 2-sulfanilamido-3-bromo-5,6-dimethylpyrazine, 2-sulfanilamide-3-chloro-5,6-dimethylpyrazine, 2-sulfanilamido-3-amino-5,6-dimethylpyrazine, and 2,3-disulfanilamido-5,6-dimethylpyrazine.

---

[8] If the acid is added too rapidly, and/or the solution has not been thoroughly chilled (0°), the compound may separate as a gray gummy mass which soon solidifies. It can be purified by crystallization from aqueous ethanol.

5. The replacement of the bromine atom in 2-amino-3-bromo-5,6-dimethylpyrazine and some of its derivatives with chlorine on treatment with aqueous hydrochloric acid in ethanol was unexpected.

EVANSVILLE, IND. RECEIVED JULY 21, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF OREGON STATE COLLEGE, AND THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA]

Strains in Methyl Amines and Hydrocarbons[1]

BY RALPH SPITZER AND KENNETH S. PITZER

H. C. Brown and co-workers have written a series of interesting articles on the anomalous basic strength of the methyl amines.[2] In order to eliminate complicating effects due to hydration, they worked in the gas phase and used trimethylboron as reference acid. They concluded that trimethylamine was weakened, in comparison with ammonia or mono- or dimethylamine, by a type of steric effect to which they referred as B-strain and which resulted from spreading of the methyl groups. We propose to show, by a semiquantitative calculation, that the magnitude of the B-strain is far too small to account for the observed anomaly and that the anomaly is probably due to ordinary steric effects of the type referred to by Brown as F-strain.

Perhaps a brief description of our understanding of Brown's use of the term F-strain is in order at this time. Under this heading are lumped all types of steric strain resulting from the interference of groups attached to two adjacent atoms, including van der Waals repulsion, increase in the bonded distance, and interference with the preferred rotational configuration about the bond. It is our opinion that strains of this type are primarily responsible for the weakness of trimethylamine.

Let us quote from Dr. Brown's paper his definition of B-strain: "There are theoretical reasons for believing that the three bonds of a trivalent nitrogen atom should be directed in space at angles of 90° to each other. In all cases which have been investigated, however, the angles are considerably greater, probably because they must be increased to accommodate the attached groups. An electron diffraction investigation of trimethylamine led Brockway and Jenkins to the conclusion that the C–N–C angle in this molecule is 108 ± 4°.[3a] In the explanation here proposed, it is assumed that the bond angle in trimethylamine is somewhat greater than the normal tetrahedral angle, probably close to the upper limit set by Brockway and Jenkins. In other words, the three rather bulky methyl groups spread the bonds of the nitrogen atom from their preferred configuration (90°) to a value greater than the tetrahedral angle.

"In the trivalent nitrogen derivative, such spreading of the bond angles is relatively easy since the fourth position in the valence shell is not occupied. However, the addition of a fourth group to the vacant position, be it a proton or a trimethylboron molecule, forces the nitrogen atom toward a tetrahedral configuration and results in a reduction of the expanded angles. The methyl groups are, therefore, crowded toward each other, setting up a strain which reduces the stability of the addition compound.

"The term B-strain is proposed for this effect. (The letter B is used to indicate that the interference which causes the strain is localized at the "back" of the molecule—trimethylamine in the case under discussion—away from the entering group; it is thus contrasted to F-strain which results from interference at the front of the molecule, at the interface between the two components of the addition compound."

Our problem is thus to calculate the energy needed to crowd the methyl groups together to tetrahedral angles. This will be accomplished by calculating the energy needed to bend trimethylamine into the tetrahedral configuration. As long as the C–N–C bond angles remain the same, the actual addition of the acid can introduce only F, not B strain. Also any B strain already in the free base at its expanded angles is not significant since it is the change in B-strain on addition of the acid which would affect the energy or equilibrium in that reaction.[3b]

Total Strain in Amines.—In order to discuss this concept, it is necessary to estimate the amount of the B-strain. Brown estimates that the total strain is about 9000 kcal. per mole in the free energy of the trimethylamine–trimethylboron complex. Although he does not divide this into B-strain and ordinary steric strain (F-strains), he implies that the B strain is of considerable im-

---

[1] Presented in part at the Northwest Regional Meeting, American Chemical Society, May, 1947. Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 118, School of Science.

[2] (a) H. C. Brown, M. D. Taylor and M. Gerstein, THIS JOURNAL, **66**, 431 (1944). (b) H. C. Brown, H. Bartholomay, Jr., and M. D. Taylor, *ibid.*, p. 435. (c) H. C. Brown and M. D. Taylor, *ibid.*, **69**, 1332 (1947).

[3a] L. O. Brockway and Jenkins, *ibid.*, **58**, 2036 (1936). More recently V. Schomaker (private communication) has obtained for the C–N–C angle, 109 ± 2° for trimethylamine, 111 ± 3° for dimethylamine, 112 ± 3 for diethylamine and 113 ± 3° for triethylamine.

[3b] We have discussed this matter at considerable length because Dr. Brown does not agree that our calculation is in accord with his definition quoted above.

portance. We shall use energy rather than free energy in our discussion in order to eliminate the complicating effects of entropy changes, and it is therefore necessary to re-estimate the strain.

Table I shows the energy of dissociation of the trimethylboronamine complexes. The addition of one methyl group increases dissociation energy by 3.9 kilocalories per mole. If we assume, with Brown, that the effect of adding more methyl groups is linear in the number of methyl groups, we may derive the third column in Table I, which shows expected dissociation energy. The last column then gives the difference between expected and observed dissociation energies, and this difference may be attributed to a steric strain of some sort. Actually, these estimates are probably high. If we accept Brown's hypothesis that methylamine is a stronger base than ammonia because of the positive inductive effect, we really should not expect the strength of the amines to increase linearly with number of methyl groups added. Whereas the dipole moment of ethyl chloride is about 10% higher than that of methyl chloride—presumably because of the positive inductive effect of the added methyl group—we find little or no additional increase in the dipole moments of isopropyl and *t*-butyl chlorides. This fact would indicate that the positive inductive effect of methyl groups falls off beyond the first. If we arbitrarily assume that the second methyl may have as little as one-half the effect of the first and that the third one-third the effect, we would obtain 0.35 and 3.3 kcal./mole for the strain energies of the last two compounds in the table. These values are used as lower limits to the strain energies in Table III.

Table I

Summary of Dissociation Energies

	Kcal. per mole		
Compound	ΔH of dissociation	Expected dissociation	Strain energy
NH_3—$B(CH_3)_3$	13.7	13.7	(0)
CH_3NH_2—$B(CH_3)_3$	17.6	17.6	(0)
$(CH_3)_2NH$—$B(CH_3)_3$	19.3	21.5	2.2
$(CH_3)_3N$—$B(CH_3)_3$	17.6	25.4	7.8

Calculation of B-Strain.—We are now ready for an approximate calculation of B-strain in the trimethylamine complex. Inasmuch as the C–N–C angle changes only a few degrees when boron trimethyl is added to trimethylamine, the energy increment due to the change in this angle should be calculable to good approximation by use of the angle bending constant for trimethylamine. It should be noted that the use of an empirical potential constant accounts for energy of methyl group compression as well as pure angle bending. If we make the extreme assumptions that the C–N–C angles in the trimethylamine and the trimethylamine–boron trimethyl complex are, respectively, 112° and 109$^1/_2$°, the angle change is 2$^1/_2$°.

Although the bending potential constants for similar molecules are known to range near 1×10^{-11} erg./radian^2, there seemed to be no good literature value for trimethylamine. We calculated the C–N–C bending constant from the Raman frequencies[4] 368, 827 and 1179 cm.$^{-1}$ which are to be identified as primarily C–N–C bending, C–N stretching and CH_3 wagging, respectively, all in the symmetry class A_1. We set up the exact equations for the A_1 class and then reduced them by making the CH_3 groups rigid and of the generally accepted dimensions. Then assuming a valence force potential, we obtained the constants 1.17×10^{-11} erg./radian^2 for C–N–C bending, 4.77×10^5 dynes/cm. for C–N stretching, and 0.70×10^{-11} erg./radian^2 for the C–C–H angles in CH_3 wagging. This result may be compared, *e. g.*, with Sutherland's[5a] estimate of the stretching and bending constants for isobutane of 4.5×10^5 dynes/cm. and 0.95×10^{-11} erg./radian.^{2}

With the bending constant 1.17×10^{-11} erg./radian^2, we find that the energy of trimethylamine increases by $25(\Delta\theta)^2$ calories per mole per C–N–C angle where $(\Delta\theta)$ is the change in degrees from the equilibrium value of the C–N–C angle. Taking the upper limit $\Delta\theta = 2^1/_2°$, we obtain a destabilization of 156 calories per angle or a total destabilization for the molecule of three times this amount. The resulting maximum value of about 0.5 kcal. per mole is certainly small compared with the 3–8 kcal. per mole estimated in Table III. This calculation indicates that B-strain is not primarily responsible for the anomalous weakness of trimethylamine.

Comparison with Related Hydrocarbons.—Having indicated that the effect of B-strain is small in the methylamines, we shall now show that hydrocarbons with structures related[5b] to the structures of the compounds discussed here show a corresponding increase in strain energy as the complexity of the structures increases. This strain must be a manifestation of F-strain, because, even if B-strain is present in the hydrocarbons which we shall discuss, it must not vary greatly from one to another because the number and nature of bonds attached to carbon is essentially constant. As we have seen in the preceding discussion, B-strain becomes manifest in such a situation as the change from trivalent to tetravalent nitrogen in which the methyl groups attached to nitrogen are forced back toward the tetrahedral angle. Table II shows the heats of formation of some hydrocarbons in the gas phase at 25°.[6] Column 3 gives the difference between the heat of formation of the given hydrocarbon and the normal hydrocarbon with the same num-

---

[4] K. W. F. Kohlrausch and J. Wagner, *Z. physik. Chem.*, **B52**, 185 (1942).

[5a] G. B. B. M. Sutherland and D. M. Simpson, *J. Chem. Phys.*, **15**, 153 (1947).

[5b] This relationship has been mentioned by H. C. Brown, H. I. Schlesinger and S. Z. Cardon, This Journal, **64**, 325 (1942).

[6] E. J. Prosen, K. S. Pitzer and F. D. Rossini, *J. Research Natl. Bur. Stds.*, **34**, 403 (1945).

ber of carbon atoms. We observe that the iso hydrocarbons are about 1.7 and the neo hydrocarbons about 4.6 kcal. per mole more stable than the related normal hydrocarbon. If we assume that the effects of branching would be additive in more complex molecules, we obtain the results in column 4 of Table II for the expected difference from the heat of formation of the normal hydrocarbon. For example, 2,2,3-trimethylbutane contains both iso and neo type configuration, and so should be more stable than *n*-heptane by 1.7 + 4.6 = 6.3 kcal. per mole. The difference between columns 4 and 3 represents destabilization which we shall attribute to steric strain of the F type. The assumption of additivity is no doubt an oversimplification. Some justification for the assumption may be derived from a consideration of 2,5-dimethylhexane. In this compound, where two iso groups are widely separated, additivity is strict. We were unable to test the assumption with regard to combinations with neo groups due to lack of data on compounds in which these groups are separated sufficiently.

TABLE II

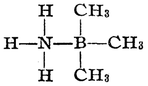
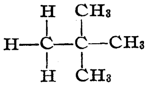
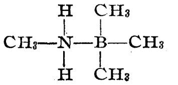
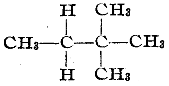
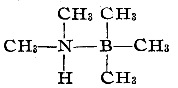
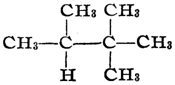
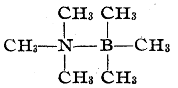
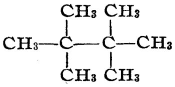
HEATS OF FORMATION OF HYDROCARBONS IN THE GAS PHASE AT 25° AND RELATED DATA

Hydrocarbon	$-\Delta H_f$	Kcal. per mole Difference from normal hydrocarbon	Expected difference from normal hydrocarbon	Steric strain
n-Butane	29.8	0.0	0.0	0.0
Isobutane	31.5	−1.7	−1.7	.0
n-Pentane	35.0	0.0	0.0	.0
Isopentane	36.9	−1.9	1.7	− .2
Neopentane	39.7	−4.7	−4.6	− .1
n-Hexane	40.0	0.0	0.0	.0
2-Methylpentane	41.7	−1.7	−1.7	.0
2,2-Dimethylbutane	44.4	−4.4	−4.6	.2
n-Heptane	44.9	0.0	0.0	.0
2-Methylhexane	46.6	−1.7	−1.8	.0
2,2,3-Trimethylbutane	49.0	−4.1	−6.3	2.2
n-Octane	49.8	0.0	0.0	0.0
2,2,3,3-Trimethylbutane	54.0	−4.2	−9.2	5.0
2-Methylheptane	51.5	−1.7	−1.7	0.0
2,5-Dimethylhexane	53.2	−3.4	−3.4	.0

The skeletons of the hydrocarbons 2,2-dimethylpropane, 2,2-dimethylbutane, 2,2,3-trimethylbutane and 2,2,3,3-tetramethylbutane are identical, respectively, with those of the addition compounds of trimethylboron with ammonia, mono-, di-, and trimethylamines if we consider B + N atoms as equivalent to C atoms, as the first two columns of Table III show. Columns 3 and 4 of the same table summarize the steric strains of the hydrocarbons and of the amine–boron compounds. This agreement as to order of magnitude makes it probable that this steric effect in the hydrocarbons, in which B-strain should be substantially eliminated, is of the same nature as that in the amine complexes.

TABLE III

COMPARISON OF STERIC STRAINS OF AMINE–TRIMETHYLBORON COMPLEXES AND RELATED HYDROCARBONS

Amine–boron complex	Hydrocarbons	Estimated strain of amine, kcal.	Estimated steric strain of hydrocarbon
 $H_3N-B(CH_3)_3$	 $H_3C-C(CH_3)_3$	0.0	−0
 $CH_3NH_2-B(CH_3)_3$	 $CH_3CH_2-C(CH_3)_3$	0.0	0.2
 $(CH_3)_2NH-B(CH_3)_3$	 $(CH_3)_2CH-C(CH_3)_3$	0.3–2.2	2.2
 $(CH_3)_3N-B(CH_3)_3$	 $(CH_3)_3C-C(CH_3)_3$	3.3–7.8	5.0

Discussion.—The comparison with the hydrocarbons does not apply to the formation of ammonium salts in water solution, in which a parallel trend has been found.[2b] Inasmuch as the situation in water is much more complex, as was recognized by Brown, it is probable that the parallelism is to some extent fortuitous. Indeed correction[7] for symmetry number changes on proton addition spoils the exact parallelism by making methylamine the strongest base. Possibly hydration energy effects are responsible for the effect in water solution.

It is clear, then, as was pointed out by Lewis (and also by Brown in his later experiments on F-strain) that the reference acid is very important in determination of the order of basic strengths.

With hydrochloric as a reference acid, Brown[8] found a regular order of base strength for the methylphosphines. His conclusion that this result supports his theory is not necessarily correct. It is quite possible that if experiments could be performed in the gas phase, the alkylamines would show the normal order of basic strength against hydrochloric acid. In any event, the structure of the hydrochlorides is so different from that of the trimethyl boron complexes that any comparison between the two must be made with caution. Also, it should be pointed out that in compounds such as the phosphines, in which the bond angles are less than tetrahedral, B-strain should have a base-strengthening effect. The change from p to sp^3 bonds caused by the addition of the acid and consequent expansion of the bond angles should relieve the B-strain, thereby making the salt or addition complex more stable compared with the free base.

---

[7] We are indebted to Prof. V. Schomaker for suggesting this point.

[8] H. C. Brown, THIS JOURNAL, **67**, 503 (1945).

B-strain may become important when groups much larger than methyl are attached to the central atom because both the angles of distortion and the angle force constant will increase.

Summary

1. It is shown, by a semi-quantitative calculation, that the B-strain postulated by H. C. Brown is too small to account for the observed weakness of trimethylamine as an acid.

2. A comparison of ordinary steric forces (F-strain) in hydrocarbons of related structure shows that the steric strains in trimethylboron-alkyl amine compounds are probably of the same nature as those in the hydrocarbons.

3. The importance of the reference acid in establishing basic strengths is re-emphasized.

4. It is pointed out that B-strain will be base-strengthening rather than base-weakening when the angles are less than tetrahedral.

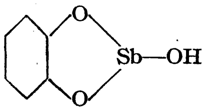
CORVALLIS, OREGON
BERKELEY, CALIFORNIA RECEIVED FEBRUARY 7, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND CO.]

Antimonylcatechol. I. Coördination of Simple Amines and Alcohols

BY L. M. WHEELER AND C. K. BANKS

The combination of inorganic, trivalent antimony with phenols and α-hydroxyacids has long been known, but only a few derivatives with alcohols have been reported[1] and these compounds are unstable in the presence of water. Since antimonylcatechol[2] (I) appeared to be of interest in the treatment of filariasis,[3] efforts were made to solubilize this compound. It is insoluble in water, aqueous ammonia, alcohol, ether, chloroform and other solvents and dissolves only in strong sodium hydroxide and concentrated hydrochloric acid. However, it was noted that in the presence of both an alcohol and an amine, antimonylcatechol readily formed solutions from which crystalline products could be isolated. Both the alcohol and the amine were combined, in some fashion, with the antimonylcatechol in the isolated products. That such combinations were not fortuitous was readily demonstrated. The ratios of combination were always the same regardless of the reactants and experiments showed that no combination occurred in aqueous solution when only the alcohol or the amine was present.



I

The atomic ratio of antimony to nitrogen was always one within experimental limits. The products dissolved readily in water to give nearly neutral solutions which could be decomposed with strong acids to yield antimonylcatechol, the alcohol and the amine salt. When both the alcohol and amine were low-boiling, prolonged heating at 100° in a high vacuum resulted in the loss of these fragments, leaving antimonylcatechol. Preparations containing ammonia or other volatile amines would lose the nitrogenous constituent during prolonged shelf storage, resulting in decreased solubility and altered crystalline properties. If the amines were relatively non-volatile, the products were stable to heat and storage.

Solutions of these compounds in water appeared to undergo hydrolysis on standing and a hydrated form of antimonylcatechol was separated. An excess of any amine would stabilize the solutions indefinitely. Aqueous solutions appeared to have all the properties of salt solutions, particularly in that they were excellent conductors of electricity, showing about forty per cent. the conductance of equimolar sodium chloride solutions.

Determinations of carbon and hydrogen in the presence of antimony were extremely variable, but both antimony and nitrogen were readily determined. To further elucidate the structures, inductive postulations were necessary.

The alcohols used were methanol, propanol, glycols, glycerol, sorbitol, mannitol, dextrose, galactose and levulose. The amines studied consisted of ammonia, diethyl- and triethylamine. The properties of the resulting products are given in Table I.

The reaction product of antimonylcatechol and tartaric acid[4] was also investigated. When equimolar amounts of the two substances were heated in water containing a four-fold excess of sodium bicarbonate, a product similar in every respect to the alcohol–amine complexes was formed.

Experimental

Alcohol–Amine–Antimonylcatechol Complexes.—Antimonylcatechol (0.2 mole) was suspended in 100 ml. of water in which had been dissolved 0.2 mole of the alcohol and 0.5 mole of amine in a 500-ml. round-bottomed flask equipped with stirrer and condenser. The temperature of the vigorously stirred solution was raised to 80–90° and was maintained at this temperature for fifteen minutes after complete solution occurred. The hot solutions were filtered rapidly and cooled. The products crystallized on cooling or on adding acetone to the cold solution. They were recrystallized from hot water, methanol or

---

[1] Meerwein, *Ann.*, **476**, 113 (1929).

[2] Causse, *Bull. soc. chim.* [3] **8**, 245 (1892).

[3] Feinberg, U. S. Patent 2,330,962, Oct., 1943.

[4] U. S. Patent 1,688,964.

TABLE I

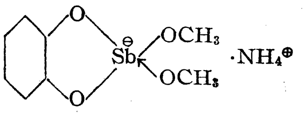
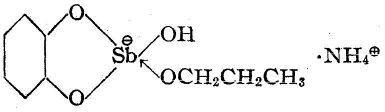
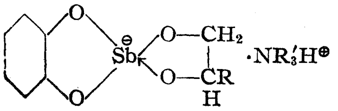
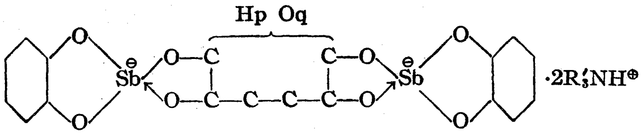
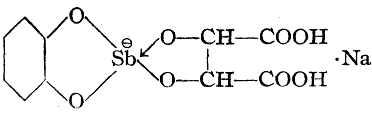
ANTIMONYLCATECHOL COÖRDINATE COMPOUNDS

Alcohol	Amine	Recrystallization solvent	M. p., °C.	Assay,[a] %		Atomic ratio Sb/N
				Antimony[b]	Nitrogen[c]	
Methanol	NH_3	Methanol	273	33.63	3.81	1.02
Propanol	NH_3	Water	274	35.14	4.05	1.00
Ethylene glycol	NH_3	Water	275	35.07	4.05	1.00
Propylene glycol	NH_3	Water	269	34.17	3.92	1.00
Glycerol	NH_3	Water	238	32.40	3.96	0.94
Mannitol	NH_3	Water	272	34.75	4.02	1.00
Glycerol	$(C_2H_5)_2NH$	Water	86–90	25.94	3.01	0.99
Sorbitol	$(C_2H_5)_2NH$	Water	170	28.44	3.29	1.00
Mannitol	$(C_2H_5)_2NH$	Water–acetone	114	28.44		
Dextrose	$(C_2H_5)_2NH$	Water–acetone	106	28.31		
Galactose	$(C_2H_5)_2NH$	Water	106	28.72	3.04	1.09
Levulose	$(C_2H_5)_2NH$	Water	106	28.93	3.23	1.03
Mannitol	$(C_2H_5)_3N$	Water	90	28.92	3.09	1.08
Dextrose	$(C_2H_5)_3N$	Water	90	28.98	3.28	1.02

[a] Analytical results are due to A. W. Spang, Margaret McCarthy Ledyard and Elizabeth Selvig. [b] Modification of the arsenic method of Cislak and Hamilton, THIS JOURNAL, 52, 638 (1930). [c] Micro-Kjeldahl method.

TABLE II

STRUCTURAL COMPARISONS

Postulated structure					Molecular weight			Composition, %			
						From assays		Antimony		Nitrogen	
				nH₂O	Formula	Sb	N	Calcd.	Found	Calcd.	Found
				3	364	362	368	33.45	33.63	3.85	3.81
				1	342	347	346	35.60	35.14	4.00	4.05
											
R	From	NR'_3H^+									
—H	Ethylene Glycol	NH_4^+		2	344	347	346	35.40	35.07	4.07	4.05
$—CH_3$	Propylene Glycol	NH_4^+		2	358	356	357	34.01	34.17	3.91	3.92
$—CH_2OH$	Glycerol	NH_4^+		2	374	376	354	32.56	32.40	3.75	3.96
$—CH_2OH$	Glycerol	$N(C_2H_5)_2H_2^+$		4	466	470	465	26.18	25.94	3.01	3.01
											
p	q	From	NR_3H^+								
10	2	Sorbitol	$N(C_2H_5)_2H_2^+$	4	858	856	852	28.34	28.44	4.26	3.29
10	2	Mannitol	$N(C_2H_5)_2H_2^+$	4	858	856		28.34	28.44		
10	2	Mannitol	NH_4^+	2	710	701	697	34.30	34.75	3.94	4.02
10	2	Mannitol	$N(C_2H_5)_3H^+$	0	842	842	907	28.92	28.92	3.33	3.09
8	2	Dextrose	$N(C_2H_5)_2H_2^+$	4	856	860		28.44	28.31		
8	2	Galactose	$N(C_2H_5)_2H_2^+$	4	856	848	922	28.44	28.72	3.27	3.04
8	2	Levulose	$N(C_2H_5)_2H_2^+$	4	856	842	922	28.44	28.93	3.27	3.04
8	2	Dextrose	$N(C_2H_5)_3H^+$	0	840	840	854	28.98	28.98	3.33	3.28
				0	401	402		30.36	29.92		

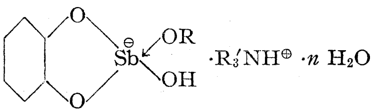
acetone–water mixtures. The properties of the compounds are listed in Table I.

Sodium Antimonyltartratecatechol.—Tartaric acid (16 g.) and sodium bicarbonate (32 g.) were dissolved in 180 ml. of water and heated to 80°. Antimonylcatechol (27.6 g.) was added slowly. After the reaction was completed, the solution was filtered hot and cooled. The product crystallized on standing and was recrystallized from water.

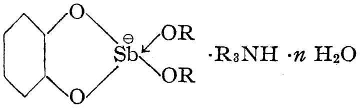
Anal. Found: Sb, 29.91, 29.92.

Discussion of Structure

The structure of antimonyl compounds has not been investigated extensively. Doak[5] has shown that arylstibonic acids and their salts conform to a coördinate ion structure which may be represented as $RSb(OH)_5^-\cdot M^+$ in which antimony exhibits a coördination number of six. Similarly, it was suggested in previous work that some benzenearsonous acids are best represented as $RAs(OH)_3^-\cdot H^+$ where arsenic has a coördination number of four.[6] Triethoxystibine in ethanol forms the ion $(C_2H_5O)_4Sb^-$ which has strong acid properties[1] and the antimony-bis-catecholates have been postulated by Bodendorf[7] to have a coördinate ion structure. By analogy, these compounds might have structures II or III.

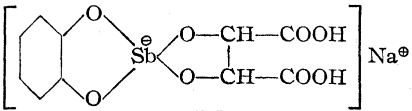


II



III

The strict one-to-one ratio of antimony to nitrogen, the water solubility, ionic type of conductance, all favor such a structural interpretation. Furthermore, the tartaric acid–antimonylcatechol complex (IV), can be explained by a similar postulation.



IV

A comparison of the experimental data with the postulated structures is given in Table II.

While these structures appear to satisfactorily explain the antimonylcatechols and related compounds, all postulations as to the structures of the antimony derivatives of tartaric, citric and malic acids are inadequate to explain the large number of variations obtained. While previous work has suggested that the compounds form complex ions, it is possible that reëxamination of the data in the light of the requirements for coördinate structures may elucidate the nature of the chemical linkages.

Summary

1. Antimonylcatechol was found to react with alcohols and amines to form antimonylcatechol–alcohol–amine complexes having the properties of salts. Fourteen such compounds involving various alcohols and amines are reported.

2. The compounds are best explained as amine salts of an antimonylcatechol coördinate acid.

Detroit, Michigan Received August 18, 1947

---

[5] G. O. Doak, This Journal, **68**, 1991 (1946).

[6] C. K. Banks, *et al.*, *ibid.*, **69**, 5 (1947).

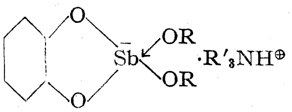
[7] K. Bodendorf, *Pharm. Press.* (Vienna), **38**, 8 (1933).

[Contribution from the Research Laboratories of Parke, Davis and Co.]

Antimonylcatechol. II. Coördinates with Aminoalcohols

By L. M. Wheeler and C. K. Banks

In the previous paper of this series[1] it was shown that antimonylcatechol would react with alcohols in the presence of amines to form compounds which could be represented by formula III. It was considered of interest to determine if aminoalcohols would also form similar compounds, and under what specific conditions.



III

Antimonylcatechol was dissolved by aqueous solutions of amino-alcohols when the aminoalcohol was in molecular excess.[2] It was frequently difficult to isolate the products directly from such reaction mixtures. They were easily isolated, however, when antimonylcatechol and the aminoalcohol reacted in aqueous suspension in the presence of an excess of ammonia or diethylamine. The product appeared to be independent of the amine used to catalyze the reaction. When the ratios of reactants were varied, the isolated products were more complex and appeared to incorporate a portion of the catalytic amine.

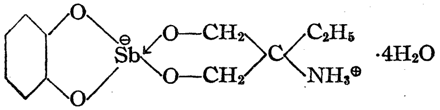
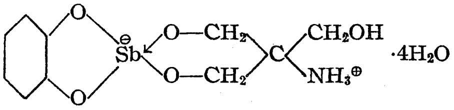
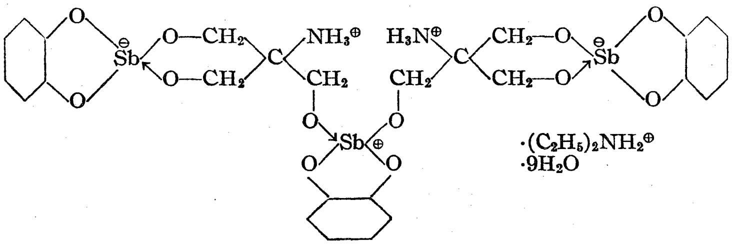
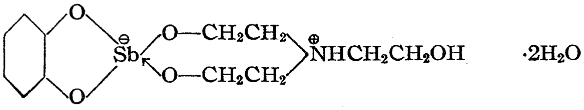
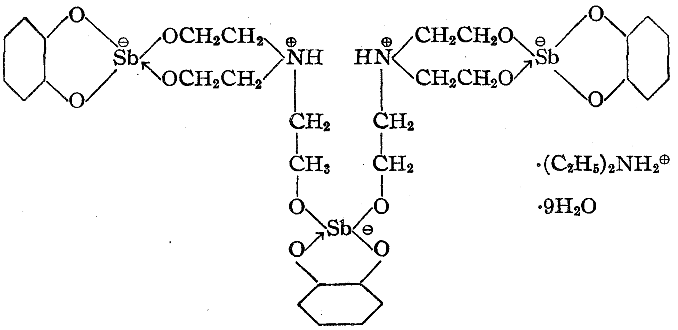
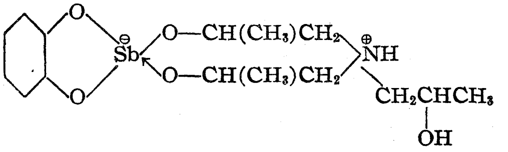
The products resulting from equimolar reaction were stable as solids and dissolved in water to give solutions which hydrolyzed slowly on standing. An excess of any amine appeared to prevent this hydrolysis. Like the products derived from amines and alcohols, the compounds appeared to have the properties of salts. When two moles of antimonylcatechol reacted with one of a poly-

---

[1] Wheeler and Banks, This Journal, **70**, 1264 (1948).

[2] J. G. Feinberg, U. S. Patent 2,330,962, Oct., 1943.

TABLE I

Reactants—moles				Assays—%			
Antimonylcatechol	Aminoalcohol	Postulated structure	M. p., °C.	Antimony Calcd.	Antimony Found	Nitrogen Calcd.	Nitrogen Found
1	1		114–115	28.99	28.95	3.33	3.45
1	1		110	28.85	28.74	3.31	3.33
2	1		174–176	31.37	31.25	3.61	3.60
1	1		258–260	29.41	29.43	3.38	3.52
2	1		107	29.91	29.80	3.44	3.48
1	1		114	28.98	28.97	3.33	3.36

hydric aminoalcohol in the presence of another amine, the products were less stable, tending to decompose in solid form. Solutions of these compounds had the same properties as before. The condensation products and their postulated structures are listed in Table I.

Experimental

Equimolar Compounds.—Antimonylcatechol (0.1 mole) was suspended in 100 ml. of water containing the aminoalcohol (0.1 mole) and 0.5 mole of ammonia or diethylamine. The temperature was raised to 80° while stirring. As soon as the reaction was complete, the solution was filtered and chilled. The products crystallized on standing and were recrystallized from acetone–water mixtures.

Antimonylcatechol (2): **Aminoalcohol** (1).—Antimonylcatechol (0.2 mole) and the aminoalcohol (0.1 mole) reacted in 100 ml. of water and 0.5 mole of diethylamine as before. The products were recrystallized from water or acetone–water mixtures.

Summary

Six coördinate complexes of antimonylcatechol with amino-alcohols have been described as to preparation, properties and possible structure.

DETROIT, MICH.

RECEIVED AUGUST 18, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

Some Chemotherapeutically Active Sulfones.[1] III. Azido Substituted Sulfones

BY C. K. BANKS AND O. M. GRUHZIT

The activity of 4,4′-diaminodiphenylsulfone against β-hemolytic streptococcal infections in mice has resulted in the preparation of innumerable sulfone derivatives of varying types. A survey of variously substituted sulfones[2] indicated that derivatives easily hydrolyzed to the parent 4,4′-diaminodiphenylsulfone, such as the di-dextrose bisulfite (Promin) and the di-formaldehyde sulfoxylate (Diamidin, Diasone), retained the same type of therapeutic activities as the parent sulfone. When groups which would hydrolyze only with difficulty were substituted on the amine groups, the activity was generally retained when one amino group remained unsubstituted, but was lost if both amine groups were substituted.

It was thought of interest to prepare related compounds in which the character of the amino group was completely changed. The triazo group was chosen since it resembles the amino group in some respects but also has some greatly different reaction properties. 4,4′-bis-Triazo-, 4-amino-4′-triazo, 4-succinylamino-4′-triazo- and 2-sulfamyl-4,4′-bis-triazodiphenylsulfone were prepared by variations in standard procedures. Both hydroxylamine and hydrazine were investigated as reactants with diazonium salts and hydrazine was found to be superior for these preparations. While the compounds generally separated from the reaction mixtures in better than 99% purities, special recrystallization techniques were necessary to remove traces of diazotizable amines. All of the compounds had very sharp explosion points when pure.

Experimental[3]

4,4′-*bis*-Triazodiphenylsulfone.—4,4′-Diaminodiphenylsulfone (25 g.) was worked into a paste with 60 g. of concentrated sulfuric acid and then poured over 100 g. of ice. The resulting suspension was cooled in an ice-bath and diazotized by the slow addition of 14 g. of sodium nitrite in 100 ml. of water. When the diazotization was nearly completed, the nitrite was added dropwise, testing the diazonium solution after each drop until an excess was indicated by starch-potassium iodide strips. A coupling solution of 100 g. of sodium acetate, 20 ml. of 85% hydrazine hydrate, 100 g. of ice and 200 ml. of water was prepared and placed in a 4-liter beaker. The diazonium solution was added all at one time with vigorous stirring, resulting in violent foaming which required octyl alcohol to prevent overflow.[4] After four hours, the yellow product was filtered off and dissolved in 600 ml. of acetone. The acetone solution was treated with two types of charcoal (Darco G 60 and Norite) and then diluted with 2 liters of water. The resulting precipitate was recrystallized from glacial acetic acid and then dissolved in a minimum of acetone, charcoaled and the solution filtered directly into a large volume of air-free water. The acetone recrystallization was repeated until no diazotizable amine was present. The product was filtered off and dried *in vacuo* over phosphorus pentoxide; yield 70%, nearly white, explosion point 156–157°.

Anal. Calcd. for $C_{12}H_8N_6O_2S$: N, 28.02. Found: N, 27.94.

4-Amino-4′-triazodiphenylsulfone.—4-Acetoamino-4′-aminodiphenylsulfone (60 g.) was suspended in 100 ml. of water, 50 ml. of concentrated hydrochloric acid added and 100 g. of ice. The hydrochloride salt precipitated and was diazotized slowly with 14 g. of sodium nitrite in 100 ml. of water using the same precautions as above to avoid an excess. The diazonium solution was added all at once to a solution of 100 g. of sodium acetate and 25 ml. of 85% hydrazine hydrate in 200 ml. of water and 200 g. of ice. The crude product was filtered off and hydrolyzed by refluxing in 300 ml. of 3 *N* hydrochloric acid until solution occurred. The solution was cooled and neutralized with ammonia to precipitate a nearly white product which was purified further by recrystallization from 70% alcohol; yield 40%, white, m. p. 130–131°, explodes immediately after melting.

Anal. Calcd. for $C_{12}H_{10}N_4O_2S$: N, 20.44. Found: N, 20.49.

4-Succinylamino-4′-triazodiphenylsulfone.—4-Amino-4′-succinylaminodiphenylsulfone (7 g.) was diazotized in 60 ml. of water and 4 ml. of concentrated sulfuric acid with 1.4 g. of sodium nitrite. The coupling was performed with a solution of 10 g. of sodium acetate, 2 ml. of 85% hydrazine hydrate, 50 ml. of water and 100 g. of ice. After coupling was completed, the solution was made alkaline to phenolphthalein paper, filtered and acidified. The product was recrystallized from 70% acetone until no diazotizable amine was found; yield 60%, white, explosion point 182–185°.

Anal. Calcd. for $C_{16}H_{14}N_4O_5S$: N, 14.92. Found: N, 14.95.

2-Sulfamyl-4,4′-*bis*-triazodiphenylsulfone.—4,4′-Diamino-2-sulfamyldiphenylsulfone (18.2 g.) was diazotized in 50 ml. of water, 50 ml. of concentrated hydrochloric acid and 100 g. of ice as in the other preparations. Coupling was performed with 50 g. of sodium acetate, 15 ml. of 85% hydrazine hydrate and 100 g. of ice in 100 ml. of water. Recrystallized from 70% acetic acid, then repeatedly from an acetone–alcohol–water (40–40–20) until no diazotizable amine test was obtained; yield 50%, nearly white, explosion point 176–178°. *Anal.* Calcd. for $C_{12}H_9N_7O_4S_2$: N, 25.88. Found: N, 25.42.

Chemotherapy

The chemotherapeutic activity of the triazosulfones was determined in albino mice injected intraperitoneally with about 5,000–10,000 lethal doses of β *Streptococcus hemolyticus* or about 750 lethal doses of pneumococcus Type I cultures, as based on the titration for virulence at the time of the tests. A "lethal dose" of either culture resulted in the death of all control animals in thirty-six hours. Treatment of the pneumococcus-infected mice was begun immediately following inoculation, and in one to one and one-half hours after *Streptococcus hemolyticus* inoculation. The mice were treated orally by cannula twice daily for three days when infected with pneumococci and

---

(1) Parts I and II, Bambas, THIS JOURNAL, **67**, 668, 671 (1945).

(2) B. F. Tullar and C. K. Banks, presented before the Division of Medicinal Chemistry of the American Chemical Society Division, Cincinnati meeting, April, 1941.

(3) Analytical determinations by Frances C. Hummel.

(4) Slow addition of the diazonium solution resulted in the formation of tars.

TABLE I

Compound	LD_{50}-oral[a] mg./mouse	Chemotherapy: β-Strep. hemolyt. salivarius[b] M. E. D.[d] × days mg./M./day	% Survival 14 days	Pneumococcus[c] mg./M./day × 3 days	% Survival 7 days
4,4'-Diaminodiphenylsulfone	12.6	0.25	80	2.5	80
disodium didextrosesulfonate[e]	130	2.8	90	10.0	56
disodium diformaldehydesulfoxylate[f]	250	10.0	90	..	..
4,4'-bis-Triazodiphenylsulfone	250	0.5	83	20.0	13
4-Amino-4'-triazodiphenylsulfone	21.4	0.5	90	5.0	12
2-Sulfamyl-4,4'-bis-triazodiphenylsulfone	>500	2.5	83	20.0	0

[a] Calcd. by the method of Dragstedt, *J. Pharmacol.*, **32**, 217 (1927–1928). [b] Lancefield's Group A, 01625. [c] Type I, 02444. [d] M. E. D. = minimal effective dose permitting survival of 80 to 90% of mice. [e] Promin. [f] Diamidin, Diasone.

once daily for three days when infected with streptococci. The animals were observed for twenty-eight days; however, the comparison of compounds was made on the basis of fourteen and seven day survival rates, respectively. Except for 4,4'-diaminodiphenylsulfone, the results tabulated in Table I are based on one or two routine tests for each compound, using ten to fifteen animals per dose level. Diaminodiphenylsulfone was used as a reference standard in all tests and the values given are the statistical average of all tests. Only those minimal doses which achieved comparable therapy are reported. The oral LD_{50} in mice was also determined for each compound.

The activities of the triazo compounds against mouse streptotoccal infections resembled those of the analogous aminosulfones but the pneumococcal activities were much less. 4,4'-bis-Triazodiphenylsulfone was of greatest interest. The acute toxicity of the triazo compound given orally in mice was much less than that of the analogous amino compound, yet the minimal dose of triazosulfone to achieve comparable therapy was only twice that required for the aminosulfone. Furthermore, no free or hydrolyzable amine could be detected in the blood of mice given up to 10 mg./mouse of 4,4'-bis-triazodiphenylsulfone orally, while the minimum oral therapeutic dose of 4,4'-diaminodiphenylsulfone (0.25 mg./mouse) gave demonstrable blood levels, indicating that conversion of any triazo group to amino *in vivo* was of a very low order.

Summary

1. Four new triazodiphenylsulfones are described. These compounds had antistreptococcal activity in mice comparable to that of the corresponding aminodiphenylsulfones.

2. 4,4'-bis-Triazodiphenylsulfone, although absorbed orally in sufficient amounts to achieve demonstrable antistreptococcal activity, was not converted *in vivo* to an amino compound in detectable amounts. It is possible that the activity of this compound functions through a different mechanism than that common to sulfa drugs in general.

DETROIT, MICH. RECEIVED OCTOBER 9, 1947

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

Reactions of Atoms and Free Radicals in Solution. XIII. The Reactions of Diacetyl Peroxide with Aliphatic Ketones. A New Synthesis of 1,4-Diketones

BY M. S. KHARASCH, HENRY C. MCBAY AND W. H. URRY

Attention has been called[1] to the fact that the free primary or secondary alkyl radicals (formed by the decomposition of the diacyl peroxides of low molecular weight) remove hydrogen atoms from solvents to form new free radicals. The relations between the structure and the properties of the new free radicals thus formed are of considerable interest. A good deal of information regarding the behavior of the free radicals formed by the removal of hydrogen atoms from acids,[1] esters,[2] nitriles,[3] acid halides,[2] alkylbenzenes and ring-substituted alkylbenzenes[4] has already been recorded. The present paper deals with the reactions of the free radicals formed by the removal of hydrogen atoms from aliphatic and aryl-substituted aliphatic ketones.

Discussion

The products and the yields of such products obtained by the decomposition of diacetyl peroxide in aliphatic ketones, can be best explained by assuming that the free methyl radical, formed by the decomposition of the diacetyl peroxide, abstracts an *alpha* hydrogen atom from the ketone molecule, and that the new free radical, thus formed, dimerizes.

$$(1)\quad \underset{\text{(A)}}{\text{RR}'\text{CHCOCHRR}'} + \text{H}_3\text{C}\cdot \longrightarrow \underset{\text{(B)}}{\text{RR}'\underset{\cdot}{\text{C}}\text{OCHRR}'}$$

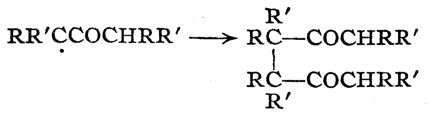
---

[1] Kharasch and Gladstone, THIS JOURNAL, **65**, 15 (1943).

[2] Kharasch, Jensen and Urry, *J. Org. Chem.*, **10**, 386 (1945).

[3] Kharasch, Smith and Urry, unpublished work.

[4] Kharasch, McBay and Urry, *J. Org. Chem.*, **10**, 401 (1945).

(2) 

$$\mathrm{RR'\dot{C}COCHRR'} \longrightarrow \begin{array}{l} \mathrm{R\overset{R'}{C}{-}COCHRR'} \\ \;\;| \\ \mathrm{R\underset{R'}{C}{-}COCHRR'} \end{array}$$

(C)

R is an alkyl radical, an aryl radical, or a hydrogen atom, and R′ is an alkyl or an aryl radical. Furthermore, since the "dimer" (C) contains hydrogen atoms (secondary or tertiary) susceptible to attack by free methyl radicals, it is to be expected that "trimers" (formed by a combination of the free radical (B) and the free radical produced by removal of a hydrogen atom from (C)) and "tetramers" (formed by the combination of two free radicals produced by removal of a hydrogen atom from (C)) should occur among the reaction products. In most of the reactions studied, both of these types of reaction product were isolated. The yields of the "dimers," "trimers" and "tetramers" are strongly influenced by the molecular ratio of ketone to peroxide. When this ratio is very high (*e. g.*, 10:1), the "dimer" predominates. With lower ratios (*e. g.*, 3:1) the yields of the "trimers" and "tetramers" are fairly high. These findings illustrate the selective action of free methyl radicals to which attention has been called in previous articles. In closely related series of compounds, the ease of removal of hydrogen atoms by free methyl radicals follows the order tertiary > secondary > primary. If the radical R in compound (A) is a hydrogen atom (that is, if the compound is $\mathrm{R'CH_2COCH_2R'}$), then its "dimer" (C), because it contains tertiary hydrogen atoms, should have a strong tendency to form "trimers" and "tetramers." A large ratio of ketone to diacetyl peroxide would therefore be required to ensure the formation of an appreciable quantity of the "dimer" (C).

Furthermore, the selective action of free methyl radicals in removing secondary or tertiary rather than primary hydrogen atoms is well illustrated by the products formed from the action of free methyl radicals on the following ketones: butanone, 3-methylbutanone, 2,4-dimethyl-3-pentanone, 2,6-dimethyl-4-heptanone, 1-phenylpropanone, methyl acetoacetate, and 3,3-dimethylbutanone. No evidence of attack on primary hydrogen atoms was found in any of these compounds (except in the case of 3,3-dimethylbutanone). It should, however, be stated that, with the methods used, even careful examination of the reaction products may have failed to detect small quantities of the substances formed by removal of primary hydrogen atoms. To settle this point another experimental procedure is needed. It is proposed to study the comparative reactivity of primary, secondary, and tertiary hydrogen atoms by labeling one of the hydrogen atoms, that is, by replacing it by a deuterium atom and determining the amounts of CH_4 and CH_3D formed.

The products formed by the decomposition of diacetyl peroxide in various ketones are indicated in Table I.

Whenever the 1,4-diketones ("dimers"), formed by the decomposition of diacetyl peroxide in ketones, were new compounds, their structure was established by conventional methods. The experimental part of this paper should be consulted for the procedures used in individual cases. This part also contains a full list of the gaseous and other products (methane, carbon dioxide, methyl acetate) formed from the diacetyl peroxide when that compound is decomposed in aliphatic ketones. Since these products are the same as those formed when diacetyl peroxide is decomposed in other solvents (acids, esters, nitriles, etc.), the mechanism of their formation is presumably the one discussed in previous articles.

"Dimers" (1,4-diketones), "trimers" (triketones), and "tetramers" (tetraketones) are formed by the action of a diacyl peroxide on ketones whenever the ketones are either aliphatic or of the type Aryl-CHR-CO-Alkyl, (in which R is a hydrogen atom or an alkyl group); they are not formed from ketones in which an aryl group is directly attached to a carbonyl group. Thus, no polymers of low molecular weight, but only higher polymers were formed when acetophenone, propiophenone, or phenyl isopropyl ketone was treated with diacetyl peroxide. Furthermore, judging by the nature of the gaseous products produced in these

TABLE I

DECOMPOSITION OF DIACETYL PEROXIDE IN KETONES

	Ketone	Major reaction product	Other products
1	Butanone	3,4-Dimethyl-2,5-hexanedione	Heavy oil, probably "trimer" and "tetramer"
2	3-Methylbutanone	3,3,4,4-Tetramethyl-2,5-hexanedione	"Trimer" and some higher polymer
3	2,4-Dimethyl-3-pentanone	2,4,4,5,5,7-Hexamethyl-3,6-octanedione	"Trimer" and some higher polymer
4	2,6-Dimethyl-4-heptanone	2,9-Dimethyl-5,6-diisopropyl-4,7-decanedione (*meso* and racemic)	Some "trimer"
5	1-Phenylpropanone	3,4-Diphenyl-2,5-hexanedione (*meso* and racemic)	Some polymer
6	2,4-Pentanedione	*sym*-Tetraacetylethane	Some polymer
7	2,5-Hexanedione		Mostly "trimer" and "pentamer"
8	3,3-Dimethylbutanone	2,2,7,7-Tetramethyl-3,6-octanedione (about 15%)	"Tetramer" and polymer
9	Cyclohexanone	2,2′-Dioxobicyclohexyl (*meso* and racemic)	High polymer

reactions (high carbon dioxide to methane ratio), it is probable that some of the free methyl radicals attach themselves to the benzene ring. If such is the fact the benzene ring must be greatly activated by the adjacent carbonyl group, for in the ketones mentioned, it competes successfully for free methyl radicals with such active atoms as the secondary and tertiary hydrogen atoms in the alkyl groups of propiophenone and phenyl isopropyl ketone, respectively. Further examination of such ketones is in progress.

Experimental

The general method for the preparation, isolation, analysis and decomposition of diacetyl peroxide in organic solvents is described in previous articles of this series.

I. The Decomposition of Diacetyl Peroxides in Organic Solvents. A. The Preparation of 3,4-Dimethyl-2,5-hexanedione, $[CH_3(CH_3CO)CH]_2$.—Diacetyl peroxide (61.0 g., 0.517 mole) was dissolved in butanone (129 g., 1.79 mole), and this solution was introduced into butanone (159 g., 2.21 moles) heated to 75°. Carbon dioxide (34.76 g., 0.79 mole), methane, (14 liters, S. C., 0.62 mole, mol. wt. 16.95), and methyl acetate (6.09 g., 0.08 mole, b. p. 56–7°) were collected and identified in the usual manner.

The first fraction obtained when the contents of the reaction flask were distilled was unchanged butanone (237.0 g., 3.30 moles, b. p. 78.5°, n^{20}_{D} 1.3800). The second fraction was collected at 57° (1 mm.) (38.3 g.). The residue in the flask weighed 4 g. The second fraction was then fractionated through a 10-plate column, and the fraction boiling at 92° (30 mm.) (n^{20}_{D} 1.4330) was collected.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.44; H, 9.56.

The analysis and the observation that the compound gave positive ferric chloride and iodoform tests suggested that the substance was the expected 3,4-dimethyl-2,5-hexanedione. The structure of the compound was established in the following manner. (a) When a sample of the presumed diketone was treated with an excess of sodium hypobromite a nearly quantitative yield of α,α'-dimethylsuccinic acid (*meso* and racemic) was obtained. The melting point of the *meso* dimethylsuccinic acid thus obtained was 206°. The recorded melting point of this acid is 209°. (b) The compound when heated with ammonium hydroxide and methyl alcohol gave 2,3,4,5-tetramethylpyrrole, which upon crystallization from methyl alcohol melted at 110°. The recorded melting point of 2,3,4,5-tetramethylpyrrole is 114°.[5] (c) The compound when treated with phenylhydrazine in ethyl alcohol gave a pyridazine derivative which melted at 127–128°. The recorded melting point for this pyridazine derivative is 130°.

Anal. Calcd. for $C_{14}H_{18}N_2$: N, 13.1. Found: N, 12.6.

B. The Preparation of 3,3,4,4-Tetramethyl-2,5-hexanedione, $[CH_3CO(CH_3)_2C]_2$.—Diacetyl peroxide (67.0 g., 0.57 mole) was dissolved in 3-methylbutanone (260 g., 3.0 moles), and this solution was introduced into 3-methylbutanone (131.0 g., 1.52 mole) heated to the boiling point of the solvent (93°). Carbon dioxide (42.25 g., 0.96 mole), methane (18.2 liters, S. C., 0.81 mole; mol. wt. 18.4), and methyl acetate (1.6 g., 0.02 mole, b. p. 57°) were collected and identified in the usual manner.

The unchanged ketone (333 g.) was recovered by distillation at ordinary pressure. The residue (64 g.) was distilled at 0.5 mm. pressure. The following fractions were collected: Fraction 1: b. p. 40° (0.5 mm.), n^{20}_{D} 1.4522, colorless oil, 23 g.; Fraction 2: b. p. 40–55° (0.5 mm.), n^{20}_{D} 1.4559, 9 g.; Fraction 3: b. p. 103–125 (0.5 mm.); n^{20}_{D} 1.4713, pale yellow sirup, 6.5 g. The residue weighed 7.0 g.

Fraction 1.—This material was shown to be the "dimer" of 3-methylbutanone (3,3,4,4-tetramethyl-3,5-hexanedione) by analysis and by the fact that it reacts with sodium hypobromite to give tetramethylsuccinic acid.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65; mol. wt., 170. Found: C, 70.94; H, 10.34; mol. wt., 179.

Fraction 1 ("the dimer") (9 g.) was treated with the calculated amount of sodium hypobromite. The white solid which separated (9 g.) was crystallized from methyl alcohol. Beautiful white needles of a compound which melted at 117° were thus obtained. The compound contained bromine and was undoubtedly the tetrabromo derivative of the "dimer" (3,3,4,4-tetramethyl-2,5-hexanedione).

Anal. Calcd. for $C_{10}H_{14}O_2Br_4$: Br, 65.79. Found: Br, 65.71.

The appearance of this type of bromo derivative when a hindered methyl ketone is treated with sodium hypobromite has been noted previously.[6]

The hypobromite oxidation was repeated using 0.5 mole of sodium hypobromite in 300 cc. of solution and 2.5 g. (0.015 mole) of the diketone. The reaction mixture was stirred for twenty-four hours at room temperature, and eight hours at 60–80°. The reaction mixture gave 2.0 g. of the tetrabromide (m. p. 113–15°) described in the preceding paragraph, and 0.25 g. of an acid which, upon recrystallization from water, melted at 200°. The melting point of this acid was not depressed by mixture with an authentic sample of tetramethylsuccinic acid. Reflux of the tetrabromoderivative of the diketone (1 g.) in a 20% solution of potassium hydroxide in ethylene glycol for five hours and subsequent acidification gave a small quantity of tetramethylsuccinic acid.

Fraction 2.—This material is probably a mixture of the "dimer" and small amounts of the "trimer."

Fraction 3.—This material is mostly the "trimer" (mol. wt. 280; calcd. mol. wt. 255) contaminated with small amounts of the "tetramer." The structure of this compound was not established, but, on the basis of previous experience in this field, we favor the structure assigned to the "trimer" in the theoretical part.

C. The Preparation of 2,4,4,5,5,7-Hexamethyl-3,6-octanedione, $[i\text{-}C_3H_7CO(CH_3)_2C]_2$. Diacetyl peroxide (64.5 g., 0.546 mole) was dissolved in 230.5 g., 2.0 moles, of 2,4-dimethyl-3-pentanone, and this solution was added to the ketone (312.5 g., 2.74 moles) heated to 135°. Carbon dioxide (40.4 g., 0.92 mole), methane (16.34 liters, S. C., 0.73 mole, mol. wt. 17.0), and methyl acetate (2.7 g., 0.036 mole, b. p. 56.5–57°; n^{20}_{D} 1.3599) were collected and identified in the usual manner.

The unchanged ketone (477 g.) was recovered by distillation at reduced pressure (40° (35 mm.)). The straw-colored residue (62.5 g.) was fractionated at a pressure of 1.5 mm. through a six-inch Vigreux column. The following fractions were collected: Fraction 1: b. p. 75–77° (1.5 mm.), n^{20}_{D} 1.4520, 30 g.; Fraction 2: b. p. 77–85° (1.5 mm.), n^{20}_{D} 1.4583, 8 g.; Fraction 3: b. p. 100–140° (1.5 mm.), n^{20}_{D} 1.4694, 10 g. The residue weighed 5 g.

Fraction 1.—This material was shown to be the "dimer" of 2,4-dimethyl-3-pentanone (2,4,4,5,5,7-hexamethyl-3,6-octanedione) by analysis and by the fact that it gave upon oxidation tetramethylsuccinic acid and acetone.

Anal. Calcd. for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58; mol. wt., 226. Found: C, 74.54; H, 11.79; mol. wt., 229.

Two grams of Fraction 1 ("dimer") was added at 0° to 100 cc. of glacial acetic acid containing 8 g. of chromic anhydride. The mixture was kept at 0° for five hours, at the end of which time it was heated to 100° and kept at that temperature for one hour. The reaction mixture was then cooled, diluted with 900 cc. of water, and the whole was extracted with 200 cc. of ether. The ether extraction was repeated five times, and the ether extracts

---

(5) Ciamician and Silber, *Ber.*, **45**, 1542 (1912); Démètre-Vladesco, *Bull. soc. chim.*, [3] **6**, 807 (1891).

(6) Fuson and Bull, *Chem. Rev.*, **15**, 275 (1934).

were combined. The ether extract was then shaken three times with a dilute solution of sodium hydroxide (20 cc. of 2% sodium hydroxide), and the alkaline extracts were combined. Upon acidification with hydrochloric acid 0.8 g. of a solid separated. When crystallized from hot water the material melted at 201°, and its melting point was not depressed by the addition of an authentic sample of tetramethylsuccinic acid.

The original aqueous solution (from which the tetramethylsuccinic acid was removed by extraction with ether) was distilled. The first 75 cc. of the distillate was collected and tested for acetone, the other expected oxidation product of the "dimer." The solution in fact gave with 2,4-dinitrophenylhydrazine a yellow crystalline product which did not depress the melting point of a known sample of the 2,4-dinitrophenylhydrazone of acetone.

D. The Preparation of 2,9-Dimethyl-5,6-diisopropyl-4,7-decanedione, $[i\text{-}C_3H_7(i\text{-}C_3H_7CH_2CO)CH]_2$.—Diacetyl peroxide (31.0 g., 0.26 mole) was dissolved in 2,6-dimethyl-4-heptanone (230.0 g., 1.62 mole), and this solution was introduced into the ketone (48.0 g., 0.34 mole) heated to 115°. Carbon dioxide (20.7 g., 0.47 mole), methane (9.0 liters, S. C., 0.40 mole, mol. wt. 17.69), and methyl acetate (2.0 g., 0.027 mole, $n^{20}D$ 1.3614) were collected and identified in the usual manner.

The unchanged ketone (232 g.) was removed at reduced pressure (b. p. 30° (1 mm.)), and the residue (48 g.) was distilled through a 6-inch Vigreux column. The following fractions were collected: Fraction 1: b. p. 95–97° (1.5 mm.), $n^{20}D$ 1.4430, clear oil, 8 g.; Fraction 2: b. p. 98–110° (1.5 mm.), mixture of crystals and an oil, 3 g.; Fraction 3: b. p. 110–114° (1.5 mm.), white crystalline material, 9 g.; Fraction 4: b. p. 114–24° (1 mm.), yellow oil, 4 g. The residue ($n^{20}D$ 1.4705) weighed 7 g.

The solid material which comprises Fraction 3 crystallizes from methyl alcohol in long white needles which melt at 87–90°. This material and the substance of Fraction 1, which is an oil, are assumed to be the *meso* and racemic forms of the "dimer" of 2,6-dimethyl-4-heptanone, namely, 2,9-dimethyl-5,6-diisopropyl-4,7-decanedione. The evidence for this assumption is based upon the difference in their boiling points, the fact that one of the isomers is a solid and the other a liquid (which resisted all our efforts to transform it into a solid), their identical analyses for carbon and hydrogen, their almost identical molecular weights, and the fact that an alcoholic solution of the liquid material of Fraction 1 could be transformed by sodium ethoxide into the solid material (m. p. 87–90°) of Fraction 3. (Note that these substances contain enolizable hydrogen atoms on the carbon atoms adjacent to the carboxyl groups.)

Anal. Calcd. for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13; mol. wt., 282. Found: (solid, m. p. 87–90°) C, 76.45; H, 11.53; mol. wt., 292. (Fraction 1) C, 76.32; H, 11.41; mol. wt. 300.

Fraction 2 is probably a mixture of the two stereoisomers of Fractions 1 and 3. The residue is a tan-yellow sirup. The molecular weight of this material is 466. It is probably a "trimer" (mol. wt. 432) admixed with some of the "tetramer."

E. The Preparation of 3,4-Diphenyl-2,4-hexanedione, $[CH_3CO(C_6H_5)CH]_2$.—Diacetyl peroxide (19.6 g., 0.17 mole) was dissolved in 1-phenylpropanone (69.4 g., 0.52 mole) and this solution was introduced dropwise into the ketone (40 g., 0.3 mole) heated to 125–30°. Carbon dioxide (11.7 g., 0.27 mole), methane (4.79 liters, S. C.; 0.21 mole; mol. wt. 18.4), and methyl acetate (2.0 g., 0.03 mole; b. p. 56.5°; $n^{20}D$ 1.3615) were collected and identified in the usual manner.

The reaction mixture, upon standing overnight, deposited white crystals. These were collected on a filter. They weighed 6.5 g. When crystallized from a mixture of methyl and ethyl alcohols they melted at 201–202°. This material is quite insoluble in methyl alcohol.

The filtrate obtained when the reaction mixture was freed of the solid material was subjected to distillation at reduced pressure (5–6 mm.), and the unchanged ketone (86 g., 0.638 mole) thus recovered. The residue in the flask when allowed to stand overnight deposited some crystals. These were collected on a filter (6.0 g.). This material when crystallized first from methanol, in which it is very soluble, and then from ligroin, melted at 98–100°.

It is submitted that the compound which melts at 201–202°, and the compound which melts at 98–100°, are stereoisomers (*meso* and racemic, respectively) of 3,4-diphenyl-2,5-hexanedione. The evidence is based upon analyses, oxidation of the material to *sym*-diphenylsuccinic acid, and the fact that both materials when treated with aniline gave the identical substituted pyrrole.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: (solid m. p. 201–202°) C, 81.37; H, 6.88 (solid m. p. 98–100°) C, 80.93; H, 6.56.

The high-melting material (201°) when treated with sodium hypobromite gave a solid which upon crystallization from water melted at 253°. The melting point of this material was not depressed when mixed with an authentic sample of *meso* diphenylsuccinic acid.

The high-melting and the low-melting forms of the 3,4-diphenyl-2,5-hexanedione were converted to the same pyrrole (m. p. 135°) when treated with aniline. The procedure employed was as follows. About 0.7 g. of the material was dissolved in 20 cc. of glacial acetic acid to which 0.5 g. of aniline had been added. The mixture was refluxed for six hours and then allowed to cool. About 200 cc. of water was then added, and the whole was extracted with ether. The ethereal solution upon evaporation gave a solid which upon crystallization from methyl alcohol separated in the form of pale straw-colored needles which melted at 133–135°. Furthermore, no depression in the melting point was noted, when the pyrroles from the two compounds were mixed. For analysis the 1,3,4-triphenyl-2,5-dimethylpyrrole was further purified by sublimation. The melting point of the sublimed material was 135°.

Anal. Calcd. for $C_{24}H_{21}N$: C, 89.12; H, 6.55; N, 4.33. Found: C, 88.95; H, 6.32; N, 4.44.

Besides the *meso* and racemic forms of 3,4-diphenyl-2,5-hexanedione there is formed a sirupy polymer. The weight of the polymer is about equal to the weight of the two stereoisomers. All efforts to obtain a crystalline material from the sirupy polymer have been unsuccessful.

F. Preparation of *sym*-Tetraacetylethane, $[(CH_3CO)_2CH]_2$.—Diacetyl peroxide (65.0 g., 0.55 mole) was dissolved in 2,4-pentanedione (229.0 g., 2.29 moles) and this solution was introduced into the diketone (191.0 g., 1.91 mole) heated to 125°. Carbon dioxide (35.80 g., 0.81 mole), methane (14.75 liters S. C., 0.66 mole, mol. wt. 17.0), and methyl acetate (4.0 g., 0.05 mole; b. p. 55–6°; $n^{20}D$ 1.3605) were collected and identified in the usual manner.

The unchanged diketone (350 g.) was removed at reduced pressure (about 25 mm.). When the residue (64 g.) was allowed to stand overnight a solid separated. This was collected on a filter, and the filtrate ("A") was reserved for further treatment. The solid material when crystallized from ethyl alcohol melted at 189–191°. The melting point of tetraacetylethane, as recorded in the literature, is 189 or 191°. The identity of the 189–191° melting material, obtained in this reaction, was further confirmed by the fact that the melting points of its furan and pyrrole derivatives corresponded with those described in the literature.

The filtrate "A" began to decompose when an attempt was made to distill it in a molecular still. Its average molecular weight as determined in carbon tetrachloride was 326.

G. Preparation of 2,2,7,7-Tetramethyl-3,6-octanedione, $t\text{-}(C_4H_9COCH_2)_2$.—Diacetyl peroxide (59.5 g., 0.50 mole) was dissolved in 3,3-dimethylbutanone (316.0 g., 3.16 moles), and this solution was introduced into the ketone (58.0 g., 0.58 mole) heated to 104°. Carbon dioxide (37.9 g., 0.86 mole), methane (16.52 liters, S. C., 0.74 mole; mol. wt. 17.12), and methyl acetate (1.2 g., 0.016 mole) were collected and identified in the usual manner.

The unchanged ketone (330 g.) was recovered from the reaction mixture at reduced pressure (35 mm.), and the residue remaining in the distilling flask (44 g. of a yellow oil) was distilled at reduced pressure through a 6-inch Vigreux column. The following fractions were collected: Fraction 1: b. p. 55–60° (0.5 mm.), $n^{20}D$ 1.4400, colorless oil, 6.5 g.; Fraction 2: 60–115° (0.5 mm.), $n^{20}D$ 1.4545, mol. wt. 258, 7.5 g.; residue: red sirup, mol. wt. 347, 20 g.

Fraction 1 was shown to be the expected "dimer," 2,2,7,7-tetramethyl-3,6-octanedione, by its reactions and analyses.

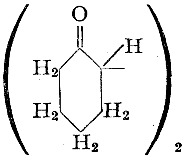
Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; mol. wt., 198. Found: C, 73.67; H, 11.09; mol. wt., 199.

The "dimer" when treated with a methyl alcohol solution of ammonium hydroxide and allowed to stand for several days gave an oil. This oil gave a positive pyrrole test with a pine splint. Furthermore, the "dimer" gave no iodoform when treated with iodine and a base.

The "dimer" (Fraction 1) (1.5 g.) when treated with phenylhydrazine (1.0 g.) and heated for several hours at 120° gave compound which upon crystallization from alcohol melted at 144–147°. This white crystalline compound is probably the di-phenylhydrazone of 2,2,7,7-tetramethyl-3,6-octanedione.

Anal. Calcd. for $C_{24}H_{34}N_4$: N, 14.83. Found: N, 14.73.

As would be expected from the considerations discussed in the theoretical part, the "dimer" should be more readily attacked than the starting material since it contains secondary hydrogen atoms, while the hydrogen atoms in the original ketone are all primary. The low yield of the "dimer" is thus readily explained. Furthermore, it follows that Fraction 2 contains some dimer and some higher polymer, while the residue is probably a "tetramer" contaminated with some "dimer." No work was done with these higher condensation products.



H. Preparation of 2,2′-Dioxobicyclohexyl.—Diacetyl peroxide (46.0 g., 0.39 mole) was dissolved in cyclohexanone (404.5 g., 4.13 moles), and this solution was introduced into the ketone (274.5 g., 2.80 moles) heated to 130°. Carbon dioxide (25.3 g., 0.57 mole), methane (10.71 liters, S. C., 0.48 mole; mol. wt. 17.79), and methyl acetate (3.4 g., 0.04 mole, b. p. 55.5–56°, $n^{20}D$ 1.3599) were collected and identified in the usual manner.

The unchanged cyclohexanone (6.22 g., 6.25 moles) was recovered from the reaction mixture by distillation at reduced pressure (1 mm.). The residue remaining in the flask (47 g.) was distilled at reduced pressure through a 6-inch Vigreux column. The following fractions were collected: Fraction 1: b. p. 114–117° (1 mm.), $n^{20}D$ 1.4958, orange oil which darkens on standing in air, 15 g; residue, dark-red glassy material, mol. wt. 605, 13 g.

The analysis and molecular weight of Fraction 1 show it to be the "dimer" of cyclohexanone.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34; mol. wt., 194. Found: C, 74.42; H, 9.21; mol. wt., 215.

If the "dimer" of cyclohexanone is 2,2′-dioxobicyclohexyl, then the compound should exist in two stereoisomeric forms. As a matter of fact, Fraction 1 upon standing deposited a crystalline material which upon crystallization from low-boiling (60°) ligroin melted at 70–71°. This melting point is that recorded by Plant[7] for 2,2′-dioxobicyclohexyl.

To confirm the structure of the solid from Fraction 1, it was converted to the 9-methyloctahydrocarbazole by heating it with methylamine in acetic acid. The melting point of the compound thus obtained was 94–95°. The recorded melting point of 9-methyloctahydrocarbazole is 94–95°.

As indicated, the residue left in the flask was a dark-red glassy material. Its high molecular weight (605) indicated that it is either a "hexamer" of cyclohexanone or a mixture of a very high molecular weight material with some materials of lower molecular weight. No further work was done with this polymer.

Decomposition of Diacetyl Peroxide in 2,5-Hexanedione.—Diacetyl peroxide (56.0 g., 0.47 mole) was dissolved in 2,5-hexanedione (273 g., 2.39 moles), and this solution was introduced into the diketone (297.5 g., 2.61 moles) heated to 145°. Carbon dioxide (34.08 g., 0.77 mole), methane, (14.47 liters, S. C., 0.64 mole; mol. wt. 17.56), and methyl acetate (5.5 g., 0.07 mole, b. p. 56°) were collected and identified in the usual manner.

The unchanged diketone (495 g.) was recovered by distillation at reduced pressure. The reddish-brown oil (72 g.) was distilled through a 6-inch Vigreux column, and the following fractions were collected: Fraction 1: b. p. 35–55 (1 mm.), 5 g.; Fraction 2: b. p. 145–155° (1 mm.), 38 g.; residue, dark-red gummy material.

Fraction 1 is the unchanged diketone.

From the molecular weight of Fraction 2 (330) it would appear that this substance is a "trimer" of the diketone (calcd. mol. wt. 338). The residue had a molecular weight of 552. The calculated molecular weight for a "pentamer" of the diketone is 562. No further chemical work was done with either Fraction 2 or the residue.

Decomposition of Diacetyl Peroxide in Acetophenone.—Diacetyl peroxide (70.0 g., 0.60 mole) was dissolved in 183 g., 1.52 mole, of acetophenone, and this solution was introduced dropwise into acetophenone (152.3 g., 1.26 mole) heated to 125°. Carbon dioxide (41.47 g., 0.94 mole), methane (8.57 liters, S. C.; 0.382 mole; mol. wt. 16.43), and methyl acetate (7.4 g., 0.10 mole, b. p. 58°, $n^{20}D$ 1.3620) were collected and identified in the usual manner. Note, however, that the amount of methane formed is about one-half of the amount formed when diacetyl peroxide is decomposed in ketones in which the carbonyl group is not adjacent to a benzene ring.

The unchanged acetophenone (300 g.) was recovered from the reaction mixture by distillation at low pressure. The residue (35 g.) was a dark red-brown gummy substance. The molecular weight of the residue was 648.

Decomposition of Diacetyl Peroxide in Propiophenone.—Diacetyl peroxide (57.8 g., 0.49 mole) was dissolved in propiophenone (187.5 g., 1.40 mole), and this solution was introduced into propiophenone (164.5 g., 1.22 mole) heated to 115°. Carbon dioxide (31.56 g., 0.717 mole), methane (10.44 liters, S. C., 0.466 mole, mol. wt. 16.38) and methyl acetate (5.4 g., 0.08 mole, b. p. 56–57°) were collected and identified in the usual manner.

The unchanged propiophenone (301 g.) was removed from the reaction mixture by distillation at reduced pressure. The residue (50 g.) was an orange-colored semi-solid resin. The molecular weight of this material (in carbon tetrachloride) was 389.

The Decomposition of Diacetyl Peroxide in Phenyl Isopropyl Ketone.—Diacetyl peroxide (72.0 g., 0.61 mole) was dissolved in phenyl isopropyl ketone (140.0 g., 0.946 mole), and this solution was introduced dropwise beneath the surface of phenyl isopropyl ketone (75.0 g., 0.51 mole) heated to 115°. Carbon dioxide (40.05 g., 0.91 mole), methane (11.41 liters, S. C., 0.509 mole, mol. wt. 22.4), and methyl acetate (11.0 g., 0.15 mole, b. p. 55–56.4°; $n^{20}D$ 1.3610) were collected and identified in the usual manner.

The unchanged phenyl isopropyl ketone (171 g.) was recovered from the reaction mixture by distillation at reduced pressure. The residue (44 g.) remaining in the flask was an orange-red sirupy material which could not be crystallized. The molecular weight of this material (in carbon tetrachloride) was 784.

---

[7] Plant, *J. Chem. Soc.*, 1595 (1930).

Summary

1. A new method for the preparation of 1,4-diketones is described.
2. A number of new 1,4-diketones have been prepared and characterized.
3. The mechanism of the formation of the 1,4-diketones is discussed.

CHICAGO, ILL. RECEIVED NOVEMBER 15, 1947

NOTES

Studies on the Mechanism of the Sulfonation of Aromatic Amines. III. Rearrangement of Barium Phenylsulfamate

BY ELLIOT R. ALEXANDER

In earlier communications, it has been shown that freezing point data and kinetic data[1] support a bimolecular mechanism for the sulfonation of aromatic amines rather than an intramolecular rearrangement of phenylsulfamic acid which has been postulated as an intermediate. There is one fact, however, that appears to be an anomaly: The dihydrate of barium phenylsulfamate can be transformed into sulfamic acid on heating at 180°.[2] It therefore seemed advisable to repeat Bamberger's experiments with carefully purified materials and to determine whether the reaction would proceed with the anhydrous salt.

On heating the dihydrate of barium phenylsulfamate in a closed vessel four and one-half hours at 175–185°, sulfonation of the aromatic nucleus was indeed found to have occurred to the extent of 26%. When the reaction was carried out with *anhydrous* barium sulfamate, however, no sulfonation occurred.

While these facts do not necessarily preclude an intramolecular rearrangement of the hydrate (since the water of hydration might have weakened and labilized certain bonds in the molecule permitting rearrangements which would not be possible in the anhydrous material), nevertheless it is interesting that this reaction is not characteristic of the anhydrous salt.

Experimental

Rearrangement of the Dihydrate of Barium Phenylsulfamate.—Barium phenylsulfamate dihydrate[3] (5.0 g., 0.00965 mole) was crushed into a fine powder and heated for four and one-half hours at 175–185° in a stoppered round-bottomed flask partially immersed in a metal heating bath. At the beginning of the heating moisture could be seen to condense on the cooler portion of the flask. As heating was continued the solid became streaked with purple but did not melt. After the heating period was completed, the flask was cooled and a mixture of 15 ml. of concentrated hydrochloric acid in 100 ml. of water was added. This mixture was digested fifteen minutes on a steam-bath and attached to a Kjeldahl apparatus. The solution was then made basic with sodium hydroxide solution and steam distilled quantitatively into 10 ml. of concentrated hydrochloric acid and 25 ml. of distilled water. The aromatic amine content of the distillate and the non-volatile portion was determined by titrating with standard sodium nitrite solution.[4] The steam-volatile portion required 28.91 ml. of 0.484 *N* sodium nitrite solution (72.6%) while the non-volatile portion required 10.38 ml. (26.1%).

Attempted Rearrangement of Anhydrous Barium Phenylsulfamate.—Anhydrous barium phenylsulfamate was prepared by drying the dihydrate for eight hours at 100° and 1 mm. It was analyzed by titration with sodium nitrite solution.[4]

Anal. Calcd. for $C_{12}H_{12}N_2S_2O_6Ba$: NH_2, 6.58. Found: NH_2, 6.55.

This salt (5.0 g., 0.00104 mole) was treated exactly as described above. Three drops of the sodium nitrite solution was required for the non-volatile portion while 42.87 ml. (99.6%) was required for the portion volatile with steam.

---

(1) Alexander, THIS JOURNAL, **68**, 969 (1946); **69**, 1599 (1947).

(2) Bamberger and Hinderman, *Ber.*, **30**, 655 (1897).

(3) Traube, *ibid.*, **23**, 1654 (1890).

(4) Kolthoff and Stenger, "Volumetric Analysis," Interscience Publishers, Inc., New York, N. Y., 1942, p. 240.

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS
RECEIVED AUGUST 25, 1947

The Preparation of 2-Amino-4-hydroxy-6-keto-5,5-dichlorodihydropyrimidine

BY R. B. ANGIER, J. H. MOWAT, J. H. BOOTHE, C. W. WALLER, J. SEMB, B. L. HUTCHINGS, E. L. R. STOKSTAD AND Y. SUBBAROW

In connection with the investigation of the synthesis of pteroylglutamic acid[1] the compound, 2-amino-4-hydroxy-6-keto-5,5-dichlorodihydropyrimidine (III), became of some interest. The corresponding 2,4-dihydroxy-6-keto-5,5-dichlorodihydropyrimidine (IV) has been prepared by several methods[2,3,4] including the direct chlorination of barbituric acid (II) in water solution.[4] Several attempts to chlorinate 2-amino-4,6-dihydroxypyrimidine (I) by the use of chlorine in a water solution were unsuccessful. A good deal of decomposition occurred and the small yield of product usually obtained was apparently a mixture of the starting material and the monochloro and dichloro substitution products. When a potassium chlorate and hydrochloric acid mixture was used as a chlorinating agent a reasonably pure

---

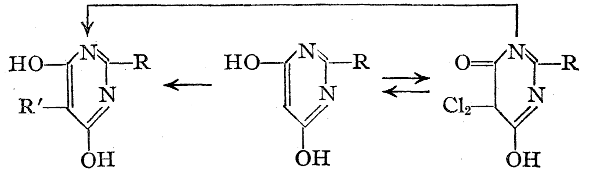
(1) Waller, *et al.*, THIS JOURNAL, **70**, 19 (1947).

(2) Behrend, *Ann.*, **236**, 64 (1886).

(3) Blitz and Hamburger, *Ber.*, **49**, 639 (1916).

(4) Bock, *ibid.*, **56B**, 1222 (1923).

sample of the monochloro derivative, 2-amino-4,6-dihydroxy-5-chloropyrimidine (V), was obtained.



V R = NH$_2$, R′ = Cl
VI R = NH$_2$, R′ = I
I R = NH$_2$
II R = OH
III R = NH$_2$
IV R = OH

Johnson[5] has described the use of a mixture of 30% hydrogen peroxide and concentrated hydrochloric acid to convert 2-amino-4-hydroxypyrimidine to 2-amino-4,6-dihydroxy-5,5-dichlorodihydropyrimidine. By applying this procedure to 2-amino-4,6-dihydroxypyrimidine (I) the desired product was obtained. Unlike the monochloro derivative or the starting material this compound was rather unstable. In hot water it dissolved and decomposed rapidly with the production of carbon dioxide.[6] Therefore in order to demonstrate that the pyrimidine ring was still intact the compound was reduced by two methods. Reduction with hydriodic acid and glacial acetic acid gave 2-amino-4,6-dihydroxy-5-iodopyrimidine (VI) while stannous chloride and hydrochloric acid gave 2-amino-4,6-dihydroxypyrimidine (I).

Experimental[7]

2-Amino-4,6-dihydroxy-5-chloropyrimidine (V).—2-Amino-4,6-dihydroxypyrimidine (2.5 g.) was suspended in a solution of 10 cc. of concentrated hydrochloric acid and 15 cc. of water; 1.6 g. of potassium chlorate was added slowly while keeping the temperature at 25–35°. After thirty minutes the product was filtered off, washed with water and dried; yield 1.0 g. This was nearly pure but to obtain an analytical sample it was dissolved in dilute ammonium hydroxide, filtered, and precipitated by adding acetic acid. This was repeated and a white crystalline product was obtained.

Anal. Calcd. for $C_4H_4N_3O_2Cl$: C, 29.74; H, 2.50; N, 26.01; Cl, 21.95. Found: C, 29.36; H, 2.52; N, 25.70; Cl, 22.38.

2-Amino-4-hydroxy-6-keto-5,5-dichlorodihydropyrimidine (III).—2-Amino-4,6-dihydroxypyrimidine (10.0 g.) was suspended in 70 cc. of cold 30% hydrogen peroxide (Superoxol) and 70 cc. of concentrated hydrochloric acid was added. While stirring or shaking the solid slowly dissolved and the solution became warm. This was allowed to react for ten to twenty minutes while keeping the temperature between 40° and 60° by cooling. During this time a crystalline precipitate appeared. (It was necessary to control the temperature of the reaction since if the solution became too hot the reaction became violent and the product decomposed. Even when the temperature was controlled during the initial reaction period if the mixture was allowed to stand at room temperature overnight the product would redissolve and decompose.) The reaction mixture was then well cooled, filtered and the precipitate washed with water, ethanol and ether and dried; yield 6.5 to 8.0 g. (42–52%). The product did not require purification.

Anal. Calcd. for $C_4H_3N_3O_2Cl_2$: C, 24.51; H, 1.54; N, 21.44; Cl, 36.18. Found: C, 24.50; H, 1.65; N, 21.63; Cl, 35.81.

This compound is insoluble in cold water and in most organic solvents but is somewhat soluble in pyridine. It is insoluble in all concentrations of cold hydrochloric acid. It dissolves in hot water or hot dilute acid solutions and immediately decomposes giving off carbon dioxide. A sample of the compound was recrystallized by dissolving it in cold ammonium hydroxide and then acidifying the cold solution with acetic acid. The product crystallized as platelets. Analytical data on this material were the same as before recrystallization.

Reduction of 2-Amino-4-hydroxy-6-keto-5,5-dichlorodihydropyrimidine (III). A. Hydriodic Acid in Glacial Acetic Acid.—2-Amino-4-hydroxy-6-keto-5,5-dichlorodihydropyrimidine (0.5 g.) was suspended in 5 cc. of glacial acetic acid; 5 cc. of hydriodic acid (sp. gr. 1.7) was added and the resulting solution was heated on the steam-bath for thirty minutes. It was then diluted to 50 cc. with water and enough sodium hydroxide added to neutralize the hydriodic acid present. The resulting precipitate was filtered off, redissolved in dilute sodium hydroxide, filtered and precipitated again by the addition of acetic acid; yield 0.4 g. (62%) of a white powder insoluble in water. This material gave a good qualitative test for iodine.

Anal. Calcd. for $C_4H_4N_3O_2I$: C, 19.00; H, 1.59; N, 16.61. Found: C, 19.37; H, 2.02; N, 16.74.

B. Stannous Chloride in Hydrochloric Acid.—To a suspension of 1.0 g. of 2-amino-4-hydroxy-6-keto-5,5-dichlorodihydropyrimidine in 10 cc. of water were added 4 g. of stannous chloride dihydrate and 15 cc. of concentrated hydrochloric acid. This was warmed to 70° for fifteen minutes, cooled, neutralized, and then made distinctly alkaline with ammonium hydroxide. This was centrifuged and filtered to remove the stannous hydroxide. The filtrate was neutralized with acetic acid and a white crystalline product appeared; yield 0.3 g. (47%). This contained no halogen and had physical properties resembling 2-amino-4,6-dihydroxypyrimidine. To further purify it, it was dissolved in dilute ammonium hydroxide, filtered, and crystallized by adding acetic acid.

Anal. Calcd. for $C_4H_5N_3O_2$: C, 37.80; H, 3.97; N, 33.06. Found: C, 37.67; H, 4.35; N, 33.19.

All of these products are characteristic of this type of pyrimidine compound in that they have no melting point but decompose slowly at high temperatures. Also they are all insoluble or only slightly soluble in water and most organic solvents.

LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK
RECEIVED OCTOBER 6, 1947

The Reaction of 2-Amino-2-methyl-1-propanol with Sulfuric Acid[1]

BY ROBERT E. BUCKLES AND GENE V. MOCK

The synthesis[2] of 2,2-dimethylethyleneimine by the dehydration of 2-amino-2-methyl-1-propanol would be expected to be analogous to Wenker's[3] synthesis of ethyleneimine. In the latter case the first step of the reaction has been shown to be the esterification of monoethanolamine by sulfuric

---

(5) Johnson, THIS JOURNAL, **65**, 1218 (1943).

(6) Although 5,5-dichlorobarbituric acid (IV) can be recrystallized from water, Blitz and Hamburger[3] have shown that it decomposes slowly in boiling water.

(7) The microanalyses were carried out by Mr. Louis Brancone and staff of this Laboratory.

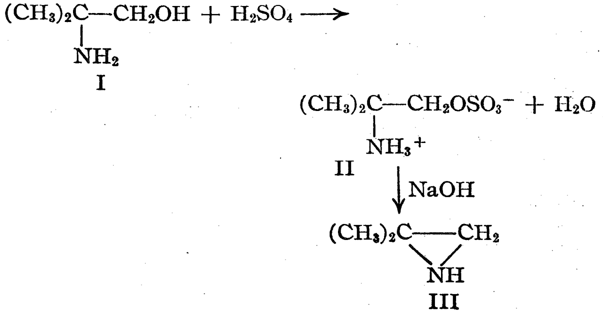
(1) Part of a thesis presented by Gene V. Mock to the Graduate College of the State University of Iowa.

(2) (a) Cairns, THIS JOURNAL, **63**, 871 (1941); (b) Karabinos and Serijan, *ibid.*, **67**, 1856 (1945); (c) Campbell, Sommers and Campbell, "Org. Syntheses," **27**, 12 (1947).

(3) Wenker, *ibid.*, **57**, 2328 (1935).

acid to give aminoethylsulfuric acid.[4] A similar procedure is used as the first step in the synthesis of 2,2-dimethylethyleneimine, but no published report of the actual identification of the reaction product has been made.

It has now been found that 2-amino-2-methyl-1-propanol (I) is esterified directly by sulfuric acid to give the expected 2-amino-2-methyl-1-propylsulfuric acid (II).



The mixture of the amine I, water and sulfuric acid was distilled slowly to remove the water according to the method of Cairns.[2a] The solid product obtained was identical with that formed during a more rapid distillation of the water similar to that described by Leighton, Perkins and Renquist[5] for the synthesis of β-aminoethylsulfuric acid. Both products yielded 2,2-dimethylethyleneimine (III) when treated with alkali.

The pure salt II was found to give no precipitate with barium chloride. This behavior parallels that of β-aminoethylsulfuric acid.[4] It was possible, however, to hydrolyze completely either β-aminoethylsulfuric acid or II in hot dilute hydrochloric acid containing barium chloride. This hydrolysis in the case of II yielded the hydrochloride of the amine I.

The possibility that the imine III might be an intermediate in the formation of the salt II was investigated. When 2,2-dimethylethyleneimine III reacted with sulfuric acid under conditions similar to those used in the preparation of II, a dark viscous product was obtained. None of the salt II could be isolated from the product, and no imine III was generated from it by alkali. It is clear from these results that the imine is not an intermediate in the preparation of II. The salt II, is formed directly from I, and III is produced by an intramolecular alkylation of II in the presence of alkali.

Experimental

2-Amino-2-methyl-1-propylsulfuric Acid (II).—A hundred grams (1.12 moles) of 2-amino-2-methyl-1-propanol (I) in 200 ml. of water was heated with 110 g. (1.06 moles) of sulfuric acid in 200 ml. of water until most of the water was distilled from the mixture. The temperature of the heating bath was then slowly raised to 175°, while the rest of the original water and that formed from the reaction was removed under the reduced pressure obtained with an aspirator. A modified method[5] was also carried out. Only about a quarter of the original amount of water was used. The solution of I was mixed with the slightly diluted sulfuric acid with cooling. The water was removed by distillation at reduced pressure over a free flame. In either case the light brown solid product was softened with 500 ml. of 95% alcohol, filtered and washed with absolute alcohol. Recrystallization from 50% alcohol yielded a white crystalline material which gave only a slight milkiness with aqueous barium chloride. The yield of purified product from the first procedure was 113 g. (63%); m. p. 253–255° (dec.).

Anal. Calcd. for $C_4H_{11}O_4NS$: C, 28.4; H, 6.56; N, 8.29. Found: C, 28.5; H, 6.48; N, 8.35.

Hydrolysis.—Two grams of II was dissolved in 25 ml. of water and 10 ml. of concentrated hydrochloric acid and 10 ml. of a saturated solution of barium chloride were added. The solution was heated overnight on a steam-bath. The barium sulfate was removed by filtration, and the filtrate was evaporated to dryness. The residue was recrystallized from absolute alcohol. The product had a m. p. 200–201° as compared with an authentic sample of 2-amino-2-methyl-1-propanol hydrochloride, m. p. 199–201°. There was no lowering of the m. p. on mixing the two. The recorded m. p. for the hydrochloride is 203–206°.[6]

Determination of Sulfur by Hydrolysis.—From 0.2 to 0.4 g. of the sulfuric ester was weighed and dissolved in 10% barium chloride solution so that there was 100% excess of barium chloride. Ten milliliters of 6 *N* hydrochloric acid was added and the solution was heated twenty hours on the steam-bath. The barium sulfate was determined gravimetrically. This analytical procedure was applied to the determination of sulfur in both II and β-aminoethylsulfuric acid.

Anal. Calcd. for $C_4H_{11}O_4NS$: S, 19.0. Found: S, 19.4, 19.8. Calcd. for $C_2H_7O_4NS$: S, 22.7. Found: S, 22.7.

Reaction of 2,2-Dimethylethyleneimine (III) with Sulfuric Acid.—A mixture of 57 g. (0.80 mole) of 2,2-dimethylethyleneimine[2] in 100 ml. of water and 79 g. (0.78 mole) of 96% sulfuric acid in 100 ml. of water was distilled with a water pump until the residue was a very viscous, black material. Treatment of some of this residue with alcohol gave no appreciable amount of crystalline product. Distillation of the residue from 40% sodium hydroxide (*ca.* 300% excess) gave some volatile material but little which distilled below 120°. 2,2-Dimethylethyleneimine boils at 70–72°.

Addendum.—It has been brought to our attention by one of the referees that J. V. Karabinos[7] has isolated 2-amino-2-methyl-1-propylsulfuric acid and β-aminoethylsulfuric acid from the reactions of the amino alcohols with sulfuric acid. Analysis of the esters for amino nitrogen by the Van Slyke method checked with the theoretical values.

---

[4] Rollins and Calderwood, THIS JOURNAL, **60**, 2312, 2751 (1938).

[5] Leighton, Perkins and Renquist, *ibid.*, **69**, 1540 (1947).

[6] Jones, *J. Assoc. Official Agr. Chem.*, **27**, 467 (1944).

[7] Karabinos, "Dissertation," Ohio State University, 1946, p. 74b.

DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA

RECEIVED OCTOBER 20, 1947

The Friedel–Crafts Reaction on Highly Methoxylated Compounds

BY H. R. FRANK[1] AND D. S. TARBELL

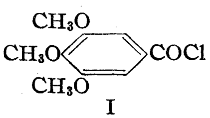
The following observations give some information about the behavior of derivatives of anisole

---

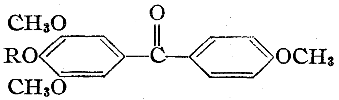
[1] Abbott Laboratories Fellow, 1946–1947.

and 1,2,3-trimethoxybenzene in the Friedel–Crafts reaction.

3,4,5-Trimethoxybenzoyl chloride (I) and anisole gave, with one and one-half moles of aluminum chloride, a mixture of the expected ketone (II) and a phenolic ketone. The position of the



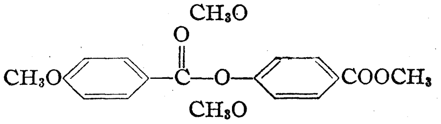
I



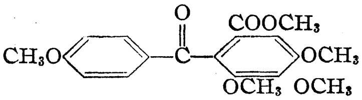
II, R = CH_3
III, R = H

phenolic group in III was not established, but was assumed to be para to the carbonyl group, since the para methoxyl in 3,4,5-trimethoxybenzoic acid is cleaved in concentrated sulfuric acid, to give syringic acid (3,5-dimethoxy-4-hydroxybenzoic acid).[2] Aluminum chloride usually cleaves the methoxyl group ortho to the carbonyl in a substituted aromatic ketone or, if no ortho methoxyl is present, a para one. Ether linkages meta to a negative group are cleaved only at higher temperatures.[3]

When the acylation of methyl 3,4,5-trimethoxybenzoate with anisoyl chloride was attempted, no reaction was observed in the presence of one mole of aluminum chloride. The addition of a second mole caused reaction to occur; the product was a neutral compound, which, on hydrolysis, yielded anisic acid and syringic acid, and hence had structure IV. None of the desired keto ester V was obtained. Similar cleavage of ether linkages



IV



V

with ester formation has been observed before in attempted acylation of aromatic ether esters.[4] In the present case, the activating effect of the methoxyl groups in methyl trimethoxybenzoate is evidently not enough to compensate for the deactivating effect of the ester group, and make the ring susceptible to Friedel–Crafts acylation. However, Friedel–Crafts acylation of a substituted benzoic ester can occur if the substituents are more favorably placed than in the present case; thus, methyl 2,6-dimethoxy-4-methylbenzoate is reported to be acylated by acetyl chloride and aluminum chloride to yield methyl 2-hydroxy-3-acetyl-4-methyl-6-methoxybenzoate.[5]

Experimental[6]

3,5,4′-Trimethoxy-4-hydroxybenzophenone (III) and 3,4,5,4′-Tetramethoxybenzophenone (II).—Freshly distilled 3,4,5-trimethoxybenzoyl chloride (I, 11.5 g., 0.05 mole) was dissolved in 10 cc. of anisole and 50 cc. of carbon disulfide. To this cooled solution was added 10 g. of aluminum chloride (0.075 mole, 50% excess) in small portions. Vigorous evolution of hydrogen chloride commenced, and a red complex formed in the solution. After refluxing on the steam-bath for ninety minutes, the reaction mixture was decomposed by ice-cold 1:3 hydrochloric acid, and the organic layer subjected to steam distillation to remove carbon disulfide and unreacted anisole. The residue was taken up in ether and extracted with dilute sodium hydroxide solution; a voluminous precipitate of the bright yellow sodium salt of the phenolic ketone, which appeared in the aqueous layer, was separated by filtration and the phenolic ketone regenerated with dilute acid. Crystallization from ethanol yielded 6.5 g. (45% yield) of colorless cubes of the phenolic ketone III, m. p. 163°. The product on methylation with dimethyl sulfate yielded the tetramethoxybenzophenone II.

Anal. (III). Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.60. Found: C, 66.59; H, 5.52.

Evaporation of the ether layer from the Friedel–Crafts reaction resulted in a sticky oil which partly crystallized when triturated with benzene or alcohol. Repeated recrystallization from methanol or ethanol yielded II, m. p. 75–77°. Since this material analyzed 1% low on carbon, it was refluxed with alcoholic alkali to remove any ester or phenolic compound. The recovered ketone melted at 76–77°, but the carbon percentage was unchanged; the phenylhydrazone was therefore prepared and analyzed. It melted at 170° after crystallization from alcohol.

Anal. Calcd. for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16. Found: C, 70.22; H, 6.35.

3,4,5,4′-Tetramethoxybenzhydrol.—Reduction of 3,4,5,4′-tetramethoxybenzophenone in alcohol with zinc and concentrated ammonia, or zinc and sodium hydroxide, yielded after refluxing for two hours almost the theoretical quantity of the substituted benzhydrol, m. p. 106°, after crystallization from ethanol.

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.13; H, 6.57.

The compound dissolves in concentrated sulfuric acid with a deep red color, which disappears on dilution with water.

2,6-Dimethoxy-4-carbomethoxyphenyl 4′-Methoxybenzoate (IV).—To a solution of 36.2 g. of methyl 3,4,5-trimethoxybenzoate in 75 cc. of benzene and 50 cc. of carbon disulfide was added 27 g. (0.16 mole) of anisoyl chloride in 100 cc. of carbon disulfide and 21.3 g. (0.16 mole) of aluminum chloride in small portions. The reagent dissolved, but no reaction was observed, even on refluxing. After cooling, another 21.3 g. of aluminum chloride was added to the reaction mixture. Evolution of hydrogen chloride took place smoothly. After the mixture had refluxed for one hour, the carbon disulfide was removed by distillation, and the residue decomposed with cold 1:1 hydrochloric acid. The neutral compound which separated was removed by filtration and washed with small portions of acetone. The benzene layer and acetone washings contained mainly starting material. The product after several crystallizations from ethanol melted at 171–173°.

Anal. Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 61.93; H, 4.93.

The structure was proved by hydrolysis with alcoholic alkali, which yielded two acids differing in their water solubility. The mixture of acids was dissolved in the minimum amount of boiling water, and cooled to 50°; anisic acid, m. p. 184°, separated. The solution, when cooled to room temperature yielded a small intermediate

---

(2) Hahn and Wassmuth, *Ber.*, **67**, 696 (1934).

(3) Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publ. Corp., New York, N. Y., 1941, p. 727–728.

(4) Limpricht, *Ann.*, **290**, 164 (1896).

(5) Okazaki, *J. Pharm. Soc. Japan*, **59**, 547 (1939); *C. A.*, **34**, 1004 (1940).

(6) Analyses by Microtech Laboratories.

fraction, and cooling in ice gave fine needles of syringic acid, m. p. 209°.[7]

---

[7] Syringic acid is reported to melt at 205° (uncor. ?).[2]

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, NEW YORK RECEIVED NOVEMBER 21, 1947

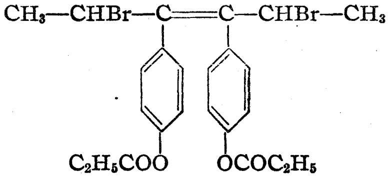
Introduction of Double Bonds into Diethyl Stilbestrol

BY M. J. FREIMAN

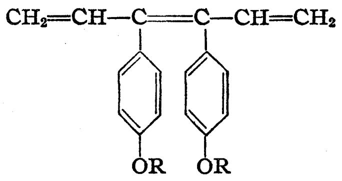
In the course of some work in this Laboratory on synthesizing substances with estrogenic activity, a 3,4 conjugated triene was prepared.

Diethylstilbestrol dipropionate was treated with 2 moles of N-bromosuccinimide to yield 3,4-bis-(*p*-propionoxyphenyl)-2,5-dibromohexene-3 (I). Two moles of hydrogen bromide were then eliminated by treatment with diethylaniline and the resulting 3,4-bis-(*p*-propionoxyphenyl)-hexatriene-1,3,5 (II) saponified to yield the free phenol (III).

The structural formulas of the new compounds are



I



II and III

II, R = C_2H_5CO—
III, R = H—

Absorption spectra of the conjugated triene dipropionate and the free phenol showed two peaks for each substance. The ester showed peaks at 273 and 280 mμ with a rather high molecular extinction coefficient of 22,860 at 280 mμ. The free phenol showed peaks at 223 and 257 mμ with a molecular extinction coefficient of 20,570 at 257 mμ.

Experimental

3,4-bis-(*p*-Propionoxyphenyl)-2,5-dibromo-hexene-3.—Thirty grams of diethylstilbestrol dipropionate dissolved in 300 ml. of carbon tetrachloride and 28.2 g. of N-bromo-succinimide were refluxed for thirty minutes in an atmosphere of nitrogen. The hot mixture was filtered and the crystals of succinimide washed with 15 ml. of carbon tetrachloride. The dried succinimide weighed 15.4 g. (theoretical recovery, 15.7 g.). The filtrate was washed with water to remove the last traces of succinimide, dried over sodium sulfate, filtered, concentrated to a volume of 85 ml. and cooled overnight. The precipitated white crystals were washed with carbon tetrachloride and dried in a vacuum desiccator at room temperature; yield, 27.3 g., m. p. 149°, green melt with decomposition. One recrystallization from carbon tetrachloride yielded small white crystals, m. p. 149.5°.

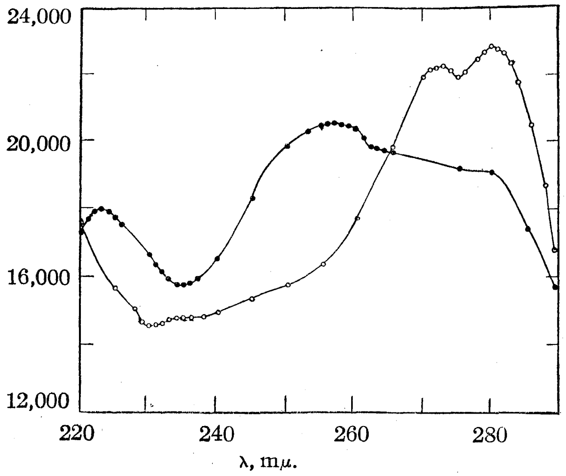


Fig. 1.—Ultraviolet absorption spectra of 3,4-bis-(*p*-propionoxyphenyl)-hexatriene-1,3,5, –○–; 3,4-bis-(*p*-hydroxyphenyl)-hexatriene-1,3,5, –●–.

Anal. Calcd. for $C_{24}H_{26}O_4Br_2$: C, 53.54; H, 4.97; Br, 29.71. Found: C, 53.48; H, 5.10; Br, 30.32.

3,4-bis-(*p*-Propionoxyphenyl)-hexatriene-1,3,5.—Twenty-one and eight-tenths grams of the above dibromo compound was heated at 150–160° for ten minutes with 220 ml. of diethylaniline. The solution darkened considerably and then was cooled to room temperature, after which it was acidified with concentrated hydrochloric acid and extracted three times with 250-ml. portions of ether. The combined ether extracts were washed with water until neutral, dried over sodium sulfate, and concentrated to a volume of 75 ml. This was then cooled to −50°, filtered and washed with a small amount of cold ether. The seven and one-tenth grams of crude crystals (m. p. 128–132°) after recrystallization from 150 ml. of petroleum ether yielded 5.4 g. of long, white needles, m. p. 134–136°.

Anal. Calcd. for $C_{24}H_{24}O_4$: C, 76.58; H, 6.43. Found: C, 76.70; H, 6.59.

When treated with bromide–bromate reagent, the triene dipropionate took up 3.84 atoms of bromine.

3,4-bis-(*p*-Hydroxyphenyl)-hexatriene-1,3,5.—Two grams of the dipropionate was refluxed for twenty minutes with 65 ml. of 10% potassium hydroxide in methanol. After this time, three volumes of water was added, and the solution made slightly acid with concentrated hydrochloric acid. At this point, the free phenol which had precipitated out, was filtered off and crystallized from ether–petroleum ether yielding 1.3 g. of slightly yellowish crystals, m. p. 196–198°. After recrystallization from aqueous isopropanol, 0.8 g. of white needles was obtained, m. p. 202–203°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.82; H, 6.11. Found: C, 81.70; H, 6.14.

Absorption Spectra.—The spectra were determined with a Beckman quartz spectrophotometer, density readings being made at 5 mμ intervals, except when in the region of maxima or minima when the readings were made at 1 mμ intervals.

The solvent used for both curves was 99% isopropanol (Carbide & Carbon). This solvent was not purified in any way since readings could be obtained when the wave length was as low as 217 mμ.

The concentration of the conjugated dipropionate was 7 mg. per liter and that of the free phenol was 7.6 mg. per liter, and the thickness of the silica absorption cells was 1.000 ± 0.002 cm.

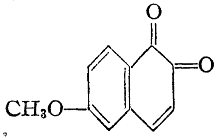
VITAMINS, INC.
CHICAGO, ILLINOIS RECEIVED SEPTEMBER 2, 1947

6-Methoxy-1,2-naphthoquinone[1]

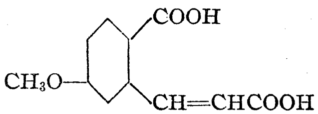
By H. E. French and Kern Sears[2]

6-Methoxy-1,2-naphthoquinone (I), required as an intermediate for a series of compounds, was prepared by the usual coupling process from 6-methoxy-2-naphthol.[3] The route to this intermediate by methylation of 2,6-dihydroxynaphthalene derived from 2-naphthol-6-sulfonic acid appeared unsatisfactory as a preparative method.[4] The claimed preparation by the hydrolysis of 6-bromo-2-naphthol with aqueous base under pressure[5] gave a tar from which a small amount of β-naphthol was isolated. Similar treatment of 6-bromo-2-methoxynaphthalene gave only traces of the desired 6-methoxy-2-naphthol. These poor results may be attributed to the positive character of the halogen.

6-Methoxy-2-naphthol was obtained in fairly good yield from 6-methoxy-2-bromonaphthalene by oxidation of the corresponding Grignard reagent according to the procedure of Kharasch.[6] Oxidation of the naphthoquinone (I) with peracetic or monoperphthalic acid gave 2-carboxy-5-methoxycinnamic acid (II). The oxidation was much less vigorous in this case than with the unsubstituted naphthoquinone.[7] When 6-methoxy-2-naphthol was oxidized with peracetic acid prepared from a mixture of acetic acid and acetic anhydride it gave a 7.4% yield of the cinnamic acid (II), whereas none of this product was obtained with peracetic acid prepared from pure acetic anhydride. On the basis of these results the oxidation may be due to unreacted hydrogen peroxide in acetic acid solution, although Böeseken obtained 2-carboxycinnamic acid from 2-naphthol by the action of peracetic acid.[8]



I



II

Experimental

6-Bromo-2-methoxynaphthalene.—6-Bromo-2-naphthol (1 mole)[9] dissolved in a solution of 80 g. of sodium hydroxide in 3000 ml. of water was methylated by heating with two portions of methyl sulfate (126 g. and 63 g.) to 70°. The mixture was thoroughly cooled after the addition of each portion. The product was filtered with suction and distilled under reduced pressure. The material boiling at 189–199° (20 mm.) weighed 170 g. (71.7%) and melted at 102–104° after crystallization from alcohol. Most of the unchanged naphthol was recovered from the aqueous solution.

6-Methoxy-2-naphthol.—A solution of 500 ml. of dry ether, 118.5 g. of 6-bromo-2-methoxynaphthalene, 123 g. of isopropyl bromide, and 300–400 ml. of dry benzene was added with stirring to a mixture of magnesium turnings (36.5 g.), 50 ml. of dry ether, and a trace of iodine. After completed reaction the mixture was stirred two hours at room temperature and one hour at reflux temperature. Dry oxygen was passed through this mixture until the visible chemiluminescence disappeared and ten minutes longer. The reaction mixture gave a negative test with Michler ketone at this point. A solution of 45 ml. of concentrated sulfuric acid in 200 ml. of water was added to the mixture with cooling, and the resulting liquid layers were separated. The naphthol was extracted from the organic layer with 1000 ml. of 10% aqueous potassium hydroxide containing some sodium hydrosulfite. It was precipitated with acid, filtered off and dried. The yield of dark yellow product was 35–37 g. (40–42%). Crystallization from water or from benzene–petroleum ether gave a white product melting at 150–151°. The m. p. has been reported as 136–137[4a] and 140.[4b]

2,6-Dimethoxynaphthalene.—Methylation of the above material with methyl sulfate in aqueous potassium hydroxide gave the known dimethyl ether which melted at 149–150.5[5] after crystallization from petroleum ether. The mixed melting point with 6-methoxy-2-naphthol (150–151°) was 118–140°.

1-Amino-6-methoxy-2-naphthol Hydrochloride.—Sulfanilic acid (42 g.) diazotized in the usual way,[3a] was added to a cold solution of 34.8 g. of 6-methoxy-2-naphthol and 61.6 g. of potassium hydroxide in 500 ml. of water. The red reaction mixture was allowed to stand for several hours and was heated to 45°. Sodium hydrosulfite (92 g.) was added, and the light yellow reaction mixture was heated to boiling, cooled to 20° in an ice-bath, and filtered. The product was crystallized and decolorized with Norite in portions from the same solution of 200 ml. of concentrated hydrochloric acid and 2 g. of stannous chloride in 800 ml. of water. The hydrochloride formed colorless needles which gradually turned purple. The yield was 30.5 g. (67.2%).

6-Methoxy-1,2-naphthoquinone.—The above aminonaphthol hydrochloride (30.3 g.) was dissolved in 2500 ml. of 0.1% aqueous hydrochloric acid by warming. The solution was filtered, cooled, and oxidized with a solution of 95 g. of ferric chloride in 75 ml. of water and 34 ml. of hydrochloric acid.[3b]

The dark orange precipitate was filtered, washed thoroughly with water and dried. The quinone, melting at 135–140°, weighed 22 g. (53.6%). Crystallization from alcohol gave red-orange needles melting at 124–127°.

Anal. Calcd. for $C_{11}H_8O_3$: C, 70.21; H, 4.23. Found: C, 69.82; H, 4.65.

3-Methoxybenzo[a]phenazine.—6-Methoxy-1,2-naphthoquinone (0.5 g.) in 20 ml. of hot glacial acetic acid was treated with a solution of 0.6 g. of *o*-phenylenediamine and 0.5 g. of sodium acetate in 20 ml. of glacial acetic acid. The crystalline phenazine was filtered off and recrystallized from aqueous acetic acid. It melted at 160–161°.

Anal. Calcd. for $C_{17}H_{12}N_2O$: C, 78.45; H, 4.66. Found: C, 78.45; H, 4.70.

2-Carboxy-5-methoxycinnamic Acid. A. Peracetic Acid Oxidation.—6-Methoxy-1,2-naphthoquinone (9.12 g.) suspended in 50 ml. of acetic acid was treated with 25 ml. of 1.4 molar peracetic acid in acetic acid.[10] A yellow

---

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Missouri.

[2] From the thesis submitted by Mr. Sears in partial fulfillment of the requirements for the degree of Master of Arts at the University of Missouri.

[3] (a) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 35; (b) *ibid.*, p. 430.

[4] (a) Windaus, *Ber.*, **27**, 1738 (1924); (b) Cabal, *Rev. acad. cien. Madrid*, **32**, 423 (1935), (c) Willstätter and Parnas, *Ber.*, **40**, 1406 (1907).

[5] Britton, U. S. Patents 1,959,283 (May 15, 1934), and 1,996,744 (April 9, 1935).

[6] Kharasch and Reynolds, This Journal, **65**, 501 (1943).

[7] Böeseken and Sloof, *Rec. trav. chim.*, **49**, 92 (1930).

[8] Böeseken, Lochman and Konigsfeldt, *ibid.*, **54**, 315 (1935).

[9] "Organic Syntheses," Vol. 20, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 18.

[10] Böeseken, Cohn and Kipp, *Rec. trav. chim.*, **55**, 817 (1936).

precipitate of the acid was filtered off after standing for three days at room temperature. It was purified through its sodium salt, and recrystallized from aqueous alcohol. The yield was 2.3 g. (23%).

Monoperphthalic Acid Oxidation.—The quinone (4.74 g.) was added to an excess of monoperphthalic acid in ether solution and the mixture was allowed to stand at room temperature for thirty hours. The precipitate of acid was filtered and the acid purified as before. The yield was 2.08 g. (31.2%).

The pure dicarboxylic acid melted at 186–190° (dec.) when the temperature of the block was raised 4° per minute.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54; neut. equiv., 111.3. Found: C, 59.32; H, 4.80; neut. equiv., 111.1.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MISSOURI
COLUMBIA, MISSOURI
RECEIVED NOVEMBER 14, 1947

A Peptide Derivative Related to Gramicidin

BY JOSEPH S. FRUTON

The studies of Hotchkiss[1] and of Gordon, *et al.*,[2] have shown that gramicidin is a cyclopeptide which is characterized by an unusually high content in D-leucine and L-tryptophan, these two components accounting for approximately one half of the total amino acids found after complete hydrolysis of gramicidin. In the course of our studies on the effect of peptides and peptide derivatives on bacterial growth, the substance D-leucyl-L-tryptophan diketopiperazine was synthesized. The synthesis involved the reaction of carbobenzoxy-D-leucyl azide with L-tryptophan methyl ester, followed by the catalytic hydrogenation of the coupling product. Treatment of the resulting dipeptide ester with ammonia gave the diketopiperazine.

If the antibacterial action of gramicidin were due solely to the presence of D-leucine or L-tryptophan residues, the synthetic diketopiperazine might have been expected to exhibit some inhibition of the growth of organisms affected by gramicidin. It has been found, however, that the diketopiperazine, when tested at concentration levels of 1 to 10 μg. per ml. of culture medium, shows no appreciable action on *Escherichia coli*, *Staphylococcus aureus*, *Clostridium welchii* or *Brucella abortus*, and only a slight antibacterial effect was noted with *Streptococcus hemolyticus*. Control experiments with gramicidin, at 1 and 5 μg. per ml., showed complete inhibition of the growth (in 12 hours) of *S. hemolyticus*. Further experiments on the antibacterial activity of peptide derivatives related to gramicidin and tyrocidine are in progress.

Experimental

N-Carbobenzoxy-D-leucyl-L-tryptophan Methyl Ester.—Three grams of carbobenzoxy-D-leucinhydrazide[3] was dissolved in a mixture of 25 ml. of water, 10 ml. of glacial acetic acid and 5 ml. of concentrated hydrochloric acid. The solution was chilled to 0° and, with shaking, there was added, in small portions, a solution of 0.7 g. of sodium nitrite in 10 ml. of water. The azide separated as an oil and was extracted with ether. The ethereal solution was washed successively with cold water, cold aqueous bicarbonate solution, and again with cold water. The ethereal layer (60 ml.) was dried briefly over sodium sulfate and added to a solution of 2.5 g. of L-tryptophan methyl ester[4] in 60 ml. of ether. The reaction mixture was left at room temperature for eighteen hours, and then washed successively with dilute hydrochloric acid, water, aqueous bicarbonate solution, and water. After being dried over sodium sulfate, the solution was concentrated to a small volume under reduced pressure. The careful addition of petroleum ether (30–60°) gave a sirup which crystallized readily. After recrystallization from ethyl acetate–petroleum ether, the substance (2.7 g.) melted at 125–127°.

Anal. Calcd. for $C_{26}H_{31}O_5N_3$: N, 9.0. Found: N, 9.2.

D-Leucyl-L-tryptophan Diketopiperazine.—One gram of the above carbobenzoxydipeptide ester was dissolved in a mixture of 15 ml. of methanol and 0.2 ml. of glacial acetic acid and was hydrogenated at atmospheric pressure in the presence of palladium black. The hydrogenation required two hours, after which time the catalyst was removed by filtration. The filtrate was added to 30 ml. of methanol which had previously been saturated with dry ammonia at 0°. The mixture was left at room temperature for two days, then concentrated under reduced pressure, and the resulting crystalline product was dissolved in 10 ml. of hot absolute alcohol. On chilling the alcoholic solution, 0.56 g. of the diketopiperazine crystallized; m. p. 218–219° (dec.).

Anal. Calcd. for $C_{17}H_{21}O_2N_3$: C, 68.2; H, 7.1; N, 14.0. Found: C, 67.9; H, 7.1; N, 14.0.

---

(1) Hotchkiss, *J. Biol. Chem.*, **141**, 171 (1941).

(2) Gordon, Martin and Synge, *Biochem. J.*, **37**, 86 (1943).

(3) This compound was prepared in the manner described for the L-form by Bergmann, *et al.*, *J. Biol. Chem.*, **109**, 325 (1935).

(4) Abderhalden and Kempe, *Z. physiol. Chem.*, **52**, 207 (1907).

DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY
YALE UNIVERSITY
NEW HAVEN, CONNECTICUT
RECEIVED DECEMBER 1, 1947

Indole from Formyl-toluidine

BY ALEXANDER GALAT AND HARRIS L. FRIEDMAN

Of the numerous methods of preparation of indole described in the literature, ring closure of *o*-formyltoluidine is the most direct and convenient. Tyson[1] has shown that yields up to 79% may be obtained with potassium alkoxides, whereas sodium alkoxides give little or no product. This is a peculiarity of the formyl group, for the higher acyl derivatives are readily dehydrated by sodium alkoxides.[2]

The use of potassium metal in the dehydration of *o*-formyltoluidine adds both expense and an element of danger to large scale preparations. It occurred to us that if the potassium *ion* had a catalytic effect in the reaction, it would be possible to use an inexpensive potassium salt with sodium alkoxide.

This possibility was tested as follows: sodium (4.6 g.) was dissolved in 100 ml. of anhydrous methanol and 27 g. of *o*-formyltoluidine was added. Complete solution resulted on warming.

---

(1) Tyson, THIS JOURNAL, **63**, 2024 (1941).

(2) Madelung, *Ber.*, **45**, 1130 (1912).

The potassium salt used was then added and methanol was distilled off with stirring to obtain a uniform dispersion. Complete removal of methanol was effected by applying reduced pressure (20–30 mm.) and the resulting solid was heated in a solder-bath between 300 and 350°. The reaction occurs at the internal temperature of 300–310° as evidenced by rapid distillation of toluidine. Reduced pressure (20–30 mm.) was applied toward the end of the reaction to remove all toluidine. The reaction mass was cooled, treated with water and the indole steam-distilled over. The product crystallized in the cooled distillate in the form of lustrous plates. Any trace of toluidine was removed by acidification and the indole was filtered, washed with water and dried; m. p. 50–51.5°.

Since half of the toluidine was recovered in every case, the yield was calculated on the basis of this recovery. The results obtained are contained in Table I.

TABLE I

g.	Added salt,	K atoms	Yield, %	Observations
None		..	6.0	
17	Anhydrous K_2SO_4	1	14.5	No stirring used; melt appears heterogeneous
35	Anhydrous K_2SO_4	2	21.0	
70	Anhydrous K_2SO_4	4	14.5	
35	Anhydrous K_2SO_4	2	34.0	Mechanical stirring used
20	Anhydrous KOAc	1	27.0	Homogeneous fluid melt
39	Anhydrous KOAc	2	37.5	

Whether the potassium acts as a catalyst or as a reactant is open to question. The data show that a potassium salt does effect a marked increase in yield, the maximum effect being obtained apparently with two atoms of potassium.

Although the yield is not as high as when potassium metal is used, the procedure is safer and much less expensive.

GALAT CHEMICAL DEVELOPMENT, INC.
61 SO. BROADWAY
YONKERS, N. Y.

RECEIVED AUGUST 4, 1947

The Preparation of 2,2,2-Trifluoroethanol

BY HENRY GILMAN AND R. G. JONES

In connection with studies of compounds containing the trifluoromethyl group, we had need of trifluoroethanol. This substance had been described by Swarts[1] who prepared it by the catalytic reduction both of trifluoroacetic anhydride and of trifluoroacetamide. Since the former method afforded him a yield of only 23%, we attempted in vain its preparation from both ethyl and *n*-butyl trifluoroacetate by hydrogenation over copper chromite catalyst at pressures up to 3500 lb./sq. in. and temperatures up to 250°. No hydrogen was absorbed and we recovered unchanged 70% of the ethyl, and 32% of the butyl ester.

In view of this failure we resorted to the latter method of Swarts, who unfortunately gave no details of his procedure other than that he hydrogenated the ethereal solution under a pressure of 40 atmospheres.

Trifluoroethanol.—A solution of 113 g. (1.0 mole) of pure amide (m. p. 74.5–75.0°) in 100 cc. of anhydrous ether in a bomb of 490-cc. capacity with 3.5 g. of Adams catalyst was agitated with hydrogen at 1500 lb./sq. in. at 90° for seven hours, the pressure dropping to 670 lb./sq. in. To the cooled bomb 1.5 g. of fresh catalyst was added and agitation at the previous temperature and pressure was continued for four hours longer, the pressure then dropping to 1080 lb./sq. in. The contents of the cooled bomb with the ether washings was fractionated in a small packed column of about 10 equivalent plates, yielding a fraction weighing 76.5 g. (76.5%) and boiling at 75–77° (740 mm.). It was necessary to heat the distilling flask with a free flame in order to drive over the trifluoroethanol. Apparently the latter forms an unusually stable solvate with the unchanged trifluoroacetamide and ammonium trifluoroacetate present. The released hydrogen in each case was allowed to bubble through concentrated hydrochloric acid, whereby a total of 36 g. of ammonium chloride (66% yield), identified by analysis, was obtained.

The platinum catalyst seemed to quickly lose its activity. In all of the runs the rate of reduction became very slow after about four hours and it was necessary to add fresh catalyst.

From several preparations, the general reaction for which may be represented as

$$CF_3CONH_2 + 2H_2 \xrightarrow{Pt} CF_3CH_2OH + NH_3$$

none of the recently described[2] trifluoroethylamine was isolated. The only products were trifluoroethanol, ammonia, unchanged trifluoroacetamide, and ammonium trifluoroacetate. The small quantity of ammonium trifluoroacetate obtained may have resulted from hydrolysis of trifluoroacetamide.[3]

Trifluoroisopropanol.[4]—Seventy-five grams (0.67 mole) of trifluoroacetone,[5] 5 g. of Adams catalyst, and 3 cc. of water, were added to the bomb previously cooled to −15°, and the whole agitated at room temperature with hydrogen at 760 lb./sq. in. pressure. The absorption of hydrogen began at once and in three hours the pressure had dropped to 250 lb./sq. in. The bomb was then opened and the contents and ether washings were dried over calcium sulfate and

---

[1] Swarts, *Compt. rend.*, **197**, 1261 (1933); *Bull. soc. chim. Belg.*, **43**, 471 (1934) [*C. A.*, **29**, 729 (1935)].

[2] Gilman and Jones, THIS JOURNAL, **65**, 1458 (1943).

[3] Although care was taken to dry the reagents and the apparatus, sufficient water may have been formed from the catalyst [$PtO_2 \cdot H_2O$].

[4] Swarts, *Bull. soc. chim. Belg.*, **38**, 99 (1929) [*C. A.*, **23**, 4440 (1929)].

[5] Swarts, *Bull. classe. sci. Acad. roy. Belg.*, **13**, 175 (1927). [*C. A.*, **22**, 58 (1928)].

fractionated. A yield of 68.5 g. (90%) of trifluoroisopropanol (b. p. 77–78°) was obtained.

CHEMICAL LABORATORY
IOWA STATE COLLEGE
AMES, IOWA
RECEIVED[6] MAY 6, 1943

---

[6] This manuscript was originally received on May 6, 1943, and after examination was accepted for publication in the Journal. It was, however, referred to the National Defense Research Committee, and at their request was withheld from publication, in a confidential file, until it was finally cleared for publication on January 14, 1946.

Preparation of Schiff Bases by Condensation of 2-Acylthiophenes with Amines

BY HOWARD D. HARTOUGH

In contrast to the circuitous procedure involved in the preparation of Schiff bases from acetophenone,[1] 2-acetylthiophene condenses directly with aniline and primary aliphatic amines, without the aid of a catalyst, in boiling toluene or xylene. 2-Butanoylthiophene condenses very slowly with aniline and the reaction apparently can be catalyzed by addition of iodine. Zinc chloride could not be used to catalyze this reaction since an insoluble complex formed with the 2-acylthiophenes. Although the best yields obtained were not greater than 46%, the original reactants could be completely recovered and the product distilled without loss due to high boiling residues.

These ketimines are readily hydrolyzed with moisture to the original components. A loosely stoppered bottle of pure crystalline N-phenyl 2-thienyl methyl ketimine stored in a humid atmosphere became semi-crystalline at the top of the bottle and the odor of 2-acetylthiophene was prevalent.

Experimental

N-Phenyl 2-Thienyl Methyl Ketimine.—A mixture of 0.5 mole each of aniline and 2-acetylthiophene was heated at reflux in 150 ml. of toluene in a flask to which was attached a conventional water take-off trap and a reflux condenser. After thirteen hours, 5 ml. of water (9 ml. calcd.) was collected in the trap. Heating at reflux an additional six hours did not increase the amount of water. The toluene was recovered by distillation at atmospheric pressure; the aniline and 2-acetylthiophene at a reduced pressure. The bright yellow product, 45 g. (46%), boiling at 155° at 5 mm. crystallized on standing and after one recrystallization from absolute alcohol melted at 69–70°.

Anal. Calcd. for $C_{12}H_{11}NS$: N, 7.0; S, 16.0. Found: N, 7.1; S, 16.1.

N-(2-Ethylhexyl) 2-Thienyl Methyl Ketimine.—An equimolar mixture (0.325 mole) of 2-acetylthiophene and 2-ethylhexylamine in 500 ml. of toluene was refluxed for twenty-two hours as above. The liquid product, 30 g. (40%), boiled at 150–157° at 4 mm.

Anal. Calcd. for $C_{14}H_{23}NS$: N, 5.91. Found: N, 6.07.

N-Phenyl 2-Thienyl Propyl Ketimine.—A mixture of 2-butanoylthiophene (0.25 mole) and aniline (0.50 mole) in 500 ml. of toluene was refluxed for four hours, but only 0.3 ml. of water was collected. The mixture was cooled, 3 g. of iodine added, and refluxed five hours more, 1.0 ml. of water being collected. The liquid product, 16 g. (28%), boiled at 128–130° at 1 mm.

Anal. Calcd. for $C_{14}H_{15}NS$: N, 6.12. Found: N, 6.19.

SOCONY-VACUUM LABORATORIES
(A DIVISION OF THE SOCONY-VACUUM OIL CO., INC.)
RESEARCH AND DEVELOPMENT DIVISION
PAULSBORO, N. J.
RECEIVED DECEMBER 15, 1947

---

[1] Claisen, *Ber.*, **29**, 2932 (1896), describes the preparation of these bases from acetophenone by condensation of amines with ketals of acetophenone.

Low Temperature Nitrogen Adsorption Studies of Silica Gel

BY ISIDOR KIRSHENBAUM AND RICHARD K. GROVER

Recently a number of papers have appeared upon the effect of sintering *in vacuo* and of grinding upon the surface area and average pore size of gel type materials. Milligan and Rachford[1] have reported that sintering a silica gel causes destruction of pores but no change in average pore size. Van Nordstrand, Kreger and Ries[2] have found that grinding Thermofor Catalytic Cracking beads to a fine powder results in a considerable decrease in both surface area and pore volume. Apparently, however, this latter phenomenon is not restricted to silica–alumina cracking catalysts. Similar observations have recently been made in our laboratories, using a Davison silica gel, activated at 650° and having a surface area of 655 sq. m./g. Upon grinding from 80+ microns to a powder containing about 40% 0–80 micron and 60% 80+ micron particles, the surface area was decreased by 8.6% to 599 sq. m./g. Typical data are summarized in Table I. Both ground and unground samples were evacuated for four hours at 290° before the nitrogen adsorption isotherms were obtained, previous work having indicated that this pretreatment is sufficient to give results reproducible to better than about 1%. The changes observed upon grinding may be due to a partial collapse of pore structure effected by the heat and/or pressure of grinding.

TABLE I

EFFECT OF GRINDING ON ACTIVATED SILICA GEL

Sample	Roller analysis		Weight loss on evacuation, %	Surface area sq. m./g.
	Microns	%		
Unground	0–20	2.8	5	655
	20–40	1.7		
	40–80	1.7		
	80+	93.8		
Ground	0–20	14.7	5	599
	20–40	10.3		
	40–80	13.7		
	80+	60.9		

This effect of grinding was also observed with a silica gel containing about 64% water. A sample of the gel was ground and then both ground and

---

[1] Milligan and Rachford, *J. Phys. Colloid Chem.*, **51**, 333 (1947).

[2] R. A. Van Nordstrand, W. E. Kreger and H. E. Ries, Jr., A. C. S. Meeting, Divn. of Petrol. Chem., New York City, September, 1947.

unground samples were evacuated at 290° for four hours. The surface area of the unground catalyst, as determined from the nitrogen adsorption isotherm, using the weight after evacuation, was 1061 sq. m./g., whereas that of the ground catalyst was 991 sq. m./g., a difference of 6.7%. Little, if any, effect was observed on the average Kelvin pore radius, as determined from the relative pressure corresponding to the steepest portion of the desorption curve. The unground sample had an average pore size of 21.1 A., whereas the ground sample had an average pore radius of 20.7Å.

STANDARD OIL DEVELOPMENT CO.
ELIZABETH, NEW JERSEY RECEIVED DECEMBER 4, 1947

Preparation and Characterization of β-Dibutylaminoethyl Chloride Hydrochloride

BY HOWARD C. KLEIN[1] AND IRVING A. KAYE

β-Dibutylaminoethyl chloride hydrochloride has been prepared by the dropwise addition of 47.2 g. (0.4 mole) of thionyl chloride to 51.9 g. (0.3 mole) of β-dibutylaminoethanol, dissolved in 150 ml. of benzene. After removal of the solvent and excess thionyl chloride under diminished pressure, the tarry residue was dissolved in dry acetone, the solution decolorized with Darco G-60, and then cooled with Dry Ice. The precipitated white hydrochloride (57.9 g., 85%) melted at 86–88°.

Anal. Calcd. for $C_{10}H_{23}NCl_2$: Cl^-, 15.41; Cl (total), 30.82. Found: Cl^-, 15.30; Cl (total), 30.92.

Recrystallization of the hydrochloride from acetone–hexane gave pearly leaflets, m.p. 87–89°.

The basic chloride boiled at 119–120° (30 mm.).[2]

---

[1] Nopco Chemical Company, Fine Chemicals Division, Harrison, New Jersey.

[2] Blicke and Maxwell, THIS JOURNAL, **64**, 429 (1942), found 114–115° (23 mm.).

DEPARTMENT OF CHEMISTRY
BROOKLYN COLLEGE
BROOKLYN, NEW YORK RECEIVED NOVEMBER 10, 1947

Synthesis of Amino-substituted Phosphonic Acids. II. α-Aminobenzylphosphonic Acid

BY GENNADY M. KOSOLAPOFF

As it was reported earlier[1] the synthesis of α-aminobenzylphosphonic acid by the reduction of *p*-nitrophenylhydrazone of diethyl benzoylphosphonate by means of hydrogen, followed by sodium sulfide, failed to yield the pure product. The contamination of the final product was caused principally by the products of incomplete reduction and led to the unusually low melting point of the substance. In order to secure the pure material it was necessary to find another reduction method which was usable in this instance. Such a procedure using the method of Fischer and Groh[2] for the reduction led to the pure substance.

The hydrazone (4 g.) in 500 cc. of ethanol was added to 10 g. of amalgamated aluminum foil immersed in 1 liter of ethanol and 200 cc. of water. The mixture was allowed to stand overnight in a loosely stoppered flask. After filtration, the precipitate was washed with 500 cc. of ethanol and the combined filtrates were treated with 300 cc. of concentrated hydrochloric acid. The solution was slowly distilled (six hours) through a Vigreux column until the volume in the still-pot amounted to approximately 50 cc. On cooling, the *p*-phenylenediamine hydrochloride was filtered off, the filtrate was evaporated to dryness by an infrared lamp and the residue was taken up in 200 cc. of ethanol. Neutralization with aniline gave the crude product which was taken up in 30 cc. of warm water, made strongly alkaline with 10% sodium hydroxide and extracted twice with 50 cc. of benzene. The aqueous solution was made just acid to congo red with 1:1 hydrochloric acid and concentrated to incipient crystallization. After cooling, the product was filtered off, washed with 5 cc. of ice-water, dissolved in 50 cc. of hot water, treated with charcoal, filtered and concentrated to 10 cc. On cooling there was obtained 1.0 g. (50%) of *dl*-α-aminobenzylphosphonic acid, in the form of tiny bunched colorless needles, which melted at 272–273°.

Anal. Calcd.: N, 7.5; P, 16.6. Found: N, 7.46; P, 16.7.

---

[1] Kosolapoff, THIS JOURNAL, **69**, 2112 (1947).

[2] Fischer and Groh, *Ann.*, **383**, 363 (1911).

CENTRAL RESEARCH DEPARTMENT
MONSANTO CHEMICAL COMPANY
DAYTON 7, OHIO RECEIVED SEPTEMBER 27, 1947

Copolymerization Rate Constants in the System 2,5-Dichlorostyrene–Methyl Acrylate

BY F. LEONARD, W. P. HOHENSTEIN AND E. MERZ

During the course of an investigation of the copolymerization of the isomeric dichlorostyrenes and acrylic esters, it became of interest to determine the copolymerization rate constants in the system 2,5-dichlorostyrene and methyl acrylate. The results of this determination are herein presented.

Experimental

2,5-Dichlorostyrene.—This monomer was obtained from the Monsanto Chemical Co. and was purified by washing with 5% sodium hydroxide solution and then with distilled water until the washes were neutral to litmus. The monomer was allowed to dry over calcium chloride overnight. It was then filtered and checked for the presence of polymer by adding a sample to methanol. If no turbidity was observed, the monomer was used *per se*.

Methyl Acrylate.—This monomer obtained from Rohm and Haas was distilled *in vacuo* through a 12″ column packed with glass helices in an all-glass system. The first 10 cc. to distil was rejected and a residue of 50 cc. was left in the distilling flask.

Polymerization and Purification.—The requisite quantities of 2,5-dichlorostyrene, methyl acrylate and benzoyl peroxide (0.5% by weight based on monomers) were weighed into Pyrex glass test-tubes. The tubes were sealed, and immersed in a water-bath held at 70 ± 0.1°. The per cent. conversion was estimated approximately by the rate of rise of air bubbles through the polymerizing mixture when the tubes were inverted. When it appeared that the desired conversion, <5%, had been reached, the tubes were immediately chilled, and the seal broken. The contents of the tubes were dissolved in methyl ethyl ketone containing hydroquinone, and this solution was slowly added with stirring to a 3 times excess of methanol. The precipitated polymer was filtered, washed copiously with methanol and allowed to dry to constant weight in a vacuum oven at 60°.

Chlorine Analysis.—The per cent. chlorine was determined using the Parr bomb.

Results and Discussion

The experimental data are summarized in Table I. The copolymerization rate constants were calculated according to the method of Alfrey and Goldfinger[1] in the usual manner.

TABLE I

DETERMINATION OF r_1 AND r_2

THE COPOLYMERIZATION RATE CONSTANTS SYSTEM 2,5-DICHLOROSTYRENE–METHYL ACRYLATE

Monomer composition: Mole fraction 2,5-dichlorostyrene	Monomer composition: Mole fraction methyl acrylate	Yield, %	Chlorine, %	Polymer composition (Exp.): Mole fraction 2,5-dichlorostyrene	Polymer composition (Exp.): Mole fraction methyl acrylate
0.90	0.10	4.4	39.95	0.950	0.050
.75	.25	3.0	39.15	.913	.087
.50	.50	3.7	37.20	.829	.171
.25	.75	4.4	32.15	.643	.357
.10	.90	4.9	22.30	.371	.629
.05	.95	4.3	14.15	.206	.794

The smooth curve in Fig. 1 represents the theoretical curve calculated from the values $\alpha = 0.25$ and $\beta = 0.15$. These correspond to the values, according to the latest nomenclature,[2] $r_1 = 4$ and $r_2 = 0.15$, respectively. The encircled points are experimentally determined from the data in Table I.

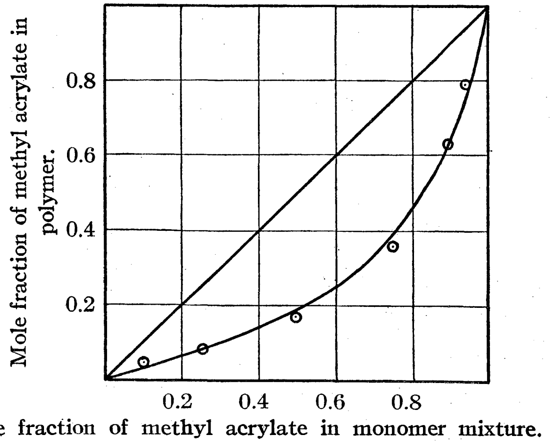


Fig. 1.—Copolymerization composition curve.

The value $r_1 = 4$ indicates that the 2,5-dichlorostyrene monomer adds to the 2,5-dichlorostyrene free radical four times as fast as the methyl acrylate monomer adds. The value $r_2 = 0.15$ indicates that the methyl acrylate monomer adds to the methyl acrylate free radical 0.15 as fast as the 2,5 dichlorostyrene monomer adds to the methyl acrylate free radical.

---

(1) T. Alfrey and G. Goldfinger, *J. Chem. Phys.*, **12**, 205 (1944).

(2) Alfrey, Mayo and Wall, *J. Polymer Sci.*, **1**, 581 (1946).

POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN, N. Y.
RECEIVED OCTOBER 20, 1947

The Preparation of 2,3,5-Triphenyltetrazolium Chloride

BY A. M. MATTSON, C. O. JENSEN AND R. A. DUTCHER

Synthesis of 2,3,5-triphenyltetrazolium chloride by the method of Pechman and Runge as modified by Bamberger and Billeter and by Kuhn and Jerchel[1] resulted in poor yields of preparations which had a greater chloride content than the desired monobasic compound. A better yield of the compound with the theoretical chloride content and a saving of time were achieved by modifying the previous procedures.

Experimental

Triphenylformazan.—Twenty-one and two-tenths grams (0.2 mole) of freshly distilled benzaldehyde was dissolved in 125 ml. of methanol. To this solution 21.6 g. (0.2 mole) of phenylhydrazine was added during mechanical agitation. The hydrazone, dissolved in one liter of methanol, was added to a solution of 50 g. of sodium hydroxide and 70 g. of sodium acetate in one liter of methanol. To this solution, cooled to 20°, benzenediazonium chloride prepared from 18.6 g. of aniline (0.2 mole), 50 ml. of concentrated hydrochloric acid, 50 ml. of water and 14–15 g. of sodium nitrite, was added slowly during agitation. Formazan was precipitated as small red crystals. A yield of 15.8 g. (23%) of triphenylformazan was obtained, m. p. 170°.

2,3,5-Triphenyltetrazolium Chloride.—Fifteen grams (0.05 mole) of triphenylformazan were dissolved in 100 ml. of chloroform and the solution was cooled to 20°. Lead tetraacetate (30 g.) was added until the red color disappeared. The chloroform was evaporated and the residue taken up in water. Hydrochloric acid was added and the lead chloride was removed by filtration. The monobasic triphenyltetrazolium chloride was removed from the filtrate by three successive extractions with chloroform (water–chloroform ratio of 3:1), leaving the more acid salt in the water. The chloroform solution was concentrated on the steam-bath. Addition of ether to this solution precipitated the tetrazolium salt in long, silky needles. Nine and seven-tenths grams (57.7% based on formazan) of 2,4,5-triphenyltetrazolium chloride was obtained, m. p. 245° (d.) (Pechman and Runge 243°).

---

(1) Pechman and Runge, *Ber.*, **27**, 2920 (1894); Bamberger and Billeter, *Helv. Chim. Acta*, **14**, 232 (1931); Kuhn and Jerchel, *Ber.*, **74B**, 941 (1941).

FREAR LABORATORIES
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PENNSYLVANIA
RECEIVED OCTOBER 6, 1947

Effects of Inhibitors on the Polymerization of Styrene[1]

BY FRANK R. MAYO AND R. A. GREGG

Inhibitors of free radical polymerization are regarded as materials which, by transfer or addition, are converted to radicals so stable they do

---

(1) This paper was presented before the Division of Organic Chemistry at the New York City Meeting of the American Chemical Society, September 15, 1947.

not add to double bonds. This note will show that benzoquinone is not an inhibitor in this sense and that even the stable radical triphenylmethyl adds readily to styrene.

Foord[2] and Goldfinger, Skeist and Mark[3] found the period of inhibition of styrene polymerization by benzoquinone was proportional to the initial quinone concentration. Assuming the consumption of inhibitor to be a direct measure of the rate of chain initiation, they calculated the activation energy for chain initiation. Since the present work shows that most of the quinone radicals add to styrene, the above assumptions are not justified. At 100°, the rate of uncatalyzed polymerization of styrene is 2.23% per hour yielding a polymer of degree of polymerization 4030.[4] The total moles of polymer per gram per hour is 5.32×10^{-8}, and is equal to the maximum number of chains which could have been initiated. At 100°, 10^{-4} g., 9.3×10^{-7} mole, of benzoquinone inhibits the polymerization of 1 g. of styrene for one hour.[3] Hence, at least 17 molecules of quinone are consumed per radical chain initiated.

Since the inhibition period, the time required to consume quinone, is directly proportional to the initial concentration of quinone, its rate of disappearance is independent of its concentration and quinone cannot be reacting directly with monomer. Let us consider the possible reactions, denoting monomer and quinone by M and Q, and the derived radicals by M* and Q*

$$2M \longrightarrow 2M^* \qquad (1)$$
$$M^* + Q \longrightarrow Q^* \qquad (2)$$
$$Q^* + M \longrightarrow M^* \qquad (3)$$
$$\left.\begin{array}{ll} 2Q^* \longrightarrow & (4) \\ Q^* + M^* \longrightarrow & (4a) \\ 2M^* \longrightarrow & (4b) \end{array}\right\} \text{non-radical products}$$

If we assume the mechanism to be described completely by Equations 1, 2, 3 and 4, then

$$-\mathrm{d}Q/\mathrm{d}t = M^2(2k_1 + k_3\sqrt{k_1/k_4})$$

The rate of disappearance of quinone should then be independent of the quinone concentration, as observed, and about 16 out of 17 quinone radicals react by Equation 3 instead of Equation 4. At higher radical concentrations Equation 4 may predominate since it is of second order while Equation 3 is of first order with respect to radicals.[5] Equation 2 may represent either chain transfer or addition of quinone to the chain (copolymerization). Reaction 4b must be unimportant or quinone would not be an inhibitor. If the termination step were 4a, then the rate of disappearance of quinone would depend on the quinone concentration.

It is desirable to have an inhibitor which will not initiate or continue chains, each molecule of which will terminate one reaction chain. Then the rate of chain initiation could be determined and, from our data,[4] the number of polymer molecules formed per chain initiated, *i. e.*, the extent of chain transfer with styrene monomer.[6] Hence, we investigated the radical triphenylmethyl hoping it would terminate chains without starting any.

Hexaphenylethane was dissolved in styrene and heated in narrow diameter tubes sealed under nitrogen. The length of the inhibition period was determined from the viscosity of the reaction mixture, measured as the time for a bubble to traverse a measured distance in the tube. Figure 1 shows that the solution viscosities after the induction period follow essentially the same course as in the blank run. The induction periods were taken as the times required for the solutions to attain a "bubble time" of thirty seconds, minus the eight and three-tenths hours required to reach this stage in the blank. The essential data and conclusions are summarized in Table I and Fig. 2. The results show that the inhibition period increases with the initial concentration of inhibitor, but less rapidly; a large concentration of inhibitor is relatively less effective than a small concentration.

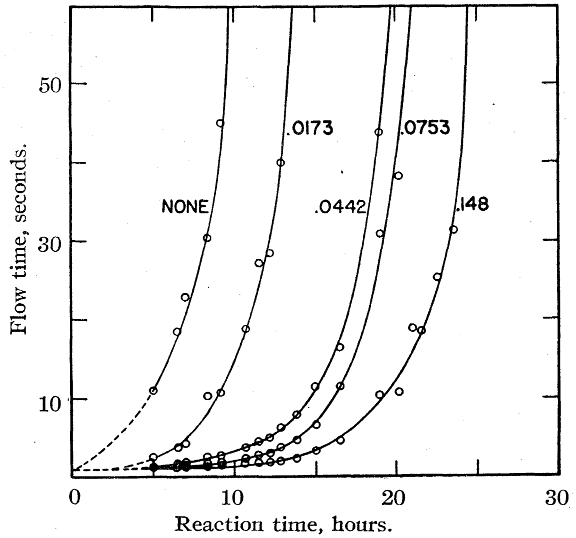


Fig. 1.—Polymerization of styrene at 100° with various initial concentrations of hexaphenylethane, as indicated in moles/liter.

TABLE I

INHIBITION OF THE POLYMERIZATION OF STYRENE AT 100° BY HEXAPHENYLETHANE

Inhibitor moles/l.	Inhibition period, hours	Hours per unit inhibitor concentration
None	None	240–300[a]
0.0173	3.9	225
.0442	9.7	219
.0753	10.9	145
.148	15.0	101

[a] Estimated from Fig. 2.

---

[2] Foord, *J. Chem. Soc.*, 48 (1940).

[3] Goldfinger, Skeist and Mark, *J. Phys. Chem.*, **47**, 578 (1943).

[4] Gregg and Mayo, THIS JOURNAL, in press.

[5] *Cf.* Cohen, *ibid.*, **69**, 1057 (1947).

[6] While this attempt failed, the transfer constant of polymerizing styrene with styrene monomer has been determined and will be published shortly.

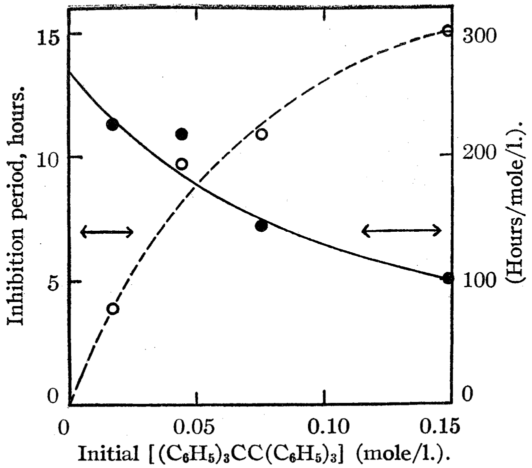


Fig. 2.—Inhibition periods in the polymerization of styrene, in hours (broken line), and in hours per unit concentration of hexaphenylethane (solid line).

This result may be due to the disappearance of hexaphenylethane in a side reaction, such as the addition to styrene; the addition of tri-biphenylmethyl to styrene to give a 2:1 product has been observed.[7] However, since our data are not consistent enough to permit analysis of the kinetics, the inhibition period per unit concentration of inhibitor has been plotted against the concentration of inhibitor in Fig. 2 and extrapolated to estimated zero concentration of inhibitor. Making the reasonable assumption that this extrapolation minimizes complications due to side reactions which consume hexaphenylethane, the results show that the induction period is of the order of two-hundred-forty to three-hundred hours per mole of substituted ethane initially present. Thus, such a solution would consume about 1/270 or 0.0037 mole of hexaphenylethane per hour. Normally, $5.32 \times 10^{-8} \times 905 = 4.8 \times 10^{-5}$ mole of polymer per liter per hour would have been produced. Hence, about 77 molecules of hexaphenylethane disappear (at zero ethane concentration) for each molecule of polystyrene that would have been formed in its absence. It follows that triphenylmethyl radicals must start nearly as many chains as they stop. The addition of hexa-arylethanes to double bonds seems to be the result of an initiation of "polymerization" by free radicals, and an even more effective termination by the same kind of radicals or by undissociated ethane, so that only *very* low molecular weight polymer is formed while triarylmethyl radicals, or undissociated ethane, remain.

We consider that this work leads to the following conclusions: Any free radical may start or terminate the polymerization of a styrene chain. Neither benzoquinone nor hexaphenylethane is suitable for measuring the spontaneous rate of chain initiation, nor for calculating its activation energy. Whether a source of free radicals will behave as a catalyst or an inhibitor depends on the balance between the rate of addition of these radicals to monomer, the rate of interaction of radicals and the rate of growth of the polymer radicals at the chosen temperature. If the radicals do not add rapidly or if they are supplied too fast, then a high radical concentration results and chain growth is restricted. If the radicals add very rapidly, or are supplied slowly enough, polymerization will result. These statements mean simply that the dividing line between catalysts and inhibitors is not clear cut; the differences between them are quantitative rather than qualitative.

GENERAL LABORATORIES
UNITED STATES RUBBER COMPANY
PASSAIC, NEW JERSEY
RECEIVED SEPTEMBER 12, 1947

---

[7] Marvel, Dec and Corner, THIS JOURNAL, **67**, 1855 (1945).

The Periodate Oxidation of Some Dihydroxyaminoalkanes[1]

BY J. F. MEAD AND E. A. BARTRON

It has been reported previously[2] that two of the contiguously substituted dihydroxyaminoalkanes and possibly dihydrosphingosine[3] can be partially identified by the periodate or lead tetraacetate oxidation of the N-acetyl derivatives with measurement of the amount of oxidizing agent consumed.

A simpler method applicable to a wide variety of related compounds is the periodate oxidation[4] of the amino glycols themselves, with isolation of at least two of the oxidation products.

The reactions of the various types of isomeric compounds with periodate can be represented as follows

Type I $R—CHNH_2—CHOH—CH_2OH + 2IO_4^- \longrightarrow R—CHO + HCOOH + HCHO + NH_3 + 2IO_3^-$

Type II $R—CHOH—CHNH_2—CH_2OH + 2IO_4^- \longrightarrow R—CHO + HCONH_2 + HCHO + 2IO_3^-$

Type III $R—CHOH—CHOH—CH_2NH_2 + 2IO_4^- \longrightarrow R—CHO + HCOOH + HCHO + NH_3 + 2IO_3^-$

Type IV $CH_2OH—C(R)NH_2—CH_2OH + 2IO_4^- \longrightarrow R—CONH_2 + 2HCHO + 2IO_3^-$

Type V $CH_2OH—C(R)OH—CH_2NH_2 + 2IO_4^- \longrightarrow R—COOH + HCHO + NH_3 + 2IO_3^-$

It will be noticed that if R is different from H (as in the case of sphingosine) all five types give different products except I and III, which can be distinguished by oxidation of the N-acetyl derivatives[2] and measurement of the amount of formaldehyde produced.

In testing the method, the simplest substrates were used, and the products isolated or identified were those most easily isolated or determined quantitatively. As can be seen from Table I, the

---

[1] This work was supported by grant No. 840 (Penrose Fund) of the American Philosophical Society.

[2] C. Niemann, A. A. Benson and J. F. Mead, *J. Org. Chem.*, **8**, 397 (1943).

[3] After completion of this note a paper appeared by Carter, Glick, Norris and Phillips, *J. Biol. Chem.*, **170**, 1 (1947), who oxidized dihydrosphingosine to obtain formaldehyde, formic acid and ammonia.

[4] E. L. Jackson, "Organic Reactions," Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1944, Chap. 8, p. 341.

method is both qualitative and quantitative. The yields, which in some cases would be greater than 100% if calculation were made on the basis of substrate actually oxidized can be explained by the differences in temperature of the oxidizing solutions resulting from the addition of the dimethyldihydroresorcinol in hot water (see below). Only one serious difficulty was experienced. In the cases in which both ammonia and formaldehyde were produced, only small yields of either could be obtained because of the formation of hexamethylenetetramine. This difficulty was partially overcome in the case of formaldehyde by an earlier addition of dimethyldihydroresorcinol, with which the formaldehyde apparently reacts preferentially. The compounds used for the reactions were selected because of availability and as examples of each type of product. Formaldehyde was isolated in each case, while acid or ammonia were titrated if the theoretical equation required their formation. If the equation and a qualitative test (for ammonia)[5] indicated the formation of an amide (II and IV), the solution was treated under hydrolytic conditions, and the acid formed was distilled and titrated.

TABLE I

Compound	% oxidized	% of theoretical amount of products isolated (based on substrate taken)			
		HCHO	NH_3	HCOOH	CH_3COOH
$CH_2OH—CHOH—CH_2OH$	94.2	91.7		93.7	
$CH_2OH—CH_2NH_2$	84.4	69.2	59.0		
$CH_2OH—C(CH_3)NH_2—CH_3$	88.0	91.2	84.0		
$CH_2OH—C(CH_3)NH_2—CH_2OH$	89.2	92.6			73.5
$CH_2OH—CHOH—CH_2NH_2$	82.2	82.1		90.8	

Experimental

Determination of Completeness of Oxidation.—The substrate, about 10^{-4} mole, in water solution or emulsion was treated with a 10% excess over the theoretical amount of a saturated solution of potassium metaperiodate (1.66×10^{-2} mole per liter) for twenty minutes. To the resulting solution was added borax–boric acid buffer solution, and potassium iodide, and the liberated iodine was titrated with standard arsenite solution.

Determination of Formaldehyde.—In the absence of ammonia, the oxidation mixture, after standing for twenty minutes, was treated with a 10% excess over the theoretical amount of dimethyldihydroresorcinol[6] in alcohol solution, brought to *p*H 4, warmed to 60°, and allowed to stand in the ice-box until precipitation was complete. The formaldehyde dimethone was collected and weighed, and the melting point taken to determine the purity of the sample.

In case ammonia was formed in the reaction, the following procedure was adopted. The substrate and periodate solutions were mixed, and dimethyldihydroresorcinol in hot water solution was added after about three minutes. After twenty minutes, the solution was brought to *p*H 4 and treated as before.

Determination of Acid.—If no ammonia was formed in the reaction, the oxidation mixture, after twenty minutes, was titrated with standard alkali. If ammonia was formed, the solution was acidified with sulfuric acid and about three-fourths of it distilled. Water was added, and the distillation repeated. The distillate was then titrated with standard alkali.

Determination of Ammonia.—If no acid was formed in the reaction, the oxidation mixture, after twenty minutes, was titrated with standard acid.

Determination of Amides.—If the formation of amide was indicated (see above), the solution, after completion of the oxidation, was made strongly acidic with sulfuric acid, refluxed for two hours and then distilled to about one-fourth volume. Water was added, and the solution was again distilled to one-fourth volume, and the distillate titrated with standard alkali. If the acid formed was known, it was necessary to distill and titrate only 10% of the solution, and calculate the total amount originally present.[7]

---

(5) J. A. Sanchez, *Anales asoc. quim. argentina*, **24**, 366 (1926).

(6) E. C. Horning and M. G. Horning, *J. Org. Chem.*, **11**, 95 (1946).

(7) L. J. Gillespie and E. H. Walters, THIS JOURNAL, **39**, 2027 (1917).

CHEMICAL LABORATORY
OCCIDENTAL COLLEGE
LOS ANGELES, CALIF.

RECEIVED SEPTEMBER 24, 1947

Crystalline Procaine Penicillins

BY CHARLES J. SALIVAR, F. HOWARD HEDGER AND ELLIS V. BROWN

There is an urgent need for a penicillin dosage form which will give prolonged penicillin blood levels with more certainty and without the objectionable features of the currently available preparations.

We have prepared procaine salts of two penicillins and have milled them in vegetable oil to give injectable mixtures. Preliminary animal and clinical trials have indicated that significant and prolonged penicillin blood levels are obtainable with these preparations. These data will be published later.

For the preparation of procaine benzylpenicillin, 10 g. of sodium benzylpenicillin dissolved in 10 ml. of water is treated with a solution of 7.6 g. of procaine hydrochloride in 10 ml. of water and the reaction product is allowed to crystallize slowly. After crystallization is completed, the product is filtered, washed with water and dried in a vacuum drier at 50°.

The practically colorless crystalline procaine salt of benzylpenicillin melts (capillary) at 129–130°. *Anal.* Calcd. for $C_{29}H_{38}N_4O_6S{\cdot}H_2O$: N, 9.52; S, 5.44. Found: N, 9.78; S, 5.35.

The biological potency obtained by the Oxford plate method[1] against *S. aureus* is 1020 U./mg. The potency as determined iodometrically[2] is 1007 U./mg. The calculated value based on 1667 U./mg. for sodium benzylpenicillin is 1008 U./mg. The optical rotation is $[\alpha]^{25}\text{D}$ +173° (1% in 50% aqueous acetone).

Procaine *n*-amylpenicillin was also prepared in the same manner from sodium *n*-amylpenicillin.[3] It melts at 113–115°. *Anal.* Calcd. for $C_{27}H_{42}N_4O_6S{\cdot}H_2O$: N, 9.86; S, 5.63. Found: N, 9.79; S, 5.97.

---

(1) W. H. Schmidt and A. J. Moyer, *J. Bact.*, **47**, 199 (1944).

(2) J. F. Alicino, *Ind. Eng. Chem., Anal. Ed.*, **18**, 619 (1946).

(3) Report presented by C. J. Salivar, V. V. Bogert and E. V. Brown at the Conference on Antibiotic Research held in Washington, D. C., January 31, 1947, under the auspices of the Antibiotics Study Section of the National Institute of Health.

The biological potency against *S. aureus* is 983 U./mg. and as determined iodometrically is 986 U./mg. The calculated potency is 955 U./mg. and the optical rotation is $[\alpha]^{25}_{D}$ +175° (1% in 50% aqueous acetone).

RESEARCH LABORATORY
CHAS. PFIZER AND CO., INC.
BROOKLYN, NEW YORK RECEIVED SEPTEMBER 20, 1947

The Friedel–Crafts Reaction of Benzene and 3,4-Dichlorohexane

BY KEIITI SISIDO AND HITOSI NOZAKI

The condensation of benzene with 3,4-dichlorohexane has been studied. The dichlorohexane was prepared from divinylacetylene by catalytic hydrogenation followed by chlorination.[1] The reaction product obtained by the usual procedure was composed of two fractions.

The analysis and molecular weight determination of the first fraction agreed with the formula $C_{12}H_{16}$, showing that it was a mono-cyclialkylated benzene. The dehydrogenation of this hydrocarbon with sulfur or with selenium under the condition not to be accompanied with anomalies[2] gave an oily product, whose picrate formed orange needles melting at 144–144.5°, alone or admixed with an authentic specimen of 1,4-dimethylnaphthalene picrate. It has often been observed, however, in the case of the picrates of naphthalene derivatives, that a mixture of two different isomers shows no depression of the melting point. But as all of the isomers of dimethylnaphthalene are already known, an examination of the literature about the characteristic data of the hydrocarbons and their picrates made it clear that the dehydrogenation product above mentioned was nothing else but 1,4-dimethylnaphthalene. From these observations, we concluded that the hydrocarbon $C_{12}H_{16}$ was a new compound, 1,4-dimethyltetralin.

In the alkylation of benzene with alkyl halogenides catalyzed by aluminum chloride, the isomerizations of the alkyl radicals are often observed. The mechanism of the present condensation is explained from this view-point that the chlorine atoms of the 3,4-positions migrate to the 2,5-positions and the resulting dichloride cyclialkylates benzene to form a six-membered carbon ring.

The second reaction product formed colorless liquid. Several attempts to crystallize it were unsuccessful. The results of its analysis and molecular weight determination gave a formula $C_{18}H_{26}$, showing that it was not 3,4-diphenylhexane[3] as expected at first, but a di-cyclialkylated benzene, *i. e.*, 1,4,5,8-tetramethyl-1,2,3,4,5,6,7,8-octahydroanthracene, -phenanthrene or a mixture of them.

Experimental

The Condensation of 3,4-Dichlorohexane with Benzene.—To a mixture of 105 g. of benzene and 24 g. of aluminum chloride was added 42 g. of 3,4-dichlorohexane in the course of about one hour under stirring, during which time the reaction temperature was maintained at 5–10°. After additional fifteen minutes the mixture was heated slowly so as to insure a uniform evolution of hydrogen chloride gas. Heating was continued for about two hours until the reaction temperature reached 25° and practically no more evolution of gas was observed. The reaction mixture was poured over crushed ice acidified with hydrochloric acid and treated as usual. The solvent was removed and the residue was distilled under reduced pressure. The following fractions were obtained.

Fraction	B. p., °C.	Pressure, mm.	Yield, g.	Appearance
I	107–131	37	11	Colorless liquid
II	79–110	9	5	Colorless liquid
III	112–140	9	1	Colorless liquid
IV	140–170	9	5	Colorless viscous oil
V	170–184	9	3	Viscous sirupy oil
VI	Residue	..	3	Viscous sirupy oil

The Mono-cyclialkylated Product: 1,4-Dimethyltetralin.—Fractions I and II were combined and the mixture was redistilled. The main fraction boiling at 216–227° under atmospheric pressure weighed 14 g. occupying 50% of the total condensate. It formed a colorless liquid with characteristic odor. The boiling point determined by the Emich method was 226°.

Anal. Calcd. for $C_{12}H_{16}$: C, 89.94; H, 10.06; mol. wt., 160. Found: C, 89.74; H, 10.21; mol. wt. (cryoscopy in benzene), 152.

The Dehydrogenation of 1,4-Dimethyltetralin with Sulfur.—A mixture of 2.4 g. of the hydrocarbon and 1.0 g. of sulfur was heated on a metal-bath at 180–250° for two and a half hours. The reaction product was immediately distilled and yellowish oil, boiling at 260–300° (bath temperature), was obtained. It was dissolved in hot alcohol and added a hot alcoholic solution of picric acid. On cooling, orange needles separated. After one recrystallization from alcohol, the picrate melted at 144–144.5° and repeated crystallizations changed the melting point no more. This fact showed that the material was already quite pure. When admixed with an authentic specimen of 1,4-dimethylnaphthalene picrate (m. p. 143–144°) it melted at 144–144.5°.

Anal. Calcd. for $C_{12}H_{12}\cdot C_6H_3O_7N_3$: C, 56.10; H, 3.92. Found: C, 55.39; H, 4.17.

The Dehydrogenation of the Dimethyltetralin with Selenium.—To 1.58 g. of the substance was added 1.62 g. of selenium and the mixture was heated on a metal-bath at 250–300° for one hour. The reaction product was shaken out and heated for additional six and a half hours at 300–350° (bath temperature). Distillation of the dehydrogenation product gave 0.57 g. of yellowish oil, which yielded the same picrate as described above.

The Di-cyclialkylated Product.—Fraction IV was redistilled under reduced pressure and the main fraction boiling at 145–160° at 9 mm. was subjected to the following experiments.

Anal. Calcd. for $C_{18}H_{26}$: C, 89.19; H, 10.81; mol. wt., 242. Found: C, 89.20; H, 10.81; mol. wt. (cryoscopy in benzene), 220.

A mixture of 4.5 g. of the substance and 2.3 g. of sulfur was heated for about three hours at 180–260°. The resulting black mass was distilled under reduced pressure. The red viscous oil, which distilled at 230–300° (bath temperature) at 5–6 mm., solidified immediately. On recrystallizations from alcohol, colorless prisms melting at 219–220°[4] separated. An analysis was impossible for lack of material.

Higher Boiling Fractions.—Fraction V and the residue separated a small quantity of crystals, melting at 197–

---

(1) Spiegler and Tinker, THIS JOURNAL, **61**, 940 (1940).

(2) Ruzicka and Peyer, *Helv. Chim. Acta*, **18**, 676 (1935).

(3) Lepin and Reich, *Chem. Zentr.*, **87**, I, 787 (1916).

(4) *Cf.* Ellison and Hey, *J. Chem. Soc.*, 1849 (1938).

198°. The detailed study of this crystalline substance was abandoned because of the low yield.

DEPARTMENT OF INDUSTRIAL CHEMISTRY
FACULTY OF ENGINEERING
KYÔTO UNIVERSITY
KYÔTO, JAPAN
RECEIVED MARCH 25, 1947

Two Derivatives of 9,10-Dimethylanthracene

BY KEIITI SISIDO AND TYÛZÔ ISIDA

In view of the fact that 9,10-dimethylanthracene[1] often cited in the literature erroneously as 9,10-dimethyl-9,10-dihydroanthracene since the discovery of this compound,[2] we have undertaken to obtain the real 9,10-dimethyl-9,10-dihydroanthracene.

9,10-Dimethylanthracene was reduced with sodium and the desired new compound was obtained. It was found that 9,10-dimethyl-9,10-dihydroanthracene on treatment with aluminum chloride is converted to 9,10-dimethylanthracene.

The acetylation of anthracene[3] gives 9-, 1- and 2-acetylanthracenes, and the treatment of 9-acetylanthracene with aluminum chloride rearranges it into 1- and 2-acetyl compounds. Nenitzescu[4] acetylated 9,10-dihydroanthracene and obtained 9-acetyl-9,10-dihydroanthracene.

Acetylation of 9,10-dimethylanthracene in the presence of aluminum chloride gave 2-acetyl-9,10-dimethylanthracene. It was shown from this experiment that the acyl group can enter also directly into the 2-position of the anthracene nucleus, and that *meso*-acylanthracene is not always necessary as an intermediate.

In the Friedel–Crafts reaction of 1,2,3,4-tetramethylnaphthalene the substitution takes place only at the β-position of the nucleus.[5] This fact is probably due to the steric hindrance caused by the methyl groups at the 1- and 4-positions. The acetylation which takes place exclusively at the 2-position of 9,10-dimethylanthracene may be attributed to the same steric factor, inasmuch as the free benzene ring in 9,10-dimethylanthracene as well as in 1,2,3,4-tetramethylnaphthalene is attached to a tetra-substituted nucleus.

During this experiment we have experienced a slight skin-eruption, presumably caused by the acetyl compound. This fact may be of interest as compared with the similar poisoning effect of benzanthrone in view of the chemical constitution.

Experimental[6]

9,10-Dimethyl-9,10-dihydroanthracene.—Into a boiling suspension of 0.62 g. of 9,10-dimethylanthracene in 6 g. of ethyl alcohol was added 2.5 g. of metallic sodium in small portions. On addition of sodium the yellow crystals disappeared and a colorless solution resulted, which, however, turned reddish brown due perhaps to the action of sodium alcoholate. After two and a half hours of boiling, the solution was decolorized with active carbon. On cooling a small quantity of colorless crystals separated out. The solution was added with water in order to precipitate the desired reaction product. On repeated recrystallizations of the material from alcohol and from glacial acetic acid colorless, rectangular or square leaflet crystals of m. p. 130° resulted, yield 0.2 g. The product is very soluble in ether, benzene, carbon disulfide, moderately soluble in alcohol and glacial acetic acid. The product gives no picrate and its solution does not show a fluorescence.

Anal. Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.45; H, 7.92.

When the crystals were mixed with aluminum chloride in the presence or absence of benzene and after thirty minutes of standing poured into water, characteristic yellow crystals separated. A benzene solution of this material exhibits a beautiful violet fluorescence and on addition of picric acid gave dark violet-brown needles, thus proving the formation of 9,10-dimethylanthracene.

2-Acetyl-9,10-dimethylanthracene.—When a mixture of 7.0 g. of 9,10-dimethylanthracene, 150 cc. of carbon disulfide, 2.7 g. of acetyl chloride and 4.5 g. of aluminum chloride was stirred for four hours at room temperature, the reaction did not take place to any appreciable extent. But as soon as the temperature was elevated to 45° the reaction ensued. The progress of the reaction was traced by the liberation of hydrogen chloride. After an additional two hours at 45° the reaction product was poured into iced water acidified with hydrochloric acid, and treated in the usual way. There was obtained a brown solid which on repeated recrystallizations from alcohol using active carbon gave fine yellow crystals of m. p. 164.5°. The product developed blue coloration in concentrated sulfuric acid, yield 6.5 g.

Anal. Calcd. for $C_{18}H_{16}O$: C, 87.28; H, 6.45; mol. wt., 248. Found: C, 87.08; H, 6.45; mol. wt., 243.

A solution of 1.0 g. of the substance in glacial acetic acid was oxidized with 3.0 g. of chromic acid in the usual way and the product was recrystallized from glacial acetic acid. There was obtained an anthraquinonecarboxylic acid of m. p. 277–280°. The mother liquor yielded the same substance. As the isomers of the acid have nearly the same melting points, for the identification we have methylated the material by the E. Fischer method. An ester of m. p. 165–166.5° resulted, which, when admixed with an authentic sample of methyl ester of anthraquinone-2-carboxylic acid, did not depress the melting point.

DEPARTMENT OF INDUSTRIAL CHEMISTRY
FACULTY OF ENGINEERING
KYÔTO UNIVERSITY
KYÔTO, JAPAN
RECEIVED NOVEMBER 23, 1946

---

[1] Barnett and Matthews, *Ber.*, **59**, 1429 (1926); Bachmann and Chemerda, *J. Org. Chem.*, **4**, 583 (1939).

[2] Angelbis and Anschütz, *Ber.*, **17**, 165 (1884); Anschütz, *Ann.*, **235**, 305 (1886).

[3] I. G. Farbenindustrie A.-G., German Patent 492,247; *Friedlaender*, **16**, 1195.

[4] Nenitzescu, *Ber.*, **72**, 819 (1939).

[5] Hewett, *J. Chem. Soc.*, 293 (1940).

[6] Microanalyses by Miss Meizyô of our Laboratory.

NEW COMPOUNDS

Di-(*p*-anisyl)-methylcarbinol

Although 1,1-di-(*p*-anisyl)-ethylene has been made from di-*p*-anisyl ketone and methylmagnesium bromide,[1,2] the corresponding tertiary alcohol, di-(*p*-anisyl)-methylcarbinol, was not isolated because the intermediate Grignard addition compound was hydrolyzed in acid solution. The alcohol has now been made by modification of the Grignard reaction.

In a dry 500-ml. 3-necked flask fitted with a stirrer, nitrogen inlet, reflux condenser and dropping funnel was placed 50 ml. of 1.2 *N* (0.058 mole) methylmagnesium bromide. To this solution was added dropwise during

---

[1] Pfeiffer and Wizinger, *Ann.*, **461**, 144 (1928).

[2] Bergmann and Bondi, *Ber.*, **64B**, 1455 (1931).

twenty minutes 12.5 g. (0.048 mole) of di-*p*-anisyl ketone (m. p. 140–142°) dissolved in 125 ml. of dry, warm thiophene-free benzene. After fifteen minutes of stirring at room temperature, a qualitative test for the Grignard reagent[3] was made to be certain that an excess had been used. Otherwise the product is difficult to purify because of the ketone present. The mixture was hydrolyzed by pouring it into 200 g. of ice and water containing 10 g. of ammonium chloride. The benzene–ether layer was separated and washed successively with 100-ml. portions of water, 2% sodium carbonate solution, and water. The solvent was removed under reduced pressure at 60° to give 10 g., 83% of the calculated yield melting 80–83°. Crystallization from 95% ethanol made alkaline to phenolphthalein with aqueous sodium hydroxide raised the melting point to 82–83.5°. To avoid dehydration the alcoholic solution was not heated above 60°.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.80; H, 6.94; mol. wt., 258. Found: C, 74.90; H, 6.74; mol. wt. (cryoscopic in benzene), 265.

One gram of this compound was oxidized by refluxing one hour in a solution of 10 ml. of glacial acetic acid, 2 drops of concentrated sulfuric acid, and 1.8 g. of chromic acid. The yield of ketone was 0.7 g., melting 141–142°. A mixed melting point with authentic di-*p*-anisyl ketone showed no depression.

Di-(*p*-anisyl)-methylcarbinol is very readily dehydrated to 1,1-di-(*p*-anisyl)-ethylene. A sample of the pure compound standing on the shelf spontaneously formed the ethylene in less than two months, whereas diphenylmethylcarbinol and di-(*p*-chlorophenyl)-methylcarbinol are stable under the same conditions. Thus, it is important in this synthesis to avoid elevated temperatures and even traces of acid.

---

(3) Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

SHERWIN-WILLIAMS LABORATORY
WESTERN RESERVE UNIVERSITY OLIVER GRUMMITT
CLEVELAND 6, OHIO DEAN MARSH

RECEIVED NOVEMBER 19, 1947

4-Benzyl-2,3-isopropylidene-D-mannosan<1,5>β<1,6> and 2-Benzyl-3,4-isopropylidene-D-galactosan<1,5>β<1,6>

4-Benzyl-2,3-isopropylidene-D-mannosan<1,5>β<1,6>.—Two and one-half grams of 2,3-isopropylidene-D-mannosan<1,5>β<1,6>[1] was dissolved in 60 ml. of liquid ammonia in a three-necked flask (fitted with a mercury-sealed stirrer, a gas inlet tube and an outlet protected by a soda lime tube) cooled in a Dry Ice–acetone cooling bath. Three grams of sodium in small pieces was added in one portion and solution was completed by gentle stirring; the blue color imparted to the solution disappeared in a few minutes. Following the addition of 2.3 ml. (about 1.6 molecular equivalents) of benzyl chloride the flask was raised from the bath and the ammonia allowed to boil off slowly while standing at room temperature; dry air was then passed through the flask for two hours and the residue, which was easily scraped from the flask, was dried overnight in an evacuated desiccator. The reaction product was washed well with water and recrystallized from 5 parts of alcohol, forming large elongated plates which melted at 99–100° and rotated $[\alpha]^{20}D$ −13.0° in chloroform (*c*, 0.83). It is soluble in acetone, chloroform, pyridine and warm alcohol and nearly insoluble in water and petroleum ether.

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.86; H, 7.07.

2-Benzyl-3,4-isopropylidene-D-galactosan<1,5>β<1,6>.—The procedure used for the benzylation of 3,4-isopropylidene-D-mannosan<1,5>β<1,6> was applied to 2.5 g. of 3,4-isopropylidene-D-galactosan<1,5>β<1,6> prepared by the pyrolysis of lactose.[2] The product remaining after removal of the ammonia was somewhat sticky and it was extracted with one 10-ml. and three 5-ml. portions of chloroform; the extract was evaporated and gave a mass of long fine needles which was stirred with 10 ml. of alcohol, cooled and filtered. The yield was 3.2 g. (89%). The compound was recrystallized from three parts of alcohol in the form of needles which melted at 84–85° and rotated $[\alpha]^{20}D$ −81.9° in chloroform (*c*, 0.85). The benzyl ether is soluble in acetone, ethyl acetate, ether, pyridine and warm alcohol and nearly insoluble in water and petroleum ether.

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.86; H, 7.05.

---

(1) Knauf, Hann and Hudson, THIS JOURNAL, **63**, 1449 (1941).

(2) Hann and Hudson, *ibid.*, **64**, 2436 (1942).

CHEMISTRY LABORATORY W. T. HASKINS
NATIONAL INSTITUTE OF HEALTH RAYMOND M. HANN
BETHESDA, MARYLAND C. S. HUDSON

RECEIVED OCTOBER 17, 1947

2,6-Di-*tt*-octyl-4-methylphenol[1]

A mixture of 214 g. (2 moles) of *p*-cresol and an equal volume of diisobutylene was placed in an ice-bath and stirred for three hours during which were added additional diisobutylene to make a total of 896 g. (8 moles) and 21 g. of 45% boron trifluoride in ether as catalyst. The mixture then was let stand at 40–50° for fifteen hours. Catalyst was removed by agitation of the reaction mixture with 350 g. of 30% aqueous sodium hydroxide. Distillation through a column packed with Raschig rings (6 theor. plates) yielded a small amount of diisobutylene at atmospheric pressure, and then, at 10 mm., fractions containing approximately 581 g. of tetraisobutylene and 283 g. 2-*tt*-octyl-4-methylphenol[2] (b. p. 143–144° (10 mm.); $n^{27}D$ 1.5105 (super-cooled); m. p. 47.0–47.8°, from petroleum ether). The viscous residue was distilled without fractionation to give 61 g. (9% yield) of crude 2,6-di-*tt*-octyl-4-methylphenol, a highly viscous yellow liquid, b.p. 168–195° (5 mm.) and $n^{27}D$ 1.5036, which slowly crystallized. Recrystallized twice from alcohol, the long needles had m. p. 51.6–52.2° and b. p. 188° (10 mm.).

Anal. Calcd. for $C_{23}H_{40}O$: C, 83.07; H, 12.13; mol. wt., 332.55. Found: C, 82.81, 82.54; H, 12.24, 12.02; mol. wt. (micro-Rast), 338.

---

(1) The 1,1,3,3-tetramethylbutyl group is designated *tt*-octyl after Niederl and Ruderman, THIS JOURNAL, **67**, 1176 (1945).

(2) W. F. Hester, U. S. Patent 2,008,017.

CHEMICAL AND PHYSICAL RESEARCH LABORATORIES
THE FIRESTONE TIRE & RUBBER COMPANY
AKRON 17, OHIO LELAND J. KITCHEN

RECEIVED NOVEMBER 7, 1947

1,4-Dimethoxy-2-butene[1,2,3] and 1,4-Dimethoxy-3-chloro-2-butanol

1,4-Dimethoxy-2-butene.—A total of 69.1 g. of 1,4-dimethoxy-2-butyne[4] was reduced in three equal batches, each dissolved in 100 cc. of methanol, with Raney nickel and hydrogen at room temperature and about 50 lb. pres-

---

(1) The work reported was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Rochester.

(2) This compound has been prepared by Johnson, *J. Chem. Soc.*, 1009 (1946). Dr. Johnson has pointed out in a private communication that the material obtained by him is undoubtedly the *trans* form, whereas the sample obtained by us by catalytic reduction must be the *cis* form.

(3) *Cf.* Campbell and O'Connor, THIS JOURNAL, **61**, 2897 (1939).

(4) This compound was prepared at Northwestern University by Professor C. D. Hurd and Dr. Otis Fancher, to whom we wish to express our appreciation. It was obtained by the action of chloromethyl methyl ether on the acetylenic Grignard (Lespieau, *Ann. chim.*, [8] **27**, 172 (1912); Dupont, *ibid.*, [8] **30**, 492 (1913)).

sure. The calculated amount of hydrogen was taken up in a few minutes, with the evolution of appreciable amounts of heat. The catalyst was removed by filtration, the batches were combined, and distilled through a column until the b. p. reached 70°. Some low-boiling petroleum ether was added, causing separation of a lower layer, which was removed, and the solution dried. The solvent was removed and the residue distilled, which yielded the following fractions:

I	II	III
3.4 g.	b. p. 100–136°	$n^{20}\mathrm{D}$ 1.4213
29.0	136–141°	1.4220
16.0	141–146°	1.4240

The analytical sample had the properties: b. p. 138–138.5°; $n^{20}\mathrm{D}$ 1.4201; d^{26}_{20} 0.8958.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.03; H, 10.42. Found: C, 62.00; H, 10.39.

1,4-Dimethoxybutane has $n^{15}\mathrm{D}$ 1.4031[5]; Johnson[2] reports $n^{20}\mathrm{D}$ 1.4220 for (*trans*) 1,4-dimethoxy-2-butene. The percentage composition calculated by this author for this compound (C, 63.2; H, 8.8) is somewhat in error.

1,4-Dimethoxy-3-chloro-2-butanol.—A 0.68 molar solution of hypochlorous acid was prepared by passing chlorine into a solution of 95 g. of sodium bicarbonate in 1140 cc. of water.[6] One hundred-cc. portions of this solution were added with stirring to 72.9 g. of 1,4-dimethoxy-2-butene while cooling with ice, a total of 1080 cc. (theoretical 930 cc.) of the hypochlorous acid solution being added. After the addition was complete, the solution was stirred for one-half hour in the ice-bath, then for three and one-half hours at room temperature, and allowed to stand overnight. At this point, a potassium iodide test showed practically no oxidizing power in the solution, and it was saturated with sodium chloride, extracted three times with ether and the residue from the ether extract distilled. A total of 69.0 g. was collected as product in several fractions, b. p. 92–98.5° (8 mm.) most of it boiling at 96–98.5°; the analytical sample had the following properties: b. p. 97–97.5° (8 mm.), $n^{21}\mathrm{D}$ 1.4542.

Anal. Calcd. for $C_6H_{13}ClO_3$: C, 42.74; H, 7.77. Found: C, 42.32; H, 7.41.

---

(5) Dionneau, *ann. chim.*, [9] **3**, 259 (1915).

(6) Wohl and Schweitzer, *Ber.*, **40**, 94 (1907).

(7) Present address, Department of Chemistry, Reed College, Portland, Oregon.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, NEW YORK
D. S. TARBELL
J. F. BURNETT[7]

RECEIVED NOVEMBER 17, 1947

COMMUNICATIONS TO THE EDITOR

THE CRYSTAL STRUCTURES OF AMMONIUM AND POTASSIUM MOLYBDOTELLURATES

Sir:

A structural study is now being made in this Laboratory of heteropoly ions of the general type $[XMo_6O_{24}]^{-n}$, in which the charge *n* depends on the metalloid X. The investigation is centered on the salts ammonium and potassium molybdotellurate, $(NH_4)_6TeMo_6O_{24}\cdot 7H_2O$ and $K_6TeMo_6O_{24}\cdot 7H_2O$, which have been described morphologically by Donnay and Mélon[1] as orthorhombic, homeomorphous and probably isostructural. A preliminary X-ray lattice study was reported by the writer to the Crystallographic Society in March 1947.[2] A more complete diffraction study since then has shown that the two salts are not isostructural, but possess entirely different and unrelated (though similar) symmetries. The final unit cell and space group data are as follows:

$(NH_4)_6TeMo_6O_{24}\cdot 7H_2O$, orthorhombic *mmm*; a_0 = 14.62 Å., b_0 = 14.91, c_0 = 14.26; space group *Pnaa* = C_{2h}^{10}; 4 formulas (as above) per cell, density calcd. 2.82, found (Donnay and Mélon) 2.78.

$K_6TeMo_6O_{24}\cdot 7H_2O$, orthorhombic *mmm*; a_0 = 14.30 Å., b_0 = 14.95, c_0 = 14.26; space group *Pbca* = C_{2h}^{15}; 4 formulas per cell, density calcd. 3.15, found (Donnay and Mélon) 3.05.

The structure problem was attacked by the preparation of Patterson maps for the ammonium salt projected on the three pinacoid faces, using diffraction intensities visually estimated from Weissenberg photographs. These maps showed sharp peaks revealing the positions of the tellurium and molybdenum atoms. Although these maps were greatly simplified by the presence of the heavy tellurium atom at a symmetry center, an ambiguity still remained which allowed the possibility of three different models. This ambiguity is represented by an indeterminacy of sign of the parameters of one of the three kinds of molybdenum atoms in the structure. Calculation of the structure factors for a certain class of reflections in each of the series (*hk*0), (0*kl*) and (*h*0*l*) which is sensitive to this change of sign, shows that a reasonable check of observed and calculated intensities is obtained with only one of the three possible models. The correct parameters for the tellurium and molybdenum atoms in the ammonium cryatals, and probably also the potassium crystals (with *x* and *z* interchanged), are

	x	*y*	*z*
Te	0	0	0
Mo_{I}	0	0.228	0
Mo_{II}	0.113	0.121	−0.168
Mo_{III}	0.113	−0.121	−0.168

The model accepted here is one originally proposed hypothetically by Anderson.[3] In it, the molybdenum atoms lie in a hexagon about the tellurium atom at the center (Te–Mo and Mo–Mo distances 3.42 Å.); the oxygen atoms lie close-

---

(1) J. D. H. Donnay and J. Mélon, *Proc. Nat. Acad. Sci.*, **20**, 327–335 (1934).

(2) H. T. Evans, Jr., *Am. Min.*, **32**, 687 (1947).

(3) J. S. Anderson, *Nature*, **140**, 850 (1937).

packed in two layers of twelve above and twelve below the plane of the hexagon, so that the tellurium and molybdenum atoms are octahedrally coördinated.

The detailed structures of both the ammonium and potassium salts are now under analysis, and will be described in full in a forthcoming paper.

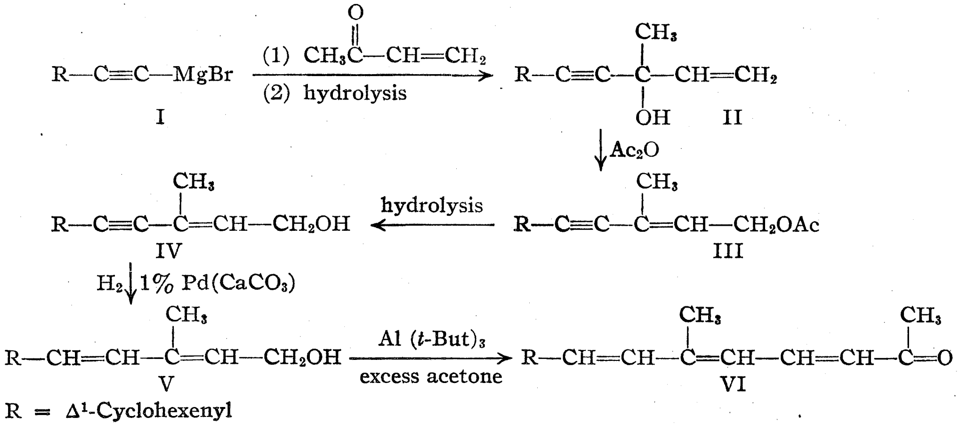
GEORGE EASTMAN LABORATORY
DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASS.
HOWARD T. EVANS, JR.

RECEIVED FEBRUARY 11, 1948

THE SYNTHESIS OF 1-[CYCLOHEXEN-1'-YL]-3-METHYL-1,3,5-OCTATRIEN-7-ONE (C_{15} KETONE)[1]

Sir:

Using the new approach to vitamin A synthesis,[2] we wish to report an alternative route which makes possible the synthesis of vitamin A and its analogs. The C_{15} ketone (VI) was thus synthesized by the following series of reactions:



The carbinol (II) was obtained in yields of 45–50%; b. p. 45–48° (10^{-4} mm.); n^{25}_D 1.5135; d^{25}_4 0.964; $\lambda_{max.}$ (alcohol), 231 mμ, log $\epsilon_{mol.}$ 4.36.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.8; H, 9.13; A. H. (Zer.), 1.0; unsaturation, 4.0 ⌈. Found: C, 81.23, 81.60; H, 9.20, 8.99; A. H. (Zer.). 0.99; unsaturation, 4.08 ⌈.

When the carbinol (II) was refluxed with acetic anhydride, the acetate (III) was obtained in 58–60% yields; b. p. 69–70° (10^{-4} mm.); n^{25}_D 1.5267; d^{25}_4 0.9938; $\lambda_{max.}$ (alcohol), 266.5 mμ, log $\epsilon_{mol.}$ 4.33.

Anal. Calcd. for $C_{12}H_{18}O$: C, 77.2; H, 8.33; unsaturation, 4.0 ⌈; saponification equivalent, 218. Found: C, 77.03; H, 8.51; unsaturation, 4.21 ⌈; saponification equivalent, 216.

The carbinol (IV) was obtained in good yields by the saponification in nitrogen of the acetate (III); b. p. 61–64° (10^{-4} mm.); n^{25}_D 1.5530; d^{25}_4 0.983; $\lambda_{max.}$ (alcohol), 266.5 mμ, log $\epsilon_{mol.}$ 4.22.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.80; H, 9.13; A. H. (Zer.), 1.0; unsaturation, 4.0 ⌈. Found: C, 81.51; H, 9.14; A. H. (Zer.), 0.9; unsaturation, 4.19 ⌈.

The carbinol (V) was obtained either by selective hydrogenation of (IV) or of (II) followed by allylic rearrangement. It boiled at 55–57° (10^{-4}–10^{-5} mm.); n^{25}_D 1.5268; d^{25}_4 0.961; $\lambda_{max.}$ (alcohol), 267 mμ, log $\epsilon_{mol.}$ 4.30.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.80; H, 10.18; A. H. (Zer.), 1.0; unsaturation, 3.0 ⌈. Found: C, 80.78; H, 10.48; A. H. (Zer.), 0.95; unsaturation, 3.16 ⌈.

The C_{15} ketone (crude) was obtained by the method previously described[2] in 90% yield; n^{25}_D 1.5765; A. H. (Zer.), 0.6. The mixture of the ketone and its aldol precursor was further dehydrated in toluene either with iodine or with *p*-toluenesulfonic acid; b. p. 75–85° (10^{-4} mm.); n^{25}_D 1.5960; $\lambda_{max.}$ (alcohol), 333 mμ; log $\epsilon_{mol.}$ 4.28.

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.30; H, 9.31; unsaturation, 4.0 ⌈. Found: C, 83.38; H, 9.27; unsaturation, 4.0 ⌈.

The C_{15} ketone formed a light yellow semicarbazone which discolors on standing in air; m. p. 162–164° (dec.).

All of the compounds (II to V inclusive) were also prepared with the methyl group in position two of the ring by Tome[3] and those with methyl groups in both two and six positions of the cyclohexene ring by other members of our group.

DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECH.
CAMBRIDGE, MASSACHUSETTS
NICHOLAS A. MILAS
FRANK X. GROSSI[4]
SIEGFRIED E. PENNER[5]
SAMUEL KAHN[6]

RECEIVED FEBRUARY 4, 1948

---

(1) Paper X on the synthesis of products related to vitamin A.

(2) Milas and Harrington, THIS JOURNAL, **69**, 2247 (1947).

(3) Tome, B.S. Thesis, M. I. T., May, 1947.

(4) Research Assistant 1942–1945. Present address, Royal Bond, Inc., St. Louis, Missouri.

(5) B.S. Thesis, M. I. T., June, 1945.

(6) M.S. Thesis, M. I. T., September, 1947. Present address, Godfrey Cabot, Inc., Boston, Massachusetts.

A GENERAL THERMODYNAMIC THEORY OF ION EXCHANGE PROCESSES

Sir:

The specific volume of a strong (sulfonic) acid resin measured in water with the following cations in the exchange position is: H^+, 1.283; Na^+, 1.655; K^+, 1.434; Cs^+, 1.388; Mg^{++}, 1.665; Ca^{++}, 1.585; Ba^{++}, 1.453; Ag^+, 1.283. When an alkali metal resin is equilibrated with solutions of the same alkali ion, the specific volume decreases with increasing concentration, and usually becomes less than the pure water-equilibrated volume of the next heavier member of this group.[1]

These and other data, in conjunction with a simple mechanical model and classical physicochemical methods, provide a basis upon which exchange phenomena may be interpreted. The resin is an osmotic system in which the fixed, non-diffusible (anionic) groups act as though restricted by a semipermeable membrane separating the inner pore volume (V_i) from the external solution. V_i varies with the swelling pressures and the elasticity of the resin structure. V_i and total resin volume (V) can be determined by pycnometric[1] and other methods.[2]

Dry resins swell in water chiefly because of hydration of the fixed and counter ions and the osmotic pressure due to the latter. If a salt of the counter ion is added to the external water, Donnan effects virtually exclude it from the internal volume; a counter osmotic pressure is established with consequent reduction in swelling. The dependence of swelling upon the (calculable) counter osmotic pressure provides access to the $p-V$ relation; other methods may also be applicable.[3]

Consider the exchange process

$$\mathrm{A_i^+ + B_0^+ = A_0^+ + B_i^+}$$

where neither A^+ nor B^+ forms a weakly-dissociated compound with the fixed anion. The virtual osmotic work for $\mathrm{A_i^+} \rightarrow \mathrm{A_0^+}$ is $\delta n\ RT \ln a_{\mathrm{A_i^+}}/a_{\mathrm{A_0^+}}$, and the virtual pV work is $\delta n p \overline{V}_{\mathrm{A_i^+}}$. $\overline{V}_{\mathrm{A_i^+}}$ may be determined experimentally.

The expressions for $\mathrm{B_0^+} \rightarrow \mathrm{B_i^+}$ are similar, and, as $\delta w = 0$

$$RT \ln \left(\frac{a_{\mathrm{A^+}}}{a_{\mathrm{B^+}}}\right)_{\mathrm{i}} \left(\frac{a_{\mathrm{B^+}}}{a_{\mathrm{A^+}}}\right)_0 = p(\overline{V}_{\mathrm{B^+}} - \overline{V}_{\mathrm{A^+}})_{\mathrm{i}}$$

where p is of course the swelling pressure. The separation factor $K_{\mathrm{D}} = a_{\mathrm{A_i^+}}a_{\mathrm{B_0^+}}/a_{\mathrm{B_i^+}}a_{\mathrm{A_0^+}}$ is then unity for $\overline{V}_{\mathrm{B_i^+}} = \overline{V}_{\mathrm{A_i^+}}$. This is the case for K^+ and NH_4^+. K_{D} is not a constant because p and the $\overline{V}$'s are not constants; the latter depend strongly upon $a_{\mathrm{A_i^+}}/a_{\mathrm{B_i^+}}$ in a manner determined by the ionic diameters.

If the fixed group is weakly acidic (—COOH) or a weakly dissociated ion-pair is formed (—SO_3Ag), the corresponding dissociation constants must be introduced into the expression above; volume change terms of the form $(\overline{V}_{\mathrm{A^+}} + \overline{V}_{\mathrm{R^-}} - \overline{V}_{\mathrm{AR}})_{\mathrm{i}}$ occur and the expression becomes too complex for development within the limits of this communication. The dissociation constant becomes a function of swelling pressure. This complication appears in the alkaline earths; the swelling of Mg^{++}, Ca^{++} and Ba^{++} resins is directly proportional to the solubility of the benzene sulfonates.

These concepts form the basis of a general theory of exchange processes, applicable also to cationic resins and non-aqueous systems,[4] which permits predictions of K_{D} from measurable physical quantities.

---

[1] H. Chaya, Thesis, Polytechnic Institute of Brooklyn, June, 1947.

[2] R. A. Gortner, "Outlines of Biochemistry," J. Wiley and Sons, Inc., New York, N. Y., 1938.

[3] E. Posnjak, *Kolloidchem. Beih.*, **3**, 417 (1912).

[4] G. Wiegner, *J. Soc. Chem. Ind.*, **50**, 55 (1931).

DEPARTMENT OF CHEMISTRY
POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN, NEW YORK HARRY P. GREGOR

RECEIVED DECEMBER 19, 1947

ON THE DYNAMIC STATE OF ANTIBODIES

Sir:

Experiments with N^{15} labeled amino acids carried out by Heidelberger, *et al.*,[1] have led these authors to the conclusion that normal serum proteins, as well as immune globulins, incorporate dietary amino acids during immunization. However, no exchanges were stated to occur with injected antibody though the authors found an excess of N^{15} in these substances which was about two to four times as high as their experimental error, and about one-fourth to one-eighth of their value for the active antibodies.

We have repeated these experiments using C^{14} leucine in the following manner:

A rabbit was actively immunized against *p*-azophenylarsonic acid-ovalbumin until the serum had a high titer of the corresponding antibodies. Ten days after the last injection (day 1) an injection of 10 cc. of concentrated rabbit pneumococcus antiserum (Type I) was given intravenously, followed by a similar injection on day 2. On the same day, an injection of 30 cc. of a 1% leucine solution was given intraperitoneally. The leucine contained C^{14} in the carboxyl group and had an activity of about 0.06 microcurie per milligram.[2] Similar injections of leucine were given on the three following days, 1.15 g. of leucine being injected in all.

Samples of serum were taken on days 5, 9 and 16. The antibodies were precipitated with the corresponding antigens, washed with saline (3x), distilled water (1x), alcohol and ether (2x), dried and analyzed for C^{14}. The results are given in the

---

[1] M. Heidelberger, H. P. Treffers, R. Schoenheimer, J. Ratner and D. Rittenberg, *J. Biol. Chem.*, **144**, 555 (1942).

[2] The C^{14} used in this investigation was supplied by the Monsanto Chemical Co. and obtained on allocation from the U.S. Atomic Energy Commission. This work was supported by a grant from the Rockefeller Foundation.

table. The numbers indicate counts per 10 mg. of substance per minute, after subtraction of the back-ground rate of 10 counts. The error was less than 1 count per minute.

	R-Azo-ovalbumin	Pneumococcus I	Serum proteins
First bleeding (day 5)	11	12	59
Second bleeding (day 9)	18	8	53
Third bleeding (day 16)	26	no antibody isolated (amount too small)	39

As a control on the purity of the precipitates, two experiments were carried out in which a small amount of pneumococcus I antiserum was added to radioactive serum containing no pneumococcus antibodies. After thorough mixing and standing for one hour in the refrigerator, the corresponding polysaccharide was added to precipitate the antibodies. The precipitate was worked up in the same way as the others but contained no C^{14} (less than 0.1 count per minute per mg.).

The order of magnitude of the radioactivity found in the passive antiserum was essentially the same as that found by Heidelberger and Schoenheimer, *viz.*, about one-fifth to one-sixth of the serum proteins. Our results are in line with theirs, though we think it very probable that an exchange takes place with the injected or passive transfer antibody.

A detailed paper on this subject will be published later.

CALIFORNIA INSTITUTE OF TECHNOLOGY
GATES AND CRELLIN LABORATORIES OF CHEMISTRY
PASADENA 4, CALIFORNIA
EDWARD C. KOOYMAN
DAN H. CAMPBELL

RECEIVED MARCH 4, 1948

NEW BOOKS

Elsevier's Encyclopaedia of Organic Chemistry. Volume 13, **Tricyclic Compounds.** Series III, **Carboisocyclic Condensed Compounds.** E. JOSEPHY AND F. RADT, EDITORS. Elsevier Publishing Company, Inc., 215 4th Avenue, New York 3, N. Y., 1946. xx + 1265 pages; 17.5 × 26 cm. Subscription Price, $78.00; Serial Price, $91.00; Single Volume Price, $104. Volume 14, **Tetracyclic and Higher-Cyclic Compounds.** Series III, **Carboisocyclic Condensed Compounds.** New York, 1940. xx + 711 pages; 17.5 × 26 cm. Subscription Price, $45.00; Serial Price, $52.50; Single Volume Price $60.00.

Elsevier is a monumental new encyclopedia of organic compounds comparable to Beilstein but written in English. The work was undertaken in Amsterdam in 1937 under the editorship of Drs. Edith Josephy and F. Radt, both formerly of the Beilstein staff. Volume 14, Tetracyclic and Higher-Cyclic Compounds, which includes sterols, sex hormones, triterpenes, and carcinogenic hydrocarbons, was selected as the first volume to be published because of the current interest in these fields. This volume was completed in 1940 but could not be published until 1946 because of the war. Volume 13, which includes anthracene, phenanthrene, the resin acids, dicyclopentadiene, trycyclene, also bears the publication date 1946 and has just become available. Further volumes are scheduled for publication at intervals of about six months. The whole range of organic compounds is to be covered in a total of twenty volumes in thirty-eight parts. The production plan provides for completion of the work by 1963.

Elsevier is no English-language version of Beilstein; it is a thoroughly excellent competitive compendium with a character all its own. The most substantial difference in the scope of the two works is that Beilstein covers the patent literature whereas Elsevier does not; the absence of references to patents in the new work is a shortcoming in some fields but of little consequence in others. Elsevier shares with Beilstein a high quality of accuracy, reliability and thoroughness. It contains more and better formulas and numerous summarizing reaction charts; it is printed on good paper in easily readable type; and the whole scheme of publication of the new compendium represents a certain advance over the classical German documentation of organic chemistry. It is my opinion, however, that the one work supplements, rather than supplants, the other. What the user of either work most urgently requires is data and references of the most recent possible date. Immeasurable research time can be saved by any combination of reference works that will expedite literature searches. Since Beilstein and Elsevier operate on different publication schedules such that new volumes of each will cover recent literature in alternate fields, the combination of the two is bound to afford a better general coverage than either alone. For this reason alone, if for no other, Elsevier can be recommended as a worthwhile investment for the library of any active center of research already equipped with Beilstein.

The avowed ultimate goal of the Elsevier publication is to include complete references to the literature until four years prior to publication. The recently published Volume 13 bears evidence that this high standard of attainment may eventually be realized. This volume, published as of 1946 under the difficult circumstances of the post-war period, covers the whole literature through 1936 and includes most or all key references concerning the structure of compounds through 1941 or 1942. This high speed of documentation is achieved in part by use of an ingenious scheme for the citation of references; each item of information in the text is followed by a parenthetical citation of the year of publication and the name of the first author. The full references are then listed by years at the end of short sections. One advantage of the scheme is that additional references of any date can be entered at the last minute without disturbance of any sequence of reference numbers. Another is the avoidance of the frequent repetition of reference citations (*cf.* Beilstein). Another is that the reader can see from a glance at the list of references for a given section the date to which the literature survey has been carried.

The data cited in Elsevier were almost all taken directly from the original papers. A total of 229 journals were consulted in the composition of Volume 14. In the case of a few papers from obscure journals both the *Chemisches Zentralblatt* and *Chemical Abstracts* were consulted.

The system of arrangement employed in Elsevier is a simple and rational one based upon structure; closely related compounds are placed together, and derivatives are described along with the parent compounds. The reader is further assisted in rapidly finding specific compounds by excellent subject and formula indexes in each volume. The subject indexes have the valuable feature of including a number of summarizing entries that list groups of compounds of similar structural and functional types: "Carcinogenic compounds," "Vitamins and provitamins," "Azido compounds." The editors showed wisdom in deliberately refraining from introducing new systems of nomenclature; the names recorded are those chosen by the investigators who built the science. Elsevier is thus a chemist's book, and it will be used and liked by those who build the science of the future. In my opinion, the contrasting disregard of chemists' preferences as expressed in established usage detracts enormously from the usefulness and lasting influence of *Chemical Abstracts*.

My wife and I have made considerable use of the section on sterols in Volume 14 and have found it excellent. The highly confused early literature has been untangled with care and skill. Good judgment has been exercised in the discussions of structures that are still controversial and in the selection of best values of physical constants. The data cited include physiological actions, specific rotations for different wave lengths and in different solvents, absorption maxima (unfortunately without specification of the solvent), axis ratios of crystals, magnetic susceptibilities. Although the sterol section is very complete, we noticed the omission of Δ^2-cholestene ("neocholestene"), discovered by Mauthner in 1909. We are sorry that Elsevier accepted Rosenheim and King's proposed names coprostene, coprostenone, and coprostenol for compounds obtained from cholesterol and more appropriately called Δ^4-cholestene, cholestenone, and Δ^4-cholestenol-3. We regret that the editors did not venture to cross the border of rigid classification and include D vitamins and the tachysterols along with ergosterol and 7-dehydrocholesterol and all the many other products of irradiation and isomerization. These are very minor points; we heartily endorse this splendid new Encyclopedia.

Louis F. Fieser

A Survey of Anti-Malarial Drugs 1941–1945. Edited by Frederick Y. Wiselogle. Subsidized by the Office of Scientific Research and Development on Recommendation by the Committee on Medical Research. J. W. Edwards, Ann Arbor, Mich. 1946. Two volumes (the second in two parts). 1921 + xi pages. 22 × 28 cm. Price, $30.00 the set.

In the Survey is presented an historical summary of the evolution of the organization developed under National Research Council auspices with funds from the Office of Scientific Research and Development for the all-out attack on the problem of the prevention and cure of malaria through chemotherapeutic means. Detailed data on the antimalarial activity of close to 15,000 substances which were examined for their response to experimental avian malarias are given. Further, pharmacological data are given on what appeared to be the more promising substances and extensive clinical data are recorded on those drugs which warranted clinical trial in man. The work is divided nominally into two volumes, the second volume appearing in two parts, making a total of three actual volumes.

In the first volume are recorded an outline of the organizational scheme whereby the whole vast undertaking was coördinated—a structure which by its flexibility and adaptability to changing emphasis may well serve as a model for future organizations; a critical and detailed discussion of the methods used in the pharmacological aspects of the problem, some of which represent for the first time a logical and rational approach to this and similar problems; and an equally detailed and rational discussion of the methods used in the clinical evaluation of the drugs which furnishes, at least as far as this reviewer is aware, one of the finest examples so far produced of the development of methods for comparison of drugs under carefully controlled and standardized conditions. Incorporated into the two latter sections are critical discussions of hypotheses of the mode of action of certain chemical classes of drugs and of the biology of the various malaria infections. For the reader interested in securing an over-all picture of the relationsip between chemical structure and antimalarial action, the summarizing tables dealing with chemical series of potential interest, which are incorporated in the discussion of the pharmacological aspects of the work, will be very useful.

The second volume (two parts) is devoted in its entirety to a tabulation of the results of the tests on all the compounds examined. The chemical classification used is novel, but after a moderate amount of study, presents no insurmountable difficulties in application. Presentation of the structural formula for every compound to which a definite structure can be assigned leaves no room for confusion regarding identity of the substances listed. One could wish that the mass of compounds listed in Volume II could have been arranged more in accordance with detailed structural variations. However, this is partially compensated for by the summarizing tables of Volume I. Of particular value is the discarding of the previously used and meaningless method of reporting antimalarial activity and toxicity as a therapeutic index and substitution therefor of absolute values in terms of selected standard substances such as quinine, sulfadiazine, etc. Also to be commended is the convention of reporting such data in exact mathematical equivalents referred to the standards rather than the use of such symbols as $^+$, $^{+++}$ or $\pm$. Of great value are the fine indices of which there are three: subject, molecular formula and Survey Number.

No details of the synthetic chemistry involved in the preparation of the drugs are given. Inclusion of this information would result in a work of inordinate size. By an arrangement whereby the authors of papers dealing with the large bulk of the synthetic chemistry list the drugs by Survey Number in their communications, sufficient cross referencing should be available to enable this gap to be conveniently filled from the chemists' point of view.

The work is clearly reproduced by the photo offset process and remarkably free from errors. It will prove of great value not only for one interested in the narrow field of the chemotherapy of malaria, but, by virtue of the mass of pure toxicity data alone as well as of the analytical methods described, to all who are interested in chemotherapy in general.

Robert C. Elderfield

Advances in Enzymology. Vol. V. 1945. Edited by F. F. Nord, Fordham University, New York, N. Y., and C. H. Werkman, Iowa State College, Ames, Iowa. vii + 268 pp. Illustrated. 15.5 × 23.5 cm. Price $5.50. Vol. VI. 1946. Edited by F. F. Nord. x + 563 pp. Illustrated. 15.5 × 23.5 cm. Price $6.50. Vol. VII. 1947. Edited by F. F. Nord. xi + 665 pp. Illustrated. 16 × 23.5 cm. Price $8.75. Interscience Publishers, Inc., 215 Fourth Ave., New York 3, N. Y.

The three most recent annual volumes of this valuable series continue the high standards set in the earlier volumes. When it is realized that these reviews were prepared while the writers were still under the stress of war conditions or were exposed to the almost equally disturbing events of the period immediately after the cessation of hostilities, the thoroughness and scientific detachment with which the topics have been discussed is the more surprising.

No adequate account of the contents of these volumes is possible in the space available. The reviewer must therefore content himself with reference to those chapters which were found to be most stimulating and informing. In Volume V, N. W. Pirie's thoroughly critical account of certain plant viruses is especially useful for its point of view. H. Blaschko's review of the amino acid decarboxylases of mammalian tissue together with that of E. F. Gale on the amino acid decarboxylases of bacteria in Volume VI summarize present day knowledge of this group of enzymes effectively. Gale's chapter is unusual inasmuch as so large a part of the material discussed derives from the work of his own laboratory. E. Stotz has given a clear account of pyruvate metabolism and F. Schlenk of the enzymatic reactions in which nicotinamide and related substances are involved in Volume V; V. A. Engelhardt has dealt with the adenosinetriphosphatase properties of myosin and F. Lipmann with acetyl phosphate in Volume VI. F. H. Johnson has discussed bacterial luminescence in Volume VII. These papers are all strictly within the field of enzymology.

However, the editor obviously interprets the extent of this field in the broadest terms and several of the reviews deal with topics that many would regard as straightforward biochemistry. For example, K. C. D. Hickman and P. L. Harris have discussed the biochemical interrelationships of tocopherol in Volume VI in a paper that is by far the clearest and most interesting account of this complex and difficult subject that has come to the reviewer's attention. Volume VII contains accounts of asymmetric synthesis by P. D. Ritchie, of hemoproteins by H. Theorell, and of the chemistry of tetrapyrroles by S. Granick and H. Gilder. However, G. Hevesy's outstanding review of the application of radioactive indicators in biochemical problems does indeed deal with reactions strictly within the field of enzymology.

Several of the reviews are concerned with topics allied with technology. In Volume VI, W. G. Frankenburg has discussed the chemical changes that take place in tobacco leaves during the process of curing, and W. F. Geddes the significance of the amylases of wheat in milling and baking. In Volume VII, F. M. Hildebrandt gives a review of industrial fermentation research in recent years.

On the whole the volumes under review are almost essential equipment for the present day biochemical laboratory. They are a mine of authoritative information. However, there is another side of the picture. Publishing costs of books are high and the marked advance in price and increase in size of the volumes means that an increasingly serious load is thrown upon the individual who feels that he must maintain his subscription to the series. To be sure, scientific journals have also increased their price, but not in the ratio of \$5.50 to \$8.75. The publishers would do well, therefore, to make every effort to diminish the cost of these volumes in the future, even if sacrifices in the length of the articles or in style of publication must be made.

H. B. Vickery

BOOKS RECEIVED

January 10, 1948–February 10, 1948

Jerome Alexander. "Life, Its Nature and Origin." Reinhold Publishing Corporation, 330 West Forty-Second Street, New York 18, New York. 291 pp. \$5.00.

J. J. Bikerman. "Surface Chemistry for Industrial Research." Academic Press Inc., Publishers, 125 East 23rd Street, New York, New York. 464 pp., \$8.00.

R. E. Burk and Oliver Grummitt. "Frontiers in Chemistry, Volume V. Chemical Architecture." Interscience Publishers, Incorporated, 215 Fourth Avenue, New York 3, New York. 202 pp. \$4.50.

H. Eilers, R. N. J. Saal, and M. van der Waarden. "Chemical and Physical Investigations on Dairy Products. Monographs on the Progress of Research in Holland." Elsevier Publishing Company, Inc., 215 Fourth Avenue, New York 3, New York. 217 pp.

C. J. Gorter. "Paramagnetic Relaxation." Elsevier Publishing Company, Incorporated, 215 Fourth Avenue, New York 3, New York. 127 pp. \$2.25.

T. H. James and George C. Higgins. "Fundamentals of Photographic Theory." John Wiley and Sons, Incorporated, 440 Fourth Avenue, New York 16, New York. 286 pp. \$3.50.

Alexander S. Levens. "Nomography." John Wiley and Sons, Incorporated, 440 Fourth Avenue, New York 16, New York. 176 pp. \$3.00.

H. Mark and E. S. Proskauer. "The Science of Plastics. Volume I." Interscience Publishers, Incorporated, 215 Fourth Avenue, New York 3, New York. 632 pp. \$9.00.

Melville Sahyun. "Proteins and Amino Acids in Nutrition." Reinhold Publishing Corporation, 330 West Forty-Second Street, New York 18, N. Y. 566 pp. \$7.50.

Ralph L. Shriner and Reynold C. Fuson. "The Systematic Identification of Organic Compounds." Third Edition. John Wiley and Sons, Incorporated, 440 4th Avenue, New York 16, New York. 370 pp. \$4.00.

J. L. Snoek. "New Developments in Ferromagnetic Materials. Monographs on the Progress of Research In Holland." Elsevier Publishing Company, Incorporated, 215 Fourth Avenue, New York 3, New York. 136 pp. \$2.50.

Frank J. Welcher. "Organic Analytical Reagents. Volume IV." D. Van Nostrand Company, 250 Fourth Avenue, New York. 624 pp. \$8.00 (\$7.00 series orders.)

"Selected Values of Properties of Hydrocarbons." (Circular of the National Bureau of Standards C46). Prepared as part of the work of the American Petroleum Institute Research Project 44 by Frederick D. Rossini, Kenneth S. Pitzer, William J. Taylor, Joan P. Ebert, John E. Kilpatrick, Charles W. Beckett, Mary G. Williams and Helene G. Werner. For Sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 483 pp. \$2.75.